

Zika Virus – An Obscure Disease Goes “Viral”

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Zika virus is an arbovirus (virus spread by arthropods), that is a member of the flavivirus family, along with other viruses including Yellow Fever, West Nile, Dengue, Japanese encephalitis and Saint Louis encephalitis viruses. First isolated in 1947, it did not appear in the Americas until early 2014 when it was identified on Easter Island (Chile).

By early 2015, an outbreak of the virus began in Brazil. As of March 31st, 2016, locally acquired cases of Zika virus had been reported from 33 countries and territories in the Americas.

Previously thought to be a generally mild illness, the ongoing epidemic has highlighted serious complications from the infection that were previously unidentified or unreported. Information about the virus, the nature of the infection and the distribution of the disease is emerging on a continual basis.

As more is learned, the Centers for Disease Control and Prevention (CDC) and state and local health departments will continue to release updated guidance to educate the public and health care providers on measures to take to prevent Zika virus transmission, as well as updated information about the health effects that result from infection with the virus.

Most Zika virus infections are asymptomatic. About one in five people infected with the virus develop the disease and symptoms are generally mild comprising any combination of fever, rash, joint pain, or conjunctivitis. Symptoms typically begin after an incubation period of a few days to a week. In most cases, symptoms resolve within a few days to a week.

Differential diagnoses for the characteristic symptoms of Zika are myriad and (given the relevant travel or exposure history) might include leptospirosis, malaria, rickettsia, group A streptococcus, rubella, measles, parvovirus, enterovirus, adenovirus, dengue fever, chikungunya (or other alpha viruses).

The current Zika epidemic has brought to light serious consequences of what was previously thought to be a benign disease. In addition to poor pregnancy outcomes (stillbirth, miscarriages) and microcephaly, there is also accumulating evidence that implicates the virus in a spectrum of neurologic syndromes in adult and adolescents including Guillaine-Barre syndrome and acute myelitis amongst others.¹⁻³ Long term consequences of Zika virus infection are yet to be determined. There is currently no vaccine to prevent, or antiviral to treat Zika virus, although studies are ongoing to develop these. Since the only natural hosts for Zika appear to be primates, previous research around Zika was limited to non-human primate models. Recently, two murine (mouse) models for Zika virus infection have been described.^{4,5} These will likely open up the door for much progress towards the development of Zika therapeutics.

Patients with Zika should be managed symptomatically. Given the similarity to Dengue virus infection, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided until dengue is ruled out in order to avoid potential hemorrhagic complications that might ensue if the patient has dengue.

Transmission

Transmission of Zika virus is primarily through the bite of infected *Aedes* mosquitos with the primary vector being *Aedes aegypti* (also known as the yellow fever mosquito). *Aedes aegypti* is also an important vector for Dengue virus and Chikungunya virus. Isolation of the virus in, or transmission by, other *Aedes* species in natural or laboratory settings has been described in the literature. Of particular interest is *Aedes albopictus* (Asian Tiger mosquito),⁶ given its relative abundance in the continental US including Delaware.

The sexual route of transmission for the Zika virus has been recently described⁷ with several Zika virus infections in the current epidemic also being linked to sexual transmission. Most cases of sexual transmission of Zika were from an infected male to a female, however, male to male transmission of Zika has been described of late.⁸ It is yet to be determined if Zika can be transmitted from a female to her sexual partners. It has also not been established which forms of sex (vaginal, anal or oral) pose the highest risk for sexual transmission of Zika virus.

A recent study demonstrated high concentrations of Zika virus in the testes of experimentally infected mice, with the concentration in the testes being higher than in any of the other tissues examined,⁴ underscoring the importance of the sexual route of transmission.

The length of persistence of the virus in semen is a subject of ongoing study by the CDC and others. Mother to child transmission of Zika virus during pregnancy and/or child birth is a third mode of transmission. Zika infection during pregnancy has been shown to result in poor pregnancy outcomes including miscarriage, stillbirths, intrauterine fetal growth retardation. Particularly concerning are the severe neurologic consequences including microcephaly that are associated with Zika infection in pregnancy.¹ In the wake of the Zika virus outbreak, Brazil has seen an unprecedented rise in cases of microcephaly.⁹ Studies have been published reporting the isolation of Zika virus from the neural tissues of stillbirths and from products of conception retrieved from women infected with Zika virus. It remains unclear during which trimester of pregnancy the risk of transmission is highest. Studies are also ongoing to determine the impact of infection at different stages of pregnancy and how frequently an infected mother will transmit the virus to her unborn child.

Transmission of Zika virus through the inadvertent transfusion of infected blood is yet another means by which the virus can spread.

As of March 31st, the continental U.S. had 312 travel-associated cases of Zika identified from 34 states, including three confirmed cases in Delaware. Apart from Puerto Rico, American Samoa and the US Virgin Islands where there is ongoing transmission, there have (as of March 31st) been no cases of mosquito-borne Zika virus infection in the U.S. Sexual transmission of Zika has been documented in 6 US states so far. No sexual transmission has been reported in Delaware as of March 31st.

