DEPARTMENT OF HEALTH AND HUMAN SERVICES

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The Role of the National Institute of Allergy and Infectious Diseases in Research on Influenza Vaccine Innovation

Testimony before the

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Madam Chair, Ranking Member Lucas, and Members of the Committee:

Thank you for the opportunity to discuss the role of the National Institute of Allergy and Infectious Diseases (NIAID) in the research and development of innovative influenza vaccines. NIAID is the lead institute at the National Institutes of Health (NIH) for conducting and supporting research on infectious diseases, including influenza.

NIAID supports a comprehensive portfolio of basic, translational, and clinical research on influenza. This research is focused on better understanding the influenza virus and the disease it causes as well as developing diagnostics, therapeutics, and vaccines to prevent and treat it. The constantly changing nature of seasonal influenza viruses and the threat of the emergence of a pandemic influenza necessitate the development of broadly reactive or "universal" influenza vaccines that could protect individuals over many years against multiple types of influenza viruses, both seasonal and pandemic. NIAID efforts in this regard are bolstered by ongoing collaborations with academia, philanthropic organizations, and biotechnology and pharmaceutical companies. NIAID conducts this work alongside key U.S. government partners, particularly the Department of Defense, the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response (ASPR), including the Biomedical Advanced Research and Development Authority (BARDA).

UNIQUE CHALLENGES PRESENTED BY INFLUENZA VIRUSES

Influenza viruses, particularly influenza A viruses, are persistent threats to global health as they cause significant illness and death every year in the United States and worldwide. Influenza viruses evolve and evade the immune system response in two major ways: "antigenic drift" and "antigenic shift." Antigenic drift occurs when small changes steadily accumulate in key proteins on the surface of the influenza virus. The human immune system focuses its response to influenza primarily on two proteins on the surface of the virus, hemagglutinin (HA) and neuraminidase (NA). Over time, minor alterations in the HA and NA proteins, usually resulting from genetic mutations, can impair the immune system's ability to recognize a specific influenza virus. This antigenic drift characteristic of seasonal influenza often necessitates the modification of the influenza vaccine from season to season. On the other hand, antigenic shifts are characterized by major genetic changes that, when they occur, are often manifested by the "spill over" of an influenza virus from an animal population to humans, who lack existing immunity to that virus. If these novel viruses can efficiently transmit from person to person, the risk of a potential influenza pandemic is high.

The mainstay of influenza prevention is vaccination. Seasonal influenza vaccination can protect an individual from illness, hospitalization, and death due to influenza. Current influenza vaccines are designed to protect against a few influenza strains. These vaccines result in highly "strain-specific" immunity. This means that updated influenza vaccines must be developed each year against the specific viruses that are predicted to circulate in the upcoming season. The effectiveness of seasonal influenza vaccines – a measure of how well the vaccines work to prevent influenza illness – has ranged from 10 to 60 percent in the last 15 years. This rate is

lower than that of many other licensed vaccines for common infectious diseases, such as the combined vaccine for measles, mumps, and rubella viruses, which has an effectiveness rate of 97 percent against measles. Suboptimal seasonal influenza vaccine effectiveness in part may be due to the six-month timeline required to grow the virus (usually in eggs) for production of vaccines. Once the vaccine production process is initiated, it is nearly impossible to begin anew if a different strain emerges. In years when circulating influenza strains drift significantly, mismatches between the vaccine and circulating viruses can occur, and this may result in low vaccine effectiveness.

In addition, due to the long time-frame for egg-based influenza vaccine production, vaccines likely would not be readily available if an antigenic shift occurs and a previously unidentified strain of pandemic influenza suddenly emerges. Currently, an updated – and sometimes a novel – influenza vaccine is needed for each new strain of influenza with pandemic potential. During the H1N1 influenza pandemic in 2009, a vaccine against the emergent virus strain was not available to the public until well after the peak of the pandemic had occurred. Continually "chasing" influenza viruses that jump from animals to humans comes at a substantial economic cost and can leave public health at risk. It is essential that we move beyond the current strain-specific influenza vaccine development strategy to address both seasonal and pandemic influenza.

