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 Oversight and Investigations

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

Thank you for the opportunity to discuss the ongoing National Institutes of Health (NIH) research response to Zika virus. 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 that pose threats to public health. NIAID funds a comprehensive research portfolio, from basic studies of the mechanisms of disease, to applied and clinical research focused on developing interventions such as diagnostics, therapeutics, and vaccines. We have a dual mandate to support research on established disease threats and to respond rapidly to newly emerging and re-emerging infectious diseases.

Emerging and re-emerging disease threats are perpetual challenges, in part due to the inherent capacity of microbial pathogens to evolve rapidly and adapt to new ecological niches. NIAID anticipates and responds to these threats by leveraging fundamental, basic research; mobilizing domestic and international research infrastructure; and partnering with governments, non-governmental and multilateral organizations, academia, and industry, both nationally and internationally.

I am pleased to be able to discuss with you our research efforts to protect the American people from Zika virus.

OVERVIEW OF ZIKA VIRUS

Zika virus is a flavivirus. These viruses typically are transmitted by mosquitoes or ticks and often can spread quickly to new geographic locations due to the abundance of these vectors. Other well-known flaviviruses include dengue virus and yellow fever virus; like Zika, these viruses are transmitted by *Aedes* mosquitoes. Zika virus, first identified in monkeys in Uganda in

1947, is endemic to Africa and Southeast Asia; however, it recently has spread to other parts of the world. An unprecedented Zika outbreak began in Brazil in May 2015 and has spread throughout South and Central America and into the United States. Widespread local transmission has occurred in U.S. territories including Puerto Rico, and limited local transmission has occurred in areas of Florida and Texas. Although recent Zika case reports in the Americas have decreased from the unprecedented spread of the virus in 2015 and 2016, continued transmission of Zika virus to a greater or lesser degree is expected throughout the western hemisphere.

While infections caused by Zika virus are usually asymptomatic, about 20 percent of infected individuals experience mild clinical symptoms such as fever, rash, muscle and joint pain, and conjunctivitis (red eyes). Increases in cases of Guillain-Barré Syndrome, a rare, acute, immune-mediated peripheral nerve disease that leads to weakness, sometimes paralysis, and infrequently, respiratory failure and death, also have been noted in association with Zika outbreaks in Brazil and elsewhere. Of most concern, the recent outbreaks of Zika virus disease have coincided with a marked 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. Recent studies have conclusively shown that Zika virus causes microcephaly in infants, as well as an array of congenital abnormalities such as eye defects, hearing loss, impaired growth, seizures, difficulty moving limbs, and other complications known collectively as congenital Zika syndrome. Although it has been established that Zika infection during pregnancy can cause congenital Zika syndrome in the infant, further research is needed to better understand the disease and how to prevent it. Currently, no FDA-licensed vaccines or specific therapeutics are available to prevent or treat Zika virus disease. Improved diagnostic tests also

are needed as Zika virus infection can be difficult to diagnose and distinguish clinically from other mosquito-borne infections, such as dengue, West Nile, and chikungunya.

DEVELOPING COUNTERMEASURES TO COMBAT ZIKA VIRUS

NIAID has responded to the Zika epidemic by accelerating ongoing flavivirus research efforts to speed the development of biomedical tools that could help control current and future outbreaks of Zika virus.

Vaccines

A safe and effective Zika vaccine would be an invaluable tool to help stop the spread of infection and prevent future outbreaks. NIAID is developing and investigating multiple Zika vaccine candidates, including vaccines based on technologies that have shown promise against other flaviviruses. The NIAID Vaccine Research Center (VRC) has developed a candidate DNA-based Zika vaccine akin to a West Nile virus vaccine that we previously developed. The DNA-based Zika vaccine candidate entered a Phase 1 clinical trial in 2016, and initial study results indicate that the vaccine is safe and induces an immune response in the range that would predict that it would protect against Zika virus. NIAID launched a multi-site Phase 2a/2b clinical trial of this vaccine in March 2017 that aims to enroll at least 2,490 healthy participants in various sites in the Americas, including the continental United States and Puerto Rico, Brazil, Peru, Costa Rica, Panama, and Mexico. The trial will further evaluate whether the experimental vaccine is safe and able to stimulate an adequate immune response, and importantly whether it can prevent disease in areas with ongoing mosquito-borne Zika transmission.

NIAID scientists also are developing live-attenuated Zika vaccine candidates using an approach similar to that taken with an experimental vaccine against the closely related dengue virus. This vaccine candidate will enter an NIAID Phase 1 trial in late 2017. Another version of

this approach, an experimental vaccine designed to protect against Zika and all four circulating strains of dengue virus, is scheduled to enter clinical testing by 2018. NIAID is working with academic partners in Brazil to plan later-stage trials of this combination vaccine referred to as a chimeric vaccine.

NIAID also is collaborating with the Biomedical Advanced Research and Development Authority (BARDA) and the Walter Reed Army Institute of Research (WRAIR) to evaluate a Zika purified inactivated vaccine (ZPIV) candidate. Multiple Phase 1 clinical trials of ZPIV began in November 2016 in several U.S. sites.

NIAID-supported researchers also are evaluating investigational mRNA vaccines, which are broadly similar to DNA vaccines. The NIAID VRC is working with academic and industry partners to evaluate various mRNA vaccine technologies to identify potential candidates for further development. These include an investigational vaccine under development by the NIAID VRC and a pharmaceutical company that may enter clinical trials in late 2017.

