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*CIDRAP Note: Below is the full final text of Dr. Osterholm's article as it is printed in the Mar/Apr 2007 issue of Foreign Affairs. A 500-word extract and a link to purchase the text below in pdf format is available on the Foreign Affairs Web site and can be reached by [clicking here](#).*

## **Unprepared for a Pandemic**

By Michael T. Osterholm

From *Foreign Affairs*, March/April 2007

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Summary: The need to prepare for an influenza pandemic has not yet sunk in, partly because disaster has not yet struck. But that good news could turn into very bad news if it leads to slacking off on necessary preparations today: although no one can predict when or how, a pandemic will occur for sure, and it will have implications far beyond its toll on human health.

*Michael T. Osterholm is Director of the Center for Infectious Disease Research and Policy, a Professor in the School of Public Health, and an Adjunct Professor in the Medical School at the University of Minnesota.*

## SOUNDING THE ALARM, AGAIN

More than a year and a half ago, *Foreign Affairs* published three articles that sounded a clarion call to prepare for the next pandemic. They warned that another pandemic could occur at any time and at a staggering cost to human health and the world economy. These facts remain incontrovertible. At the time, many public health scientists believed that recent outbreaks of the H5N1 influenza virus in birds in Asia, Europe, and Africa, with occasional infections in humans, were precursors to the next pandemic. They still do today.

Like earthquakes, hurricanes, and tsunamis, influenza pandemics are recurring natural disasters. The natural reservoir of influenza virus is wild aquatic birds. But for a human influenza pandemic to occur, a strain of an avian influenza virus must develop to which humans have no preexisting immunity and undergo critical genetic changes that allow it to be readily transmitted from person to person. The H5N1 strain of the influenza virus has had a limited impact on human health so far, but a human influenza pandemic could occur -- and be devastating -- if a current strain underwent the right genetic changes.

For decades, scientists believed that the only way for an avian influenza virus to become transmittable between humans was through a process known as reassortment. Reassortment occurs when an avian virus and a human virus both infect the same cells of an animal (a pig, for example) or a person and swap genes, creating a new virus adapted

to humans. (This is how the 1957 and 1968 influenza pandemics began.) Over the past two years, however, studies of tissue samples from 1918-19 influenza victims have suggested that an influenza virus can also become a pandemic strain after undergoing genetic mutations of its own. Recent studies of the virus' genetic material have demonstrated that the 1918-19 virus likely evolved by a process known as adaptation, a series of critical mutations that rendered it capable of being transmitted between humans.

Although it is impossible to know for sure whether H5N1 will ever evolve into the next human pandemic virus, more and more of the genetic changes documented in the 1918-19 virus have also been found to have occurred in recent H5N1 strains affecting both birds and people. Meanwhile, the spread of H5N1 infections to more avian species and to more humans continues to point to H5N1 as a likely strain of the next pandemic.

No one can predict when the next pandemic will occur or how severe it will be. But it will occur for sure, and because of the interdependence of the global economy today, its implications will reach far beyond its toll on human health. A recent study by the Lowy Institute for International Policy, which provides the most comprehensive estimate yet, found that a mild pandemic similar to that of 1968 would kill 1.4 million people and cost approximately \$330 billion (or 0.8 percent of global GDP) in lost economic output. Were a pandemic as severe as that of 1918-19 to occur, over 142.2 million people would die, and the world's GDP would suffer a loss of \$4.4 trillion.

Yet the issue has generated only limited attention in both the public and the private sectors worldwide because preparing for a pandemic is a daunting challenge to begin with and because disaster has not yet struck. But that good news could turn into very bad news if it leads to slacking off on preparedness activities today. In a world filled with competing international priorities, preparing for something that may not happen in the next year may seem hard to justify in terms of both financial resources and time, but that is no excuse for inaction.

