DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

The Role of the National Institute of Allergy and Infectious Diseases in Research Addressing Seasonal and Pandemic Influenza

Testimony before the

House Committee on Energy and Commerce

Subcommittee on Oversight and Investigations

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February 3, 2015

Mr. Chairman and members of the Committee, thank you for the opportunity to discuss the response of the National Institutes of Health (NIH) to the public health threats posed by seasonal and pandemic influenza. The National Institute of Allergy and Infectious Diseases (NIAID) is the lead NIH institute for conducting and supporting research on infectious diseases, including influenza.

For more than six decades, NIAID has made important contributions to the understanding of infectious, immunologic, and allergic diseases, from basic research on disease pathogenesis to applied research to develop diagnostics, therapeutics, and vaccines. NIAID has a dual mandate that balances research addressing current biomedical challenges with the capacity to rapidly respond to new threats from emerging and re-emerging infectious diseases.

Among these emerging and re-emerging infectious diseases are the occasionally unpredictable seasonal influenzas and the largely unpredictable pandemic influenzas. As we are well-aware, the strain of H3N2 influenza A that is circulating during the currently relatively severe influenza season is poorly matched to the H3N2 virus contained in this season's influenza vaccine. This divergence has contributed to a lower-than-usual level of vaccine effectiveness and to elevated influenza activity. Historically, in influenza seasons when novel H3N2 viruses have predominated, we have observed higher hospitalization rates and increased mortality.

This experience, together with the constant threat of pandemic influenza, underscores the importance of NIAID's longstanding commitment to influenza research as well as the need for a universal influenza vaccine that could protect people against numerous strains of influenza over multiple influenza seasons. NIAID has built on knowledge gained from past experiences with pandemic influenza—most recently, the 2009 H1N1 pandemic—to enhance the research

infrastructure that will enable our rapid response should another influenza virus with pandemic potential emerge. Critical to these efforts are NIAID's partnerships with academia and with biotechnology and pharmaceutical companies, and collaborations with other Federal organizations, particularly the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Office of the Assistant Secretary for Preparedness and Response (ASPR), including the Biomedical Advanced Research and Development Authority (BARDA), and the National Vaccine Program Office within the Department of Health and Human Services.

Seasonal and Pandemic Influenza

Each year in the United States, 15 to 60 million people experience symptomatic influenza illness, and more than 200,000 are hospitalized. Annual influenza-related deaths in the United States ranged from about 3,000 to 49,000 over a recent 30-year period. Very young children, pregnant women, people 65 years of age and older, and individuals with underlying chronic health conditions are particularly susceptible to severe outcomes of influenza, including death. As influenza circulates around the globe each year, the genes of the influenza virus mutate and sometimes reassort or exchange genes with other influenza strains; this causes proteins on the surface of the virus to undergo varying degrees of structural changes. These changes, which are usually small, accumulate over time to cause "antigenic drift" that allows an influenza virus to evade in part the protection people may have built up against influenza viruses due to previous influenza vaccinations or prior influenza exposure. Antigenic drift in human influenza viruses causes the changes in seasonal influenza viruses that we see from year to year, and it is the reason why, each year, we must re-evaluate which influenza virus strains should be included in

the seasonal influenza vaccine. Occasionally, more profound changes in the genetic makeup of the influenza virus lead to "antigenic shift," which results in larger changes in the structure of its surface proteins. Because the vast majority of the population typically does not have existing immunity against a virus that has undergone an antigenic shift, a pandemic can ensue, as we saw with 2009 H1N1 pandemic influenza. We must constantly address these small and large evolutionary changes in order to be prepared for both seasonal and pandemic influenza.

Annual influenza vaccination is the primary method to prevent seasonal influenza. Current manufacturing typically requires growth of influenza vaccine strains in eggs, a laborious and time- consuming process. Recently, the growing of virus in cell lines for certain influenza vaccines is somewhat of an improvement in vaccine production over growing the virus in eggs; however, it still requires the tedious process of growing the virus. Influenza vaccine technology of the future, based on research largely supported by NIAID, is employing modern molecular biological techniques to circumvent this outdated approach.

Basic and Clinical Research

NIAID has a longstanding commitment to basic and clinical research on influenza to better understand how influenza viruses replicate, stimulate immune responses, and evolve into new strains. Results from these research studies inform the design of new and improved influenza vaccines, diagnostic tools, and antiviral drugs applicable to both seasonal and pandemic influenza strains. Partnerships between government, academia, and the biotechnology and pharmaceutical industries are critical to speeding the development of these countermeasures.

