POLICY ANALYSIS

Zika Virus Update: More on an Emerging Arboviral Disease in the Western Hemisphere

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ABSTRACT

Zika virus has captivated the world with its quick spread throughout the Western Hemisphere. Increased emphasis has been placed on the infection of pregnant women and subsequent adverse and severe effects in the developing fetus and newborn. This article supplements a previous article and provides updated information on new and evolving evidence that strengthens the association between Zika virus and unique congenital and neurologic diseases, updates what is known about the epidemiology of the disease, and provides new and updated material for primary care providers as they counsel patients who may be exposed or infected. With the extent of disease spread, it is expected that Zika virus will become endemic to the Western Hemisphere and will change the public health parameters and approach in this area of the world. (*Disaster Med Public Health Preparedness*. 2017;11:163-167)

Key Words: Zika virus, microcephaly, neurologic disease, arbovirus, sexual transmission

In March 2016, I submitted an overview article on the emergence of Zika virus (ZIKV) in the Western Hemisphere.[1] Because of the World Health Organization public health declaration related to ZIKV and the explosive spreading nature of the agent throughout the world, there is a tremendous focus on studies related to prevention, epidemiology, and control of the disease. Updated information, guidelines, and recommendations have been released.[2-7] As ZIKV is a developing issue, this article provides updated information that supplements the previous report.

As of May 13, 2016, the epidemic has spread to 38 countries or territories throughout the Western Hemisphere.[8] In addition, active transmission is being reported in 6 Pacific or Indian Ocean island nations and on the Cape Verde islands of Africa.[9] Within the United States, only travel-related cases have been reported from 43 states and the District of Columbia, and 8 cases are considered sexually transmitted cases.[10] Autochthonous transmission is occurring in Puerto Rico, where more than 770 cases have been reported, including 110 pregnant females and 1 death attributed to ZIKV.[11]

On May 6, 2016, US Major League Baseball (MLB) and the MLB Players Association postponed and relocated a baseball game series from Puerto Rico to Florida.[12] These games were organized to honor Roberto Clemente who was from Puerto Rico. Other upcoming sporting events held in the Americas, to include the 2016 Summer Olympics and Paralympics in Brazil, are a concern to hosting and supporting countries and public health officials. A recently published phylogenetic analysis compared the lineage of viruses recovered from ZIKV cases in Bahia, Brazil.[13] From this analysis the authors estimate and suggest that the common ancestor virus was present in Bahia, Brazil, as early as mid-2014, further supporting virus introduction coinciding with other international sporting events held in Brazil during 2014.

Updates and considerations based on new and evolving discoveries, cases studies, and other epidemiologic and laboratory research is provided to update previous information about a not-so-well understood arboviral disease.

MICROCEPHALY AND OTHER CONGENITAL DEFECTS

Of note with ZIKV clinical effects is the increasing evidence of the association between maternal infection and fetal congenital defects. Recently published studies included an ongoing ecologic study of 104 infants with microcephaly during 2015 from 2 hospitals located in Pernambuco, Brazil.[14] Associated abnormalities included severe central nervous system defects, brain dysgenesis, and intracranial calcifications.

Other case studies included a Finnish woman who visited Mexico and Central America while pregnant and a Slovene woman who became pregnant while working in Bahia, Brazil.[15,16] Both became ill consistent with ZIKV infection during the first trimester. Both had normal ultrasonography during the early second trimester and both showed fetal anomalies in the late second or early third trimester to include intracranial calcifications and microcephaly. Both pregnancies were terminated.

A recently released, retrospective review of the 2013-2014 French Polynesia outbreak identified 19 cases of fetuses and newborns with cerebral malformations.[17] Eight of these had severe microcephaly. Seven total cases were tested for ZIKV and 4 of these tested positive; all 4 of the 5 microcephalic cases tested had microcephaly.

The most compelling evidence that points toward a link for causality between ZIKV and birth defects was published by a team from the Centers for Disease Control and Prevention (CDC).[18] In this analysis, the investigators applied Thomas Shepard's criteria for human teratogenicity[19] and also presented Austin Bradford Hill's criteria for evidence of causation.[20] Under both standards, evidence was presented for which the conditions were met to support that prenatal ZIKV exposure/infection causes birth defects (ie, microcephaly and other brain abnormalities). The authors concluded, "…that a causal relationship exists between prenatal Zika virus infection and microcephaly and other serious brain anomalies."

