

Pandemic Influenza

How Worried Should We Be?

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Pandemic influenza is once again on the radar of the public health community. For most people, the destruction and upheaval caused by the 1918-19 flu pandemic is an obscure historical event, but the 2003 SARS epidemic and the smoldering H5N1 avian influenza epizootic in Asia have renewed interest in a flu pandemic and brought dire predictions of its imminent recurrence. At the same time, most of us in public health would like to avoid a repeat of 1976, when ominous forecasting about swine flu led to public anxiety, expenditure on mass vaccination, and embarrassment when the pandemic never materialized. So just how real a possibility is a worldwide crisis caused by a flu pandemic, and what can be done to prepare?

Despite causing 36,000 deaths in a routine US winter, in the public consciousness flu remains an inaccurate name for the common cold and not something to be feared. But people are still alive today who lived through the fall and winter of 1918-19 when a novel H1N1 strain of influenza virus emerged and spread so rapidly and with such virulence that it killed between 20 and 50 million people and affected life in every corner of the world. Up to 20 percent of the world's population was infected, and an estimated 675,000 people died of influenza in the US alone. Unlike a typical flu year when most deaths occur in infants and the elderly, during this pandemic the young and healthy were disproportionately affected. Current theories attribute the high mortality both to the lack of population immunity to the strain as well as the vigorous immune response produced by the virus in the respiratory tract, resulting in rapid development of acute respiratory distress syndrome (ARDS), highly lethal in this era before mechanical ventilation. The large percentage of the population affected in each country overwhelmed the capacity of health care systems as well as the ability to safely dispose of the large number of dead. In the US at first, the war propaganda effort and official denial of the problem in many areas prevented a rapid response to the epidemic. Eventually widespread, and widely unpopular, authoritarian measures were implemented, including banning public gatherings, closing schools, and limiting funerals to 15 minutes.

Influenza strains

Pandemic influenza is caused by a strain of influenza A virus that is new to humans and to which, therefore, there is almost no pre-existing population immunity. The strain must also possess the ability to produce sustained human-to-human transmission, as occurs with the strains that cause the yearly flu epidemics. Small changes in either

hemagglutinin (H) or neuraminidase (N) surface proteins, resulting from point mutations (genetic drift), account for some of the antigenic variation between influenza strains, allowing evasion of circulating antibodies and facilitating person-to-person transmission. However, major gene reassortments (genetic shift) result in viruses so antigenically different that they are unrecognizable to the immune system. These new strains are given a different H or N designation. Typically, it is the emergence of novel hemagglutinin subtypes that characterize a pandemic strain. The three major pandemics of the twentieth century were caused by the emergence of strains with a novel hemagglutinin protein: 1918 (H1N1), 1957 (H2N2), and 1968 (H3N2). Currently, only H1, H2, and H3 subtypes are circulating among humans; typically H5, H7, or H9 infect primarily birds.

Why worry?

Novel strains can emerge as a result of reassortment of genes between viruses with different host species (including birds and pigs), as in 1957 and 1968. However, avian viruses may also adapt to transmit directly from birds to humans, as in 1918 and recently with H5N1. The natural reservoir for avian influenza is wild ducks and geese, which are infected asymptotically and spread the virus easily to other species. These avian strains can be of either low or high pathogenicity when they infect domestic poultry. The extraordinary transmissibility and high mortality among poultry of pathogenic strains such as H5N1 give rise to the concern that if such a strain adapts to the human respiratory tract, a pandemic will result.

Much of this concern arises from the steady increase in epizootic activity with avian influenza strains in the past few years and the accompanying increase in human infections with these strains. The first dramatic H5N1 epizootic was in 1997 in Hong Kong, which resulted in 18 human cases with 6 deaths, and was interrupted only through the culling of millions of chickens. The H5N1 epizootic recurred in 2003 in eight Asian countries and was again slowed by mass culling, but it has recurred in Cambodia, China, Vietnam, Indonesia, Malaysia, Thailand, and North Korea. In July 2005, an outbreak of avian influenza in Siberia killed hundreds of poultry. Although the cost to the poultry industry in these countries has already been dramatic, from the public health perspective the most concerning aspect is the increasing numbers of human infections. As of August 2005, 109 human H5N1 infections have been confirmed, with 55 deaths (50 percent mortality) occurring in Cambodia, Indonesia, Thailand,

and Vietnam. All of these cases appear to have developed through contact with infected birds, with the exception of one probable case of human-to-human transmission in Vietnam. These numbers are, of course, only as good as the countries' surveillance system for human cases. Given that many cases occur in rural areas among farmers, who may not report their illnesses, the true number of infections could be higher.

