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

House Democratic Steering and Policy Committee

Anthony S. Fauci, M.D.

Director

National Institute of Allergy and Infectious Diseases

National Institutes of Health

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Leader Pelosi and Members of the Committee:

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 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, announced a request to Congress for approximately $1.9 billion in emergency funding to enhance ongoing efforts to prepare for and respond to outbreaks of the Zika virus, both domestically and internationally. This includes funding for the development of vaccines and diagnostics and to improve scientific understanding of Zika virus disease.

The overarching mission of NIAID is to conduct and support research to better understand, treat, and prevent infectious and immunologic diseases. This is accomplished through an array of research, from basic studies of the mechanisms of disease, to applied research focused on developing interventions such as diagnostics, therapeutics, and vaccines. NIAID has a dual mandate that encompasses both research on current biomedical challenges and the capability to respond rapidly to newly emerging and re-emerging infections such as Zika virus.

These emerging and re-emerging disease threats, whether man-made or naturally occurring, are perpetual challenges, in part due to the inherent capability of microbial pathogens to evolve rapidly and adapt to new ecological niches. NIAID addresses the challenges posed by emerging infectious diseases by employing targeted, disease-specific research as well as broad-spectrum approaches. NIAID maximizes its efforts by prioritizing the development of drugs

effective against multiple pathogens, and cross-cutting technologies to facilitate rapid development of vaccines and diagnostics applicable to multiple infections.

NIAID is well-positioned to respond rapidly 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 provides preclinical research resources to 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, lowering the scientific, technical, and financial risks incurred by industry, and incentivizing them to partner with us in the development of effective countermeasures. NIAID also supports a research network of Vaccine and Treatment Evaluation Units (VTEUs) that conduct clinical trials to investigate promising therapeutic and vaccine candidates when public health needs arise. We also collaborate with other federal agencies, including through the Department of Health and Human Services (HHS) Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), to help advance progress against newly emerging public health threats. In addition, partnerships with academia, the biotechnology and pharmaceutical industries, international researchers, and organizations such as the World Health Organization (WHO) and the Pan American Health Organization (PAHO), a WHO regional office, are integral to these efforts.

OVERVIEW OF ZIKA VIRUS

Zika virus is a flavivirus. These viruses typically are transmitted by mosquitoes or ticks 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 these viruses are transmitted by *Aedes* mosquitoes. Zika virus, first identified in monkeys in Uganda in 1947, is endemic in 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 outbreaks.

Infections caused by Zika virus are usually asymptomatic. About 20 percent of infected individuals experience clinical symptoms such as fever, rash, muscle and joint pain, and conjunctivitis (red eyes). Symptoms of Zika virus infection in humans are usually mild and brief, with very low hospitalization and fatality rates. However, the recent 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. Recent studies have provided compelling evidence confirming a causal link between Zika virus and microcephaly. Furthermore, Zika virus infection has been associated with other problems in infants, including eye defects, hearing loss, and impaired growth. 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 and elsewhere in association with Zika outbreaks.

Further research is needed to better understand the effects of Zika virus infection on the body, particularly during pregnancy to investigate the relationship between Zika infection and congenital abnormalities, including microcephaly; to explore the relationship between Zika infection and GBS and other neurological conditions; 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 or no symptoms at all, and it can be difficult to distinguish clinically from other mosquito-borne infections, such as dengue, malaria, and chikungunya. Moreover, current antibody screening tests can be falsely positive or inconclusive due to cross-reactivity 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 currently 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 infection, Japanese encephalitis, tick-borne encephalitis, and yellow fever. This research has improved 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.

The emergency funding for NIH would support development of vaccines to prevent Zika virus infection, from the discovery phase through preclinical and clinical testing. In addition, the funds would support basic research to understand the natural history, viral biology and pathogenesis of Zika virus disease. In addition, we will explore the impact of infection during pregnancy; the establishment of animal models to test candidate countermeasures; the development of rapid, sensitive, and specific diagnostic tests; and the discovery and development

of new therapeutics to treat disease in people infected with Zika virus. This research is necessary to better understand this emerging infection and uncover optimal ways to diagnose, treat, and prevent Zika virus disease.

NIAID and other NIH Institutes are working to accelerate research on Zika and have issued several notices to researchers highlighting NIH's interest in supporting such research. The notices outline high priority areas of interest, including research on optimal screening and management in pregnancy; the mechanisms by which the virus can affect the developing nervous system and cause microcephaly and other congenital abnormalities; basic research to understand viral replication, pathogenesis, and transmission, as well as the biology of the mosquito vectors; potential role of prior exposure to other flaviviruses such as dengue and yellow fever; development of animal models of Zika virus infection; and novel vector control methods. NIH also has issued two funding opportunity announcements to solicit Zika virus research proposals, including basic research into Zika and its complications; vector competence studies; and 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.

