Testimony
Before the Subcommittee on Labor, Health and Human Services, Education and Related Agencies, Committee on Appropriations
United States House of Representatives

The Role of NIH Biomedical Research in Pandemic Influenza Preparedness

Statement of

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For Release on Delivery

Expected at 10:00AM
Tuesday, April 12, 2005

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 National Institute of Allergy and Infectious Diseases (NIAID), a component of NIH, holds the primary responsibility for carrying out the duties assigned to NIH under the Department of Health and Human Services (DHHS) Draft Pandemic Influenza Preparedness and Response Plan, which outlines a coordinated national strategy to prepare for and respond to an influenza pandemic.

Between influenza pandemics, when annual influenza activity occurs, the role of NIAID in influenza research 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 has the potential to cause a pandemic), NIAID is responsible for developing and clinically evaluating specific candidate vaccines against the emergent strain, testing the activity of antiviral drugs, and, in some cases, supplying vaccine manufacturers and the research community with viral reference strains and other reagents to speed vaccine development.

Background

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-associated complications. As influenza viruses circulate annually through the human population, they undergo small changes in their surface proteins. If enough of these small changes accumulate, the influenza virus is able to escape the human immune response that was primed by prior exposure to influenza viruses or by vaccination. This phenomenon is referred to as “antigenic drift” and is the basis for the well-recognized patterns of influenza disease that occur every year. Influenza vaccines are changed or updated each year on the basis of these drifts.

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

When an influenza virus jumps species from an animal such as a chicken to a human, it is usually a “dead end” infection because the virus cannot readily transmit further from human to human. Mutations in the virus could result in an increasing efficiency in the ability of the virus to spread from human to human. 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 potentially deadly influenza virus that is transmissible between humans and hence has “pandemic potential.” 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 acquire the ability to 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 79 people in Vietnam, Thailand, and Cambodia; 49 of these people died of the disease. More ominously, there has been at least one probable case of human-to-human transmission of the H5N1 virus, and it is possible that more such transmissions have occurred.

Historically, pandemic influenza is a proven threat. Three deadly 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. This 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 another pandemic. Given the poor conditions 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

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 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 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 today, 35 genomic sequences of influenza viruses have been made available 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 an additional $120 million to support pandemic preparedness activities. These activities 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 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 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, the efficacy of candidate vaccines.

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 could work against many influenza virus strains. Some of these target viral entry into human cells, while others specifically attack and degrade the viral genome.

Pandemic Influenza Preparedness

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, NIAID has contracted with Chiron Corporation to produce 40,000 doses of an inactivated H9N2 vaccine, which will be clinically evaluated in the coming months.

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. Trials of the Sanofi-Pasteur preparation are imminent in the NIAID VTEU network; trials of the Chiron-produced doses are expected to begin later this year. In the early phases of these trials, healthy adult volunteers will receive vaccine; elderly people and children will be involved in later phases.

In addition to these relatively small pilot lots, DHHS contracted with Sanofi-Pasteur to produce two million doses of their 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-approved influenza vaccine marketed as FluMist. Building on their experience with 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; initial human trials are planned for later this year.

Antiviral Therapies

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 doses of oseltamivir, which is approved for use in individuals older than one year. Development and testing in animals of a combination antiviral regimen against H5N1 and other potential pandemic influenza strains are under way.

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 would 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.