Good morning Chairman Murphy, Ranking Member DeGette, and members of the Subcommittee. Thank you for the opportunity to testify before you today on the effects of Zika virus in pregnant women and how clinicians are responding to this virus threatening the United States and the rest of the Americas. This virus has received international attention predominantly because of its effects on the developing fetus, specifically the association with microcephaly and abnormal intracranial findings.

The Zika virus is a mosquito-borne flavivirus closely related to yellow fever, West Nile and dengue viruses. It was first identified in 1947 in rhesus monkeys and subsequently noted to cause mild disease in humans throughout Africa and Asia. The first significant outbreak occurred in 2007 in the Yap Islands of Micronesia. French Polynesia in 2013-2014 reported that 10% of its population was infected - several cases of Guillain-Barre syndrome and 2 cases of vertical transmission were identified. It was not until May 2015 that local transmission of the virus in the Americas was reported in Brazil. This virus has now spread throughout South and Central America and the Caribbean following the global distribution of the *Aedes aegypti* mosquito. While the continental United States has not identified a case of local transmission of Zika, there are now greater than 100 confirmed travel-related cases, several of these pregnant women.

Transmission of Zika virus is primarily through infected *Aedes aegypti* mosquitos and, less common *Aedes albopictus* mosquitos. These mosquitos are found in the United States and are daytime biters. Once a person is infected, the incubation period is up to 2

weeks. Transmission may also rarely occur through infected blood and laboratory accidents. Vertical transmission from a pregnant mother to her fetus has been confirmed and transmission at the time of delivery may also occur. Viral RNA has been found in breast milk though no virus has been isolated and no case of transmission from breastfeeding has been reported. Finally cases of sexual transmission of Zika from an infected person to an uninfected sexual partner are increasingly being identified, currently all from an infected male to an uninfected female. All infected males were symptomatic within 2 weeks of travel to Zika affected areas.

The majority of persons infected with Zika virus are asymptomatic – only 20% develop symptoms and these symptoms are usually mild. Acute onset of fever, maculopapular rash, arthralgias and conjunctivitis are the predominant symptoms though myalgias, headache, retro-orbital pain, pruritis and vomiting have also been reported. Symptoms last up to a week and infection rarely results in serious illness or death. The primary concern of Zika virus infection is to the pregnant woman and her developing fetus.

Zika virus effects on pregnancy women and the developing fetus

Data regarding Zika virus infection and pregnancy are limited and it is imperative that resources are directed to elucidating the pathophysiology of infection in pregnancy, rate of fetal transmission, influence of timing of infection in relation to pregnancy on fetal manifestations of disease, and long term consequences of fetal infection. While it is

unknown at this time if pregnant women are more susceptible to Zika virus, the disease does not appear to be any worse in pregnant women compared to non-pregnant individuals. Zika infects pregnant women in any trimester and the virus has been found in tissues from fetal losses, amniotic fluid, placenta, and in the brain of infected neonates.

The Brazilian outbreak of Zika virus was associated with a significant rise in microcephaly cases, first recognized in September 2015. The Brazil Ministry of Health established a microcephaly registry and task force and on November 17, 2015 they reported a possible association of Zika virus infection during pregnancy and microcephaly. By December, Zika virus RNA was reported in the amniotic fluid of two pregnancies in the third trimester in which fetal microcephaly was diagnosed. The virus was also found in tissues from an infant with microcephaly who died soon after birth. January 22, 2016 Brazil reported 35 cases of Zika-virus related microcephaly; 74% of the mothers reported a rash during pregnancy and all women lived in Zika affected areas.

Microcephaly is diagnosed when the head is significantly smaller than would be expected at a specific gestational age and sex. There are many causes of microcephaly and in the United States, microcephaly is reported in 2 to 12 infants per 10,000 live births. Microcephaly has been associated with genetic abnormalities e.g. chromosome and single-gene disorders, environmental factors such as exposure to toxic substances during pregnancy e.g.mercury, severe malnutrition, maternal alcohol use in pregnancy

and infections such as rubella and cytomegalovirus (CMV). It can also occur when there is an insult to the fetus during development and the brain stops growing normally. In the case of infection, it takes weeks to months after the infection for microcephaly to develop. The reason microcephaly develops in association with Zika infection is currently under investigation.

Infants with microcephaly can have a wide range of long-term complications depending on the severity of the microcephaly and the associated abnormalities. Seizures, developmental delay including speech and motor abnormalities, cerebral palsy, intellectual disability, feeding problems and vision and hearing loss are not uncommon in these infants. There is no known cure or standard treatment for microcephaly. Because microcephaly can range from mild to severe, treatment options vary. Significant resources will need to be available for the long-term care of these affected infants.

