



Testimony
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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 the ongoing threat of a human influenza pandemic, the immediate threat from H5N1 avian influenza, and research being conducted and supported by the National Institutes of Health (NIH) that is improving our ability to respond effectively not only to an influenza pandemic, but to seasonal influenza epidemics as well.

Seasonal outbreaks of influenza occur almost every year in the United States and impose a substantial burden of morbidity and mortality on the population. Influenza viruses circulate constantly around the globe, 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 epidemics cause an annual average of about 200,000 hospitalizations and 36,000 deaths in this country, mostly among people aged 65 years and over and those with chronic health conditions. Globally, an estimated 250,000 to 500,000 influenza-related deaths occur each year.

As influenza viruses circulate, the genes that determine the structure of their surface proteins undergo small changes called mutations. As these mutations accumulate (a process called “antigenic drift”), the immunity created by prior exposure to older circulating influenza viruses or by prior vaccination no longer can reliably prevent 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 waterfowl. These avian viruses may begin to infect domestic poultry, farm animals such as pigs, or, very rarely, humans. When an avian 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 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—a process known as reassortment—resulting in a virus that may be 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, mutation or reassortment, a global influenza pandemic can result.

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 in our modern society. The consequences likely will be severe throughout the world, in developed nations but especially in poor countries that do not have adequate public health systems.

Of known influenza viruses, the highly pathogenic H5N1 avian influenza virus currently spreading among domestic and migratory birds in Asia, Africa, and the Middle East is of greatest concern. Although the H5N1 virus remains primarily an avian pathogen, 269 people are known to have been infected, usually from direct contact with infected poultry; 163 of the people diagnosed with H5N1 avian influenza infection have died. At this time, the virus does not efficiently spread from birds to humans, and transmission from one person to another is rare. 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, a human pandemic could become a reality. The degree of threat from such a virus would depend on the extent to which the virus retained its current virulence and how transmissible it became.

In late 2005, the President announced the National Strategy for Pandemic Influenza, and 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 effort to prepare for and respond to a human influenza pandemic that includes a National Implementation Plan and preparedness and response plans from other federal agencies. Within HHS, the National Institutes of Health, 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 development of therapies, diagnostic tests and devices, and vaccines to help prepare for a potential human influenza pandemic.

In my testimony today, I will present an overview of the ongoing scientific research and development efforts of NIH and our progress and priorities in creating the countermeasures needed to reduce the threat posed by both seasonal and pandemic influenza.

Basic Research

NIH supports numerous basic research projects intended to increase our understanding of how influenza viruses replicate, interact with their hosts, stimulate immune responses, and evolve into new strains. Although many questions remain unanswered, results from these basic research studies are laying the foundation for the design of new antiviral drugs, diagnostics, and vaccines, and are applicable to seasonal epidemic and pandemic strains alike. For example, NIH-supported scientists recently used a massive database to complete the most comprehensive analysis to date of the critical sites on influenza viruses that are recognized by the immune system. Because the work reveals

at the molecular level exactly where the immune system targets the viruses, it will help scientists design new vaccines, diagnostics and immune-based therapies against influenza. Moving from the molecular to the population level, NIH-supported modeling studies of the dynamics of influenza infection in large human populations are providing important insights into how the virus spreads, the effects of air travel and commuting patterns on how fast epidemics move, and the potential value of antiviral drugs and nonpharmaceutical interventions in controlling outbreaks. In addition, several NIH programs are describing the detailed immune responses to seasonal influenza vaccination in humans to define the immune correlates of protection and to understand the lack of efficacy in the elderly and other immunocompromised individuals.

To better understand the varied and ever-changing genetic blueprints of influenza viruses, NIH launched the Influenza Genome Sequencing Project in the fall of 2004. The goal of this collaboration between NIH (NIAID and the National Library of Medicine), St. Jude Children's Research Hospital, the Wadsworth Center, the Institute for Genomic Research, the Centers for Disease Control and Prevention (CDC), and several other organizations is to determine the complete genetic sequences of different influenza viruses from around the world and to rapidly provide these sequence data to the scientific community. The project has determined genomic sequences of close to 2,000 animal and human influenza viruses, all of which are freely available to researchers via the NIH website; more than 200 new sequences are being added every month. The data flowing from this program will enable scientists to track how influenza viruses evolve as they spread through their host populations and across geographic

regions, and to match viral genetic characteristics with virulence, ease of transmissibility, and other clinical properties. The end result will be a clearer understanding of how influenza epidemics and pandemics emerge.

