



Testimony
Before the Subcommittee on Health
Committee on Energy and Commerce
United States House of Representatives

***The Role of NIH Biomedical
Research in Pandemic
Influenza Preparedness***

Statement of
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Introduction

Mr. Chairman and Members of the Committee, thank you for the opportunity to discuss with you the role of the National Institutes of Health (NIH) in preparing the Nation for the next influenza pandemic. The Department of Health and Human Services (DHHS) Draft Pandemic Influenza Preparedness and Response Plan outlines a coordinated national strategy to prepare for and respond to an influenza pandemic, and assigns specific roles to various Federal agencies; the National Institute of Allergy and Infectious Diseases (NIAID) holds the primary responsibility for carrying out those duties assigned to NIH.

In this capacity, NIAID provides the scientific input required to facilitate the development of both new influenza vaccine technologies and novel antiviral drugs against influenza viruses. Under this Administration, we have made extraordinary progress. DHHS began investing in new technologies, securing more vaccines and medicines, and preparing stronger response plans. Total NIH funding for influenza research has grown more than five-fold in recent years, from \$20.6 million in FY 2001 to an estimated \$119 million in FY 2005. This is part of the largest investment ever made by the Federal government in protecting against influenza.

Influenza epidemics typically occur during the winter months in the United States and other temperate regions of the world and cause significant morbidity and mortality. On average, 36,000 people in this country die each year and 200,000

are hospitalized due to influenza and influenza-related complications. Each year, influenza viruses undergo small changes in their surface proteins as they circulate through the human population. As these small changes accumulate, the influenza virus gains the ability to overcome immunity created by prior exposure to older circulating influenza viruses or by vaccination. This phenomenon, called “antigenic drift,” is the basis for the well-recognized patterns of influenza disease that occur every year, and is the reason that influenza vaccines must be updated each year.

Influenza viruses can also change more dramatically; viruses may emerge that can jump species from natural reservoirs such as wild ducks to infect domestic poultry, farm animals, or humans. This type of significant change in the antigenic makeup of the virus that infects humans is referred to as “antigenic shift.”

In most instances when influenza virus jumps species from an animal such as a chicken to infect a human, the result is a “dead end” infection that cannot readily be transmitted further from human to human. Mutations in the virus, however, could increase the efficiency of human-to-human transmission. Furthermore, if an avian influenza virus and another human influenza virus were to simultaneously co-infect a person, the genes of the two viruses might reassort, resulting in a virus that is readily transmissible between humans and against which the population would have no natural immunity. In addition, the reassortant virus could reflect the virulence of the avian virus. Such a virus could potentially cause an influenza pandemic.

Historically, pandemic influenza is a proven threat. Three influenza pandemics have occurred in the 20th century: in 1918, 1957, and 1968. The 1918-1919 pandemic was by far the most severe, killing approximately 500,000 people in the United States and 20-40 million people worldwide—almost two percent of the global population at that time. Worldwide, the pandemics that began in 1957 and 1968 killed approximately 2 million and 700,000 people, respectively.

H9N2 and H5N1 influenza are two avian viruses that have jumped directly from birds to humans and have significant pandemic potential. In 1999 and 2003, H9N2 influenza caused illness in three people in Hong Kong and in five individuals elsewhere in China, but the virus did not spread from human to human. H5N1 influenza, often referred to as “bird flu,” appears to be a significantly greater threat than H9N2. This virus was first detected in humans in Hong Kong in 1997. Since January 2004, it has spread widely among wild and domestic birds and has infected at least 97 people in Vietnam, Thailand, and Cambodia; 53 of these people have died of the disease. Ominously, H5N1 viruses are evolving in ways that increasingly favor the start of a pandemic, including becoming more stable in the environment and expanding their host species range. Moreover, there has been at least one highly probable case of human-to-human transmission of the H5N1 virus, and it is possible that other such transmissions have occurred recently.

The deadly experience with past influenza pandemics explains our current high level of concern about the appearance of virulent H5N1 avian influenza viruses in

Asia, which by a variety of mechanisms could adapt themselves to efficiently spread from human to human and result in the next pandemic. Given the poor condition of public health systems in many underdeveloped regions and the speed of modern air travel, the consequences of such an event, should it result in an influenza pandemic, would be severe.

