Committee on Energy and Commerce
Subcommittee on Oversight and Investigations

Hearing on
"Flu Season: U.S. Public Health Preparedness and Response""

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The Honorable Brett Guthrie (R-KY)

1. The National Institutes of Health's (NIH) written testimony states that the National Institute for Allergy and Infectious Diseases (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.

   a. Is NIAID's research also examining how the immune systems of adults respond over time to influenza vaccinations?

   NIAID Response:
   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 better understand how repeat vaccinations and immune memory affect the ability to mount an immune response to different influenza subtypes. Humans encounter numerous influenza virus strains and vaccinations throughout their lifetime, with immune responses determined by the genetics of the virus, as well as by intrinsic host factors, such as genetics, age, health, and immune status. Recent data provide critical evidence that infection with influenza virus strains circulating during one's childhood elicits a lifelong immunologic imprint. The lifelong imprint then influences subsequent responses to novel strains or vaccinations, as well as helps the body mount an immune response against unfamiliar hemagglutinin (HA) subtypes from the same phylogenetic group as the original infecting virus. This phenomenon is termed "immunologic imprinting." While imprinting can induce protective immunological memory that may be helpful to combat influenza strains similar to the "imprint," some evidence suggests that imprinting may limit the generation of protective responses to novel influenza virus strains or vaccines that are considerably different from the original imprinting viruses.

   An improved understanding of how immunity develops and evolves over time in different age cohorts is one of the key scientific questions that NIAID identified in our 2018 *Strategic Plan for a Universal Influenza Vaccine*. The emergence of transformative new

technologies such as high-throughput sequencing and single-cell sorting provides the opportunity to better understand the fundamental basis for viral evolution and human immune repertoires. While the long-term studies discussed above will focus on children, the results could benefit people of all ages as researchers use the findings to investigate vaccine strategies that provide improved lifelong immunity against different strains of the influenza virus.

In addition, the NIAID-supported Human Immunology Project Consortium (HIPC) and Center for Human Immunology (CHI) are helping to evaluate different vaccine formulations and administration regimens, as well as identify markers of vaccine safety and effectiveness in different populations. HIPC scientists have identified molecular signatures that were predictive of influenza vaccine responses. Interestingly, these signatures appeared to be inversely correlated between younger and older individuals, suggesting that distinct mechanisms may be responsible for the lower response to influenza vaccination observed in older individuals. Findings from the HIPC and CHI studies could lead to the prediction of immune responses before vaccination and offer the possibility of modulating an individual's immune state before vaccination to improve the resulting antibody response.

NIAID-supported scientists in the Division of Intramural Research (DIR) and in the Centers of Excellence for Influenza Research and Surveillance (CEIRS) program are performing studies to help understand the adult immune response to influenza vaccinations over time. CEIRS scientists analyzed samples from a four-year study of serial annual influenza vaccinations in young adults and elderly adults. The researchers demonstrated that although younger individuals produced a better immune response after the first vaccination, age was less relevant after successive vaccinations. This finding suggests that the difference between the two age groups in their response to vaccination may be the result of the different vaccination and infection histories between these groups, in addition to the effect of an aging immune system.

NIAID recently launched the Collaborative Influenza Vaccine Innovation Centers (CIVICs) program, a new network of research centers that will work together in a coordinated, multidisciplinary effort to develop more durable, broadly protective and longer-lasting influenza vaccines. The CIVICs will focus on designing novel vaccine candidates and delivery platforms with an emphasis on cross-protective vaccine strategies that could be used in healthy adults as well as populations at high risk for the most serious outcomes of influenza, including children, older adults, and pregnant women. The CIVICs program also will conduct detailed immunologic analysis of samples collected from clinical trials of vaccine candidates and from human challenge studies. These analyses will help to define the immune responses required for broad and durable protective immunity and identify clear correlates of protection.

Collectively, these studies in children and adults are helping to improve our understanding of how the body responds to influenza infection or vaccination. This knowledge will inform our efforts to develop more broadly protective, or "universal"

influenza vaccines that could protect against a number of influenza strains over longer periods of time.

b. Do we have a good understanding on how repeat vaccinations affect the ability of adults to mount an immune response to different influenza subtypes?

