DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Research Conducted and Supported by the National Institutes of Health (NIH) in Addressing Zika Virus Disease

Testimony before the

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Subcommittee on Africa, Global Health, Global Human Rights, and International Organizations and Subcommittee on the Western Hemisphere

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Chairman Smith, Chairman Duncan, Ranking Member Bass, Ranking Member Sires, and Members of the Subcommittees:

Thank you for the opportunity to discuss the National Institutes of Health (NIH) research response to Zika virus, an emerging public health threat of international concern. I direct the National Institute of Allergy and Infectious Diseases (NIAID), the lead institute of the NIH for conducting and supporting research on infectious diseases, including flaviviruses such as Zika virus.

NIAID's mission is research to better understand, treat, and ultimately 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 research on ongoing health issues as well as the capability to respond rapidly to newly emerging and re-emerging infectious diseases such as Zika virus. NIAID's collaborations with other Federal Agencies such as the Centers for Disease Control and Prevention (CDC), the Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response (ASPR), including the Biomedical Advanced Research and Development Authority (BARDA), and the Food and Drug Administration (FDA), among others, help advance progress against these newly emerging public health threats. In addition, partnerships with academia, the biotechnology and pharmaceutical industries, and international organizations such as the World Health Organization (WHO) and the Pan American Health Organization (PAHO) are integral to these efforts.

The Administration is taking every appropriate measure to protect the American people, and as you know on Monday announced that we are asking the Congress for more than

$1.8 billion in emergency funding to enhance our ongoing efforts to prepare for and respond to the Zika virus, both domestically and internationally, including work on the development of vaccines and diagnostics and to improve scientific understanding of the disease.

OVERVIEW OF ZIKA VIRUS

Zika virus is a flavivirus. These viruses typically are transmitted predominantly by mosquitoes and often have the ability to spread quickly to new geographic locations because of the widespread prevalence of this vector. Like Zika virus, other well-known flaviviruses including dengue virus and yellow fever virus also are transmitted by *Aedes* species mosquitoes. Zika virus was first 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. Recently, however, Zika virus outbreaks have coincided with increases in two serious medical conditions: Guillain-Barré syndrome (GBS), and microcephaly in infants born of mothers who were infected with Zika virus while pregnant. GBS is a rare, acute, immune-mediated peripheral nerve disease that leads to weakness, sometimes paralysis, and infrequently, respiratory failure and death. During a 2013-2014 outbreak of Zika virus in French Polynesia, 42 cases of GBS were detected, well above expected levels.

More recently, the outbreak of Zika virus disease in Brazil has coincided with an 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 GBS 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 the potential relationship between Zika infection and GBS; and to develop better diagnostics, candidate treatments and vaccines, and novel 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 when conducting antibody screening. 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.

THE SCOPE OF 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 will be critical in 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. For example, NIAID-supported experts have begun characterizing the

molecular structure of Zika virus to inform drug and vaccine development efforts. Ongoing genetic studies are examining Zika virus strains from outbreaks in 2015, 2013, and the 1940s to understand the differences in host immune response and disease pathogenesis of different strains.

NIAID maintains a program that provides preclinical research resources for the use of scientists worldwide to advance translational research against emerging and re-emerging diseases. These resources are designed to bridge gaps in the product development pipeline and lower the scientific, technical, and financial risks incurred by industry. NIAID flavivirus resources include laboratory screening services for drug compounds and repositories containing viral strains from a variety of vector and human sources. Currently, two human-derived and six mosquito-derived strains of Zika virus are available for distribution through NIAID-supported repositories. In addition, NIAID is focusing new efforts on the development of animal models to better understand the effects of Zika virus in humans, especially during pregnancy. NIAID intends to expand these resources and make their availability widely known to the international scientific community to foster Zika virus research and product development.

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 and 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 (NICHD), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Dental and Craniofacial Research (NIDCR), to accelerate Zika virus research as it relates to the mother-infant pair. The Institutes are planning to issue 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.

Vector Control

For many years, NIAID has supported extensive research to understand the biology of mosquitoes to help develop tools to limit the spread of deadly mosquito-borne diseases such as dengue and malaria. This research aids in vector control strategies to reduce mosquito bites or limit mosquito populations. In the Americas, Zika virus is transmitted primarily by *Aedes aegypti* mosquitoes, and vector control or other methods to prevent exposure to these mosquitoes are currently the only ways to prevent Zika infection. NIAID plans to support vector competence studies to test various mosquito species for their ability to carry and transmit Zika virus and for insecticide resistance. Understanding the specific mosquito species involved in Zika outbreaks and which insecticides may be effective against them will aid current vector control efforts and may inform novel mosquito control strategies in the future.

