Mr. Chairman, Ranking Member DeGette, and members of the Subcommittee, thank you for the opportunity to discuss the response of the National Institutes of Health (NIH) to the public health threat posed by influenza. I direct the National Institute of Allergy and Infectious Diseases (NIAID), the lead NIH institute for conducting and supporting research on established and emerging infectious diseases, including influenza.

NIAID funds a longstanding, comprehensive portfolio of basic, translational, and clinical research on influenza focused on better understanding the virus and the disease that it causes as well as developing diagnostics, therapeutics, and vaccines to prevent and treat it. The current, remarkably severe influenza season, the consistently changing nature of seasonal influenza viruses, together with the ever-present threat of pandemic influenza, underscore the importance of this research to improve on our current influenza vaccines, as well as to lead us on a pathway toward the development of a universal influenza vaccine. The latter would provide long-lasting protection against multiple seasonal and pandemic influenza viruses. NIAID efforts in this regard are bolstered by ongoing collaborations with academia, philanthropic organizations, biotechnology and pharmaceutical companies, as well as U.S. government partners, particularly the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the Office of the Assistant Secretary for Preparedness and Response (ASPR), including the Biomedical Advanced Research and Development Authority (BARDA).

Fundamental Research to Understand Influenza Evolution and Immunity

NIAID-supported basic research on influenza provides the foundation for developing new and improved diagnostics, antiviral therapies, and vaccines for influenza caused by both seasonal and pandemic virus strains. Detailed studies of how our immune system responds to influenza viruses and influenza vaccines are stimulating novel approaches for developing vaccine candidates that can elicit robust immune responses and provide broad protection against a variety of influenza virus strains.

Surveillance (CEIRS) study the emergence and spread of novel influenza viruses worldwide to lay the groundwork for new and improved control measures for circulating influenza viruses. The CEIRS global network of research sites has characterized newly detected influenza virus strains and has evaluated potential vaccine approaches for emerging influenza viruses, including those of avian origin. CEIRS investigators also have recapitulated influenza virus evolution in the laboratory, allowing them to predict viral mutations that may occur in nature. This information can be used to help design seasonal influenza vaccines that optimally match circulating strains. Influenza virus surveillance programs using next-generation genomic technologies supported by NIH also are providing an in-depth view of influenza virus evolution and insights into reducing the disease burden of seasonal and pandemic influenza.

Influenza Vaccines

Challenges Presented by Current Influenza Vaccines

Licensed annual influenza vaccines, the primary tool for prevention of seasonal influenza, are updated each year to address the strains that experts deem likely to circulate during the upcoming influenza season. These vaccines are updated annually through supplements to their FDA licenses, which must be approved by FDA prior to distribution of the vaccines. The overall efficacy of seasonal influenza vaccines ranges from 40 to 60 percent when there is a good match between the vaccine and circulating influenza viruses, although they may be significantly less effective when varying degrees of mismatches occur between the circulating strains and the vaccine. These mismatches can be caused by the constant evolution of circulating influenza strains, as was observed in the 2014-2015 influenza season, or by mutations that occur when

viruses from humans are adapted to grow in eggs, a requirement for the egg-based vaccine manufacturing process, the predominant technology used for influenza vaccines globally.

The public health response to influenza becomes particularly challenging when a pandemic strain emerges. This happens when the vast majority of the population has not been exposed to a newly emerging influenza strain and lacks immunity to it, as occurred with the 2009 pandemic H1N1 influenza virus. The less than optimal efficacy of vaccines against seasonal influenza together with the constant threat that a pandemic strain may emerge, and the risk of seasonal influenza vaccine mismatches, emphasize the need for additional strategies to address both seasonal and pandemic influenza. A more broadly protective, or universal, influenza vaccine would be a valuable tool in our efforts to generate more durable protection against multiple influenza strains. It would also be important as we are pursuing the development of a universal influenza vaccine to improve on the efficacy of our current vaccines since it will take several years to develop a universal influenza vaccine ready

correlate with protection against influenza; and supporting the rational design of universal influenza vaccines. Targeted investments in each of these research areas will be required to generate the critical information necessary to enable the development of universal vaccines effective against both seasonal and pandemic influenza.

