



Testimony
Committee on Appropriations
Subcommittee on Foreign Operations, Export
Financing, and Related Programs
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**Pandemic Influenza: The Road
to Preparedness**

Statement of

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Mr. Chairman and members of the Subcommittee, thank you for the opportunity to speak to you today about H5N1 avian influenza, the ongoing threat of a human influenza pandemic, and research being conducted by the National Institutes of Health that is improving our ability to respond effectively not only to an influenza pandemic, but to seasonal influenza epidemics as well.

Influenza viruses constantly circulate through the human population, and influenza cases occur sporadically throughout the year. Influenza epidemics, in which the number of cases peaks sharply, usually occur in winter months. These seasonal influenza epidemics cause an annual average of about 36,000 deaths in the United States, mostly among people aged 65 years and over and those with chronic health conditions.

As influenza viruses circulate, the genes that determine the structure of their surface proteins undergo small changes. As these mutations accumulate—a process called “antigenic drift”—immunity created by prior exposure to older circulating influenza viruses or by vaccination can no longer reliably and optimally ward off infection. Antigenic drift is thus the basis for the predictable patterns of seasonal influenza seen in most years, and is the reason that we must update influenza vaccines annually.

Influenza viruses also can change more dramatically. For example, viruses sometimes emerge that can infect species other than their natural animal

reservoirs, typically migratory birds. These viruses may begin to infect domestic poultry, farm animals such as pigs, or, very rarely, humans. When an animal influenza virus develops the ability to infect humans, the result is usually a “dead-end” infection that cannot readily spread further in the human population.

However, the virus could mutate in ways that allow human-to-human transmission of an animal influenza virus to occur more easily. Furthermore, if an animal influenza virus and a human influenza virus were to simultaneously co-infect a person or animal, the two viruses could exchange genes, resulting in a virus that is readily transmissible between humans, and against which the human population may have no pre-existing immunity. When such an “antigenic shift” occurs by either of these mechanisms, a global influenza pandemic can result. After a significant proportion of the global population has been exposed to the new virus and has thereby acquired immunity to it, the death rate would almost certainly fall and drifted variants of the new virus would become the new seasonal viruses.

Historically, pandemic influenza is a proven threat. In the 20th century, influenza pandemics occurred in 1918, 1957, and 1968. The pandemics of 1957 and 1968 were serious infectious disease events that killed approximately two million and 700,000 people worldwide, respectively. The 1918-1919 pandemic, however, was catastrophic: epidemiologists estimate that it killed more than 50 million people worldwide, including more than 500,000 people in the United States, and caused enormous social and economic disruption. In all three of these

pandemics, for reasons that remain unclear, a much greater proportion of young adults were killed than is typical of seasonal influenza. Given this history, we can expect that a new influenza virus will emerge and another pandemic will occur at some point in the future. Although the precise timing of the next pandemic remains unknown, when it arises, it is likely to spread rapidly due to the speed of modern air travel. The consequences will be severe throughout the world, in developed nations and especially in underdeveloped regions that do not have adequate public health systems.

Of known influenza viruses, the highly pathogenic H5N1 avian influenza that is currently spreading among domestic and migratory birds in Asia, Africa, the Middle East and Europe is of greatest concern. Although the H5N1 virus is primarily an animal pathogen, it nonetheless has infected more than 170 people; more than half of the people diagnosed with H5N1 avian influenza infection have died. At this time, the virus does not efficiently spread from animals to humans, and it spreads even less efficiently from one person to another. However, if the H5N1 virus mutates further or exchanges genes with a human influenza virus to acquire the ability to spread from person to person as efficiently as the viruses that cause seasonal influenza epidemics, the feared human pandemic could become a reality. The degree of threat from such a virus would depend on the extent to which the virus retains its current virulence and how transmissible it becomes.

On November 1, 2005, the President announced the National Strategy for Pandemic Influenza, and the next day U.S. Department of Health and Human Services (HHS) Secretary Michael O. Leavitt released the HHS Pandemic Influenza Preparedness and Response Plan, an integral component of the National Strategy. These two documents are part of a blueprint for a coordinated national strategy to prepare for and respond to a human influenza pandemic which will include a National Implementation Strategy and preparedness and response plans from other federal agencies. Within HHS, the National Institutes of Health (NIH), and the National Institute of Allergy and Infectious Diseases (NIAID) in particular, were given primary responsibility for the conduct of scientific research and clinical trials to foster product development, particularly vaccines and antiviral drugs, to prepare our nation for a potential human influenza pandemic.

In my testimony today, I will describe some of the ongoing scientific research and development efforts of the NIH, much of which is in collaboration with the private sector to counter the threat of pandemic influenza, focusing on projects and programs that will help to ensure that effective influenza vaccines and antiviral drugs will be available to counter any human influenza virus with pandemic potential that could emerge. I will close with a brief discussion of how our efforts to prepare for pandemic influenza are closely tied to those directed at seasonal influenza.