THE NEED FOR INNOVATIONS IN INFLUENZA VACCINOLOGY

The optimal influenza vaccination strategy would deploy universal influenza vaccines that protect broadly and durably against seasonal influenza strains and those with pandemic

potential. NIAID has prioritized the development of universal influenza vaccines and has outlined its research strategy toward this goal in our *Strategic Plan for a Universal Influenza Vaccine. The Strategic Plan* focuses on three research areas: improving knowledge of the transmission, natural history, and pathogenesis of influenza infection; characterizing influenza immunity and immune factors that correlate with protection against influenza; and supporting the rational design of universal influenza vaccines. NIH will continue targeted investments in each of these research areas to generate critical information for the development of universal vaccines effective against both seasonal and pandemic influenza. Currently, we face two main challenges when designing such innovative influenza vaccines: improving vaccine production strategies and moving beyond strain-specific vaccines to vaccines with universal influenza strain coverage.

Improving Vaccine Production Strategies

Most existing influenza vaccines are produced by growing the virus in eggs. This is a time-honored, but time-consuming process. Furthermore, the vaccine undergoes a process of adaptation to grow in eggs that may in itself lead to mutations that make the resulting vaccine less effective. In recognition of these limitations, the President signed the *Executive Order on Modernizing Influenza Vaccines in the United States to Promote National Security and Public Health* on September 19, 2019. Broadly, the Executive Order directs BARDA, CDC, NIH, and FDA to accelerate the adoption of improved influenza vaccine technologies. In alignment with the goals of the Executive Order, NIAID is conducting and supporting research to develop state-of-the-art vaccine platform technologies that could be used to develop universal influenza vaccines as well as to improve the speed and agility of the influenza vaccine manufacturing process. These platform technologies include DNA, messenger RNA (mRNA), virus-like

particles, vector-based, and self-assembling nanoparticle vaccines. For example, NIAID-supported scientists are investigating an mRNA vaccine candidate that would allow for a more rapid and flexible response to both seasonal and pandemic influenza than do existing vaccine production strategies.

Moving Beyond Strain-specific Influenza Vaccines

In addition to research into how we can improve influenza vaccine manufacturing, NIAID is working to advance from strain-specific vaccines to vaccines that would provide near universal influenza virus strain coverage. This effort aligns with NIH responsibilities outlined in the Executive Order mentioned previously. The HA protein of influenza is made up of a head and a stem, analogous to a mushroom cap and its stem. Strain-specific vaccines primarily generate an immune response to the head region, which mutates easily and differs between influenza virus strains. NIAID scientists and NIAID-supported researchers are working toward designing vaccines that generate an immune response to multiple influenza strains by targeting conserved parts of the virus – those that are less likely to differ among strains. A key target is the stem region of the HA protein, which is more similar from strain to strain than the head region of HA. The NA surface protein has been identified as another potential vaccine target. Recently, NIAID-supported scientists demonstrated in an animal model that monoclonal antibodies targeting NA of one influenza virus strain can also provide protection against several other strains of influenza. NIAID scientists also are working on new ways of displaying conserved parts of the virus to the immune system to induce a stronger and broader immune response.

The process of moving beyond strain-specific influenza vaccines will be iterative and progressive. The initial stage of development will focus on vaccines against all versions of a single subtype. For example, one vaccine may target all strains of subtype H3N2, whereas another vaccine may target all strains of subtype H1N1. All influenza A viruses fall within two broad groups. Following the initial stage, efforts would progress toward development of vaccines against all subtypes within a specific group. These vaccines would target influenza A viruses throughout either "group 1" (which includes subtypes H1N1 and H5N1, among others) or "group 2" (which includes subtypes H3N2 and H7N9, among others). The final iteration of development would provide a truly universal vaccine that would protect against all influenza A viruses.