Reassortment of avian and human genes has not yet been observed in circulating avian strains in Asia. All genes in strains isolated from birds and human infections are of avian origin. However, the H5N1 strains currently circulating are antigenically heterogeneous and distinct from 1997, 2003, and 2004 strains, which is an indicator of the extreme mutability of the influenza virus. There also appears to be an increasing ability of circulating avian viruses to infect mammals such as tigers and domestic cats. Finally, although H5N1 appears to be the most active current avian strain, there is no guarantee that it will cause the next pandemic, nor that it will emerge from Asia. In recent years, there have been concerning poultry outbreaks (with accompanying human infections) with other strains and in other areas, such as in the Netherlands in 2003 (H7N7) and in British Columbia in 2004 (H7N3).

Potential for pandemic

The SARS epidemic in 2003 demonstrated that in this era of widespread international jet travel, in a matter of days, an epidemic can transform from a crisis in one province to a widespread public health crisis in at least six countries, with accompanying worldwide disruptions in trade and travel. Influenza is a much more contagious virus than the SARS-associated coronavirus and can be expected to cause severe disease in a much higher proportion of infected individuals.

It is impossible to accurately predict many of the features of the next pandemic, but some features can be anticipated. As with all recorded flu pandemics, it is likely that the disease will come in waves, such that the degree of contagiousness and severity of illness may vary over time. In the best case scenario, this may also allow enough advance warning time to put resources in place and possibly develop an effective vaccine that will reduce the extent of the pandemic.

It is nearly certain that in the early phases, existing flu vaccine will not be effective, since the strain is likely to be too different from the currently circulating strains that comprise the yearly vaccine. Antiviral medications do hold some promise, though circulating H5N1 strains in Asia have demonstrated resistance to widely available amantidine and rimantidine. Neuraminidase-inhibitors (such as oseltamivir and zanamivir) can be effective at limiting illness severity if given immediately after symptom onset, which presents its own challenge, as many will be infected by others with asymptomatic infections and may not realize they are ill until it is too late for these medications to be effective.

Will our response be effective?

As in 1918, we can expect that the capacity of the health care system will be overwhelmed. Even now with

advanced intensive care techniques, ARDS has a mortality approaching 50 percent, and US hospitals do not have nearly the beds and ventilators to care for the number of people with respiratory failure that would accompany a repeat of 1918. Mathematical models using current population figures have estimated the number of US deaths could range from 88,000 to 227,000.

There also are some critical shortcomings in current US preparedness. The reliability of the vaccine supply is such that the timely availability of an effective vaccine once the pandemic strain is identified cannot be guaranteed, given the reliance on a labor- and resource-intensive egg-based viral culture method. Work is going on to develop the capacity for cell culture-based production methods, but the full implementation of such methods is thought to be at least five years into the future. Clinical trials of H5N1 and H9N2 vaccines are also underway, which may conceivably be available in time for the next pandemic. Certainly the current supply of neuraminidase-inhibitors is inadequate to protect even a small percentage of the population and would likely need to be limited to the public safety and health care sectors. Oseltamivir has been added to the Strategic National Stockpile of pharmaceuticals, and negotiations are under way to markedly increase the production capacity of these medications, but this will also take years to implement.

A looming question concerns the role of isolation (of cases) and quarantine (of contacts) during a pandemic. These techniques were used with varying success during the SARS epidemic, but there is little precedent in recent decades for the US political system supporting public health in implementing these politically unpopular measures. Since September 11, 2001, public health officials have been working to revamp enabling public health legislation. For example, Alaska recently revised its public health statutes based on the Model Public Health Act, developed by Gostin and Hodge through a national Turning Point collaborative. Among other things, the new law clarifies and updates quarantine and isolation powers.

Given the history of influenza, it is a certainty that there will be a pandemic. Whether it will have the plague-like severity of 1918-19, with the accompanying social upheaval, is impossible to predict. In the US we were spared much of the disruption caused by SARS, but countries with large numbers of SARS cases experienced a taste of the chaos that will likely accompany a severe influenza pandemic, and many in the public health community took notice. Certainly the possibility of a pandemic is being taken seriously on an official level. But it remains to be seen if we are willing to expend the resources necessary to even start to prepare for a true influenza pandemic. ■

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The views expressed by the author may not represent the official position of the Indian Health Service or the US Department of Health and Human Services.