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Preparing for the Next Pandemic

Michael T. Osterholm, Ph.D., M.P.H. Annual influenza epidemics are like Minnesota winters — all are challenges, but some are worse than others. No matter how well we prepare, some blizzards take quite a toll. Each year, despite our efforts to increase the rates of influenza vaccination in our most vulnerable populations, unpredictable factors largely determine the burden of influenza disease and related deaths. During a typical year in the United States, 30,000 to 50,000 persons die as a result of influenzavirus infection, and the global death toll is about 20 to 30 times as high as the toll in this country. We usually accept this outcome as part of the cycle of life. Only when a vaccine shortage occurs or young children die suddenly does the public demand that someone step forward to change the course of the epidemic. Unfortunately, the fragile and limited production capacity of our 1950s egg-based technology for producing influenza vaccine and the lack of a national commitment to universal annual influenza vaccination mean that influenza epidemics will continue to present a substantial public health challenge for the foreseeable future.

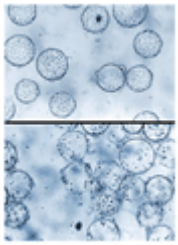
An influenza pandemic has always been a great global infectious-disease threat. There have been 10 pandemics of influenza A in the past 300 years. A recent analysis showed that the pandemic of 1918 and 1919 killed 50 million to 100 million people,[1] and although its severity is often considered anomalous, the pandemic of 1830 through 1832 was similarly severe — it simply occurred when the world's population was smaller. Today, with a world population of 6.5 billion — more than three times that in 1918 — even a relatively "mild" pandemic could kill many millions of people.

Influenza experts recognize the inevitability of another pandemic. When will it begin? Will it be caused by H5N1, the avian influenzavirus strain currently circulating in Asia? Will its effect rival that of 1918 or be more muted, as was the case in the pandemics of 1957 and 1968? Nobody knows.

So how can we prepare? One key step is to rapidly ramp up research related to the production of an effective vaccine, as the Department of Health and Human Services is doing. In addition to clinical research on the immunogenicity of influenza vaccines, urgent needs include basic research on the ecology and biology of influenzaviruses, studies of the epidemiologic role of various animal and bird species, and work on early interventions and risk assessment.[2] Equally urgent is the development of cell-culture

technology for production of vaccine that can replace our egg-based manufacturing process. Today, making the 300 million doses of influenza vaccine needed annually worldwide requires more than 350 million chicken eggs and six or more months; a cell-culture approach may produce much higher antigen yields and be faster. After such a process was developed, we would also need assured industrial capacity to produce sufficient vaccine for the world's population during the earliest days of an emerging pandemic.

(Figure)



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Cell-Culture–Based Production of Influenza Vaccine.

Microcarriers with Vero cells are shown before (top) and after (bottom) infection with influenzavirus.

Baxter Vaccine.

Beyond research and development, we need a public health approach that includes far more than drafting of general plans, as several countries and states have done. We need a detailed operational blueprint of the best way to get through 12 to 24 months of a pandemic.

What if the next pandemic were to start tonight? If it were determined that several cities in Vietnam had major outbreaks of H5N1 infection associated with high mortality, there would be a scramble to stop the virus from entering other countries by greatly reducing or even prohibiting foreign travel and trade. The global economy would come to a halt, and since we could not expect appropriate vaccines to be available for many months and we have very limited stockpiles of antiviral drugs, we would be facing a 1918-like scenario.

Production of a vaccine would take a minimum of six months after isolation of the circulating strain, and given the capacity of all the current international vaccine manufacturers, supplies during those next six months would be limited to fewer than a billion monovalent doses. Since two doses may be required for protection, we could vaccinate fewer than 500 million people — approximately 14 percent of the world's population. And owing to our global "just-in-time delivery" economy, we would have no surge capacity for health care, food supplies, and many other products and services. For example, in the United States today, we have only 105,000 mechanical ventilators, 75,000 to 80,000 of which are in use at any given time for everyday medical care; during a

garden-variety influenza season, more than 100,000 are required. In a pandemic, most patients with influenza who needed ventilation would not have access to it.

We have no detailed plans for staffing the temporary hospitals that would have to be set up in high-school gymnasiums and community centers — and that might need to remain in operation for one or two years. Health care workers would become ill and die at rates similar to, or even higher than, those in the general public. Judging by our experience with the severe acute respiratory syndrome (SARS), some health care workers would not show up for duty. How would communities train and use volunteers? If the pandemic wave were spreading slowly enough, could immune survivors of an early wave, particularly health care workers, become the primary response corps?

Health care delivery systems and managed-care organizations have done little planning for such a scenario. Who, for instance, would receive the extremely limited antiviral agents that will be available? We need to develop a national, and even an international, consensus on the priorities for the use of antiviral drugs well before the pandemic begins. In addition, we have no way of urgently increasing production of critical items such as antiviral drugs, masks for respiratory protection, or antibiotics for the treatment of secondary bacterial infections. Even under today's relatively stable operating conditions, eight different antiinfective agents are in short supply because of manufacturing problems. Nor do we have detailed plans for handling the massive number of dead bodies that would soon exceed our ability to cope with them.

