February 24, 2016

Zika Virus: Addressing the Growing Public Health Threat

Committee on Health, Education, Labor and Pensions, United States Senate, One Hundred Fourteenth Congress, Second Session

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February 24, 2016

Witness: Anne Schuchat, MD (RADM, USPHS)

Testimony before the Senate Committee on Health, Education, Labor and Pensions on Zika Virus

Introduction

Good morning Chairman Alexander, Ranking Member Murray, and members of the Committee. Thank you for the opportunity to testify before you today on Centers for Disease Control and Prevention's (CDC's) efforts to prepare for and respond to the Zika virus outbreak, which threatens the United States and the rest of the Americas. The Administration has requested approximately $1.9 billion in emergency funding to respond to the Zika virus outbreak, including $828 million for CDC, in support of both the domestic and international response, with particular attention to emergency assistance to the Commonwealth of Puerto Rico and other U.S. Territories and States with local transmission of Zika virus.

CDC is the nation's health protection agency, working 24-7 to save lives and protect people against unpredictable threats such as the Zika virus. Nature is a formidable adversary, and Zika is our newest threat, particularly to pregnant women. CDC has some of the world's leading experts both in diseases spread by mosquitos and in birth defects. We must act swiftly to stop the spread of the Zika virus, both domestically and globally. While we are learning more about the Zika virus every day, there are many things we do not know yet about Zika. These include our understanding of the spectrum of effects of Zika infection during pregnancy, the risk the virus may play in microcephaly, Guillain-Barré syndrome and other possible complications, the duration of Zika infectivity in semen, and determining what other factors may play a part in the consequences associated with the virus. In addition to answering these questions, we are also working to accelerate optimal mosquito control strategies, improve testing and assure preparedness for rapid detection, control, and prevention within the United States and U.S. territories.

We are making advancements in these areas and will need the additional requested funding to do so. We are figuring out more about Zika literally every day, and will share information – and adjust our guidelines and recommendations – as we learn more. That is the nature of a scientific response to an emerging health threat. The doctors, scientists, entomologists, and others at CDC are working nonstop to protect Americans from this and other health threats. We have already made significant progress identifying the Zika virus in brain tissue of affected deceased infants, developing new diagnostic tests, issuing guidance, conducting epidemiological investigations along with affected countries, and improving monitoring and surveillance in the United States including in the Commonwealth of Puerto Rico and the other U.S. territories. Much of what we know about Zika and similar viruses today is based on the work that's been done by CDC scientists. But there are still many things we do not yet know. We will continue to use the best of modern science to protect the American people. I understand that Zika virus and the emergence of serious birth defects cause concern. We are committed to

providing the American people with the most accurate and timely information about Zika virus and the current outbreak.

CDC is working in collaboration with other components of the Department of Health and Human Services (HHS), including the Office of the Assistant Secretary for Preparedness and Response (ASPR) and its Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health, and the Food and Drug Administration (FDA). We are also working with partners across the U.S. Government to communicate with travelers and health care providers, update travel alerts and clinical guidance, and develop improved mosquito-control methods.

Zika and its history

Zika is a flavivirus, which is closely related to dengue, yellow fever and West Nile viruses. Zika virus is primarily spread to people through the bite of infected *Aedes* species mosquitos, particularly *Aedes aegypti*. The *Aedes aegypti* mosquitos, which also transmit dengue and chikungunya viruses, are extremely difficult to control. They bite during the day, indoors and outdoors, and they preferentially feed on humans. And they need only the smallest bit of water to breed – just a bottle cap is enough. The mosquitos become infected when they bite a person with Zika virus. These infected mosquitos can then spread the virus to other people through bites. Case reports of other modes of transmission include spread through sexual transmission and blood transfusion. Of great concern, Zika virus infection in a pregnant woman has been linked to issues in fetal development, and the virus has been detected in association with fatal brain malformation in newborns as well as in miscarriages.

While its adverse effects were unforeseen, Zika is not a new virus. It was first recognized in 1947 and has caused occasional illness in Africa and Asia, but the first outbreak we know of occurred in 2007 in the small Pacific island of Yap. Last May, the first local transmission of Zika in the Americas was reported in Brazil, and by the end of 2015, Brazilian authorities estimated that the outbreak there involved perhaps a million suspected cases of Zika virus. In recent months, the virus has spread rapidly throughout Latin America and the Caribbean, as well as to parts of the Pacific. As of February 18, 2016, 32 countries and territories, including the Commonwealth of Puerto Rico, a United States Territory, the U.S. Virgin Islands, and American Samoa have reported local transmission of the Zika virus.

