House Energy and Commerce Committee

Subcommittee on Oversight and Investigations

"The State of U.S. Public Health Biopreparedness: Responding to Biological Attacks, Pandemics, and Emerging Infectious Disease Outbreaks"

Friday, June 15, 2018

The Honorable Gregg Harper

1. **What do we need to do as a country to be better prepared for an outbreak of pandemic influenza in the U.S.?**

NIAID response:

The National Institute of Allergy and Infectious Diseases (NIAID), the lead institute for research on influenza at the National Institutes of Health (NIH), is conducting and supporting basic, translational, and clinical research that will improve our ability to prepare for and respond to potential pandemic influenza outbreaks. A particular challenge in preparing for an outbreak of seasonal or pandemic influenza is that current influenza vaccines do not provide protection that is long-lasting or effective against a large number of influenza virus strains. To address this challenge, NIAID is prioritizing the development of universal influenza vaccine candidates that could provide long-lasting protection against multiple influenza strains including those with pandemic potential.

NIAID is galvanizing research efforts to develop universal influenza vaccine candidates and convened influenza experts from the U.S. and throughout the world at a research agenda-setting workshop in 2017. Following this meeting, NIAID outlined its universal influenza vaccine research priorities in a strategic plan that focuses on three key areas: improving knowledge of the transmission and pathogenesis of influenza infection; characterizing influenza immunity and immune factors that correlate with protection against influenza; and supporting the design of universal influenza vaccines. NIAID is actively engaging federal partners, including U.S. Department of Health and Human Services agencies and other key domestic and international stakeholders involved in influenza vaccine research, to coordinate and advance activities outlined in the strategic plan. For example, NIAID continues to collaborate with the Biomedical Advanced Research and Development Authority (BARDA) to advance the development and clinical testing of promising influenza vaccine candidates. The additional $40 million in funding for universal influenza vaccine research provided through the Consolidated Appropriations Act, 2018 (P.L. 115-141) will support targeted research investments for the development of universal influenza vaccines that could protect vaccinated individuals against seasonal or pandemic influenza virus strains.

In addition to pursuing universal influenza vaccine strategies, NIAID is working to develop novel vaccine production strategies – such as recombinant DNA manufacturing techniques – that may allow for a more rapid production of targeted vaccines in response to newly emerging or changing strains of influenza virus than current egg and cell-based technologies. These vaccine production techniques could help to speed the availability of vaccines that protect against new or evolving pandemic influenza virus strains.

While investing in research to improve influenza vaccines, NIAID also continues to support the development of novel diagnostics to rapidly identify influenza viruses, including potential pandemic strains, and antiviral drugs that could help to limit influenza morbidity and mortality in a pandemic. NIAID will continue to play a key leadership role in seasonal and pandemic influenza outbreak preparedness and response efforts by conducting and supporting the basic, translational, and clinical research needed to identify and develop effective medical countermeasures.

2. **In your testimony, you mentioned that there will be several iterations of a 'universal' flu vaccine. How many universal vaccine candidates are currently being developed at, or supported by, NIAID and what strains will they target? Where does this research currently stand? How many iterations of a universal flu vaccine does NIAID ultimately envision?**

NIAID response:

A truly universal influenza vaccine would represent a groundbreaking advance in the fight against influenza by providing protection against a number of seasonal and pandemic influenza virus strains. NIAID currently is exploring at least 10 different strategies toward the development of universal influenza vaccine candidates. Each of these strategies may have multiple vaccine candidates in various stages of development that are being investigated by NIAID intramural researchers or NIAID-supported grantees in academia and industry. Notable highlights of NIAID universal influenza vaccine research include the development of a ferritin nanoparticle-based vaccine candidate by the NIAID Vaccine Research Center (VRC), Phase I clinical trials of a VRC-developed DNA vaccine candidate using a prime-boost strategy with a standard inactivated seasonal influenza vaccine, and the recent launch of a NIAID-sponsored Phase II clinical trial to evaluate the M-001 vaccine candidate, which contains several influenza fragments recognized by the immune system that are common among multiple influenza virus strains. Additionally, NIAID is sponsoring a Phase I clinical trial to evaluate the safety and immunogenicity of a prime-boost regimen using an intranasal vaccine candidate followed by a licensed, quadrivalent seasonal influenza vaccine.