Since the microcephaly association was first noted several months ago, a number of other fetal abnormalities have been identified. Fetal growth restriction, intracranial calcifications, abnormal brainstem and cerebellum development, almost complete agyria with brain atrophy, absence of the corpus callosum and thalami have all been documented. The majority of the infants with microcephaly have at least one of these other abnormalities. Eye abnormalities have been identified in 35% of the Brazilian cohort. The Zika virus is neurotropic, targeting the brain. The complications identified to

date reflect this. Autopsy specimens have identified the virus in the brain of affected fetuses and infants. It is unknown whether infants infected late in pregnancy that have not had time to develop microcephaly and other abnormalities prior to delivery will have long term sequelae.

Recommendations for pregnant and reproductive age women

Soon after the association between Zika virus infection and fetal microcephaly was identified, the Centers for Disease Control and Prevention (CDC) sent out a Health Alert and brought together subject matter experts including virologists with arbovirus expertise, public health personnel and Obstetricians/Gynecologists who specialize in infectious diseases in pregnancy. While data were limited, interim guidelines were rapidly developed to inform physicians caring for pregnant women. Management strategies addressing pregnant women who had traveled to Zika affected areas were disseminated and educational materials describing preventative measures were made widely available to physicians and the general public. These guidelines have been updated several times as new information has been elucidated. The CDC also maintains a hotline available to clinicians 24/7 for Zika related questions.

There is no vaccine or medication to prevent the acquisition of Zika virus. The CDC recommends that all pregnant women or women considering pregnancy postpone travel to areas of ongoing Zika virus transmission

(http://wwwnc.cdc.gov/travel/notices). If they have to travel to affected areas, avoid mosquito bites by wearing protective clothing, using U.S. EPA-registered insect repellent and stay in screened in or air-conditioned areas. DEET and permethrin can be used throughout pregnancy.

Pregnant women that do travel to areas of ongoing Zika virus transmission should be evaluated regardless of symptomatology. The CDC algorithms detail the laboratory evaluation that should be performed. While this initially could only be done at a central CDC laboratory, they have rapidly made the testing available to a number of state health departments and are rapidly expanding the laboratories able to perform the tests. Ultrasound guidance to evaluate the fetus for evidence of Zika infection has been developed in conjunction with the Society of Maternal-Fetal Medicine (SMFM) and the American College of Obstetricians and Gynecologists (ACOG). The CDC has also developed guidance for pregnant women living in endemic areas and to evaluate neonates born to mothers infected by Zika.

There have now been several confirmed and suspected cases of sexual transmission in the Unites States, all from men who traveled to areas of ongoing Zika virus transmission to female non-travelers. The concern now is that this is a more common mode of transmission than was previously suspected. Men who have a pregnant partner should either not travel to affected areas or if they do travel, abstain from sexual activity or use condoms “consistently and correctly” for the duration of the pregnancy. Pregnant

women who do engage in unprotected sexual activity with a partner who traveled to an affected area and who had symptoms of Zika infection during travel or within 2 weeks of return should be offered evaluation.

Zika virus infection is a notifiable disease in the United States, allowing for better surveillance of the disease burden. The CDC has developed a registry of U.S. pregnant women with confirmed Zika infection. They released a report February 26,2016 detailing the initial results of the testing in pregnant women travelers. Of 257 Zika tests performed for pregnant women, 3% tested positive. The nine pregnant women with confirmed infection all reported symptoms (100% had a rash). Six women were infected in the first trimester: two had an early pregnancy loss, two elected to terminate their pregnancy, one delivered an infant with microcephaly and one is ongoing. Two women were infected in their second trimester: one woman delivered a healthy infant and one pregnancy is ongoing. One woman was infected in the third trimester and delivered a healthy infant.

While this initial report is an important first step, much more is needed for the physician to be able to effectively counsel a pregnant woman at risk for infection. Support for both national and international research targeting key populations e.g. pregnant women is imperative. Until effective treatments and/or a vaccine are developed, prevention of maternal infection is necessary to prevent the devastating consequences of fetal infection.

Conclusion

The Zika virus epidemic is a unique situation: it is a mild disease in adults of little consequence to date except for the uncommon complication of Guillain-Barre. However, maternal Zika infection during pregnancy can have enormous consequences to a developing fetus. As such, the Centers for Disease Control and Prevention has moved quickly to respond to this global threat. As we move into the warmer months in the United States and the mosquito population increases, we expect to see locally transmitted infections. Mobilizing resources to better characterize this disease is imperative.

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