Symptoms and Adverse Outcomes

Many people exposed to Zika virus will have only mild symptoms - such as fever, rash, joint pain, and red eyes or conjunctivitis - that will last no more than a week. In past outbreaks, about four out of five people infected with Zika appear not to have had symptoms at all, although we do not know if that is the pattern in this outbreak.

Increasing evidence suggests that Zika virus infection may be associated with more serious health outcomes. In October 2015, Brazilian authorities recognized a concerning increase in microcephaly, which has occurred in

close sequence to Brazil's outbreak of Zika virus. Microcephaly is a usually rare, serious condition where a baby's head is smaller than expected based on age and sex. Microcephaly is not a diagnosis in and of itself, but a sign that the brain did not develop as it should in the womb. Babies with microcephaly can have a range of problems, including seizures, developmental delay, feeding problems and hearing loss. In some cases these problems can be fatal.

Laboratory tests at CDC strongly suggest a link between Zika virus infection during pregnancy and microcephaly. We do not fully understand the nature of this relationship, or if there are important cofactors. We also do not know what, if any, other outcomes might be associated with Zika infection during pregnancy among infants who do not have microcephaly. Microcephaly in infants can be devastating to the affected families, and this ongoing outbreak is concerning to everyone, especially for pregnant women, and their families who may travel to or live in the infected areas. The association between Zika virus and microcephaly is unexpected. A new infectious cause of fetal malformations has not been identified in decades. Zika virus spread in the Americas and its effect on pregnancy are developments that we are working with partners to better understand.

Our key priority at this point is to reduce the risk to pregnant women of Zika virus infection. Given the potential risks associated with maternal Zika infection, prevention is key for this response, with a parallel approach of acting based on what we know now and, at the same time, discovering more so that we can better prevent adverse health outcomes in the future. That's why, during the same week we identified Zika in brain tissue specimens from affected infants, we issued a warning to advise pregnant women not to travel to affected areas. That's why we are working intensively with the Commonwealth of Puerto Rico and other areas to get support to women who are or who may become pregnant and do what we can to reduce the threat of Zika there. And that's why we are engaging in studies with international partners so that we can more fully understand the magnitude of risk and the range of outcomes associated with Zika virus infection during pregnancy.

Health authorities in Brazil and elsewhere have also reported an increase in suspected cases of Guillain-Barré syndrome, a rare neurologic disorder in which a person's own immune system damages nerve cells, leading to nerve damage or paralysis that lasts for several weeks or several months. Most people fully recover, but it can take a few months or even years to do so. Some people with Guillain-Barré syndrome have permanent damage and, in rare cases, people have died. It is difficult to determine if any particular pathogen "caused" or "triggered" Guillain-Barré syndrome. Currently, we do not know if Zika virus infection causes Guillain-Barré syndrome. However, the development of Guillain-Barré syndrome is a recognized after-effect of a variety of different infections. CDC is currently collaborating with public health officials in Brazil to investigate whether there is any causal link between Zika infection and Guillain-Barré syndrome.

Domestic Activities

While we are working to better understand these health outcomes, transmission, diagnostics, and mosquito control, CDC is moving quickly to respond. We have moved our Emergency Operations Center to the highest

alert level for Zika virus to further enhance our response activities in areas with current local transmission and to accelerate preparedness efforts in anticipation of local transmission in the continental United States.

For the Commonwealth of Puerto Rico as well as the U.S. Virgin Islands and American Samoa, a surge in resources is urgently needed. The population of *Aedes aegypti* mosquitos is widespread on these islands, protective environmental factors such as window screens are not as prominent, and the density of people puts people there at high risk for transmission. All three areas have already reported local Zika transmission, with Puerto Rico alone reporting at least 30 cases. Furthermore, recent outbreaks of dengue and chikungunya suggest that Zika virus may spread extensively and rapidly in these areas. CDC has deployed staff to the U.S. Virgin Islands, American Samoa, and Puerto Rico to support response activities and provide technical assistance to health departments there. CDC and the CDC Foundation are also partnering to create Zika prevention kits. Containing educational materials, and initial supplies of prevention tools such as insect repellant, the purpose of these kits is to help pregnant women in areas with local Zika transmission protect themselves and their pregnancies. Five thousand of these kits have been dispatched to the Commonwealth of Puerto Rico, the U.S. Virgin Islands, and American Samoa; and CDC plans to distribute more than 45,000 kits to these areas in the future.