We anticipate that progress toward the goal of a universal influenza vaccine will occur in several stages, with each intermediary stage represented by several vaccine candidates that protect against progressively greater numbers of influenza virus strains. NIAID is pursuing strategies that could protect against all strains of a single subgroup of influenza virus, such as the H3N2 strains. This could be considered a universal influenza vaccine Version 1.0. As we make progress towards more broadly protective influenza vaccines, a Version 2.0 could protect against two or more subgroups of influenza, such as all H1N1 strains and all H3N2 strains. This may lead to developing a universal influenza vaccine candidate that by itself could durably protect against all subgroups of influenza, thereby protecting against virtually any influenza strain. Each universal influenza vaccine candidate will need to be evaluated over several influenza seasons to determine the level of protection that is induced, and the durability of that protection. Version 1.0 of a universal influenza vaccine may be available in a few years, representing an incremental improvement on currently available influenza vaccines. A universal influenza vaccine that covers all major influenza strains may be many years away, with several iterations may be likely needed to ultimately achieve a broadly protective vaccine against all or nearly all influenza strains.

3. **What are the present challenges that are preventing the broader utilization of cell-based influenza vaccines, and what steps can be taken to become less reliant on egg-based vaccines?**

NIAID response:

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. Barriers to the broader utilization of cell-based and recombinant technologies to produce influenza vaccines include differences in manufacturing needs, development costs, and public awareness of alternatives to egg-based influenza vaccines.

NIAID is working to address these challenges through the support of basic and translational research for the development and manufacture of novel influenza vaccine strategies. NIAID scientists have devised a new method to manufacture an experimental whole virus inactivated influenza vaccine using a cell-based system. This method would provide another alternative to currently licensed egg-based and cell-based influenza vaccines. NIAID researchers also are developing and evaluating an additional cell-based system for whole virus influenza vaccine candidates to try to determine the most efficient cell-based system to produce influenza vaccines, both in terms of manufacturing time and cost. Data from these NIAID-supported studies will help improve vaccine manufacturing processes and vaccine efficacy, leading to the design of better influenza vaccines. NIAID also 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.

In addition to supporting the development of innovative seasonal influenza vaccines, NIAID has made a strategic shift toward a research paradigm that features broader, more flexible vaccine platform technologies such as recombinant DNA manufacturing techniques that can be rapidly mobilized when pandemic influenza viruses emerge. NIAID continues to support the early development of candidate pandemic influenza vaccine candidates that can be transitioned to BARDA for advanced development, with the goal of Food and Drug Administration (FDA) licensure and potential inclusion in the Strategic National Stockpile. NIAID also will continue to work closely with industry partners to advance promising influenza vaccine candidates, including cell-based and recombinant vaccine strategies.

The Honorable Michael C. Burgess

1. **Dr. Fauci, the National Institute of Allergy and Infectious Diseases is on the front lines of vaccine development, especially in the wake of Ebola and Zika hitting the United States. You wrote an article in the Journal of the American Medical Association in November 2017 that detailed the critical role of biomedical research in pandemic preparedness. Can you share with us some of the research approaches NIAID uses to prepare for pandemics, such as a new flu strain, that have yet to hit our shores?**

NIAID response:

As outlined in the 2017 article in the Journal of the American Medical Association, *The Critical Role of Biomedical Research in Pandemic Preparedness*, comprehensive pandemic preparedness requires a multifaceted approach. A critical component is biomedical research to support the development of vaccines, diagnostics, and therapeutics that may be quickly deployed in response to an emerging or re-emerging infectious disease of pandemic potential. NIAID supports a comprehensive portfolio of basic research on microbiology and immunology to better understand the mechanisms of pathogenesis and immune responses, as well as applied and clinical research to evaluate candidate diagnostics, therapeutics,

and vaccines. This strategic effort includes the pursuit of several research approaches, including: (1) research targeting specific pathogens; (2) prototype pathogen efforts, in which fundamental research to understand the disease caused by one pathogen may inform the development of countermeasures for a closely related pathogen; and (3) development of platform-based technologies and broad-spectrum products that may be easily and quickly deployed against multiple pathogens. NIAID research complements other elements of pandemic preparedness by improving understanding of infectious disease pathogenesis and by developing candidate medical countermeasures that could be used in a pandemic.

NIAID supports a broad portfolio of pathogen-specific basic, translational, and clinical research. NIAID investments in pathogen-specific research include priority pathogens of the United States Government as designated by the Centers for Disease Control and Prevention (CDC), as well as other emerging and re-emerging diseases identified as priority pathogens by NIAID. For example, NIAID supported development of m102.4, a candidate monoclonal antibody treatment for Nipah virus infection. NIAID also is supporting the development of improved influenza vaccine candidates, including universal influenza vaccines that could provide broad protection for a range of pandemic and seasonal influenza strains. Additionally, it was an NIAID investment in basic research nearly 40 years ago that enabled the development of the novel influenza antiviral Xofluza (baloxavir marboxil), which was approved for use in Japan in early 2018 and is currently undergoing FDA priority review for use in the United States.