What if an H5N1 influenza pandemic began not now but a year from now? We would still need to plan with fervor for local nonmedical as well as medical preparedness. Planning for a pandemic must be on the agenda of every public health agency, school board, manufacturing plant, investment firm, mortuary, state legislature, and food distributor. Health professionals must become much more proficient in "risk communication," so that they can effectively provide the facts — and acknowledge the unknowns — to a frightened population.[3]

With another year of lead time, vaccine might have a more central role in our response. Although the manufacturing capacity would still be limited, strategies such as developing antigen-sparing formulations — that is, intradermal formulations that take advantage of copious numbers of dendritic cells for antigen processing or formulations including adjuvants to boost the immune response — might extend the vaccine supply. Urgent planning efforts are required to ensure that we have the syringes and other essential equipment, as well as the workforce, for effective delivery. Finally, a detailed plan for vaccine allocation will be needed — before the crisis, not during it.

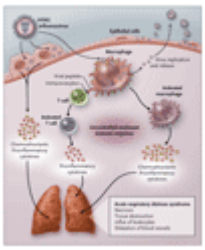
What if the pandemic were 10 years away and we embarked today on a worldwide influenza Manhattan Project aimed at producing and delivering a pandemic vaccine for everyone in the world soon after the onset of sustained human-to-human transmission? In this scenario, we just might make a real difference.

The current system of producing and distributing influenza vaccine is broken, both technically and financially. The belief that we can greatly advance manufacturing technology and expand capacity in the normal course of increasing our annual vaccination coverage is flawed. At our current pace, it will take generations for meaningful advances to be made. Our goal should be to develop a new cell-culture–based vaccine that includes antigens that are present in all subtypes of influenzavirus, that do not change from year to year, and that can be made available to the entire world population. We need an international approach to public funding that will pay for the excess production capacity required during a pandemic.

Today, public health experts and infectious-disease scientists do not know whether H5N1 avian influenzavirus threatens an imminent pandemic. Most indications, however, suggest that it is just a matter of time: witness the increasing number of H5N1 infections in humans and animals, the documentation of additional small clusters of cases suggestive of near misses with respect to sustained human-to-human transmission, the ongoing genetic changes in the H5N1 Z genotype that have increased its pathogenicity, and the existence in Asia of a genetic-reassortment laboratory — the mix of an unprecedented number of people, pigs, and poultry.

It is sobering to realize that in 1968, when the most recent influenza pandemic occurred, the virus emerged in a China that had a human population of 790 million, a pig population of 5.2 million, and a poultry population of 12.3 million; today, these populations number 1.3 billion, 508 million, and 13 billion, respectively. Similar changes have occurred in the human and animal populations of other Asian countries, creating an incredible mixing vessel for viruses. Given this reality, as well as the exponential growth in foreign travel during the past 50 years, we must accept that a pandemic is coming — although whether it will be caused by H5N1 or by another novel strain remains to be seen.

Should H5N1 become the next pandemic strain, the resultant morbidity and mortality could rival those of 1918, when more than half the deaths occurred among largely healthy people between 18 and 40 years of age and were caused by a virus-induced cytokine storm (see diagram) that led to the acute respiratory distress syndrome (ARDS).[4] The ARDS-related morbidity and mortality in the pandemic of 1918 was on a different scale from those of 1957 and 1968 — a fact that highlights the importance of the virulence of the virus subtype or genotype. Clinical, epidemiologic, and laboratory evidence suggests that a pandemic caused by the current H5N1 strain would be more likely to mimic the 1918 pandemic than those that occurred more recently.[5] If we translate the rate of death associated with the 1918 influenzavirus to that in the current population, there could be 1.7 million deaths in the United States and 180 million to 360 million deaths globally. We have an extremely limited armamentarium with which to handle millions of cases of ARDS — one not much different from that available to the front-line medical corps in 1918.



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Proposed Mechanism of the Cytokine Storm Evoked by Influenzavirus.

The key element in generating the storm is an uncontrolled exuberant immune response to the virus, in which there is an outpouring of proinflammatory cytokines and chemoattractants. An animated version of this figure is available at www.nejm.org.

Is there anything we can do to avoid this course? The answer is a qualified yes that depends on how everyone, from world leaders to local elected officials, decides to respond. We need bold and timely leadership at the highest levels of the governments in the developed world; these governments must recognize the economic, security, and health threats posed by the next influenza pandemic and invest accordingly. The resources needed must be considered in the light of the eventual costs of failing to invest in such an effort. The loss of human life even in a mild pandemic will be devastating, and the cost of a world economy in shambles for several years can only be imagined.

Source Information

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An interview with Dr. Osterholm can be heard at www.nejm.org.

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