While we have not yet seen transmission of the Zika virus by mosquitos within the continental United States, we expect many returning travelers will have Zika infection. As a potential benchmark, we received reports of 3,270 travelers from 49 states with laboratory confirmed cases of chikungunya infection in 2014 and 2015. There are about 40 million people travelling between the continental U.S. and Zika-affected areas each year. Therefore, all U.S. jurisdictions must be prepared to evaluate, test, and manage patients with potential Zika virus infection, particularly pregnant women. Furthermore, *Aedes aegypti* is found in many areas of the United States, raising the risk of local transmission. The most recent data available suggest that *Aedes aegypti* are found in 13 states and *Aedes albopictus* are found in 31 states and the District of Columbia. Recent chikungunya and dengue clusters in the United States suggest that Zika outbreaks in the U.S. mainland may be relatively small and localized due to protective factors like window screens and less dense living conditions; however, any local outbreaks will be of deep concern to the people living there, and we must be prepared for different scenarios including more extensive transmission risk.

CDC is working with health departments across the country to ensure coordination and to expand capacity for detecting and responding to Zika virus. Surveillance is essential to monitor and quickly identify areas with local transmission. We conduct multi-faceted surveillance for arboviruses, including Zika, through ArboNET, an integrated network which funds, through our Epidemiology and Laboratory Capacity cooperative agreements, staff in 49 states, the Commonwealth of Puerto Rico, and six large municipalities to conduct human case investigations, collect and test mosquitos, and perform laboratory analysis on arboviruses including Zika. Zika virus is now a nationally notifiable disease, meaning states report the virus to CDC, which will aid Zika

surveillance efforts. CDC is also working with several states and the Commonwealth of Puerto Rico to determine a baseline prevalence of microcephaly so that any increase, should it occur, can be quickly and accurately identified.

With support from the President's emergency request, CDC will build on its current efforts to provide financial and technical resources to states and territories through its cooperative agreements to strengthen their capacity to prepare for and respond to emerging insect-borne threats such as Zika virus. These resources may be used to help health departments expand their capability to manage cases of local Zika virus transmission in their areas and to implement community education and prevention programs to reduce human-mosquito contact and subsequently, the risk of Zika transmission. Resources will also be used to implement mosquito control strategies, including mosquito surveillance. Current mosquito surveillance capacity is uneven across the country, which makes our knowledge about the locations of the two mosquito vectors that transmit Zika virus potentially incomplete. To effectively track the spread of the outbreak, it is critical that states and territories receive specimens and test for Zika virus to diagnose and report travel-related and locally acquired cases of Zika. Under the emergency request CDC will expand its efforts to assist public-health labs nationwide to test for Zika and to provide the guidance on how to interpret test results. In addition, CDC is available to provide testing of any Zika samples upon request. We are working to expand the number of health departments that have the ability to perform testing, but will need to increase the existing capacity to meet the projected demand for Zika testing. Given that, last year, it is estimated that approximately 500,000 travelers to areas of current Zika transmission were pregnant women and 36,000 pregnant women are currently living in the Commonwealth of Puerto Rico, the expansion of testing capacity in public health labs nationwide, included in the request, is urgently needed in order to ensure that every pregnant woman needing testing for Zika virus has access.

Recognizing the potential for Zika virus transmission through blood transfusions, CDC is collaborating with FDA to ensure the safety of the blood supply from Zika virus, particularly in regions experiencing local outbreaks. CDC has sent experts to the Commonwealth of Puerto Rico to assess the steps needed to assure both that Puerto Rico's blood supply needs are met and that transfusion-transmitted Zika is prevented.

CDC experts are working intensively to learn more about the outbreak and provide people with the information they need to protect themselves. We will continue to issue travel alerts for the affected areas as confirmation of the virus is reported, and we'll keep the American people informed as the situation changes. We recognize people are eager for information, and our website has exceeded half a million views in recent days.

