

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

The Role of the National Institutes of Health
in Preparing for Emerging Infectious Disease Threats

Testimony before the
Senate Committee on Appropriations
Subcommittee on Labor, Health and Human Services, Education, and Related Agencies

Anthony S. Fauci, M.D.
Director of the National Institute of Allergy and Infectious Diseases

March 14, 2019

Mr. Chairman, Ranking Member Murray, and members of the Subcommittee, thank you for the opportunity to discuss the role of the National Institutes of Health (NIH) in the research response to emerging and re-emerging infectious diseases. I direct the National Institute of Allergy and Infectious Diseases (NIAID), the lead NIH institute for conducting and supporting infectious disease research. Infectious pathogens are a perpetual challenge to human health because of their diversity and inherent capacity to adapt and evolve, allowing them to emerge and re-emerge in different populations, different circumstances, and new geographic locations. NIAID addresses this ongoing challenge with basic research to better understand mechanisms of pathogenesis and immunity, as well as applied and clinical research to evaluate candidate diagnostics, therapeutics, and prevention strategies, including vaccines. NIH funding for emerging infectious disease research was approximately \$2.8 billion in fiscal year 2018.

PANDEMIC PREPAREDNESS: A MULTIFACETED APPROACH

Preparedness for emerging and re-emerging diseases and the potential epidemic and pandemic threats they pose requires a multifaceted approach. 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. NIAID-supported biomedical research includes several approaches:

- a) Targeting specific pathogens that are likely threats that might emerge. Examples are Ebola virus, Lassa virus, Middle East Respiratory Syndrome (MERS) coronavirus, and Nipah virus.
- b) Prototype pathogen research, in which basic research on one microbe may inform the development of countermeasures for a closely related pathogen. A typical example is the

intensification of research on viruses of the *Flavivirus* genus. The flaviviruses have been extensively studied by NIAID and effective vaccines for Japanese encephalitis virus, yellow fever virus, and tick-borne encephalitis virus have been successfully developed. This experience has positioned us well in attempts to develop vaccines for the related flaviviruses West Nile virus, dengue virus, and Zika virus.

- c) Developing flexible platform-based technologies. The field of vaccinology is advancing from the historical requirement of growing a virus and either inactivating it or attenuating it for use as a vaccine, an approach that is cumbersome and often fraught with delays in production. Now, various novel vaccine “platforms” that have been intensively studied employ recombinant DNA technology that bypasses the need to grow the virus. Such 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 rapidly deployed against a variety of pathogens.

NIAID builds upon more than 60 years of experience and lessons learned from prior outbreaks to inform our biomedical research response to emerging pandemic threats. In doing so, NIAID coordinates with its Federal partners, such as the Centers for Disease Control and Prevention (CDC); the Food and Drug Administration (FDA); and the Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR) and its Biomedical Advanced Research and Development Authority (BARDA).

PANDEMIC PREPAREDNESS: BUILDING INFRASTRUCTURE

NIAID advances its research through a robust research infrastructure that includes long-term partnerships with individual scientists, scientific organizations, and governments worldwide. NIAID has prioritized research on pathogens with known or suspected pandemic potential in cooperation with international organizations such as the World Health Organization (WHO) and the Coalition for Epidemic Preparedness Innovations (CEPI). NIAID is poised to leverage its existing research investments to develop and test candidate vaccines and therapeutics. Critical to these efforts are longstanding NIAID clinical research networks such as the NIAID Vaccine and Treatment Evaluation Units (VTEUs), which conduct clinical trials on candidate interventions, and the Centers of Excellence for Influenza Research and Surveillance (CEIRS), which advance our understanding of influenza viruses and support early identification of emerging viruses with pandemic potential.

PANDEMIC PREPAREDNESS: RESPONSE TO SELECTED EMERGING DISEASES

Ebola. Ebola was first identified in the Democratic Republic of the Congo (DRC) in 1976, and 27 additional Ebola outbreaks have subsequently occurred. The largest Ebola outbreak occurred in West Africa from 2014 - 2016, with more than 28,600 infections and 11,300 deaths. NIAID built upon biodefense research investments made after the 2001 anthrax attacks to rapidly launch a robust research response to the West African Ebola outbreak. A critical component of that response was the Partnership for Research on Ebola Virus in Liberia (PREVAIL), an agreement between HHS and the government of Liberia that enabled the evaluation of candidate vaccines and therapeutics during the outbreak. These NIAID-supported

Ebola studies showed the feasibility of conducting scientifically and ethically sound clinical research during a major public health emergency.

NIAID has incorporated the lessons learned in conducting research during the West African outbreak into its response to the most recent re-emergence of Ebola in the DRC. The current outbreak began in August 2018 and already is the second largest in history. Many Ebola cases are occurring in an area of armed conflict and tenuous security, which is hindering response efforts. Data from prior NIAID-supported studies, including large-scale vaccine trials conducted by PREVAIL, have provided evidence supporting the use of candidate Ebola countermeasures during the current outbreak. NIAID has entered a memorandum of understanding with the WHO to facilitate a research response to emerging infectious diseases; this collaboration underpins the Institute's efforts in the DRC.

Safe and effective Ebola vaccines will be crucial tools in the response to future Ebola outbreaks, especially for situations in which conflict or other factors limit the healthcare response. The rVSV-EBOZ Ebola vaccine candidate evaluated by the PREVAIL 1 study currently is being used in a ring vaccination campaign in the DRC to immunize frontline workers, people potentially exposed to Ebola virus, and individuals who may have been in contact with them. NIAID is supporting continued development of additional vaccine candidates through its intramural and extramural research programs, including a prime-boost strategy combining the Ad26.ZEBOV and MVA-BN-Filo vaccines that is being evaluated by the ongoing PREVAIL partnership.