NIAID has built upon increased understanding of infectious disease pathogenesis to move strategically toward a medical countermeasures research paradigm that features broader, more flexible platform technologies that can be used to respond to several biological threats. High-throughput sequencing and platform-based technologies are facilitating the development and manufacture of vaccines, targeted antibody therapeutics, and broad-spectrum antibiotics and antivirals by significantly decreasing the time from identification of a public health threat of an emerging infection to clinical evaluation of candidate countermeasures. For example, in 2015-2016 when Zika virus emerged in the Americas, clusters of microcephaly and other birth defects were identified, and a Public Health Emergency of International Concern was declared by the World Health Organization. NIAID scientists rapidly used Zika virus genetic sequence information to develop a DNA-based vaccine candidate that moved from concept to a first-in-human trial in less than four months. The experimental DNA-based Zika vaccine, which currently is in Phase II/IIb clinical testing, was developed with a readily deployable DNA vaccine platform that is a form of gene-based immunization previously used by NIAID to develop a candidate vaccine for West Nile virus. The development of a broadly applicable platform technology facilitated an accelerated response to a previously unrecognized public health threat. As mentioned in the 2017 article in the Journal of the American Medical Association, NIAID is supporting development of additional vaccine platform technologies, including nanoparticle, virus-like particles, and mRNA platforms. NIAID also supports development of broad-spectrum therapeutics, including antiviral and antibacterial agents that have demonstrated activity against multiple viral or bacterial pathogens.

Together with academia, industry, and Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) partners, NIAID remains committed to meeting public health emergency needs by advancing high-priority research to support development of medical countermeasures for emerging and re-emerging infectious diseases, including influenza viruses with pandemic potential. NIAID-supported research into specific pathogens, prototype pathogens, and the development of platform-based technologies will continue to play an essential role in PHEMCE pandemic preparedness and response efforts.

The Honorable Frank Pallone, Jr.

1. **How can we plan long-term for therapeutics and vaccines in order to respond to outbreaks that we cannot yet anticipate?**

NIAID response:

NIAID supports a comprehensive portfolio of basic research on microbiology and immunology to better understand the mechanisms of pathogenesis and immune response, as well as applied and clinical research to evaluate candidate diagnostics, therapeutics, and vaccines. This strategic effort includes the pursuit of foundational platform approaches that could be used to develop medical countermeasures against multiple pathogens.

NIAID is pursuing the development of platform approaches including molecular biological technologies that could be rapidly mobilized to generate candidate vaccines against emerging infectious disease threats. For example, during the 2015-2016 Zika virus outbreak in the Americas, NIAID scientists developed a novel DNA-based vaccine for Zika virus using viral genetic sequence information. The candidate vaccine moved from concept to a first-in-human trial in less than four months, and currently is in a Phase II/IIb trial. In order to respond so quickly, NIAID utilized a readily deployable DNA vaccine platform that was previously used by NIAID to develop a candidate vaccine for West Nile virus. These types of genetic platforms could be used to respond similarly to multiple emerging and re-emerging infectious disease threats.

NIAID investments in basic, translational, and clinical research also are contributing to the development of novel broad-spectrum therapeutics that can target several pathogens. For example, NIAID has supported early-stage development of broad-spectrum antiviral agents such as BCX4430 (galidesivir), which has demonstrated activity against Ebola and other RNA viruses, and broad-spectrum antibacterial products, including a compound with activity against the two different bacteria that cause tularemia and plague. Such broad-spectrum therapeutics may decrease the time necessary to identify and distribute an effective treatment during an outbreak setting.

NIH, led by the Fogarty International Center and NIAID, also supports the development of research infrastructure and partnerships in foreign countries to aid in the identification, monitoring, and response to the emergence and reemergence of infectious diseases. Long-standing international investments in disease monitoring and response made by NIH were vital in the immediate response to the 2014-2016 Ebola outbreak in West Africa and provided critical in-country expertise that helped to contain the spread of the disease. In addition, the clinical research partnership between NIAID and the government of Liberia, the Partnership for Research on Ebola Virus in Liberia (PREVAIL), demonstrated the ability to do rigorous scientific research in developing countries. The PREVAIL partnership enabled in-country clinical trials testing of several Ebola virus therapeutic and vaccine candidates, among them the ZMapp™ therapeutic, the Merck VSV vaccine, and the cAd3-EBOZ vaccine developed by the NIAID VRC in partnership with industry. NIAID, through a partnership with the French National Institute of Health and Medical Research (Inserm), the London School of Hygiene and Tropical Medicine, and the host country governments, has launched the Partnership for Research on Ebola VACcination (PREVAC), a Phase II clinical trial comparing three experimental Ebola vaccination strategies in Mali, Guinea, Sierra Leone, and Liberia. Medical countermeasures tested by the PREVAIL partnerships were recently deployed in the Democratic Republic of the Congo to help address an Ebola outbreak from May to July 2018, emphasizing the key contributions of this effort. NIAID-supported international research partnerships also contribute to the development of site infrastructure and sustainable research capacity in developing countries, enhancing

