DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases Research Addressing the Public Health Threat of Influenza

Testimony before the

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Mr. Chairman, Ranking Member DeGette, and members of the Subcommittee, thank you for the invitation to discuss the National Institutes of Health's (NIH) response to the public health threat posed by influenza. The National Institute of Allergy and Infectious Diseases (NIAID) is the lead NIH institute for research on immunologic, allergic, and infectious diseases, including influenza.

The NIAID mission balances basic, translational, and clinical research addressing current biomedical challenges with the capacity to rapidly respond to new threats from emerging and re-emerging infectious diseases, including seasonal and pandemic influenza. Given the morbidity and mortality of influenza in the United States every year, and the disease's economic burden, we recognize the importance of research to develop new tools to diagnose, treat, and prevent seasonal influenza, as well as prepare for the next influenza pandemic. NIAID's longstanding influenza research program includes efforts to develop a universal influenza vaccine that could provide durable protection against a variety of seasonal and pandemic influenza viruses. Important to these NIAID efforts are ongoing collaborations with academia, the biotechnology and pharmaceutical industries, and other Federal partners, 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.

Basic Research

NIAID support for basic research on influenza continues to inform the development of new and improved vaccines, diagnostic tools, and antiviral drugs applicable to both seasonal and pandemic influenza strains. As part of this focus, NIAID supports fundamental research to better

understand the evolution and pathogenesis of influenza viruses in animals and humans. Researchers supported by NIAID's Centers of Excellence for Influenza Research and Surveillance (CEIRS) program are studying the global emergence and spread of novel influenza viruses, critical information that is provided to the World Health Organization (WHO). Influenza virus surveillance and sequencing using next-generation genomic technologies supported by NIH have begun to provide a more detailed picture of the evolution of the influenza virus and insights into controlling the impact of influenza outbreaks. Additionally, further understanding of the way our immune system responds to influenza and influenza vaccines is resulting in new approaches to the development of vaccines that have more breadth in their ability to protect against a variety of influenza viruses.

Diagnostics Development

NIAID supports research aimed at improving influenza diagnostics to make them faster, more accurate, and usable wherever patients seek medical care. In particular, NIAID is funding the development of diagnostic platforms to examine the molecular makeup of influenza viruses to quickly distinguish between seasonal strains and those with pandemic potential. NIAID also supports development of influenza clinical assays to determine viral sensitivity to neuraminidase inhibitors – drugs that both lessen the severity and duration of illness in those infected, and potentially prevent infection in close contacts. To help ensure that patients receive prompt and effective care, NIAID will continue to develop rapid diagnostic tools that distinguish one influenza strain from another and also detect resistance to antiviral drugs.

Antiviral Therapies Development

Antiviral medications are important tools in treating and preventing complications of influenza infection. Three antiviral drugs (neuraminidase inhibitors) currently are recommended for the treatment of influenza in the United States. The emergence of antiviral-resistant influenza strains, however, requires the development of new and better treatment options. NIAID continues to pursue novel influenza therapeutics, including broad-spectrum antiviral drugs, and has advanced several candidates into clinical trials. NIAID supports the development of RNA polymerase inhibitors, peptide inhibitors, and next-generation neuraminidase inhibitors. NIAID also is developing monoclonal antibodies against hemagglutinin (HA), a protein on the surface of the influenza virus that enables it to attach to the cells lining the respiratory tract. Blocking the interaction between the virus and human cells with an antibody could prevent or lessen influenza disease. In addition, three NIAID clinical trials are underway to assess the effectiveness of novel influenza therapeutics in high-risk populations. These therapeutics include human plasma containing high levels of anti-influenza antibodies, concentrated immunoglobulin with high levels of anti-influenza antibodies, and a combination of three licensed influenza antiviral drugs.

Vaccine Development

Universal Influenza Vaccines

Annual influenza vaccination is the primary method to prevent seasonal influenza. Because influenza viruses evolve as they spread from person to person, the strains used in the influenza vaccine must be re-evaluated every year. When significant changes occur among circulating influenza strains after vaccine recommendations have already been made, the seasonal influenza vaccine may not be as effective in preventing influenza infection, as was the case with the H3N2

influenza A virus during the 2014-2015 influenza season. When genetic changes in the influenza virus cause substantial changes in the structure of its surface proteins, the strain that emerges can lead to a pandemic because a majority of the population lacks immunity to the new strain, as occurred with the 2009 H1N1 pandemic. We must constantly monitor evolutionary changes in circulating influenza viruses to be prepared for both seasonal and pandemic influenza. While recent analyses suggest that the strains in the current seasonal influenza vaccine match the circulating influenza strains, the mismatch experienced during the 2014-2015 influenza season underscores the importance of NIAID's sustained support for influenza research. In particular, the recent mismatch reminds us of the need for a more broadly cross-protective or "universal" influenza vaccine that could generate long-lasting protection against several influenza strains over multiple seasons.

NIAID research on universal vaccines is focused on several concepts, but the common principle behind each concept is to identify those parts of the influenza virus that are similar across multiple influenza strains and then maximize the immune system's ability to respond to them. Research on the HA protein has revealed that most influenza virus antibodies target the "head" of the HA protein structure, portions of which differ from strain to strain of influenza. In comparison, the "stem" of the HA protein is relatively stable among diverse influenza strains, suggesting that strategies to generate immune responses against the HA stem could elicit broader protection against multiple influenza strains. To explore this concept, NIAID is investing in universal influenza vaccine research and development focusing on the HA stem region, including early clinical trials of several vaccine candidates.