Diagnostics

Accurate diagnostic tests for Zika virus infection are needed to distinguish it from other flavivirus infections and to identify women who have been infected with Zika virus and may be at risk for developing complications during pregnancy. Blood, organ, and tissue donor screening tests are also needed to assure the safety of transfusion and transplantation in areas of active mosquito borne virus infections. Currently, Zika virus itself can often be detected during the acute phase of infection and up to seven days after the onset of symptoms using diagnostic tests for viral RNA (RT-PCR test). While prior infection can be detected by testing for the presence of antibodies against Zika virus, assays for Zika antibodies may also detect or cross-react with antibodies against other flaviviruses, particularly dengue virus. For this reason, a positive antibody test does not definitively confirm prior Zika virus infection in the setting of possible co-infection or prior infection with dengue and other related viruses, and separate confirmatory testing is required. This is a particular concern in South America where there is a high level of exposure to other flaviviruses such as dengue virus.

To facilitate the development of improved Zika virus diagnostic tests, NIAID grantees are working to generate antibodies that can distinguish between Zika virus and dengue virus. They also are working to identify biosignatures unique to Zika infection that could form the basis of additional rapid, specific, and sensitive diagnostic tests. In addition, NIAID is pursuing the development of a mouse model of Zika virus infection that could be used to test new diagnostic tools.

Vaccines

A safe and effective Zika vaccine would be a critically important tool to 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 is pursuing a DNA-based vaccine for Zika virus that is similar to the West Nile virus vaccine previously developed by NIAID. In Phase 1 testing, this 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, building on a similar approach used for the closely related dengue virus. That dengue vaccine candidate showed an excellent safety profile and generated strong immune responses in early-phase clinical trials; in January, a large Phase 3 dengue vaccine trial was launched in Brazil in collaboration with the Butantan Institute. Finally, 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 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.

Therapeutics

NIAID has an active program to screen for antiviral drugs active against viruses in the flavivirus family, including dengue, West Nile, yellow fever, Japanese encephalitis, and hepatitis C viruses. NIAID has enhanced these efforts with the recent development of an assay to test compounds for antiviral activity against Zika virus. NIAID will make this test available to the research community and will soon test 10 antiviral compounds with activity against other

flaviviruses to determine if they are effective against Zika virus. Promising drug candidates identified by the assay could be further tested in a small animal model of Zika virus infection developed with NIAID support. The ultimate goal of NIAID-supported flavivirus therapeutic research is to develop a broad-spectrum antiviral drug that could be used against a variety of flaviviruses, including Zika.

Emergency Request for Vaccine Research and Diagnostic Development and Procurement

As I noted in the introduction to my testimony, the Administration has announced an emergency-funding request of more than $1.8 billion to combat the Zika virus both domestically and internationally. Included in the request are resources for Zika-related vaccine research, rapid advanced development, and commercialization of new vaccines and diagnostic tests for Zika virus. The funding will allow NIH to build upon existing resources and work to develop a vaccine for Zika virus and the chikungunya virus, which is spread by the same type of mosquito. Funding will accelerate this work and improve scientific understanding of the disease to inform the development of additional tools to combat it. The request also includes resources for FDA to support Zika virus medical-product development, including the next-generation diagnostic devices. We look forward to working with the Congress to implement this request.

COLLABORATIONS

Investigation of emerging and re-emerging infectious diseases requires expertise from a variety of fields. In the case of Zika virus, studies of virology, immunology, natural history, neurology, and neonatology will be required to fully understand the pathogenesis of this infection. As mentioned previously, NIAID is partnering with other NIH institutes including NICHD and NINDS to better understand the potential association between Zika virus infection

and neonatal defects. In addition, NIAID will partner with NINDS to investigate microcephaly linked to Zika virus infection and how these cases may differ from microcephaly caused by other infections.

NIAID also is employing partnerships with research institutions in South America to advance research on Zika virus infection; additional collaborations with academic, industry, and government partners are under active exploration. NIAID held a joint meeting in December 2015 with Brazilian research institute Fiocruz in which Zika was a key area of concentration. In addition, NIAID is collaborating with other HHS agencies in responding to the Zika epidemic. For example, NIAID, CDC, BARDA, ASPR, and FDA are jointly convening a Zika virus workshop on March 28-29, 2016, where the latest information on Zika virus will be discussed by experts from Federal Agencies, academia, and pharmaceutical and biotechnology companies. Topics to be addressed at the workshop include virology, epidemiology, possible links to microcephaly, and efforts to develop diagnostics, therapeutics, and vaccines.

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. As Agencies of the U.S. Government work together to address this new public-health concern, NIH will move quickly to conduct and support research to combat Zika virus and

inform the global public health response in partnership with the affected communities and academic and industry researchers worldwide.