global preparedness to respond to unanticipated outbreaks and to conduct clinical research to better understand the disease and to test candidate countermeasures during these outbreaks.

2. **In your view, are there specific pathogens or diseases we should be most concerned with?**
    a. **With so many dangerous pathogens, how do we prioritize research to try to target those posing the greatest threat?**

NIAID response:

NIAID prioritizes research and early-stage development of medical countermeasures against bioterror threats and emerging and re-emerging infectious diseases of public health importance. The persistent threat of pandemic influenza and other respiratory viruses that may spread quickly and cause significant morbidity and mortality, such as severe acute respiratory syndrome coronavirus (SARS-CoV) or Middle East respiratory syndrome coronavirus (MERS-CoV) remain a particular area of concern. NIAID maximizes its efforts to develop effective medical countermeasures against these, and other potential emerging and re-emerging diseases, by prioritizing research into broad-spectrum antibiotics and antiviral drugs, as well as efficient platform technologies to more rapidly develop vaccines and diagnostics for a variety of threat pathogens.

NIAID's efforts to develop a broader, more flexible research paradigm is yielding scientific advances that will facilitate public health emergency preparedness and our ability to respond to emerging public health threats. NIAID is supporting the development of diagnostics platforms capable of distinguishing between several pathogens, as well as broad-spectrum therapeutics, including novel antiviral agents, effective against several pathogens. In addition, NIAID is prioritizing the development of several vaccine platforms that could be used to quickly develop vaccine candidates against newly identified threats. This includes the DNA-based platform used to develop a candidate vaccine against Zika virus that moved from concept to a first-in-human trial in less than four months. The development of these and other broad-spectrum therapeutics and platform technologies remains a NIAID priority.

In addition to supporting the development of platform technologies and broad-spectrum therapeutics that may decrease response time in the event of a pandemic, NIAID also supports a targeted portfolio of basic, translational, and clinical research on priority pathogens with pandemic potential, including influenza and other respiratory viruses. This includes detailed studies of immune system responses to infection, as well as research to better understand the transmission, evolution, and pathogenesis of the viruses to inform the development of vaccines, diagnostics, and therapeutics that could be deployed during a pandemic. The NIAID Vaccine and Treatment Evaluation Units currently are conducting two Phase II clinical trials of a new vaccine candidate to protect against emerging H7N9 influenza virus strains, and NIAID intramural scientists are conducting clinical studies of prime-boost vaccine regimens for swine (H1) and avian (H7) influenza viruses.

NIAID is galvanizing research efforts to support the development of universal influenza vaccine candidates. A universal influenza vaccine that is effective against both seasonal and pandemic influenza strains would be a vital tool to prepare for future pandemics, as well as to improve our ability to prevent seasonal influenza. In addition, NIAID is supporting novel antiviral therapies for influenza, including RNA polymerase inhibitors, peptide inhibitors, and next-generation neuraminidase inhibitors. NIAID support for influenza diagnostics research has led to the development of a rapid molecular *in vitro* assay recently cleared by the FDA to accurately distinguish influenza A from influenza B in nasal swab specimens.

NIAID continues to make progress against other respiratory viruses with pandemic potential. NIAID is supporting early-stage clinical trials of antibodies designed to treat people infected with MERS-CoV, as well as development of a vaccine candidate for MERS-CoV based on information from previous vaccine studies on SARS-CoV. NIAID-funded researchers also have identified a novel SARS-related virus, swine acute diarrhea syndrome coronavirus (SADS-CoV). SADS-CoV was responsible for 25,000 piglet deaths in China in 2016-17; however, no infections in humans have been identified. The identification of pathogens with zoonotic potential such as SADS-CoV that may emerge as human diseases contributes to our preparedness, as it may facilitate early identification if the pathogen becomes capable of causing disease in humans. NIAID will continue to prioritize research on pathogens with pandemic potential such as influenza and other respiratory viruses and support the development of platform-based technologies and broad-spectrum products that may be easily and quickly deployed against multiple pathogens.