With increasing information about the disease, updated guidance is provided on the definitions for microcephaly[21] as well as the methods for detecting microcephaly.[22,23] Other serious outcomes discussed and considered include brain disruption sequence in fetuses and neonates leading to the collapse of the skull and further development of complications that affect hearing.[23,24]

GUILLAIN-BARRÉ SYNDROME AND OTHER NEUROLOGIC CONDITIONS

Along with adverse neurologic effects in fetuses and neonates, Guillain-Barré syndrome continues to be reported in additional case reports and study reviews,[25,26] thus strengthening this causal relationship with ZIKV. Other reports of neurologic conditions associated with ZIKV cases include a case review study in Recife, Brazil, describing another brain disease as acute disseminated encephalomyelitis[27] and another report of 2 cases of encephalopathy in Martinique.[28]

PATHOGENESIS

With the increased emphasis on neurologic effects in fetal development, neonates, and adults, additional studies have been published focusing on the microscopic and cellular level of ZIKV. Garcez et al released a study in which they used neural stem cells to form neurospheres and brain organoids.[29] When infected with ZIKV, cellular death occurred in the neural stem cells, and during the growth phase in which neural stem cells are stimulated to form neurospheres and brain organoids, ZIKV reduced their growth. The outcomes of this study showed that ZIKV targets human brain cells and suggested that it inhibits neurogenesis during cellular development.

Another study published by Nowakowski et al reviewed the entry receptor proteins expressed by cells through which the ZIKV would enter the cell.[30] The outcome of that study suggests that cells that express high levels or concentrations of the AXL receptor protein are susceptible to ZIKV infectivity. These include human radial glial cells, astrocytes, endothelial cells, and microglia in the developing human cortex as well as progenitor cells in the developing retina. The authors hypothesized that after the virus moves across the placental-fetal barrier and reaches the brain, it invades the developing neural cells, killing the cells or stunting their growth, thus producing microcephaly and other congenital defects.

SEXUAL TRANSMISSION

The mosquito vector continues to be the primary mode of transmission for the ZIKV. The CDC released an updated distribution map for *Aedes aegypti* and *A. albopictus* in the United States that expands the geographic range for mosquito transmission.[31] In areas of the world where intense vector-borne transmission is occurring, it is challenging to differentiate between mosquito-borne or sexual transmission. Thus, sexual transmission is primarily being identified and highlighted in countries or territories where autochthonous vector-borne transmission is not occurring.

New to sexual transmission is a reported case of male-to-male sexual transmission.[32] In this case, one male partner had visited Venezuela and returned to the United States where he had anal sex with the other male partner. Both patients developed fever, pruritic rash, and conjunctivitis. Other symptoms exhibited included myalgia, headache, lethargy, malaise, and small joint arthritis.

PREGNANCY COUNSELING AND TESTING

The CDC published an updated guidance article for providing preventive and protective guidance to women and men who desire to have children and for caring for women of reproductive age that may travel to or reside in areas with active ZIKV transmission or who have been exposed to ZIKV.[7] This article provides testing algorithms based on exposure and infection of pregnant women. It defines exposure as travel to or residence in an area with active ZIKV transmission or having had sex with an exposed partner.

Preconception Counseling

For women who do not reside in transmission areas, but have a possible exposure to ZIKV and become infected, the CDC recommends waiting at least 8 weeks after symptom onset to attempt conception. If a woman has been exposed but remains asymptomatic, the recommendation is the same: to wait 8 weeks after the exposure to attempt conception. Similarly, men who have been exposed but remain asymptomatic should be counseled to wait at least 8 weeks since exposure before attempting conception. Men who have been infected should be counseled to wait at least 6 months after

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symptom onset before attempting conception. Routine ZIKV testing is not currently recommended for men and women attempting conception who may have been exposed and remain asymptomatic.

Testing of Pregnant Women With Possible Exposure

If the ZIKV test result is positive or inconclusive, serial fetal ultrasounds are recommended to detect abnormalities. For pregnant women with a negative test result, if fetal ultrasound abnormalities are detected, the mother should be retested. If fetal abnormalities are not detected, routine prenatal care is recommended. Fetal ultrasound abnormalities include intracranial calcifications, microcephaly, or other brain abnormalities.

Testing of Pregnant Women Who Reside in ZIKV Transmission Areas

If the pregnant woman **reports clinical illness**, she should be tested for ZIKV. If the test result is positive or inconclusive, serial fetal ultrasounds are recommended. For women with a negative test result, if abnormalities are present on fetal ultrasound, the pregnant woman should be retested for ZIKV infection. If fetal abnormalities are not present, then routine prenatal care should continue. The mother should be retested during the second trimester and additional fetal ultrasounds should be considered as part of the care.