Scientists also are working to understand the virus that caused the devastating 1918 pandemic, and in the process are gaining new insights into what might happen with the H5N1 avian influenza virus. Using pathology samples from victims of the 1918 pandemic, NIH intramural and extramural scientists and their collaborators have determined the complete genetic sequence of this virus, and have assembled viruses that bear some or all of these genes. The sequence revealed that the pandemic virus probably did not arise through a reassortment of animal and human viruses but rather was an entirely avian-like virus that adapted to infect humans. Infection of mice and non-human primates with the complete 1918 virus resulted in a damaging inflammatory response in the lungs, with aberrant levels of expression of immune regulatory molecules. This result might explain the extraordinary mortality among young adults in the 1918 pandemic because young adults have a strong and robust immune system and a stronger immune response would lead to increased pathological consequences. Of note, immunological responses similar to those seen with reconstructed 1918 viruses in animals have been seen with recent H5N1 virus infections in humans.

Ongoing sequence analysis of human influenza viruses from before and after 1918 seeks to place the emergence of the 1918 virus in its historic context. Understanding how long the pandemic virus circulated in humans before it emerged in full force in 1918

has important implications for pandemic planning, including more effective nonpharmaceutical interventions. Knowledge of how highly virulent influenza viruses kill could lead to new strategies for the development of novel antiviral drugs and other therapies.

Vaccines

Vaccines are essential tools for the control of influenza. NIH efforts to facilitate the creation of effective H5N1 influenza vaccines are based on isolates of the currently circulating H5N1 virus. Since there is no H5N1 pandemic among humans at this time, such vaccines are referred to as pre-pandemic H5N1 vaccines. Should an H5N1 virus emerge that can be easily transmitted among humans, a vaccine based on the newly emerged strain would need to be developed. However, development of pre-pandemic H5N1 vaccine candidates, which is proceeding rapidly, serves two important purposes. As the H5N1 virus mutates, even imperfectly matched prototype vaccines may prime the immune system to respond to related H5N1 viruses and offer enough protection to reduce the severity of disease, and therefore serve as an important preliminary component of pandemic control. In fact, recent results from a small study indicated that a previously administered dose of H5N1 vaccine successfully served as immunologic priming for a vaccine against an antigenically drifted strain given seven to eight years later. Such a strategy could buy precious time while a vaccine that more closely matches the pandemic strain is produced and distributed. Producing prototype H5N1 vaccines also provides an opportunity to create the infrastructure, processes, and production capacity to manufacture enough vaccine should a worldwide pandemic

ensue.

In early 2004, NIH-supported researchers used a technology called reverse genetics to create an H5N1 reference vaccine strain from a Vietnamese H5N1 isolate. NIH then contracted with sanofi pasteur and Chiron Corporation to use this reference strain to manufacture small-scale lots of inactivated virus vaccine for use in clinical trials. These pre-pandemic vaccine candidates have now been clinically tested in healthy adults, elderly people, and children, and the results provided both good and sobering news. The good news is that the vaccine is well tolerated, and induces an immune response that is similar in all age groups and is suggestive of protection against infection with the immunizing strain. The sobering news is that the doses of vaccine needed to elicit the levels of immune responses usually thought to predict protection were larger than those used for seasonal influenza vaccines. In addition, these predictably protective responses were elicited in only approximately half of the vaccinated individuals. The need for larger doses of vaccine reduces the number of people who could be immunized with the amount of vaccine that can be produced in a given timeframe. In addition, it is important to elicit a protective immune response in a greater percentage of vaccinated individuals.