NIAID grantees also are in the early stages of developing a Zika virus vaccine candidate based on a recombinant vesicular stomatitis virus – the same animal virus used successfully to create an investigational Ebola vaccine. This Zika vaccine construct will be evaluated in tissue culture and animal models. NIAID is supporting diverse early-stage Zika vaccine strategies to maximize our chances of success in rapidly reaching the goal of a licensed vaccine.

While these multiple approaches are promising, it is important to realize that the development of investigational vaccines and the clinical testing required to establish their safety and effectiveness take time. The pace of these trials in reaching a conclusion will depend on both the inherent effectiveness of the vaccine and the amount of Zika virus transmission near clinical trial sites. If a Zika outbreak occurs during the phase 2a/2b vaccine trial, it is conceivable that we

will have an indication of whether the vaccine works within 1 to 1.5 years. However, with the recent decline in Zika cases across the Americas, Zika vaccine clinical trials may require more time to discern whether the vaccine candidates are successful in preventing Zika virus infection. While we have begun clinical testing of several Zika vaccine candidates, a safe, effective, and fully licensed Zika vaccine likely will not be available for several years.

Therapeutics

NIAID has accelerated its program originally designed to screen for antiviral drugs with activity against viruses in the flavivirus family, including dengue, West Nile, yellow fever, and Japanese encephalitis viruses, as well as the closely related hepatitis C virus. NIAID has enhanced these efforts by developing an assay to test compounds for antiviral activity against Zika virus, and has made this test readily available to the broader research community. As of April 30, 2017, NIAID has tested 679 antiviral molecules and identified 39 compounds with high or moderate activity against Zika virus. Promising drug candidates identified by this assay are being further tested in animal models of Zika virus infection developed with NIAID support. For example, NIAID evaluated BCX4430, a broad-spectrum antiviral drug originally developed by a pharmaceutical company as a candidate therapeutic for Ebola and Marburg viruses, and found that the drug protected mice and non-human primates from Zika virus.

NIAID-supported researchers also have identified a human antibody, ZIKV-117, that neutralizes multiple strains of the Zika virus. ZIKV-117 reduces levels of the virus in reproductive tissues and decreases fetal disease in a pregnant mouse model of Zika infection, suggesting that such broadly neutralizing Zika antibodies could be used to treat or prevent Zika virus infection in humans.

Diagnostics

Accurate diagnostic tests are needed to distinguish Zika virus infection from other flavivirus infections and to identify women who have been infected with Zika virus during pregnancy and may be at risk of having an infant with fetal complications. Currently, molecular diagnostic tests for viral RNA can detect Zika virus during the acute phase of infection and for a limited period after the onset of symptoms. After this limited period, prior infection can be detected by testing for the presence of antibodies against Zika virus. However, assays for Zika antibodies also may 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, particularly in geographic areas with ongoing dengue virus infection. In cases of possible co-infection or prior infection with dengue and other related viruses, separate confirmatory testing is required. This is a particular concern in South America, where people have a high level of exposure to other mosquito-borne viruses, especially dengue and chikungunya.

NIAID is facilitating the development of improved Zika virus diagnostic tests through support for NIAID investigators and grantees working to generate antibodies and recombinant protein antigens that can be used to distinguish between Zika virus and dengue virus. Studies also are underway to create new diagnostic methods that simultaneously measure antibody responses to several flaviviruses to clearly distinguish which virus caused a recent infection. In addition, NIAID grantees are working to identify unique biosignatures for Zika infection that could form the basis of other rapid diagnostic tests.

IMPROVING UNDERSTANDING OF ZIKA VIRUS TRANSMISSION

NIAID conducts and supports research on the natural history and transmission of Zika virus. These studies will increase our understanding of the effects of Zika virus during pregnancy and help identify strategies to limit mosquito-borne transmission of the virus.

Natural History

NIAID is partnering with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Environmental Health Sciences, and the Brazilian research institute Fiocruz to study the link between Zika infection and adverse outcomes such as the congenital Zika syndrome. This study, Zika in Infants and Pregnancy (ZIP), is a multi-center, international, prospective study of 10,000 women in Zika-affected regions. Enrollment of women early in their pregnancy is ongoing, and their children will be followed for at least one year after birth. The information gained from this study will help improve our understanding of congenital Zika syndrome, enhance care for pregnant women and their infants, and guide interventions for affected children.

Vector Control

For many years, NIAID has supported extensive research on the biology of mosquitoes to help develop tools to limit the spread of deadly mosquito-borne diseases such as dengue and malaria. This research informs 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 is supporting vector competence studies to test various mosquito species for their ability to carry and transmit Zika virus, as well as research to prevent resistance of mosquitoes to

insecticides and identify the emergence of resistance early so it can be managed appropriately. Understanding the specific mosquito species involved in Zika outbreaks and which insecticides may be effective against them will aid current vector control efforts. In addition, NIAID is supporting innovative vector control research, including evaluation of novel repellents, mosquito traps, and the use of bacterial symbionts to affect mosquito biology and reproduction.

CONCLUSION

NIH is committed to robust collaborations with partners across the U.S. government, academia, and industry to further advance research to address Zika virus infection. As part of its mission to respond rapidly to emerging and re-emerging infectious diseases globally, NIAID is elucidating the biology of Zika virus and developing tools to diagnose, treat, and prevent disease caused by this virus. As a high priority, NIAID will continue to pursue the development of safe and effective vaccines and therapeutics against Zika virus. All of these efforts will expand our understanding of this current public health threat, improve our preparedness for the next emerging infectious disease outbreak, and continue to provide evidence-based strategies to promote public health.