

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Research Conducted and Supported by the National Institutes of Health (NIH) in
Addressing Emerging and Re-emerging Infectious Diseases Including Zika Virus Disease

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

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Mr. Chairman, Ranking Member Murray, and Members of the Subcommittee:

Thank you for the opportunity to discuss the research response of the National Institutes of Health (NIH) to emerging infectious diseases threats to our nation and the world. The current case in point is our response to the outbreak of Zika virus disease in the Americas. I direct the National Institute of Allergy and Infectious Diseases (NIAID), the lead NIH institute for conducting and supporting research on emerging and re-emerging infectious diseases, including those caused by flaviviruses such as Zika virus.

The Administration is taking appropriate action to protect the American people and, as you know, on February 8 it announced a request to Congress for more than \$1.8 billion in emergency funding to enhance ongoing efforts to prepare for and respond to the Zika virus, both domestically and internationally. This includes funding for work on the development of vaccines and diagnostics and to improve scientific understanding of the disease.

The overarching NIAID mission is to conduct and support research to better understand, treat, and prevent infectious and immunologic diseases. This is accomplished through a spectrum of research, from basic studies of the mechanisms of disease to applied research focused on developing diagnostics, therapeutics, and vaccines. As part of this mission, NIAID has a dual mandate encompassing both research on ongoing public health issues and the capability to respond rapidly to newly emerging and re-emerging infectious diseases such as those caused by Zika virus.

These emerging and re-emerging disease threats, whether man-made or naturally occurring, are perpetual challenges, in part due to the capacity of microbial pathogens to evolve rapidly and adapt to new ecological niches that most often result from human activity. To address the challenges posed by emergent infectious diseases, NIAID employs both targeted,

disease-specific research as well as broad-spectrum approaches. NIAID maximizes its efforts by prioritizing the development of drugs effective against multiple bacteria or viruses, and “platform” technologies to facilitate rapid development vaccines and diagnostics for multiple infections.

NIAID is well-positioned to rapidly respond to infectious disease threats as they emerge by leveraging fundamental, basic research efforts; domestic and international research infrastructure that can be quickly mobilized; and productive partnerships with industry. NIAID maintains a program that provides preclinical research resources for use by scientists in academia and private industry worldwide to advance translational research against emerging and re-emerging infectious diseases. These resources are designed to bridge gaps in the product development pipeline and lower the scientific, technical, and financial risks incurred by industry in order to incentivize them to partner with us in the development of effective countermeasures against these emerging infectious disease threats. NIAID also supports the Vaccine and Treatment Evaluation Units (VTEUs), a research network for conducting clinical trials to quickly investigate promising therapies and vaccine candidates when public health needs arise. NIAID collaborations with other federal agencies, including those undertaken within the Department of Health and Human Services (HHS) Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), help advance progress against newly emerging public health threats. In addition, partnerships with academia, the biotechnology and pharmaceutical industries, and international researchers and organizations such as the World Health Organization (WHO) and WHO’s regional office, the Pan American Health Organization (PAHO), are integral to these efforts.

OVERVIEW OF ZIKA VIRUS

Zika virus is a flavivirus. These viruses typically are transmitted by mosquitoes and often have the ability to spread quickly to new geographic locations because of the widespread prevalence of these vectors. Other well-known flaviviruses include dengue virus and yellow fever virus; like Zika virus they are transmitted by mosquitoes of the *Aedes* species. Zika virus was discovered in monkeys in Uganda in 1947 and is now endemic to Africa and Southeast Asia. During the past decade it has emerged in other areas of the world, including Oceania, the Caribbean, and Central and South America, where countries, notably Brazil, are currently experiencing unprecedented Zika transmission.

Infections caused by Zika virus are usually asymptomatic. About 20 percent of infected individuals experience clinical symptoms such as fever, rash, joint pain, and conjunctivitis (red eyes). Symptoms of Zika virus infection in humans are typically mild and brief, with very low hospitalization and fatality rates. The recent outbreak of Zika virus disease in Brazil has coincided with a reported increase in the number of infants born with microcephaly, a birth defect characterized by an abnormally small head resulting from an underdeveloped and/or damaged brain. In addition, increases in suspected cases of Guillain-Barré syndrome (GBS), a rare, acute, immune-mediated peripheral nerve disease that leads to weakness, sometimes paralysis, and infrequently, respiratory failure and death, have been noted in Brazil and other countries in the Americas.

Further research is needed to better understand the effect of Zika virus infection on the body, particularly during pregnancy; to investigate the potential relationship between Zika infection and microcephaly, as well as explore the potential relationship between Zika infection

and GBS; and to develop better diagnostics, vaccines and treatments, and new methods of vector control. Currently, no vaccines or specific therapeutics are available to prevent or treat Zika virus disease. Improved diagnostic tests also are needed because Zika virus infection causes non-specific symptoms and can be difficult to distinguish from other mosquito-borne infections such as dengue, malaria, and chikungunya in antibody screening tests. Moreover, current antibody screening tests can be falsely positive or inconclusive if the individual was previously infected with related viruses such as dengue, which is prevalent in South America and the Caribbean. Therefore, a positive result with the antibody screening test requires an additional test to confirm the diagnosis.

NIH RESEARCH ON ZIKA VIRUS

NIAID has a longstanding commitment to flavivirus research, including extensive efforts to combat diseases such as dengue, West Nile virus, and yellow fever. This research has informed our understanding of the viral genetics, vector biology, and pathogenesis of flaviviruses and provides a strong foundation for our efforts to learn more about Zika virus. NIAID has responded to the newly emerging Zika virus disease outbreak by expanding our portfolio of basic research on Zika virus and other flaviviruses. NIAID also is accelerating efforts to develop improved diagnostics and candidate therapies for Zika virus as well as prioritizing the development of Zika virus vaccines. In addition, screening tests and pathogen reduction technologies are critically important to assure safety of the U.S blood supply.