NIAID Response:
NIAID is supporting research to better understand the role of repeat vaccination on the adult immune response to different influenza subtypes. Recently, NIAID-supported CEIRS investigators demonstrated that study participants receiving repeat influenza vaccinations exhibited a reduced ability to develop high-affinity antibodies to an important HA domain of all three influenza virus strains tested, regardless of the vaccine platform being used. Although the sample size of this study was small, the results suggest additional work is needed to determine whether repeat vaccination may contribute to lower vaccine effectiveness of seasonal influenza vaccines in humans.

NIAID-supported CEIRS investigators analyzed blood samples from a cohort of adults after the administration of seasonal influenza vaccine and observed that previously vaccinated individuals had lower post-vaccination levels of HA-specific antibodies against all influenza subtypes tested. The levels of two subtypes of T-cells known to play an important role in the antibody response to influenza vaccination and infection also were reduced after vaccination in the previously vaccinated group. However, some degree of protection was still afforded by the vaccine. These findings suggest that the dampening of the antibody response observed in repeat vaccine recipients may be related to diminished T-cell responses.

Although additional studies are needed to better understand the role of repeat vaccination in the development of immune responses to different influenza subtypes, it is important to note that seasonal vaccines remain the best way to prevent influenza virus infection. The CDC recommends that everyone six months of age and older should get an influenza vaccine every season with rare exception. Annual influenza vaccination is especially important for people in high-risk groups, such as seniors, pregnant women, and young children, as well as people who are in close contact with those at high risk.

The Honorable Jeff Duncan (R-SC)

1. You stated that "historically, the worst bioterrorist has been nature itself" referring to pandemic flu and in your March 14, 2019 testimony to the Senate Appropriations Committee, you testified that stockpiling flu vaccine is not yet possible because it changes from season to season and thus you have supported going "full speed ahead on the platform technologies." Combined with the government's stated goal of procuring a vaccine in 12 weeks:

   a. Do you support pursuing multi-modal platform technologies capable of responding not only to influenza but additional biological threats such as Ebola?

NIAID Response:
A critical component of preparedness is biomedical research to develop medical countermeasures that could be rapidly deployed in response to a naturally occurring or deliberately introduced infectious disease outbreak. This includes NIAID-supported research to develop multi-modal, or platform-based, technologies. Novel vaccine platforms that have been intensively studied employ recombinant DNA technology that bypasses the need to grow the virus. These platforms include recombinant proteins, viral vectors containing genes that express specific viral proteins, virus-like particles that can be manufactured, nanoparticles with high immunogenicity, and genetic approaches such as DNA and RNA that code for viral proteins. These platforms can be quickly modified for use against a variety of pathogens.

For example, NIAID scientists used newly identified Zika virus genetic information to rapidly develop a Zika vaccine candidate using a DNA vaccine platform that progressed from sequence selection to a first-in-human clinical trial in less than four months. The NIAID Zika vaccine candidate was developed with a readily deployable DNA vaccine platform that was previously used by NIAID to develop a West Nile virus experimental vaccine. Using this broadly applicable platform technology, NIAID was able to accelerate its response to a previously unrecognized public health threat. This particular platform, or a similar multi-modal technology, could be used to address other public health threats in the future.
NIAID will continue to support the development of multi-modal, or platform, technologies to enhance pandemic preparedness and response efforts.

b. How important is the speed with which we respond to a pandemic determine our ability to effectively combat it?

NIAID Response:
When novel influenza viruses have the capacity to spread efficiently among humans, the risk of a potential influenza pandemic is high. The speed with which we are able to respond to a potential pandemic is crucial to minimizing potential mortality and morbidity. Our best tool to prevent the next influenza pandemic is a safe and effective vaccine. Unfortunately, a vaccine likely would not be immediately available if a previously unidentified strain of pandemic influenza suddenly emerges, as has been the case in previous influenza pandemics.

Most existing influenza vaccines are produced by growing the virus in eggs. This is a time-honored, but time-consuming process. 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 get ahead of future outbreaks of pandemic influenza.

c. Do you think it's important to support pursuing multiple, novel technologies to ensure we can produce vaccines rapidly following a pandemic declaration?

NIAID Response:
NIAID has prioritized 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. 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. NIAID's developments of vaccine platform technologies that significantly reduce the time to production for novel vaccines, including development of a universal influenza vaccine, are crucial to decreasing the response time in the event of a future pandemic.