Strategies for Universal Influenza Vaccines

Current NIAID research on universal influenza vaccines pursues multiple strategies that target parts of the influenza virus common across multiple influenza strains in an effort to broaden the immune system response and cover multiple, diverse influenza viruses. One scientific challenge in developing a truly universal vaccine relates to the influenza surface protein hemagglutinin (HA). Most antibodies against LQIOXHQ]D YLUXV WDUJHW WKH mushroom-shaped HA³KHDG´ RI protein, which differs from strain to strain of influenza viruses and is constantly changing by mutation. In contrast WKH ³VWHP´ RI WKH mushroom-shaped HA protein remains relatively constant among diverse influenza virus strains, suggesting that strategies to generate immune responses against the HA stem could elicit broader protection against multiple influenza virus strains.

Scientists at the N

In addition, VRC researchers have conducted several clinical trials of another influenza vaccine strategy designed to elicit enhanced and broadly reactive antibody responses. Recent NIAID Phase I clinical trials have tested an initial vaccinali i4tested

would be publicly available, we expect that progress toward that goal will occur in iterative and progressive steps. NIAID-supported research already has produced promising results. However, we anticipate that it will require significant scientific effort, and multiple refinements along the way, to achieve long-lasting, broadly protective vaccines that can be used in all populations. As we develop such vaccines, promising candidates will need to be evaluated over several influenza seasons to determine the extent and durability of the protection that they induce.

Improving Current Influenza Vaccines

Concurrent with efforts to develop a universal influenza vaccine, NIAID supports the development of flexible vaccine manufacturing processes, including the use of molecular biological techniques, to help shorten manufacturing times and increase production efficiency for current and future influenza vaccines. NIAID and industry partners are investigating recombinant

In addition, NIAID has supported studies of improved vaccine strain selection and optimized high-yield vaccine strains as part of the Seasonal Influenza Vaccine Improvement (SIVI) initiative, an interagency collaboration launched in 2016. The SIVI initiative builds upon the success of the Influenza Vaccine Manufacturing Improvement (IVMI) initiative, a collaboration with ASPR/BARDA, CDC, FDA, and vaccine l P7(/B)7f*EMC /P /MCID 58>BDC BT1 0 0 5mrul15(y)20(ti)f*E

Pandemic Hemagglutinin test is a new immunoassay for seasonal and pandemic influenza vaccines that can identify multiple HA subtypes, including H5, H7, and H9. This assay represents an improvement over current tests because it can be deployed rapidly to determine and monitor the potency of a greater number of vaccine formulations, such as adjuvanted vaccines and dose-sparing vaccine preparations.

Pandemic Vaccine Approaches

For decades, NIAID has supported research to prepare for the possible emergence of pandemic influenza. NIAID, in collaboration with BARDA, has evaluated candidate vaccines against pandemic influenza viruses such as the 2009 H1N1 and potential pandemic infl

viruses, and collaborating with industry and BARDA to develop live, attenuated vaccines against influenza viruses with pandemic potential.

Influenza Diagnostics

NIAID supports the development of influenza diagnostics with improved speed, accuracy, and usability in settings where patients seek medical care. NIAID is helping to develop molecular diagnostic platforms capable of quickly distinguishing between seasonal strains. For example, a rapid molecular test system developed with longstanding NIAID support was recently cleared by the FDA to accurately distinguish influenza A from influenza B in nasal swab specimens. NIAID also supports the development of clinical assays to determine

Several of these antibodies are currently in Phase II clinical trials, including a novel monoclonal antibody targeting the stem of the influenza HA protein. In addition, NIAID has launched three clinical trials 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.

Conclusion

NIAID has a long history of comprehensive and cutting-edge influenza research to develop better diagnostics, therapeutics, and vaccines. Sustained support of NIAID ¶ basic, translational, and clinical influenza research will generate the knowledge needed to reach the goal of safe and effective influenza vaccines that provide durable protection against multiple strains of influenza virus and help us prepare for the next potential pandemic. NIAID will continue to collaborate with government, academic, and industry partners to develop improved tools to prevent, diagnose, and treat influenza infection. Importantly, NIAID will use its new Strategic Plan for a Universal Influenza Vaccine to guide future investments in influenza research to accelerate progress toward broadly protective influenza vaccines.