For pregnant women who reside in ZIKV transmission areas **and do not report clinical illness**, health care providers should test for ZIKV upon initiation of prenatal care. If the test result is positive or inconclusive, consider serial fetal ultrasounds to detect fetal abnormalities. If the ZIKV test result is negative, the pregnant woman should be tested again during the second trimester. Additionally, if fetal abnormalities are detected or if the follow-up ZIKV test result is positive or inconclusive, continue serial fetal ultrasounds. If the fetal ultrasounds do not show abnormalities and the ZIKV test result is negative in the pregnant woman, continue with routine prenatal care with additional fetal ultrasounds being considered. If any of the ultrasounds show fetal abnormalities, the pregnant woman should be retested for ZIKV infection.

LABORATORY TESTS

Commercially available laboratory tests are still not on the market. The FDA has provided an Emergency Use Authorization for the CDC Zika MAC-ELISA test[33] and the CDC, Focus Diagnostics, and altona Diagnostics real-time RT-PCR assay, test, and kit, respectively (Trioplex Real-time RT-PCR Assay,[34] Zika Virus RNA Qualitative Real-Time RT-PCR[35], and RealStar® Zika Virus RT-PCR Kit U.S.[36]). The real-time RT-PCR test is the preferred test for ZIKV detection and is generally performed on serum, cerebral spinal fluid, and urine.

On May 10, 2016, the CDC released interim guidance on testing urine for the detection of ZIKV using the Trioplex rRT-PCR assay.[2] Urine specimens should be tested in conjunction with serum specimens at less than 7 days after symptom onset and urine can be tested up to 14 days after symptom onset.

Another successful reported method of collecting blood in resource-limited settings is by using filter paper with dried blood spots.[22] This mode of collection can facilitate storage and shipping of the specimen to reference laboratories with testing capabilities.

Most recently, the FDA provided an investigative new drug clearance for the utilization of screening tests for screening blood donations in locations with active vector-borne transmission (ie, Puerto Rico).[37] The FDA and American Association of Blood Banks recommendations for blood donors have not changed and remain in place.[38-40]

ANTIBODY-DEPENDENT ENHANCEMENT

Many of the geographic areas where ZIKV is being transmitted are endemic for dengue virus and chikungunya virus. A recent study considered the effects of prior dengue virus infection immunity on the response to ZIKV infection.[41] Would prior infection with dengue virus antigenically overlap and be protective for ZIKV infection or would there be an antibody-dependent enhancement effect? The study compared the in vitro response of ZIKV to anti-dengue virus antibodies. The authors concluded that preexisting immunity to dengue virus will increase or enhance the in vivo severity of ZIKV infection. Additional studies will need to be performed to determine any specific caveats to individual antibody-dependent enhancement of ZIKV infection.

RESERVOIRS

Other arboviral diseases have a sylvatic transmission cycle where the virus is transmitted between the arthropod vector and a vertebrate animal reservoir in the wild and a corresponding urban/suburban mosquito to human biological transmission cycle.[23] For ZIKV, nonhuman primates are suspected of being the sylvatic reservoir host in Africa and Asia[22]; however, more needs to be studied on the subject.

A March 2016 report from Ecuador identified ZIKV in a howler monkey from a group of monkeys that had mysteriously and acutely died.[42] No other causes of mortality had been reported at the time of the report. Then an April 2016 article described the identification of ZIKV in Neotropical primates: in marmosets (4/15; 27%) and capuchin monkeys (3/9; 33%) from Northeast Brazil.[43] The marmosets were free-ranging or cohabiting with humans and the capuchins were pets. The authors proposed that this is the first evidence in the Western Hemisphere of a sylvatic reservoir similar to the yellow fever sylvatic cycle.

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CONCLUSION

New and recently published information about ZIKV creates a more complete picture of the agent–host–environment interaction of the disease. The reports of virus recovery from New World primates supports the epidemiology of other similar arboviruses (ie, yellow fever) with sylvatic and urban transmission cycles. Understanding the nature of the virus to gravitate to, enter, and negatively impact neural cells reinforces and strengthens the connection of the virus with Guillain-Barré syndrome, microcephaly, and other neurologic disease conditions. Finally, these disease elements combined with understanding the modes of transmission (ie, sexually) informs the preventive and clinical counseling, testing, and recommendations at the patient level. It is expected that ZIKV will continue to spread and become endemic in the Western Hemisphere and other locations throughout the world. An increased understanding of adverse fetal/neonatal outcomes has placed ZIKV into a different disease category that will continue to influence future public health decisions.

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