In addition, NIAID is partnering with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the Brazilian research institute Fiocruz to study the link between Zika infection and adverse pregnancy outcomes. This study, Zika in Infants and Pregnancy (ZIP), is a multi-center, international, prospective study of 10,000 women in Zika-affected regions. Women will enroll early during pregnancy and their children will be followed for one year.

DEVELOPING COUNTERMEASURES TO COMBAT ZIKA VIRUS

NIAID has responded to public health concerns about Zika virus by accelerating 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 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 thought to be 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 adequately. 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 during pregnancy and may be at risk for developing fetal complications. 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 transmission. Currently, Zika virus often can 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, especially dengue virus.

Therefore, NIAID is facilitating the development of improved Zika virus diagnostic tests through support for NIAID investigators and grantees working to generate antibodies that can distinguish between Zika virus and dengue virus. Studies also are underway to create novel recombinant Zika virus proteins that are less cross-reactive to other flaviviruses. In addition, NIAID grantees are working to identify biosignatures unique to Zika infection that could form the basis of additional rapid diagnostic tests.

Vaccines

A safe and effective Zika vaccine would be an extremely 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 against 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 in people, the West Nile virus vaccine candidate was safe and generated a strong immune response, offering a model for Zika vaccine development. NIAID scientists also are designing live, attenuated vaccines, 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 February 2016, a large Phase 3 trial assessing the dengue vaccine candidate was launched in Brazil in collaboration with the Butantan Institute. In addition, NIAID is collaborating with BARDA and the Walter Reed Army Institute of Research (WRAIR) to make a whole-particle, inactivated virus vaccine. Preclinical testing of the vaccine candidate is underway, and human clinical studies, supported by NIAID and WRAIR, are expected to start in the fall of 2016. NIAID grantees also 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. 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 their safety and effectiveness take time. Although we plan to begin early-stage clinical testing of one or more NIAID-supported vaccine candidates in the fall of 2016, a safe and effective, fully licensed Zika vaccine will likely not be available for several years

Therapeutics

NIAID has an active program 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 with the recent development of an assay to test compounds for antiviral activity against Zika virus, and is making this test available to the broader research community. NIAID has so far tested 87 antiviral compounds and identified 14 compounds with high or moderate activity against Zika

virus. Promising drug candidates identified by the assay are being further tested in a small animal model of Zika virus infection developed with NIAID support. For example, NIAID recently evaluated BCX4430, a broad-spectrum antiviral drug originally developed by Biocryst Pharmaceuticals as a candidate therapeutic for Ebola and Marburg viruses, and found the drug protected immune-deficient mice infected with Zika virus. 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 approximately $1.9 billion to combat the Zika virus both domestically and internationally. Included in the request are resources for Zika-related research, rapid advanced development, and commercialization of new vaccines and diagnostic tests for Zika virus. The funding will allow NIH to build on existing resources and work to develop a vaccine for Zika virus. Funding will allow this work to move forward on schedule and improve scientific understanding of the disease to inform the development of additional tools to combat it. 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 to better

understand the association between Zika virus infection and neonatal defects, particularly microcephaly. In addition, NIAID is working with CDC, DOD, and USDA to develop and advance promising vector control technologies and strategies.

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 underway or are being actively explored. NIAID held a joint meeting in December 2015 with the Brazilian research institute Fiocruz in which Zika was a key area of discussion. The meeting has helped to inform ongoing Zika research collaborations with Fiocruz, including the planned ZIP study. NIAID also is collaborating with other HHS agencies in responding to the Zika epidemic. For example, NIH, CDC, BARDA, ASPR, and FDA jointly convened a Zika virus workshop on March 28-29, 2016, where the latest information on Zika virus was discussed by experts from federal agencies, academia, and pharmaceutical and biotechnology companies. Topics addressed at the workshop included virology, epidemiology, links to microcephaly, and efforts to develop diagnostics, therapeutics, and vaccines. The information exchanged through this workshop continues to inform ongoing research collaborations and progress toward Zika virus countermeasures.

CONCLUSION

NIH is committed to continued collaboration with other HHS agencies and additional partners across the U.S. government to advance 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 Zika, dengue, and chikungunya viruses. Such efforts also help to expand our knowledge base and improve our continued preparedness for the next emerging disease outbreak.