We, therefore, have pursued the use of vaccine additives called adjuvants that amplify the immune response. Results from a Phase I clinical trial of a candidate vaccine for H9N2 influenza—another avian virus that has caused human deaths—indicated that an adjuvant called MF59 increases the immune response and could thus reduce the

required dose. In 2006, GlaxoSmithKline announced encouraging results indicating that its H5N1 influenza vaccine, using a proprietary adjuvant, achieved a high immune response at a low dose of antigen. Preliminary results from NIH-supported clinical trials of H5N1 pre-pandemic vaccine with adjuvants will soon be available. In addition, NIH-supported basic research into a family of immune system proteins called Toll-like receptors—molecules that are among the immune system’s “first responders” —is providing important insights into how adjuvants work, and may illuminate new opportunities for improved dose-optimization strategies. In addition, recent research has shown non-Toll-like receptors to be potential new targets for adjuvant function. This finding and other promising approaches to developing new vaccine adjuvants are being studied by NIH-supported innate immunity research programs.

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

Although egg-based manufacturing methods have served us well for more than 40 years, they are logistically complex, can lead to delays if the vaccine strain of influenza virus will not grow efficiently, and cannot be rapidly expanded in response to increased demand for vaccine. To build a more reliable domestic manufacturing capacity that could be rapidly mobilized in response to the emergence of a pandemic virus, we are working to expand and accelerate the development of additional manufacturing methods, such as growing the vaccine strain in cell culture. New technologies for producing influenza vaccines in cell cultures are promising and such technologies are currently used in licensed vaccines for other diseases. However, the successful development of production methods and licensure of influenza cell-based products are likely several years in the future, and therefore, support for current egg-based technologies should also continue.

Our strategic plans have articulated the goal of developing the capacity to provide 300 million people in the United States with the needed doses of pandemic vaccine within a six-month time frame. Our success in reaching this goal will depend to some extent on the success of efforts to understand and expand the use of effective and safe adjuvants and other dose-optimization strategies, and efforts to develop other technologies for vaccine preparation.

In this regard, NIH is collaborating with industry to pursue several other vaccine strategies in addition to inactivated virus H5N1 vaccines. From the mid-1970s to the early 1990s, NIH intramural and extramural researchers developed a cold-adapted, live

attenuated influenza vaccine strain that led to the product now marketed by MedImmune, Inc. as FluMist®. NIH intramural researchers are now working with colleagues from MedImmune Vaccines under a Cooperative Research and Development Agreement to produce and test a library of similar live vaccine candidates against all known influenza subtypes with pandemic potential, allowing a head start and faster response should a strain from any of these subtypes emerge as a pandemic threat. Tests in mice and ferrets showed that two doses of a live attenuated H5N1 candidate vaccine protected the animals from infection and death by a wide array of H5N1 isolates—an encouraging result indicating that this type of vaccine might protect even if not precisely matched to the circulating strain. Human studies of candidate cold-adapted, live attenuated H5N1 vaccines are underway.

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 approaches that insert the genes of influenza virus into a different, harmless virus (a “vector”) that is used as a vaccine. A human trial of a DNA vaccine, developed at the NIAID Vaccine Research Center and designed to prevent H5N1 infection, began last month at the NIH Clinical Center. Planning is also underway to test intradermal injection as an alternate delivery technique for this vaccine, and to evaluate alternative vaccine candidates, such as recombinant adenoviral vectors containing H5N1 genetic sequences and recombinant H5N1 proteins.

An important NIH research goal is to develop a vaccine that raises immunity to parts of the influenza virus—so called epitopes—that vary little from season to season and from strain to strain. This is a challenging task because the invariant epitopes of influenza viruses generally do not elicit a vigorous immune response. Nonetheless, there is a great deal of interest in so-called Vaccine Common Epitope (VCE) vaccines against influenza, especially based on the influenza M2 protein. The fundamental strategy is to present the common antigen to the immune system in a way that stimulates a robust and protective immune response. Such a vaccine might not only provide continued protection over multiple seasons but also might offer considerable protection against a newly emerged pandemic influenza virus. This would substantially increase the overall immunity of the population to influenza A, and make the country far less vulnerable to a new influenza A virus.