NIAID supports efforts to gain basic understanding of how influenza strains emerge, evolve, and infect animals and humans. NIAID's Centers of Excellence for Influenza Research and Surveillance (CEIRS) Program is supporting domestic and international influenza researchers studying the factors that control the emergence and transmission of influenza viruses among animal reservoirs, and the immunological determinants of whether an influenza virus causes only mild illness or results in severe disease or death. The CEIRS Program continually monitors cases of animal and human influenza worldwide to rapidly detect and characterize viruses that may have pandemic potential, such as the avian influenza strains H5N1 and H7N9.

In addition, NIH scientists are characterizing human influenza infection through studies in healthy volunteers who are challenged under controlled conditions with influenza virus to gain a better understanding of the basic biology of human influenza infection. Information gained from these studies will include how much time elapses between a known exposure to influenza virus and the start of viral shedding (a sign of contagiousness), the onset and duration of influenza symptoms, and the development of an immune response. These investigations also provide a scientific basis for more rapid, cost-effective clinical trials to evaluate new influenza drugs or to determine the efficacy of candidate vaccines for both seasonal and pandemic influenza.

Diagnostics

NIAID supports research to design influenza diagnostics that are faster and more accurate, cost-effective, and portable than current diagnostic tools. NIAID has worked to develop diagnostic platforms capable of examining influenza viruses at the molecular level and rapidly identifying a wide variety of virus types and subtypes. With NIAID support, researchers are developing clinical assays to determine whether influenza viruses are sensitive to neuraminidase inhibitors, a

class of antiviral drugs that inhibit influenza virus replication. Rapid influenza diagnostics that allow healthcare professionals to quickly distinguish one strain from another at the point of patient care and to detect resistance to antiviral drugs would ensure that patients receive the most appropriate care.

Antiviral Therapies

Antiviral medications are an important tool to control influenza by treating infection and helping to prevent severe illness. The neuraminidase inhibitors oseltamivir (Tamiflu®), zanamivir (Relenza®), and peramivir (Rapivab™) are the three antiviral drugs recommended for the treatment of influenza in the United States. When administered within 48 hours of onset of illness, these drugs can reduce the duration and severity of illness. However, experience tells us that resistance to influenza antiviral medications can emerge, and new and better treatments are needed.

NIAID continues efforts to develop and test the next generation of influenza treatments, including broad-spectrum antiviral drugs. NIAID has supported antiviral candidates at various stages of the development pipeline; several have entered clinical trials supported by NIAID and its government and industry partners. For example, NIAID supported initial Phase I clinical studies of a novel neuraminidase inhibitor, peramivir, which was recently approved by the FDA to treat influenza infection in adults. This is the first neuraminidase inhibitor available in IV formulation. NIAID has advanced the development of additional next-generation neuraminidase inhibitors, as well as influenza RNA polymerase inhibitors and monoclonal antibodies targeting the critical influenza surface protein hemagglutinin (HA). Three NIAID clinical trials are underway to explore the effectiveness of novel influenza therapeutics in high-risk populations,

including human plasma containing high levels of anti-influenza antibodies, concentrated immunoglobulin with high levels of anti-influenza antibodies, and a "cocktail" of three licensed influenza antiviral drugs.

Vaccines

New Vaccine Development Technologies

As mentioned above, antigenic drift and shift create significant challenges for those who must forecast which influenza virus strains are the most suitable targets for seasonal vaccine development. One way to address these challenges is to create flexible manufacturing processes that could respond rapidly to emerging seasonal or pandemic influenza strains. NIAID is pursuing technologies that could increase the efficiency of vaccine production and shorten manufacturing times. NIAID and industry partners have made progress in moving from the current egg-based, and to some extent cell-based, influenza vaccine production methods to recombinant DNA manufacturing that could be rapidly mobilized with the emergence of a pandemic virus. NIAID also has participated in the Influenza Vaccine Manufacturing Improvement Initiative in collaboration with ASPR/BARDA, CDC, FDA, and vaccine manufacturers. As part of this effort, NIAID is supporting accelerated and flexible vaccine production through development of novel assays, improved influenza strain selection, and optimized high-yield influenza virus vaccine strains.