CDC has also provided guidance for doctors and other clinicians on evaluation, treatment and follow-up care of pregnant women and infants with possible exposure to Zika virus, partnering with organizations from around the health care community to help distribute this information as widely as possible. Our guidance will continue to be updated as our knowledge increases. We have recently updated our guidance to provide recommendations for the clinical care and management of pregnant women living in areas where Zika transmission is widespread, with special consideration to the ongoing risk of maternal Zika virus infection throughout pregnancy. These guidance

documents were prepared in consultation with the American College of Obstetricians and Gynecologists, the Society for Maternal Fetal-Medicine, and the America Academy of Pediatrics.

CDC also wants to ensure that the general public knows what it can do to protect itself. Pregnant women should postpone travel to regions with ongoing Zika virus transmission. If they must travel, or if they live in affected areas, CDC recommends pregnant women talk to their doctors or other healthcare providers first and strictly follow steps to prevent mosquito bites. Reducing exposure to mosquitos is important for anyone traveling to or residing in areas where the virus is circulating. Wearing long sleeves, long pants, using EPA-registered repellents such as DEET and permethrin-treated clothing (both of which are safe to use in pregnancy), and using other protections such as air-conditioning will reduce exposure to mosquito bites. Given the potential for Zika virus to be spread through sex, pregnant women and their male partners living in or who have been to Zika-affected areas should abstain from sex or use condoms for the duration of pregnancy. This is a rapidly changing situation and our understanding of the risks concerning Zika virus infection is incomplete and evolving. As we get new information, we will update our advice.

Global Activities

On February 1, the World Health Organization (WHO) declared the recent cluster of microcephaly cases and other neurological disorders (such as Guillain-Barré syndrome) and their possible association with Zika virus, a public health emergency of international concern, a reflection of the seriousness of this unfolding health threat. CDC is coordinating its response with the U.S. Agency for International Development, as well as the Pan American Health Organization (PAHO), the regional arm of the World Health Organization (WHO), and other parts of WHO, and is collaborating with many international partners to learn more about this outbreak. We are working with the Brazilian Ministry of Health on investigation and research partnerships. Specifically, one partnership involves studying the link between Zika virus infection and microcephaly, while another is examining the relationship between Zika virus and Guillain-Barré syndrome. Research teams from CDC are also in other countries, including Colombia, to explore collaborations that will shed light on the risk of microcephaly in relation to Zika virus infection during pregnancy.

In addition, CDC is offering support to all countries so that they can test samples from microcephaly cases for serologic evidence of Zika virus infection, and CDC is helping countries throughout the Americas establish in-country diagnostic capacity. To that end, we are currently, and in conjunction with PAHO, providing training to laboratorians in South and Central America on diagnostic tests, including two recent workshops in Brazil and Nicaragua.

CDC's Central American office has also facilitated the verification of Zika cases in several countries throughout Latin America, including Colombia, Venezuela, and Nicaragua. At the request of the Department of State's Bureau of Medical Services, staff from CDC's Global Disease Detection Center in Guatemala has been involved

in communication efforts to ensure that new information regarding Zika virus and its possible link to birth defects is communicated to U.S. Mission Health Unit staff throughout the Americas.

The Global Health Security Agenda, with critical support from Congress, is collaborating with countries around the world so that we can find, stop, and prevent health threats when and where they first emerge. Zika has been present in Africa for decades, and it's possible that it could become linked to microcephaly there as well. The sooner we detect a problem, wherever it occurs, the more rapidly we can respond to it and prevent it from spreading. It is in all of our best interests to work with others to improve public health capacity around the world.

Improving the tools and information for responding to Zika

We need a better understanding of the epidemiology of Zika and potential Zika-associated birth defects and other adverse health outcomes. We need better diagnostic methods that can quickly and clearly differentiate between similar viruses to detect evidence of past Zika infection. Testing for current Zika infection is only reliable in the first week of illness. A Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test can provide a definitive diagnosis of Zika, but only if it is performed within about seven days of symptom onset. The tests we have available for Zika in persons who are no longer ill may have cross-reactivity with similar flaviviruses, particularly dengue, which can lead to false-positive or inconclusive results and confirmatory testing is required. Diagnosis is particularly challenging with Zika virus since most people will not experience symptoms. We also need to determine how long a man who has been infected with Zika may continue to be able to sexually transmit the virus to a partner, and we need better tools to screen the blood supply.