Antiviral Therapies

Antiviral medications are an important counterpart to vaccines as a means of controlling influenza outbreaks, both to treat infection after it occurs and under certain circumstances to prevent infection prior to or immediately after exposure. Four drugs currently are available for the treatment of influenza, three of which are also licensed in the United States for influenza prevention in certain populations. Efforts to test and improve these existing anti-influenza drugs are in progress. H5N1 strains circulating in Southeast Asia, Africa, and elsewhere are generally resistant to two older drugs—rimantadine and amantadine—but the majority of isolates are sensitive to a newer class

of drugs, called neuraminidase inhibitors. This class of drugs includes oseltamivir (marketed as Tamiflu®), currently approved for treatment and prophylaxis 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. NIH is also collaborating with the Department of Defense and Department of Veterans Affairs (VA) in a VA-funded research project to examine if probenecid co-administration with oseltamivir can increase the effective supply of oseltamivir. In addition, NIH has collaborated with the World Health Organization, the Wellcome Trust, and other institutions in Indonesia, Thailand, Vietnam, and the United Kingdom to develop the South East Asia (SEA) Influenza Clinical Trial Network, which is developing in-country research capacity in a region directly affected by the H5N1 influenza outbreak and conducting studies of antivirals in people infected with the H5N1 virus.

NIH-supported research to identify additional anti-influenza drugs that work through a variety of mechanisms is progressing rapidly. An NIH program that screens both licensed compounds and new drug candidates—first in cell culture systems and then in animal models—has identified several promising anti-influenza candidates. NIH is collaborating with the private sector to further develop three promising candidates out of the 32 that were screened in mice in 2006:

- FluDase binds host cell receptors to prevent viral entry;
- T-705 inhibits replication of viral RNA; and
- Peramavir inhibits viral neuraminidase.

Furthermore, NIH is collaborating with industry to develop 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. In animal models, treatment with a monoclonal antibody is effective against what would otherwise be a lethal dose of H5N1 virus, even if given up to three days after infection, indicating that passive administration of antibodies might be a useful strategy to contain an H5N1 pandemic. NIH is exploring the possibility that one may be able to develop a high-titer anti-H5N1 antibody preparation as a treatment for patients with avian influenza through the hyperimmunization of healthy volunteers. Studies are also in progress to evaluate long-acting next-generation neuraminidase inhibitors. The development and testing in animals of combination antiviral regimens against H5N1 and other potential pandemic influenza strains is also a top research priority.

Diagnostics

Inexpensive, fast, accurate, and precise methods to diagnose influenza infection in its earliest stages continue to be a focus of ongoing research. If a pandemic influenza virus were to emerge, diagnostic tools capable of quickly and definitively identifying infected people would be extremely valuable, helping to slow the spread of the virus and maximizing the efficiency with which stockpiled antivirals are used. If available for routine use, such diagnostics would also help to diagnose and treat seasonal influenza, which clinically can mimic many other diseases.

Recently, NIH-supported scientists from the University of Colorado at Boulder, working in collaboration with researchers at the CDC, showed that a potentially revolutionary diagnostic device, called the MChip, is capable of quickly identifying many influenza viruses, including H5N1 avian influenza. The MChip has a number of strengths that could allow it to become a valuable tool in global influenza control efforts. The materials for each chip cost less than ten dollars. It tests for the influenza matrix gene, which varies relatively little between strains and over time, so the test likely would not have to be updated as frequently as tests based on other genes. The researchers already have automated the process of reading the test's output, allowing accurate assessment of many samples in a short time. Discussions are already under way to commercialize its manufacture, and in the future researchers hope to adapt this technology for handheld field use.

Conclusion

In closing, I would like to emphasize that our efforts to successfully prepare for an influenza pandemic—with a sufficient supply of effective vaccines and antiviral drugs, efficient infection control, and clear public communication—will benefit our ability to cope with seasonal influenza. It is clear, however, that we have not yet optimized our preparedness and responsiveness to this recurring disease. There is a 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.

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.