NIAID, in collaboration with BARDA, is continuing to support the development of HA stem-based universal influenza vaccines and other promising universal influenza candidates. NIAID intramural researchers also have developed a ferritin nanoparticle vaccine based on a stabilized HA stem from an H1N1 influenza virus. The vaccine, which lacks the HA head to more effectively elicit an immune response against the stem, protected against lethal influenza infection in animal models. Notably, the vaccine protected against a different HA subtype (H5) than the H1 subtype it was based upon, providing proof-of-concept that vaccines targeting the HA stem can offer broad protection against diverse influenza subtypes.

NIAID Vaccine Research Center (VRC) scientists also have conducted several clinical trials of another novel influenza vaccination strategy to assess whether it can induce enhanced and broadly reactive antibody responses. In this strategy, an initial vaccination with an influenza virus DNA vaccine known as a "prime" is followed by a "boost" with traditional seasonal influenza vaccine in an effort to improve the potency and durability of seasonal influenza vaccination. Three recent Phase I clinical trials investigating a regimen of an HA-based DNA influenza vaccine prime followed by a boost with either traditional seasonal influenza vaccine or a monovalent influenza vaccine found the vaccines were safe and produced an immune response. NIAID scientists also have discovered that mice inoculated with a virus-like particle vaccine were protected from infection with a wide range of influenza A strains, including strains not contained in the vaccine, suggesting another potential strategy to develop a universal influenza vaccine. NIAID is evaluating these vaccine strategies to better understand how they could contribute to universal influenza vaccine design.

Although we cannot predict when a universal influenza vaccine would be publicly available, NIAID-led efforts have generated encouraging progress toward this goal. It is important to note that as we develop universal influenza vaccines, promising candidates will need to be evaluated over several influenza seasons to determine the extent and durability of their protection.

New Vaccine Development Technologies and Pandemic Vaccine Approaches

NIAID is supporting efforts to develop and test a flexible vaccine manufacturing process for influenza vaccine development, including use of modern molecular biological techniques to help increase production efficiency and shorten manufacturing times. NIAID and industry partners are investigating recombinant DNA manufacturing that could be rapidly mobilized with the emergence of a pandemic virus. In addition, NIAID has supported investigation of improved strain selection and optimized high-yield vaccine strains as part of the Influenza Vaccine Manufacturing Improvement Initiative, a collaboration with ASPR/BARDA, CDC, FDA, and vaccine manufacturers. NIAID also supported the development of antigenic cartography, a computational method to understand evolutionary changes in influenza; this new method is now being applied to data from WHO Collaborating Centers to help provide information relevant to the composition of the annual seasonal influenza vaccine. An NIAID-supported computational method known as "antibody landscaping" has enabled scientists to visualize how the human immune system responds to a lifetime of influenza infections; this technique is now being used to aid in the design of "antigenically advanced" vaccines that may allow us to vaccinate against influenza strains that have not yet emerged in nature.

For decades, NIAID has conducted and supported research to prepare for the possible emergence of pandemic influenza. NIAID is currently supporting clinical trials of vaccines against H5N1,

variant strains of H3N2, and H7N9 to assess the immune responses these candidate vaccines induce in humans. Furthermore, NIAID is partnering with BARDA to investigate the safety and immunogenicity of an inactivated H5N8 vaccine with and without two stockpiled adjuvants designed to boost immune responses. H5N8 influenza is a novel strain of highly pathogenic avian influenza that has caused some of the outbreaks of disease in U.S. poultry populations and wild birds that have occurred since late 2014. These studies will inform potential "dose-sparing" strategies to maximize the supply of stockpiled vaccines in the event of a pandemic. In addition, NIAID intramural scientists are conducting clinical studies of prime-boost vaccine regimens for swine (H1) and avian (H7) influenza viruses, and collaborating with industry and BARDA to develop live, attenuated vaccines against potentially pandemic influenza viruses.

Other Clinical Research

NIH scientists are investigating human influenza infection under controlled conditions through clinical research with healthy volunteers challenged with influenza virus. These studies will help scientists more precisely define the timeframe between exposure to influenza virus and viral shedding, and the timing for the onset and duration of influenza symptoms as well as the development of an immune response. The scientists also are searching for factors correlated with protection against influenza. The findings of these studies are informing the design of clinical trials to evaluate candidate influenza countermeasures. For example, building upon NIAID research, an ongoing Phase II trial at the NIH Clinical Center is evaluating the efficacy of a novel monoclonal antibody targeting the stem of the influenza HA protein. In addition, NIAID, through its Vaccine and Treatment Evaluation Units (VTEUs), the Institute's longstanding clinical trials network for rapid testing of candidate vaccines and therapeutics, recently conducted a Phase II

clinical trial of a candidate H7N9 avian influenza vaccine. The study investigators found that two doses were able to generate immune responses in up to 84 percent of volunteers, but only if the vaccine was mixed with an immune-boosting adjuvant. The VTEU trial results provide additional clues to the development of effective H7N9 vaccines.

Conclusion

NIAID has a long history of research to develop better influenza diagnostics, therapeutics, and vaccines. Sustained support of NIAID's basic, translational, and clinical influenza research will contribute important information toward the advancement of an effective universal influenza vaccine that could provide lasting protection against multiple strains of influenza as well as prepare us for the next influenza pandemic. NIAID will continue to focus on advancing new tools to combat influenza in collaboration with government, academia, and industry partners.