NIAID has a longstanding vaccine clinical trials infrastructure, the NIAID Vaccine and Treatment Evaluation Units (VTEUs), ready to test vaccine produced through both new and traditional influenza vaccine manufacturing platforms. When NIAID, in close coordination with

CDC, BARDA, and FDA, moved rapidly to respond to the 2009 H1N1 influenza pandemic, the VTEUs conducted pivotal trials of 2009 H1N1 pandemic influenza vaccine. These studies determined the safety and appropriate dose of the vaccine to induce a predictably protective immune response in normal adult volunteers as well as in high-risk populations such as children, pregnant women, the elderly, and people who are immunocompromised.

Universal Influenza Vaccines and Other Vaccine Approaches

NIAID also invests in a major effort to develop a "universal" influenza vaccine that induces a broad and potent immune response to the common elements of the influenza virus that change very little from strain to strain. A universal influenza vaccine potentially could provide protection against numerous strains of influenza, including those that drift or even shift, such that protection could be sustained over multiple seasons. Advances in our understanding of the structure and immunological characteristics of hemagglutinin (HA) —a protein on the surface of the influenza virus that is targeted by the protective effect of the immune system—have shed light on the basic science behind universal influenza development. Using advanced genetic and structure-based technologies, scientists have determined that most antibodies against the influenza virus target the "head" of the mushroom-shaped HA protein structure; the head of the HA protein is also the component of this important protein subject to the antigenic drift that necessitates the generation of a new influenza vaccine every season. In contrast, researchers have discovered that the "stem" or stalk region of the HA protein is relatively unchanged among different influenza strains. Given this stability, an immune response against this stem could elicit a broad immune response effective against multiple influenza strains. NIAID has intensified universal influenza vaccine research and development focusing on the HA stem region, and

NIAID intramural and extramural researchers are advancing several promising universal influenza vaccine concepts into early clinical trials.

NIAID, in collaboration with BARDA and CDC, is planning a Phase I clinical trial in the VTEU network to investigate the human immune response to HA stem-based universal influenza vaccines. CDC has generated seed virus constructs for two stem-based vaccines developed by NIAID-funded scientists, and BARDA has supported production of clinical lots of the vaccine. In addition, NIAID Vaccine Research Center (VRC) researchers have carried out several Phase I/II clinical trials of a potential universal influenza vaccine by assessing an initial, "prime" vaccination with influenza virus DNA vaccine followed by a "boost" with a conventional, licensed seasonal influenza vaccine to induce enhanced and broadly reactive antibody responses. The study investigators are now evaluating data from those trials. NIAID VRC scientists also have developed an HA-ferritin nanoparticle vaccine to improve the potency and durability of seasonal influenza vaccination. This approach has shown promise in animal models, and the VRC team is assessing the vaccine strategy for further development, including potential application to universal influenza vaccine design.

While pursuing multiple strategies to develop a universal influenza vaccine, NIAID-funded researchers also are pursuing complementary strategies to improve seasonal influenza vaccines. For example, researchers are developing alternative vaccine delivery systems; identifying additional vaccine components that could elicit universal protection; and assessing the contribution of adjuvants, vaccine additives that can help create a more vigorous immune response to a vaccine. NIAID research efforts are yielding important information about the influenza virus that we hope will lead to an effective universal influenza vaccine. It is not

possible to predict when a universal influenza vaccine may be available, and candidates will need to be rigorously evaluated over multiple influenza seasons to determine durability of protection. However, progress in recent years is encouraging.

Finally, NIAID continues its efforts to prepare for pandemic influenza including the potential for wider spread of emerging strains of avian influenza such as H5N1 and H7N9. For example, NIAID intramural scientists, in collaboration with BARDA and industry, are working to develop live attenuated vaccines against influenza viruses with pandemic potential. In addition, NIAID is supporting clinical trials to understand human immune responses to H5N1 and H7N9 vaccines. These efforts include collaborations with BARDA on studies in the elderly of the safety and immunogenicity of an inactivated H7N9 vaccine developed by Sanofi Pasteur, with and without two different stockpiled adjuvants. Such studies will help to determine "dose-sparing" strategies to maximize the supply of stockpiled vaccines for pandemic preparedness.

Conclusion

NIAID plays a critical role in the comprehensive efforts of the Federal Government to combat influenza by supporting basic and translational research to inform the development of new and improved influenza diagnostics, therapeutics, and vaccines. A major focus of these efforts is the development of a universal influenza vaccine that could provide long-lasting protection against multiple strains of influenza, including seasonal and pandemic influenza. As we face the current severe and widespread seasonal influenza epidemic, NIAID will continue its ongoing and productive collaborations with partners in government, academia, and industry to develop and test novel and effective influenza countermeasures.