Vaccines

Vaccines are essential tools for the control of influenza. The current seasonal influenza vaccine is based on an inactivated influenza virus grown in fertilized chicken eggs. Unfortunately, current domestic capacity for the manufacture of influenza vaccines can meet only a small fraction of the expected demand should a pandemic virus emerge. For this reason, we are conducting research that will help to increase U.S.-based pandemic influenza vaccine production capacity, and lead to new vaccines and manufacturing methods that will allow faster and more flexible influenza vaccine production. The ultimate goal is to have the capacity to produce sufficient pandemic influenza vaccine to protect every American within six months of the emergence of a new pandemic virus.

Advanced development efforts to create an effective H5N1 influenza vaccine are currently based on an H5N1 virus isolated from a Vietnamese patient that was infected from a chicken in 2004. Since there is no pandemic among humans, this vaccine is referred to as a pre-pandemic H5N1 vaccine. Should a pandemic virus emerge that can be easily transmitted among humans, a vaccine based on that specific strain may have to be developed; until that time, we cannot delay vaccine preparedness and development of pre-pandemic H5N1 vaccine candidates is proceeding rapidly. This effort serves two important purposes. As the H5N1 virus mutates, the imperfectly matched prototype vaccines may offer enough protection to prime the immune system and reduce the severity of infection. This could buy precious time while a vaccine that closely matches the

pandemic strain is produced and distributed. Producing prototype H5N1 vaccines also provides a trial run in developing the infrastructure and production capacity to manufacture enough vaccine should a worldwide pandemic ensue.

In early 2004, NIAID-supported researchers used a technology called reverse genetics to create a H5N1 reference vaccine strain from the Vietnamese isolate. NIAID then contracted with sanofi pasteur and Chiron Corporation to use this reference strain to manufacture pilot lots of inactivated virus vaccine for use in clinical trials. These vaccine candidates are now undergoing clinical testing in healthy individuals: adults, elderly people, and children.

Preliminary results from clinical trials of the H5N1 pre-pandemic vaccine provide both good and sobering news. The good news is that the vaccine is well tolerated, and induces an immune response that is predictive of being protective against the H5N1 virus. The sobering news is that two large doses were needed to elicit this level of immune response. The requirement for larger than normal doses of vaccine essentially reduces the amount of vaccine we are able to produce in a given timeframe. However, preliminary results from a Phase I clinical trial of a candidate vaccine for H9N2 influenza—another avian virus that has caused human deaths—indicate that addition to the vaccine of a substance called an adjuvant can increase the immune response and thereby reduce the required dose. Clinical trials of H5N1 pre-pandemic candidates employing adjuvants and other dose-saving strategies are now in progress.

When a pandemic virus is identified and isolated, making a sufficient quantity of pandemic vaccine as quickly as possible will be a matter of great urgency. To ensure that the manufacturing techniques, procedures, and conditions used for large-scale production yield a satisfactory product, HHS contracted with sanofi pasteur and Chiron to use standard, egg-based techniques to produce inactivated H5N1 vaccine for the Strategic National Stockpile. Moving to large-scale production of the candidate vaccine in parallel with clinical testing of pilot lots is unusual, and an indication of the urgency with which we are addressing H5N1 vaccine development. The doses of H5N1 pre-pandemic vaccine being produced could be used to vaccinate certain at risk populations in affected areas before a pandemic vaccine becomes available.

Although egg-based manufacturing methods have served us well for more than 40 years, they are logistically complex, can fail if the vaccine strain will not grow efficiently, and cannot be rapidly expanded in response to increased demand for vaccine. The best hope for building a more reliable domestic manufacturing capacity that could be rapidly mobilized in response to the emergence of a pandemic virus lies in expanding and accelerating the development of manufacturing methods that grow the vaccine strain in cell culture. It is important to note, however, that while the technology for producing influenza vaccine in cell cultures is promising, successful development of the production methods and licensure of the product are years in the future and by no means guaranteed.

Moreover, how quickly we reach the production goal of 300 million doses of pandemic vaccine within a six-month time frame will depend to some extent on the success of efforts to develop adjuvants and other dose-sparing techniques that reduce the amount of vaccine needed to protect the U.S. population.

In addition to inactivated virus vaccines, NIAID is collaborating with industry to pursue several other vaccine strategies. From the mid-1970s to the early 1990s, for example, NIAID intramural and extramural researchers developed a cold-adapted, live attenuated influenza vaccine strain that later became the influenza vaccine now marketed by MedImmune, Inc. as FluMist®. NIAID intramural researchers are now working with colleagues from MedImmune under a Cooperative Research and Development Agreement to produce and test a library of similar live vaccine candidates against all known influenza strains with pandemic potential, allowing a head start and faster response should any of these strains actually appear. Other strategies under development include recombinant subunit vaccines, in which cultured cells are induced to make various influenza virus proteins that are then purified and used in a vaccine; DNA vaccines, in which influenza genetic sequences are injected directly into a person to stimulate an immune response; and vector approaches that insert the genes of influenza virus into another harmless virus (the vector) and injecting the vector vaccine as a carrier to present the influenza proteins to the vaccine recipient

The goal of a particularly important ongoing effort is to develop a vaccine that raises immunity to parts of the influenza virus that vary very little from season to season and from strain to strain. Although this is a difficult task, such a “universal” influenza vaccine would not only provide continued protection over multiple seasons, it might also offer considerable protection against a newly emerged pandemic influenza virus and thus substantially increase the immunity of the population—making the country far less vulnerable to a new influenza virus.