We also need to advance our ability to control the mosquito population. Existing methods for mosquito control all have shortcomings, especially in areas where the population of *Aedes* mosquitos is rampant. Furthermore, in some areas like the Commonwealth of Puerto Rico, mosquitos may have developed resistance to certain insecticides, which could reduce the range of substances that can be used to effectively decrease mosquito populations. We need to implement the best tools we have today, improve current vector control strategies, and identify better options. We also need better mosquito surveillance to determine the location of mosquitos and areas with mosquito resistance to insecticides, which would inform the implementation of new mosquito control techniques.

Finally, a vaccine is needed to protect people at risk of Zika virus infections, particularly preventing infection among women of childbearing age. At CDC, our scientists developed both a West Nile virus vaccine, which is currently in use for animal protection in the United States, and a dengue vaccine, which is currently in clinical trials. The President's request will increase Zika research, improve diagnostics and support advancements in vector control methods. Although availability of a licensed Zika vaccine is several years away, we do not know how long Zika will be a problem in the Americas nor whether the mosquito control efforts that must be implemented will yield durable results.

Conclusion

Microbes continue to be formidable adversaries. To protect Americans, the Zika emergency request invests in the laboratories, disease detectives, disease tracking systems, mosquito control, and investigations needed to continue to improve these essential tools.

The emergence and reemergence of health threats, including those spread by mosquitos and other vectors is not a unique event but something we expect to continue to see in the future. These outbreaks cannot be expected to occur in isolation of one another. The Commonwealth of Puerto Rico and Hawaii were already responding to outbreaks of dengue when Zika virus arose as an urgent health threat. We need to address the threat of mosquito-borne diseases systematically, rather than episodically. Thank you again for the opportunity to appear before you today. I appreciate your attention to this concerning outbreak and I look forward to answering your questions.

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

Senate Health, Education, Labor, and Pensions Committee

Anthony S. Fauci, M.D.

Director

National Institute of Allergy and Infectious Diseases

National Institutes of Health

February 24, 2016

Mr. Chairman, Ranking Member Murray, 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, it 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 work on the development of vaccines and diagnostics and to improve scientific understanding of the 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 a spectrum of research, from basic studies of the mechanisms of disease to applied research focused on developing interventions such as 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 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 capacity of microbial pathogens to evolve rapidly and adapt to new ecological niches. To address the challenges posed by emerging 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 of vaccines and diagnostics applicable to 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 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 and lower the scientific, technical, and financial risks incurred by industry in order to incentivize them to partner with us in the advanced development of effective countermeasures. NIAID also supports our Vaccine and Treatment Evaluation Units (VTEUs), a research network that conducts clinical trials to quickly investigate promising therapeutic 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 *Aedes* mosquitoes. 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 congenital abnormalities including microcephaly, as well as to 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 or no symptoms at all and can be

difficult to distinguish by antibody screening tests from other mosquito-borne infections such as dengue, malaria, and chikungunya. 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 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 funds would support basic research to understand the natural history, viral biology and pathogenesis, 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, NIH is soliciting 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 (NICHD), the National Institute of Neurological Disorders and Stroke (NINDS), 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 and other congenital abnormalities.

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 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 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, particularly 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 and therapeutic tools.

Vaccines

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. The West Nile vaccine candidate was shown in Phase 1 testing 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. 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 plan 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, 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. 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 approximately $1.9 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, particularly microcephaly.

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. In particular, NIAID will pursue the development of safe, effective vaccines to prevent disease caused by Zika and chikungunya viruses.