## FOWL PLAY

Avian influenza caused by H5N1 first received widespread attention in 1997, when an outbreak in poultry in Hong Kong subsequently spread the virus to humans. Eighteen human cases were recognized; six of the patients died. (There was no evidence of person-to-person transmission.) In the fall of 2003, H5N1 avian influenza appeared in domestic poultry farms in Asia. After subsiding briefly, it reemerged in the summer of 2004 in Cambodia, China, Laos, Thailand, and Vietnam, where it persists today despite the widespread vaccination of poultry. Studies of recent H5N1 isolates in Southeast Asia have indicated that the virus' predominant lineage today originated in southern China. Other lineages are believed to have emerged in Southeast Asia, which suggests that the virus has been present in the region for a long time. A report by the UN Food and Agricultural Organization published in September 2004 found that existing reservoirs of the H5N1 influenza virus in ducks, wild birds, and -- potentially -- pigs are already resilient enough to "pose a serious challenge to eradication."

In 2005, H5N1 expanded beyond Asia. It was identified in Kazakhstan, Mongolia, and Russia in July, and in Turkey and western Europe in October. By February 2006, it had reached northern Nigeria; it has since been documented in several other African nations. As of August 2006, over 220 million birds had been killed by H5N1 or culled to prevent its spread.

H5N1 is believed to spread geographically mostly through the movement of domestic poultry and wild migratory birds. Wild birds are thought to be the principal transporters of H5N1 from infected areas to new geographic locations. Once introduced, the virus is then disseminated more widely by poultry, especially domestic ducks and geese. (According to the World Health Organization, mallard ducks are the "champion" vectors of its spread.) The spread of H5N1 from Siberia to the Black Sea basin is consistent in time and location with the movements of migratory birds. In Africa, it most likely spread through the trade of poultry for human consumption, although migratory birds may have contributed to the problem there as well. There has been no documented spread of H5N1 to migratory birds or poultry in the Americas, but that may change: Asian and European flyways overlap in the Arctic regions of North America, and the importation of poultry and other birds from Asia and Europe into any American country could result in the infection of indigenous bird populations.

## SPREAD THICK

The H5N1 virus has also been spreading to more humans. As of January 15, 2007, it had infected 265 people, 159 of whom died, in ten countries over the previous three years. Cases of human infection have occurred in Azerbaijan, Cambodia, China, Djibouti, Egypt, Indonesia, Iraq, Thailand, Turkey, and Vietnam. Seventy-nine fatalities were confirmed in 2006, compared with 42 in 2005, 32 in 2004, and 4 in 2003. As the number of cases has risen, the mortality rate has remained stable, at roughly 60 percent.

Several studies have now confirmed that H5N1 infection in humans is fundamentally different from infections caused by the current seasonal influenza strains. H5N1 infection typically involves progressive primary viral pneumonia, acute respiratory distress, and liver and kidney damage. Some studies have suggested that in contrast to seasonal influenza, which primarily involves lung infection, the H5N1 virus might be disseminated throughout the body and affect multiple organs thanks in part to a condition of the immune system known as a cytokine storm. This is a significant finding since clinical studies of cases from the 1918-19 pandemic have indicated that the presence of cytokine storms helps explain why that pandemic was so deadly.

H5N1 has several other alarming features. Studies comparing samples over time have indicated that the virus has become progressively more pathogenic for poultry. The current strain of the virus can survive in the environment several days longer than could earlier strains. Its range of mammalian hosts appears to be expanding. It has been found in more and more dead migratory birds, which supports the conclusion that it is becoming more virulent. Recent genetic work performed on viral isolates from Turkey found

evidence of two mutations that may enhance its transmission from birds to humans and between humans.

One critical question that remains is whether the virus would become less lethal if its ability to spread among humans developed. According to a September 2006 report by the World Health Organization, "Should the virus improve its transmissibility by acquiring, through a reassortment event, internal human genes, then lethality of the virus would most likely be reduced. However, should the virus improve its transmissibility through adaptation as a wholly avian virus [as what occurred with the 1918 pandemic strain], then the present high lethality could be maintained during a pandemic." Even the former outcome is no reason for comfort: with six in ten infected people currently dying from the virus, an H5N1 pandemic caused by a virus that had lost much of its disease-causing characteristics as it adapted to humans would still have catastrophic consequences.