NIH Influenza Research Activities

Between influenza pandemics, when influenza activity occurs regularly on a seasonal basis, the role of NIAID is to conduct basic research into the viral biology, pathogenesis, and epidemiology of influenza viruses and to study host immune responses to these agents. Concomitant with these basic research studies, NIAID conducts applied research to develop new or improved influenza vaccines and production methods; to identify new anti-influenza drugs; and to support surveillance for previously unknown influenza viruses in animals and characterize any that are found. When a new influenza virus begins to infect humans (and thereby gains the potential to cause a pandemic), NIAID's role is to develop and clinically evaluate specific candidate vaccines against the emergent strain, test the activity of antiviral drugs, and, in some cases, supply vaccine manufacturers and the research community with viral reference strains and other reagents to speed vaccine development.

Basic Research

NIAID supports many 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. Results from these studies lay the foundation for the design of new antiviral drugs, diagnostics, and vaccines, and are applicable to seasonal epidemic and pandemic strains alike.

NIAID also supports two special research programs to better understand the diversity of influenza viruses. The Influenza Genome Sequencing Project, launched in the fall of 2004, is a collaboration between NIAID, the Centers for Disease Control and Prevention (CDC) and several other organizations to determine the complete genetic sequences of thousands of influenza virus isolates and to rapidly provide these sequence data to the scientific community. This program 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 properties. As of May 24, 2005, 182 genomic sequences of influenza viruses had been made available through this program to researchers via the NIH website, and many more are in the pipeline.

NIAID also supports a long-standing program based in Hong Kong to detect the emergence of influenza viruses with pandemic potential. This program, led by Dr. Robert Webster of St. Jude Children's Research Hospital in Memphis, Tennessee, conducts extensive surveillance of influenza viruses in animals in Hong Kong, analyzes new influenza viruses when they are found, and helps to

generate candidate vaccines against them. In January, the scope of this surveillance program was expanded to include Vietnam, Thailand, and Indonesia.

Vaccines

Vaccines are essential tools for the control of influenza. NIAID supports numerous research projects and other initiatives to foster the development of new influenza vaccine candidates and manufacturing methods that are simpler, more reliable, yield more broadly cross-protective products, and provide alternatives to the egg-based technology currently used to grow the vaccine viruses.

In the Fiscal Year 2006 budget request, DHHS has requested \$120 million to support pandemic influenza preparedness activities. These activities build on previous initiatives that include making chicken eggs available year round to provide for a secure supply and surge capacity for vaccine production and supporting efforts to shift vaccine manufacture to new cell-culture technologies. Moreover, a technique developed by NIAID-supported scientists called reverse genetics allows scientists to manipulate the genomes of influenza viruses and to transfer genes between viral strains. This technique allows the rapid generation of vaccine candidate strains that precisely match a selected epidemic strain. By removing or modifying certain virulence genes, reverse genetics also can be used to convert highly pathogenic influenza viruses into vaccine candidates that

are safer for vaccine manufacturers to handle. Other vaccine strategies for influenza, including protein subunit and gene-based vaccines, are also being actively pursued. On the NIH campus in Bethesda, the NIAID Vaccine Research Center (VRC) has initiated a program to develop gene-based vaccines against influenza. Should proof-of-concept studies prove successful, the VRC expects to expand and accelerate the development of gene-based and recombinant influenza vaccines.

In addition to supporting the development of new vaccine strategies, NIAID maintains an extensive capacity for evaluating candidate vaccines in clinical trials. For example, NIAID's Vaccine and Treatment Evaluation Units (VTEUs) comprise a network of university-based research medical centers across the United States that conduct clinical trials to test candidate vaccines for many infectious diseases. These units support both academic and industrial vaccine evaluation, including safety, immunogenicity, and ultimately, efficacy of candidate vaccines.

Although a pandemic alert has not yet been declared, NIAID has taken a number of steps to develop and clinically test vaccines against H5N1 and H9N2 influenza, two specific avian viruses that have significant pandemic potential. For example, in August 2004, NIAID contracted with Chiron Corporation for the production of 40,000 doses of an inactivated H9N2 vaccine. A Phase I clinical trial of this vaccine began on March 31, 2005, and is fully enrolled.