Antiviral Drugs

Antiviral medications are an important counterpart to vaccines as a means of controlling influenza outbreaks, both to prevent infection prior to or immediately after exposure and to treat infection after it occurs. Four drugs are currently available for the treatment of influenza, three of which are also licensed in the United States for influenza prevention for certain populations. Efforts to test and improve these existing anti-influenza drugs are in progress. For example, researchers have determined that H5N1 strains circulating in Vietnam and Thailand are resistant to two older drugs—rimantadine and amantadine—but are sensitive to a newer class of drugs, called neuraminidase inhibitors. This class of drugs includes oseltamivir (marketed as Tamiflu®), currently approved for treatment of individuals older than one year. Studies to test the efficacy of higher doses of neuraminidase inhibitors, and to further characterize the safety profile of oseltamivir in very young children, are in the advanced planning stages. Of note,

the most recently isolated strains of H5N1 from China and Turkey are sensitive to all four drugs.

NIAID also supports research to identify new anti-influenza drugs through the screening of existing drug candidates in cell-culture systems and in animal models; in the past year, seven promising candidates have been identified. Efforts are also underway to design new drugs that precisely target viral proteins and inhibit their functions. NIAID is also developing novel, broad-spectrum therapeutics that might work against many influenza virus strains. Some of these target viral entry into human cells, while others specifically attack and degrade the influenza virus genome. Studies are also in progress to evaluate long-acting next-generation neuraminidase inhibitors, as are development and testing in animals of combination antiviral regimens against H5N1 and other potential pandemic influenza strains.

NIAID International Influenza Research

Pandemic influenza is a global threat. International cooperation in research is thus a key component of pandemic preparedness, and NIAID participates in several international efforts. Under the International Partnership on Avian and Pandemic Influenza, which the President launched in September 2005, we are coordinating our vaccine research with activities of other nations and private companies outside the United States. The World Health Organization Secretariat recently sponsored the first of what we hope will be a series of meetings to allow

us to exchange information with and learn from our colleagues in other countries who are conducting various stages of research on human vaccines against the H5N1 virus. NIAID also is working to establish a clinical trials network in Southeast Asia to conduct research on emerging infectious diseases, with an initial emphasis on influenza. Lastly, NIAID and the HHS Office of Public Health Emergency Preparedness provide technical assistance to the Government of Vietnam as it proceeds with the development of a human H5N1 vaccine.

Because a pandemic influenza virus could emerge anywhere in the world, NIAID helps to conduct global surveillance and molecular analysis of circulating animal and human influenza viruses. For example, NIAID funds a long-standing program to detect the emergence of influenza viruses with pandemic potential, in which researchers in Hong Kong and at St. Jude Children's Research Hospital collect and analyze influenza viruses from wild birds and other animals and generate candidate vaccines against them. A recent genetic sequence analysis of some of the viruses collected through this program yielded important clues that may explain why H5N1 avian viruses cause such severe disease in humans, which may in turn yield new avenues for the creation of effective vaccines and treatments. In 2004, NIAID launched a broader effort to determine the complete genetic sequences of thousands of influenza virus isolates from throughout the world and to rapidly provide these sequence data to the scientific community. This program, a collaboration between NIAID, the Centers for Disease Control and Prevention (CDC) and several other organizations called the Influenza

Genome Sequencing Project, will enable scientists to better understand the emergence of influenza epidemics and pandemics by observing how influenza viruses evolve as they spread through the population and by matching viral genetic characteristics with virulence, ease of transmissibility, and other clinical properties. To date, the complete genetic sequences of 831 influenza viruses have been published.

Conclusion

In closing, it is important to note that our ability to cope with a pandemic—with a sufficient supply of effective vaccines and antiviral drugs, efficient infection control, and clear public communication—will to a large extent depend on how well we cope with seasonal influenza. It is clear, however, that we have not yet optimized our preparedness and responsiveness to this recurring disease. For example, the serious vaccine shortage that occurred in the 2004/05 influenza season underscored the difficulties we face in annually renewing the influenza vaccine supply, and highlights the pressing need to move toward adoption of newer vaccine manufacturing techniques and other strategies that can improve the surge capacity, flexibility and speed with which vaccines are made. Moreover, increasing the proportion of the population that is vaccinated annually with seasonal influenza vaccine will help to pave the way for the more intense vaccination effort that would accompany an influenza pandemic. The recent recommendation of the Advisory Committee on Immunization Practices to

routinely vaccinate children fro 2 to 5 years old is an important step in that direction.

Fortunately, much of the research on influenza vaccines and antivirals that has been undertaken in response to the emergence of H5N1 avian influenza is directly applicable to both seasonal and pandemic preparedness, and efforts to improve our response to one will invariably improve our ability to manage the other.

Thank you for the opportunity to testify before you today. I would be pleased to answer any questions that you may have.