Written Testimony
Committee on Health, Education, Labor, and Pensions
United States Senate

"ASPR's Role in the Zika Response"

Statement of

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ASPR
ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

For Release on Delivery
Expected at 10:00 a.m.
Wednesday, February 24, 2016

Chairman Alexander, Ranking Member Murray, and Members of the Committee, thank you for the opportunity to testify before you again. As you may recall, within the Department of Health and Human Services (HHS), I serve as the Director of the Biomedical Advanced Research and Development Authority (BARDA) and as a Deputy Assistant Secretary for Preparedness and Response (ASPR). Through ASPR and the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE), BARDA leads the advanced development of medical countermeasures to prepare for and respond to emerging infectious diseases, man-made national security threats, and other public health emergencies. In ASPR we have been working to advance a mission delineated by the Pandemic and All-Hazards Preparedness Act (PAHPA) and realize our full leadership capabilities. ASPR and BARDA have matured and flourished in many diverse ways over the past nine years. We operate efficiently and from a position of strength with the ability to manage numerous lines of effort including the water situation in Flint Michigan, the recent Ebola epidemic, and the current Zika outbreaks. With this testimony I intend to provide a progress report on our current efforts and hope to clarify our capabilities in the context of Zika.

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 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 work on the development of vaccines and diagnostics and to improve scientific understanding of the disease. While I will briefly describe some of ASPR's activities overall, as the BARDA director, I will focus my remarks on the development of vaccines and diagnostics.

The Zika virus is primarily a mosquito vector-borne viral disease threatening the United States and our neighbors in Latin America and other parts of the world. Zika is a flavivirus in the same family as dengue, West Nile virus, and Yellow Fever, diseases we have been monitoring and combating for years. On February 1, the World Health Organization (WHO) declared clusters of microcephaly and other neurological disorders, and their possible association with Zika virus, a public health emergency of international concern. Named after the Zika Forest in Uganda, Zika includes common symptoms such as fever, skin rash, joint pain, or conjunctivitis. However, eighty-percent of people with Zika do not appear to have symptoms at all. Considering recent outbreaks in the Pacific Islands, Central America, South America, and the Caribbean, we anticipate that the number of Zika cases among travelers visiting or returning to the United States is likely to increase. We have already seen cases of travelers returning to the United States with confirmed Zika virus disease and are particularly concerned about the virus becoming endemic in the Commonwealth of Puerto Rico, the U.S. Virgin Islands, the American Samoa, with potential for local outbreaks in parts of the southern United States. Moreover, the Brazilian Ministry of Health estimates that between 440,000 and 1.3 million suspected cases of Zika occurred in Brazil in 2015.

There is still much that we do not know about Zika and its adverse health effects on a population. Evidence associating Zika with birth defects like microcephaly and other adverse health conditions such as Guillain-Barré Syndrome is growing; however, there is still much to learn including whether additional factors are involved. HHS is actively monitoring the Zika virus, investigating outbreaks, and working with domestic and international partners to update health

care providers and the general public. In addition, HHS is providing laboratory and diagnostic tests both domestically and internationally.

As we learned with Ebola and pandemic influenza, one of our key responsibilities in addressing an infectious disease is effective communication. This involves delineating a leadership structure and updating information as soon as possible using principles of risk communication and using multiple including translated materials for non-English speaking communities and enhanced outreach to vulnerable populations. Clear, concise, and accurate information can reduce the level of concern among the general population and support appropriate action by health care providers. With that in mind, HHS and our federal partners are stressing a coordinated response to this emerging threat.

ASPR is fulfilling its leadership roles both through the Disaster Leadership Group (DLG) through the PHEMCE to develop and provide medical countermeasures. Both were created to effectively improve coordination within the Department and with our external stakeholders, including nonprofits, other federal departments, the private sector, and the international community. Specifically, the DLG is comprised of leadership from across HHS to advise and coordinate policy on critical issues related to preparedness and response. Additionally, the the Secretary's Operations Center serves as the focal point for International Health Regulation, and for communication across government. The PHEMCE, chaired by the ASPR, serves as the focal point for coordinating medical countermeasure development.

I will focus the remainder of my testimony on BARDA's role. BARDA has a mandate from PAHPA to transition medical countermeasure candidates from early development across the "Valley of Death" into advanced research and development towards FDA approval. BARDA has established four strategic goals to address medical countermeasure needs for the Zika response domestically and globally. These are prevention of Zika virus infection through new vaccines; detection of acute and previous Zika virus infections through new rapid diagnostics; ensuring a safe blood supply from Zika virus through screening and virus inactivation; and activation of our National Medical Countermeasure Response Infrastructure to aid medical countermeasure developers.