## THE FOG OF WAR

The Foreign Affairs articles published in July 2005 contributed to a flurry of calls to prepare for a pandemic. In September 2005, President George W. Bush announced an international partnership on avian and pandemic influenza before the General Assembly of the United Nations, and in November of that year he issued the National Strategy for Pandemic Influenza, setting out measures to prepare the United States for a pandemic. President Bush also submitted a request to Congress for a \$7.1 billion emergency budget supplement to invest in, among other things, international health surveillance and containment efforts, medical stockpiles, and the production of emergency supplies of vaccines and antiviral medications. (In the end, the Pandemic Influenza Act, which was signed into law in 2006, only provided \$3.8 billion.) In May 2006, the White House released the Implementation Plan for the National Strategy for Pandemic Influenza -- more than 300 recommendations to coordinate the federal government's response to the threat of pandemic influenza. A month later, Congress passed the president's budget for fiscal year 2007, which includes a \$2.3 billion allowance for implementing the next phase of the Bush administration's pandemic preparedness strategy. Australia, Canada, France, Israel, Japan, New Zealand, Singapore, Switzerland, and the United Kingdom have announced similar plans.

As positive as these steps may seem, there are critical problems with the preparedness plans worldwide. Many crucial questions remain unanswered and even unaddressed. What are the technological challenges and barriers to achieving a higher state of preparedness? What steps should be taken to significantly reduce the impact of a global pandemic? How does one measure preparedness? Who should pay for it? What are the economic costs of being more prepared compared to the costs of being less prepared? In some ways, a fog of confusion has settled over these issues. Like soldiers in battle, policymakers and planners in the private sector are overwhelmed by the many uncertainties and complexities surrounding the threat and by the question of how to anticipate and respond to such a catastrophe.

Partly as a result, the issue has not retained people's attention as much as it should have (or as much as, say, terrorism has), and preparedness continues to compete for priority on the agendas of policymakers. President Bush and other U.S. officials held numerous conferences and meetings on pandemic preparedness throughout 2005, but in 2006 discussion of the issue all but disappeared. No major midterm election debates or position papers mentioned it, and Congress held no relevant hearings. (In the last months of 2006, the media lost interest, too. A LexisNexis search of general news articles on H5N1 in 50 major international newspapers yielded more than 850 articles for October 2005 but fewer than 75 articles for November 2006.) The same is true in virtually all developed countries. And it is unclear whether the surge in H5N1 activity in birds and humans documented in Asia in January 2007 will increase awareness among the media, governments, private-sector leaders, and the public of the urgent need for pandemic preparedness.

Some public health experts had anticipated that planning fatigue would quickly set in if a pandemic did not materialize shortly after the first warnings. Lassitude is a normal reaction to the perception that public health experts have been crying wolf and to the challenge of staying on high alert over a sustained period of time. But the price of such apathy will be very high, because avoiding the consideration of key issues will compound the devastating effects of the next pandemic. For one thing, not enough attention is being paid to developing an effective vaccine and an effective way to produce it and deliver it to both developed and developing countries. For another, little thought is being given to what effects the structure of the world economy will have on the spread of a pandemic -- and, in turn, what effects a pandemic will have on the basic functioning of the world economy. Meanwhile, the private sector has been largely left to its own devices as it prepares for a calamity, even though its collaboration with the public sector will be critical to any prevention campaign or emergency response.

## HIT ME WITH YOUR BEST SHOT

Ideally, the risk of pandemic influenza could be eliminated today with a protective vaccine available to everyone that could be administered in advance of the pandemic. But that possibility is years away at best. Currently, licensed influenza vaccines are produced using chicken eggs, and output is limited to approximately 350 million doses a year. To supplement production down the road, more than a dozen international drug companies are researching new vaccines (27 human clinical trials of new vaccines against several strains of avian influenza are under way). But most of them, although using cell cultures rather than egg cultures, are growing a vaccine antigen similar to that grown in chicken eggs. In other words, these second-generation vaccines are just a fancy way of producing the antiquated first-generation vaccines used over the last 50 years. Moreover, cell-culture vaccines, like egg-culture vaccines, provide maximum protection against a pandemic when they are produced using the virus strain causing it. This means that although cell-culture vaccines can supplement egg-culture vaccines during the first three or four months of a pandemic, no production can start until after the pandemic itself has begun. And it will take years of research and clinical trials before cell-culture vaccines are approved and years after that before they can be widely produced. Then, because the