STRATEGIES FOR DEVELOPING UNIVERSAL INFLUENZA VACCINES

NIAID is pursuing multiple strategies for the development of universal influenza vaccines that target common parts of the influenza virus in order to elicit a protective immune response against diverse influenza viruses. The NIAID Vaccine Research Center (VRC) is conducting a Phase 1 clinical trial of a universal influenza vaccine that uses a nanoparticle-based platform technology to display the stem region of the HA protein. Proteins displayed on nanoparticles are highly immunogenic. The vaccine candidate incorporates the stem region of an H1 influenza virus subtype that in animal models provided protection against influenza viruses from other subtypes within "group 1." These results suggest that vaccines targeting the stem of the HA protein could offer broader protection than existing strain-specific influenza vaccines. In 2020, VRC scientists plan to evaluate a similar nanoparticle-based vaccine candidate designed to protect against "group 2" influenza viruses. Additionally, the NIAID Division of Intramural

Research (DIR) is evaluating multiple universal influenza vaccine candidates. In collaboration with industry partners, NIAID scientists recently completed a Phase 2 clinical trial assessing a novel peptide-based candidate in a human influenza challenge model. DIR investigators also plan to launch two Phase 1 trials of other promising universal influenza vaccine candidates in early 2020. The first candidate comprises a cocktail of inactivated avian influenza viruses and the second candidate targets the NA influenza surface protein.

NIAID also supports diverse efforts by extramural researchers to develop universal influenza vaccine candidates. NIAID continues longstanding support for its Vaccine and Treatment Evaluation Units (VTEUs), which are currently conducting multiple clinical trials evaluating candidate universal influenza vaccines. In 2018, NIAID began a Phase 2 VTEU clinical trial to evaluate the M-001 vaccine candidate made by the company BiondVax that contains several influenza fragments common among multiple influenza virus strains. In addition, NIAID is sponsoring a Phase 1 VTEU clinical trial to evaluate the safety and immunogenicity of a regimen using an investigational live, attenuated intranasal influenza vaccine followed by a boost with a licensed, quadrivalent inactivated seasonal influenza vaccine. NIAID has recently expanded the capacity of the VTEUs to conduct human influenza challenge studies to assess how levels of pre-existing influenza antibodies impact the timing, magnitude, and duration of symptoms following exposure to influenza virus. These challenge studies also will facilitate the future evaluation of novel universal influenza vaccine candidates.

Recently NIAID initiated the Collaborative Influenza Vaccine Innovation Centers (CIVICs) network to foster a coordinated, multidisciplinary effort to develop more broadly

protective and longer-lasting influenza vaccines. Network researchers will conduct preclinical studies, clinical trials, and human challenge studies to explore approaches to improve seasonal and universal influenza vaccines, such as alternative vaccine platforms or new adjuvants (substances added to vaccines to boost immunity). In addition, NIAID is supporting research to examine how the immune systems of young children respond over time to their initial influenza infection and their first vaccination. These long-term cohort studies will help us understand how repeat vaccinations and immune memory affect the ability to mount an immune response to different influenza subtypes. Insights from this research will inform the design of more effective influenza vaccines and vaccination strategies.

CONCLUSION

Recent NIAID-supported advances in the areas of influenza virology, structural biology, protein engineering, immunology, and vaccinology have made possible the goal of advancing beyond strain-specific vaccines toward a universal influenza vaccine. The recent Executive Order has helped to focus and reinvigorate NIAID's longstanding partnerships with government, academic, and industry partners dedicated to the improvement of vaccines that protect against influenza. In support of the objectives of the Executive Order and guided by *the Strategic Plan for a Universal Influenza Vaccine*, NIAID will continue to accelerate research toward the development of modern vaccines that can protect against both seasonal and pandemic influenza.

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Dr. Fauci was appointed Director of NIAID in 1984. He oversees an extensive research portfolio of basic and applied research to prevent, diagnose, and treat established infectious diseases such as HIV/AIDS, respiratory infections, diarrheal diseases, tuberculosis and malaria as well as emerging diseases such as Ebola and Zika. NIAID also supports research on transplantation and immune-related illnesses, including autoimmune disorders, asthma and allergies. The NIAID budget for fiscal year 2019 was approximately $5.5 billion.

Dr. Fauci has advised six Presidents on HIV/AIDS and many other domestic and global health issues. He was one of the principal architects of the President's Emergency Plan for AIDS Relief (PEPFAR), a program that has saved millions of lives throughout the developing world.