Reporting Zika Virus Infection

Zika virus infection has been made a nationally notifiable disease. It is a reportable disease in Delaware. It is important to identify and report cases or suspected cases of Zika virus infection to local public health authorities both for the benefit of the individual patient and for the public's health. It is also critical to report pregnant women who have had potential exposures to Zika virus. Exposure of a pregnant woman would include travel to areas with ongoing Zika virus

infection at any time during her pregnancy or 8 weeks prior to conception (6 weeks prior to last menstrual period). Unprotected sex, during her pregnancy, with a man known to have Zika virus infection would also constitute exposure for a pregnant woman. Such individuals should be referred for laboratory testing (available at the Delaware public health lab for Delaware residents).

Most non-pregnant people do not have serious consequences from Zika virus infection. Nonetheless, it is important to refer individuals with relevant travel or exposure and consistent symptoms for laboratory testing. This referral will allow state and local public health authorities and mosquito control experts to apply measures to help protect the public's health.

Laboratory Testing

Testing for Zika virus is accomplished by real-time Reverse Transcriptase Polymerase Chain Reaction (PCR) and by serology (IgM enzyme linked immunosorbent assays- ELISA). The results of this testing depends on time since infection with PCR having the best yield earlier in the course of illness (first one week). IgM ELISA is able to detect infection between 2-12 weeks after infection but is less reliable earlier on. Because of the significant cross reactivity between serologic tests for Zika and related flaviviruses, confirmatory testing for those that return positive on IgM ELISA is required. This is accomplished using Plaque Reduction Neutralization Testing (PRNT) which reliably differentiates Zika infection from primary infection due to dengue and other flaviviruses. It is important to note, however, that previous flavivirus infection or prior immunization against flaviviruses (yellow fever or Japanese encephalitis vaccination) may make PRNT results difficult to interpret.

As of the time of this publication, the Delaware Division of Public Health laboratory is performing PCR testing for Zika virus on serum and urine specimens and is expecting to add on Zika IgM ELISA within the next several weeks. PRNT is currently being done at the CDC laboratories.

Given the overlapping epidemiology and symptomatology of Zika, Dengue and Chikungunya viruses, it is important that individuals suspected of having Zika also be tested for Dengue and Chikungunya. The FDA recently approved a triplex PCR that is able to test for these three viruses simultaneously and this is available at the Delaware public health laboratory.

Priority for testing is given to pregnant women. Thus, testing of non-pregnant individuals in Delaware will be limited to those who have symptoms consistent with Zika virus infection PLUS a history of travel to areas with ongoing transmission of Zika virus. Testing will be performed on pregnant women who have concerning exposures (consistent travel or unprotected sex with a male Zika case) regardless of whether or not the woman has symptoms. This includes women who traveled to affected areas within 8 weeks prior to becoming pregnant (or within 6 weeks prior to their last menstrual period). It is important that such women are referred early as serologic tests are most reliable within 2-12 weeks following exposure. To arrange for laboratory testing in Delaware, health care providers should call 888-295-5156 or 302-744-4990 or email Reportdisease@state.de.us

Prevention

Because a lot is still unknown about the pathophysiology and persistence of Zika virus in various tissues and bodily fluids, the CDC recommends that women who desire to conceive be

counselled to wait at least 8 weeks after exposure (or after symptoms first appear) prior to attempting to conceive. Men who have been diagnosed with Zika virus or who have consistent symptoms should be advised to wait at least 6 months after symptoms first appeared before having unprotected sex.

The primary means of preventing Zika virus infection is by mosquito avoidance including personal protective measures (such as use of insect repellants, mosquito screens and permethrin treated clothing) and reduction of mosquito breeding habitats around the home. It is also important to counsel pregnant women to avoid travel to areas with ongoing transmission if at all possible and to avoid unprotected sex with men who have traveled to such areas. In addition, persons with confirmed Zika virus infection should practice mosquito avoidance measures for the first week of illness. This prevents movement of Zika into the local mosquito population and thus prevents transmission of the infection to others.

Zika Pregnancy Registry

To understand more about Zika virus infection, CDC established the U.S. Zika Pregnancy Registry and is collaborating with state, tribal, local, and territorial health departments (Including Delaware's DPH) to collect information about Zika virus infection during pregnancy and about congenital Zika virus infection.

The data collected through this registry will be used to update recommendations for clinical care, to plan for services for pregnant women and families affected by Zika virus, and to improve prevention of Zika virus infection during pregnancy.

Please contact the Division of Public Health (Office of Infectious Disease Epidemiology) to enroll patients in the Zika pregnancy registry, to report cases or to arrange for laboratory testing by calling 888-295-5156 or 302-744-4990 or emailing Reportdisease@state.de.us

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