H5N1 virus is rapidly changing, it is unclear whether the vaccines now in research and development -- which are based on strains of the H5N1 virus that have circulated in Vietnam, Indonesia, and Turkey -- will offer any protection against new strains of the virus. A working group of the World Health Organization recently cautioned countries purchasing "prepandemic vaccines" that these may offer only limited, if any, benefit.

Unfortunately, the U.S. and other governments have not made a major financial commitment to the research and development of new kinds of influenza vaccines and to building extensive production capacity; they are treating vaccine research and development as though it were about business as usual, not a pending catastrophe. Over the past two years, all the governments in the world have collectively invested less than \$2.5 billion in developing new influenza vaccine technologies, including third-generation, or universal, vaccines. This is too little, but it is hoped that ongoing research will demonstrate that it might be possible to develop such vaccines, which would be effective against an array of influenza viruses, and to start doing so before a pandemic strain is at hand.

The availability of an increasing amount of antiviral drugs, particularly Tamiflu, represents welcome news for preparedness. Roche, the pharmaceutical company that makes Tamiflu, recently announced that it will be able to make up to 400 million doses per year beginning in 2007. Although it remains unclear whether the drug will be as effective against H5N1 as it is against current seasonal influenza, it appears to be effective in preventing H5N1 infections in animal subjects when taken before exposure.

Unfortunately, even if enough of the right kind of vaccines were produced, most of the world's population would not have access to them in the throes of a pandemic. In the United States, the effects of a pandemic would likely be compounded by the country's ailing health-care system -- which itself would be further weakened by the crisis. More than 30 percent of the 5,000 hospitals in the United States are losing money. Almost half of all emergency departments report being continually at or over capacity; 100,000 additional registered nurses are needed. Last year, some 550,000 critically ill or injured Americans -- an average of one person every minute -- were diverted from the emergency rooms nearest to them because these were full. It would take only a mild pandemic to overwhelm the United States' health-care system. And in many communities it is unclear whether even basic nursing care would be available during a severe one.

## IT'S A SMALL WORLD

The interconnectedness of the global economy today could make the next influenza pandemic more devastating than the ones before it. Even the slightest disruption in the availability of workers, electricity, water, petroleum-based products, and other products or parts could bring many aspects of contemporary life to a halt. The global economy has required wringing excess costs out of the production, transport, and sale of products. Inventories are kept to a minimum. Virtually no production surge capacity exists. As a consequence, most of the developed world depends on the last-minute delivery of many critical products (such as pharmaceuticals, medical supplies, food, and equipment parts)

and services (such as communications support). In the United States, approximately 80 percent of all prescription drugs come from offshore and are delivered to pharmacies just hours before they are dispensed. An increasing number of U.S. hospitals now receive three rounds of deliveries of drugs and supplies a day to meet their needs. With such long and thin supply chains, a pandemic that closed borders, caused worker attrition, and suspended travel or the transport of commercial goods would seriously disrupt the delivery of everyday essentials.

Yet the consideration of such disturbances has been largely absent from preparedness planning. This oversight is partly due to past experience with disasters, such as earthquakes or hurricanes, for which relief supplies from nonimpacted areas were quickly available for impacted ones. Such disasters are limited in time, meaning that rescue and recovery can begin in short order. A pandemic, on the other hand, would affect the whole world for months, and relief efforts would put a strain on resources everywhere. Unfortunately, there are no easy answers to solve the supply-chain problem; it may simply be too big. None of the published models estimating the macroeconomic consequences of pandemic influenza fully account for it, reflecting a lack of imagination on the part of both the private and the public sectors.