The emergency funding request for NIH would support development of vaccines to prevent Zika virus infection, from the discovery phase through preclinical and eventually clinical testing. In addition, the request would support basic research to understand the natural history and pathogenesis of the virus, including potential links to microcephaly; establishment of animal

models to test candidate countermeasures; development of rapid, sensitive, and specific diagnostic tests; and discovery and preclinical development of new therapeutics to treat disease caused by Zika virus. This research is necessary to better understand this emerging infection and uncover the best ways to diagnose, treat, and prevent Zika virus disease.

In January 2016, NIAID issued a notice to researchers highlighting NIH's interest in supporting research and product development to combat Zika virus. Areas of high priority include basic research to understand viral replication, pathogenesis, and transmission, as well as the biology of the mosquito vectors; potential interactions with co-infections such as dengue and yellow fever viruses; animal models of Zika virus infection; and novel vector control methods. In addition, the notice indicates that NIH will pursue Zika virus research to develop sensitive, specific, and rapid clinical diagnostic tests; drugs against Zika virus as well as broad spectrum therapeutics against multiple flaviviruses; and effective vaccines and vaccination strategies.

NIAID also is partnering with other NIH institutes, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Neurological Disorders and Stroke, and the National Institute of Dental and Craniofacial Research, to accelerate Zika virus research as it relates to the mother-infant pair. The Institutes issued a notice that indicates NIH's interest in supporting research to understand transmission, optimal screening and management in pregnancy, and the mechanisms by which Zika virus affects the developing nervous system, including potential links to microcephaly.

DEVELOPING TOOLS TO COMBAT ZIKA VIRUS

In response to public health concerns about Zika virus, NIAID has accelerated ongoing flavivirus research efforts to speed the development of tools that could help control current and future outbreaks of Zika virus. A safe and effective Zika vaccine would be a very valuable tool to

help stop the spread of infection and prevent future outbreaks. NIAID is investigating multiple Zika virus vaccine candidates, including vaccines based on technologies that have shown promise in targeting other flaviviruses. The NIAID Vaccine Research Center (VRC) is pursuing a DNA-based vaccine for Zika virus that is similar to a West Nile virus vaccine previously developed by NIAID. In Phase 1 testing, the West Nile vaccine candidate was shown to be safe and generated a strong immune response in humans, offering a model for Zika vaccine development. NIAID scientists also are designing a live, attenuated vaccine, using an approach similar to that used for making a vaccine against the closely related dengue virus. The dengue vaccine candidate showed an excellent safety profile and generated strong immune responses in early-phase clinical trials. In January, a large Phase 3 trial assessing the dengue vaccine candidate was launched in Brazil in collaboration with the Butantan Institute. In addition, NIAID grantees are in the early stages of developing a Zika virus vaccine based on a recombinant vesicular stomatitis virus – the same animal virus used successfully to create an investigational Ebola vaccine candidate – that expresses the Zika E glycoprotein. Plans are underway to evaluate this potential vaccine construct in tissue culture and animal models.

While these approaches are promising, it is important to realize that the development of investigational vaccines and the clinical testing to establish whether they are safe and effective takes time. Although a safe and effective, fully licensed Zika vaccine will likely not be available for a few years, we hope to begin early-stage clinical testing of one or more NIAID-supported vaccine candidates in 2016.

DEVELOPING VACCINES TO PREVENT CHIKUNGUNYA VIRUS

Chikungunya virus is transmitted to humans primarily via the bite of infected *Aedes* mosquitoes, the same mosquitoes that transmit Zika virus. Chikungunya virus causes a

sometime-serious illness characterized by fever and severe joint pain, which can last for months and be disabling. Since 2013, chikungunya virus has spread rapidly in the Caribbean, as well as Central and South America. No licensed vaccines or therapeutics are available to prevent or treat chikungunya virus infections. NIAID has responded to the emergence of chikungunya virus by accelerating research on diagnostics, therapeutics, and vaccines to combat the disease.

The emergency funding request for NIH would support efforts to develop a safe and effective chikungunya vaccine to prevent this debilitating mosquito-borne disease. Additional funds would enable animal model and human clinical tests of promising vaccine candidates. This research will build upon efforts of scientists at the NIAID VRC, who have developed a candidate chikungunya vaccine based on a DNA vaccine that leads to the production of virus-like particles. The NIAID VRC vaccine candidate was safe and generated an immune response in a Phase 1 clinical trial. The vaccine is currently in Phase 2 clinical testing at six study sites in the Caribbean. NIAID also is planning a Phase 1 trial of a live, attenuated measles virus-vectored vaccine candidate to be conducted through the NIAID VTEUs. Several additional chikungunya vaccine candidates will be evaluated for safety, ability to generate immune responses, and efficacy in preclinical and animal model studies; if promising, these candidates will advance to clinical testing.

CONCLUSION

NIH is committed to continued collaboration with HHS agencies and other partners across the U.S. government in advancing research to address Zika virus infection, and we look forward to working with the Congress to implement the President's emergency funding request. As part of its mission to respond rapidly to emerging and re-emerging infectious diseases throughout the world, NIAID is expanding our efforts to elucidate the biology of Zika virus and

employ this knowledge to develop needed tools to diagnose, treat, and prevent disease caused by this virus. In particular, NIAID will pursue the development of safe, effective vaccines to prevent disease caused by chikungunya and Zika viruses.