3. Can you briefly explain the barriers that make it harder for scientists to discover new antibiotics?

NIAID response:

NIAID supports a comprehensive basic research portfolio on antibiotic resistance to aid in the discovery of new antibiotics. NIAID antimicrobial resistance research includes the elucidation of major mechanisms of pathogenesis, host-pathogen and drug-pathogen interactions, and the identification of new candidate antibiotics. NIAID has found that the major challenges in the development of new antibiotics are in the later stages of clinical development of these drugs. NIAID has identified three main barriers to the advanced development of new antibacterial therapeutics: 1) the scarcity of new antibacterial drug candidates effective against Gram-negative infections; 2) the challenge of enrolling patients in clinical trials needed to show efficacy of new therapeutics, especially in the case of Gram-negative drug-resistant infections; and 3) a lack of market incentives for pharmaceutical companies to invest in the final stages of antibiotic development and licensure. NIAID is working to address these challenges in several ways, including through the support of basic, translational, and clinical research to identify and advance promising antibacterial candidates to late-stage development. NIAID estimates that more than 25 percent of the antibacterial candidates currently in clinical development previously received some form of NIAID support.

NIAID is addressing these challenges by supporting early-stage development and clinical trials of new therapeutics to help offset the investment required to successfully test these therapeutics and bring them to market. The NIAID-supported Antibacterial Resistance Leadership Group (ARLG) has supported over 35 clinical studies investigating new therapeutics, optimized treatment regimens, diagnostic devices, and projects on antimicrobial stewardship. The ARLG places a priority on research involving Gram-negative bacteria that represent a major antimicrobial resistance threat. NIAID-supported scientists also completed two Phase I clinical trials for a new class of antibiotics (CRS3123) to treat *Clostridium difficile* infections, which are increasingly difficult to treat effectively. In addition, NIAID is supporting clinical trials to evaluate the efficacy of new therapeutic candidates, as well as new treatment regimens that utilize existing antibiotics in new combinations or regimens. NIAID also has solicited research for the development of tools to advance drug discovery of agents against Gram-negative pathogens through the "Partnerships for the Development of Tools to Advance Therapeutic Discovery for Select Antimicrobial-Resistant Gram-Negative Bacteria" program. NIAID is facilitating scientific discussions and partnerships to address key questions and challenges in the development of new antibiotics. NIAID and The Pew Charitable Trusts sponsored the 2017 scientific workshop entitled, "Challenges in the Discovery of Gram-

negative Antibacterials: The Entry & Efflux Problem." The goal of the workshop was to identify next steps and opportunities for collaborations to determine factors that affect the entrance of antibiotics into, and accumulation within, Gram-negative bacteria to inform the identification and design of new types of antibiotics. Resolving these early-stage research questions will help address the growing threat of resistant Gram-negative bacteria by facilitating the later-stage development of promising new therapeutic candidates.

NIAID also addresses barriers to the advanced development of new antibacterial therapeutics by helping to de-risk antibacterial product development for researchers in industry and academia through targeted research support and services. NIAID supports the National Database of Resistant Pathogens, which contains genomic data for more than 205,000 drug-resistant microbes. This database was established by the NIH, in partnership with FDA and CDC, as a publicly available resource that scientists from all over the world can access to inform the development of novel antibacterial products. NIAID also funds the Centers of Excellence for Translational Research that have recently discovered a new class of antibiotics produced by soil-dwelling bacteria. These antibiotics, known as malacidins, have a unique mechanism of action that may make the development of resistance less likely. NIAID also supports CARB-X, a unique public-private partnership led by BARDA. CARB-X is dedicated to accelerating the development of innovative antibacterial products from target/candidate identification and characterization through Phase I clinical trials. CARB-X is currently supporting 29 therapeutic candidates, including 11 new classes of antibiotics, as well as 6 diagnostics products. To facilitate the discovery and development of promising therapeutic candidates, NIAID provides unique no-cost preclinical and clinical services that include screening tests for antimicrobial activity and access to research reagents to assist in product testing. Additionally, NIAID supported preclinical development and first-in-human Phase I clinical testing of VNRX-5133, a novel beta-lactamase inhibitor (BLI). VNRX-5133 is the first BLI in clinical development that inhibits all known classes of beta-lactamases – bacterial enzymes involved in resistance to the beta-lactam class of broad-spectrum antibiotics such as penicillin.

NIAID continues to support the development of antibacterial products in collaboration with academia, industry, and federal partners. A concerted research effort is required to combat the growing public health threat of antibiotic resistance. NIAID remains committed to facilitating the development of new antibiotics by supporting innovative research and offsetting the development costs of industry and academia.