Building on existing and new partnerships and lessons learned from the H1N1 and Ebola responses, we are implementing our Zika medical countermeasure strategy through the advanced development and manufacturing of new Zika-specific vaccine candidates. In collaboration with NIH, FDA, and the Walter Reed Army Institute of Research, we are working on vaccine development, pre-clinical and clinical testing, and commercial scale production, including vaccine manufacturing through our Centers for Innovation in Advanced Development and Manufacturing. We are also providing technical assistance to our global partners in Brazil for Zika vaccine development and commercial scale manufacturing. We are supporting industry partners to develop and utilize new and innovative vaccine platform technologies to address public health emergencies for multiple emerging infectious diseases including new Zika vaccine candidates. We are collaborating with CDC, FDA, and NIH to facilitate the development of rapid point-of-care and laboratory-based serological assays for Zika to determine who has been infected previously, especially pregnant women. With regard to the blood supply, we are

collaborating with FDA to support the development and implementation of rapid high-throughput molecular diagnostic screening and pathogen reduction technologies. We're particularly concerned about blood supplies at risk due to recent Zika virus outbreaks in the Commonwealth of Puerto Rico and potentially other parts of the United States. As we did for the Ebola response, we are assisting medical countermeasure developers through our National Medical Countermeasure Response Infrastructure, which is comprised of six core service assistance programs that provide animal and human clinical testing, product development and manufacturing, and regulatory and modeling needs. This infrastructure could potentially be used to develop vector protection countermeasures such as mosquito repellants.

We are also encouraging and receiving numerous inquiries from academic and industrial stakeholders for potential medical countermeasures through our Tech Watch program. Moreover, contracting for ASPR's medical countermeasure programs has been designed to be transparent and responsive to industry but also ensure that we have appropriate internal controls for the contracting process overall. We're able to efficiently move from the idea and proposal stage to acquisition. Considering a government-wide benchmark of 180 days to award a contract, ASPR is consistently awarding major acquisition contracts within 128 days. During the height of the Ebola response we were awarding contracts within 60 days. This success is a demonstration of the mature contracting function that ASPR has implemented and one that is fulfilling its requirements to support our industry partners and the medical countermeasure enterprise.

Recognizing the domestic impact of global public health emergencies, we have strengthened our international partnerships as cited above for vaccine development with Brazil. Whether it is pandemic influenza, Ebola, or a vector-borne disease like Zika, public health emergencies have no borders. We have forged trusted networks and relationships with key international partners and continue to receive and share information with the WHO, the United Nations, the United States Agency for International Development, the U.S. Department of State, and countries around the world about best emergency preparedness practices and surveillance data on infectious diseases. We maintain regular communications and coordination with the G7 countries, Mexico, and the European Commission on public health measures, including the development and deployment of medical countermeasures. These collaborations range from discussing domestic preparedness activities of other countries to the medical evaluation and coordination of medical countermeasure development. Our weekly Americas' Call teleconference involves eighteen countries from North America, Central America, South America and the Caribbean. Thanks to this mode of outreach and coordination, we learned that Panama had Zika samples they were willing to share for research, which was a big step forward in helping to identify the strain for diagnostic comparisons. The Global Health Security Initiative (GHSI) is another success story for international coordination. Established shortly after the September 11, 2001, terrorist attacks, GHSI is an assembly of Ministers, Secretaries, Health Commissioners and other senior health officials from the European Commission, France, Germany, Italy, Japan, Mexico, the United Kingdom, the United States ,and the WHO to address global health security issues. GHSI played a crucial role in bringing countries together for the Ebola response and is already turning its focus to Zika. An early focus has been on sample sharing, which is critical to the development of vaccines and diagnostics. The next ministers

meeting is taking place this week in the United States, and Zika will be one of the main topics of discussion.

In closing, our foremost concern is protecting public health from known or emerging threats. Zika is our newest threat, but not our last. Congressional approval of the Administration's approximately $1.9 billion funding request will ensure an effective and rapid response to outbreaks that threaten the health of the American people and can accelerate our ability to prevent, detect, and respond to Zika and other emerging infectious diseases. Thanks to our combined efforts and with lessons learned from previous challenges, we are a better prepared and more resilient nation with the flexibility to successfully address a variety of public health threats. Thank you again and I look forward to your questions.