NIAID also is supporting a randomized controlled trial of candidate Ebola therapeutics in the DRC through a partnership between NIAID and the DRC's National Institute of Biomedical Research (INRB). The trial is comparing three candidate therapeutics with a control treatment,

the investigational monoclonal antibody cocktail ZMapp™ that showed signs of efficacy in NIAID-supported testing during the West African outbreak. The three additional investigational therapeutics being evaluated in the DRC are the broad-spectrum antiviral remdesivir, a cocktail of monoclonal antibodies known as REGN-EB3, and mAb114. The monoclonal antibody mAb114 was isolated from a survivor of the 1995 Ebola outbreak in Kikwit, DRC, and further developed by scientists at the NIAID Vaccine Research Center (VRC) in partnership with the DRC's INRB and the U.S. Department of Defense. The isolation and development of mAb114 as an Ebola therapeutic highlights the future promise of strategic deployment of monoclonal antibodies to prevent and treat emerging infectious diseases and potentially alter the course of epidemics. These advances are made possible by investments in pathogen-specific research that have improved our ability to identify precisely tailored monoclonal antibodies to combat infectious diseases.

Zika. Zika virus was first identified in Uganda in 1947 and was considered a relatively minor threat until a major outbreak occurred in the Americas. Increased case numbers in the 2015 - 2016 Zika outbreak led to the identification of a previously undetected risk of microcephaly and other birth defects in the children of women infected with Zika virus during pregnancy. NIAID responded to this outbreak by quickly establishing a broad Zika research portfolio using a prototype-pathogen approach that built upon decades of research on closely related viruses of the *Flavivirus* genus that cause diseases such as dengue fever, Japanese encephalitis, and West Nile virus disease. Experienced investigators and a wealth of knowledge about flaviviruses contributed to robust basic research on Zika virus and the disease it causes, as well as efforts to develop diagnostics, therapeutics, and vaccines to address the outbreak.

For example, NIAID has supported several natural history studies to better understand the long-term consequences of Zika virus infection. This includes the Zika in Infants and Pregnancy (ZIP) study, which has enrolled women throughout the Americas to follow the effects of Zika virus during pregnancy on the growth and development of affected infants. NIAID scientists also used Zika virus genetic information to rapidly develop a vaccine candidate using a DNA vaccine platform that moved from sequence selection to a first-in-human trial in less than four months. A Phase II/Ib clinical trial of the vaccine candidate has completed enrollment in several countries in the Americas, and analysis of the vaccine's safety and ability to prompt an immune response is ongoing. The NIAID Zika vaccine was developed with a readily deployable DNA vaccine platform that was previously used by NIAID to develop a candidate vaccine for West Nile virus. Using this broadly applicable platform technology, NIAID was able to accelerate its response to a previously unrecognized public health threat.

Influenza. NIAID has a longstanding research program to address the constant threat of seasonal and pandemic influenza, including studies to understand influenza pathogenesis and develop effective antiviral treatments. Influenza poses a challenge to vaccine developers because the virus can undergo significant mutational changes to its surface proteins (the target of current influenza vaccines). This phenomenon was highlighted by recent experience with H7N9 influenza, which was identified as a potential pandemic strain when it first emerged in China in 2013. HHS preparations to address the possibility of a pandemic included the development and stockpiling of an H7N9 vaccine. In 2017, a new H7N9 strain was detected and studies showed that the stockpiled 2013 H7N9 vaccine did not provide adequate protection against the new 2017 strain. NIAID has sought to avoid such challenges in the future by developing broadly protective

influenza vaccines that would be effective against existing strains as well as newly emerging strains. Broadly protective, or “universal,” influenza vaccines would be vital tools to prepare for future pandemics, as well as to improve our ability to prevent seasonal influenza.

NIAID recently published a strategic plan for universal influenza vaccine development 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; and supporting the design of universal influenza vaccines. NIAID is actively engaging Federal partners, including HHS agencies and other key domestic and international stakeholders involved in influenza vaccine research, to coordinate and advance activities outlined in the strategic plan. Novel vaccine platforms are particularly suited to the development of a universal influenza vaccine. Notable accomplishments in this area include the development of a ferritin nanoparticle-based vaccine candidate by the NIAID VRC; the formulation of a vaccine cocktail of virus-like particles by NIAID scientists that protects against diverse influenza strains in animal models; and the launch of an NIAID-sponsored Phase II clinical trial to evaluate the M-001 vaccine candidate, which contains several influenza fragments or peptides common among multiple influenza virus strains.

The development of a truly universal influenza vaccine may take years to achieve, but clear progress is being made. To continue to make steady progress toward that goal, NIAID continues to support the development of improved vaccines for influenza strains with pandemic potential. NIAID is partnering with BARDA to develop multiple candidate vaccines through the NIAID VTEUs, including an updated H7N9 vaccine.

NIAID also is supporting the development of a number of novel influenza therapeutics to support pandemic preparedness. An investment in NIAID basic research nearly 40 years ago

enabled the development of Xofluza™, an important new drug recently licensed for influenza treatment. Xofluza™ became the first influenza antiviral with a novel mechanism of action to gain FDA approval in nearly 20 years.

CONCLUSION

Together with academia, industry, and national and international partners, NIAID will continue to meet public health emergency needs by advancing high-priority research for infectious disease threats. These efforts include pathogen-specific research, the application of a prototype-pathogen approach, and the development of platform technologies, to enhance pandemic preparedness and response efforts. NIAID remains committed to supporting biomedical research to advance pandemic preparedness and enhance international research capacity to respond to emerging and re-emerging infectious diseases.