A related problem is the lack of planning for business continuity in the event of a pandemic. The private sector has been involved to varying degrees in pandemic preparedness planning. Some companies have attempted to account for all the contingencies that could affect their employees, their supply chains, and even their customers. Typically, the biggest challenge they face is anticipating how workers, suppliers, buyers, infrastructure providers, and the government would respond. Given the interdependence of all those players, figuring out what would happen if disaster struck and how to prepare for it is a Rubik's Cube-like brainteaser. With so many unknowns, one leading business continuity planner said at an off-the-record meeting at Harvard University recently, "Planning for a pandemic is so different from anything we've done in business before that we're writing the book as we go -- and it won't be finished until the virus is finished." Some companies require their suppliers to sign affidavits indicating that they have a workable pandemic plan in place. But most of these statements are barely worth the paper they are printed on, because suppliers are in no better position to prepare for a pandemic than are their buyers. Even well-intentioned efforts, in other words, have been largely ineffectual. As a September 2006 report by the Department of Homeland Security put it, "Eighty-five percent of critical infrastructure resources reside in the private sector, which generally lacks individual and system-wide business continuity plans specifically for catastrophic health emergencies such as pandemic influenza."

Many questions remain. Would consumers willingly pay a higher price for products sold by a company that invested substantially in pandemic preparedness, or would competitors gain market share by taking advantage of its increased costs? How should the stockpiling of critical emergency products be promoted in this global just-in-time economy? If solutions to these problems cannot be developed, expectations about how much can be done should be revised.

## NOW OR LATER

The world will experience another pandemic, and it will get through it, as it has all previous ones. The challenge is to figure out now how to minimize the number of deaths and the economic and psychological devastation it will cause. It is a particularly complicated problem because preparing for a pandemic challenges the very basis of the global just-in-time economy. Recent scientific findings about H5N1 infection in animals and humans have also challenged a number of facts about influenza that scientists had previously held sacred. So one must expect the unexpected. Winston Churchill once said, "It is no use saying, 'We are doing our best.' You have got to succeed in doing what is necessary." The difficulty in confronting the possibility of an H5N1 pandemic is figuring out what is necessary.

In the short term, people around the world must understand that when a pandemic unfolds, their communities will largely be on their own to get through the crisis. They should plan now and learn to depend on themselves, their families, their neighbors, and their co-workers. In the medium term, governments should devise national strategies. In the United States, either President Bush or Congress should create a national commission of elected officials and senior leaders in the fields of public health, vaccine and drug research, emergency management, law enforcement, business continuity, and economics, and it should issue, within 120 days of its creation, a report on the status of pandemic preparedness in the public and private sectors in the United States. It should also detail an aggressive agenda for additional investment.

Finally, the long-term goal must be to develop universal influenza vaccines. The impetus must come from an initiative as bold as the man-on-the-moon agenda that President John F. Kennedy articulated in May 1961. The fact that no world leader has called for such an effort reflects a lack of comprehension about the devastation an influenza pandemic would wreak. The opportunity to save millions of lives cannot be passed up. Even if such efforts come too late to stave off the next pandemic, at least they would help in the one after that.

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## Unprepared for a Pandemic

[Michael T. Osterholm](#)

From *Foreign Affairs*, [March/April 2007](#)

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Summary: The need to prepare for an influenza pandemic has not yet sunk in, partly because disaster has not yet struck. But that good news could turn into very bad news if it leads to slacking off on necessary preparations today: although no one can predict when or how, a pandemic will occur for sure, and it will have implications far beyond its toll on human health.

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For decades, scientists believed that the only way for an avian influenza virus to become transmittable between humans was through a process known as reassortment. Reassortment occurs when an avian virus and a human virus both infect the same cells of an animal (a pig, for example) or a person and swap genes, creating a new virus adapted to humans. (This is how the 1957 and 1968 influenza pandemics began.) Over the past two years, however, studies of tissue samples from 1918-19 influenza victims have suggested that an influenza virus can also become a pandemic strain after undergoing genetic mutations of its own. Recent studies of the virus' genetic material have demonstrated that the 1918-19 virus likely evolved by a

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