In January 2004, researchers at St. Jude Children's Research Hospital obtained a clinical isolate of the highly virulent H5N1 virus that was fatal to humans in Vietnam in late 2003 and early 2004 and used reverse genetics to create an H5N1 candidate vaccine from this strain. Immediately after NIAID received this vaccine last June, it was sent to two companies, Sanofi-Pasteur (formerly Aventis-Pasteur) and Chiron, which have NIAID contracts to manufacture pilot lots of eight and ten thousand vaccine doses, respectively. The vaccines will be tested in Phase I and II clinical trials that will assess safety and the appropriate dose to optimize immunogenicity, as well as provide information about how the immune system responds to this vaccine. The Sanofi-Pasteur trial, which began on April 4, 2004, will test the vaccine in approximately 450 healthy adults between the ages of 18 and 64. This trial is already fully enrolled and the safety data are being analyzed. If data from this study indicate the vaccine is safe and able to stimulate a certain immune response, NIAID expects to test the vaccine in other populations, such as the elderly and children, in late summer 2005. Trials of the Chiron-produced vaccines are expected to begin later this year.

In addition to these relatively small pilot lots, DHHS contracted with Sanofi-Pasteur to produce two million doses of its H5N1 vaccine, in order to ensure that the manufacturing techniques, procedures, and conditions that would be used for large-scale production will yield a satisfactory product. Moving to large-scale production of the vaccine in parallel with clinical testing of pilot lots is an

indication of the urgency with which we have determined that H5N1 vaccine development must be addressed. Waiting for the results of the initial clinical trials, which would be the normal procedure, would delay our ability to make large quantities of vaccine by at least six months. These doses, which have now been delivered, could be used to vaccinate health workers, researchers, and, if indicated, the public in affected areas.

From the mid 1970s to the early 1990s, researchers in the NIAID Laboratory of Infectious Diseases developed a cold-adapted, live attenuated influenza vaccine strain that later became the FDA-licensed influenza vaccine marketed as FluMist. Building on their experience with attenuated influenza vaccines, researchers from the same laboratory recently made three candidate attenuated H5N1 vaccine strains and an attenuated H9N2 vaccine strain that are now in advanced development. NIAID plans to start the clinical trial of the attenuated H9N2 candidate vaccine this summer. These researchers also hope to test one of the candidate attenuated H5N1 vaccines in a Phase I study this year.

Antiviral Therapies

Antiviral medications are an important counterpart to vaccines as a means of controlling influenza outbreaks, both to prevent illness 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 for prevention of illness. NIAID actively supports identification of new anti-influenza drugs through the screening

of new drug candidates in cell culture systems and in animal models. In the past year, seven promising candidates have been identified. Efforts to design drugs that precisely target viral proteins and inhibit their functions also are under way. In addition, NIAID is 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 viral genome.

Efforts also are underway to test and improve antiviral drugs to prevent or treat H5N1 influenza. Last year, researchers determined that although H5N1 viruses are resistant to two older drugs—rimantadine and amantadine—they are sensitive to a newer class of drugs called neuraminidase inhibitors, including oseltamivir, which is marketed as Tamiflu. DHHS has stockpiled approximately 2.3 million treatment courses of oseltamivir, which is approved for use in individuals older than one year. Scientists are planning to conduct studies to further characterize the safety profile of oseltamivir in infants; and studies are also in progress to evaluate novel drug targets, as well as long-acting next-generation neuraminidase inhibitors. In addition, development and testing in animals of a combination antiviral regimen against H5N1 and other potential pandemic influenza strains are under way.

Conclusion

In closing, Mr. Chairman, I would like to emphasize that although we cannot be certain exactly when the next influenza pandemic will occur, we can be virtually

certain that one will occur and that the resulting morbidity, mortality, and economic disruption will present extraordinary challenges to public health authorities around the world. We are working diligently in close coordination with our colleagues at CDC, FDA, other federal agencies, and in industry to ensure that we can meet these challenges in the most successful manner possible.

Thank you for this opportunity to appear before you today, and I would be pleased to answer any questions you may have.