

Zika Virus: A Global Threat

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ABSTRACT

Zika virus is an enveloped, non-segmented, icosahedral single-stranded, negative-sense RNA virus. It belongs to the Flaviviridae and was first isolated in 1947 from a monkey in the Zika forest, Uganda, then in mosquitoes (*Aedes africanus*) in the same forest in 1948 and in a human in Nigeria in 1952. Before 2007, viral circulation and a few outbreaks were documented in tropical Africa and in some areas in Southeast Asia. In 2015, Zika viral disease outbreaks were reported in Brazil of South America for the first time and it is now considered as an emerging infectious disease. This ongoing outbreak of Zika virus that began in Brazil has spread to much of South and Central America (except Canada and Chile) and the Caribbean. According to the CDC, Brazilian health authorities reported more than 404 cases of microcephaly between October 2015 and January 2016. Seventeen of those cases have a confirmed link to the Zika virus. Its natural reservoir is yet to be unknown. Transmission mainly by mosquito *Aedes aegypti* but it can be transmitted from human to human by blood transfusion, saliva, urine and sexual contact. Most dangerous transmission is mother to fetus through placenta. Its actual pathogenesis is not clear but the pathogenesis of the virus is hypothesized to start with an infection of dendritic cells near the site of inoculation, followed by a spread to lymph nodes and the bloodstream. Other than congenital malformation (microcephaly) disease symptoms are usually mild and short-lasting self-limiting febrile illness of 4-7 days duration without severe complications. No commercial diagnostic method against Zika virus are available. The virus constitutes an important public health threat in America and also worldwide as no effective treatment or vaccine is available till now. The World Health Organization (WHO) has declared the microcephaly condition, linked to the mosquito-borne virus, a global public health emergency.

Key Words: Zika virus, microcephaly, *Aedes aegypti*, global threat

Introduction

Zika virus is the causative agent of the ongoing epidemic in America¹. Zika virus disease is an emerging disease caused by a virus from the Flaviviridae family and *Aedes* mosquitoes are considered as main vectors. There are two Zika viral lineages: the African lineage and the Asian lineage which has recently emerged in the Pacific and the Americas². Before 2007, viral circulation and a few outbreaks were documented in tropical Africa and in some areas in Southeast Asia. Since 2007, several islands of the Pacific region have experienced outbreaks. In 2015, Zika viral disease

outbreaks were reported in Brazil of South America for the first time and it is now considered as an emerging infectious disease³. A significant increase of patients with Guillain-Barré syndrome (GBS) was reported during the 2014 outbreak in French Polynesia. A similar increase along with an unusual increase of congenital microcephaly was observed in some regions in north eastern Brazil in 2015. Causal relationships are currently under investigation⁴. Though Zika infections are generally confined to America, there is always a risk of spreading to the rest of the world and at present there is no

prophylaxis, treatment or vaccine to protect against infection³. Therefore, preventive personal measures are recommended to avoid mosquito bites during the daytime⁵.

History and Geographical Distribution

Zika virus was first isolated in 1947 from a monkey in the Zika forest, Uganda, then in mosquitoes (*Aedes africanus*) in the same forest in 1948, and in a human in Nigeria in 1952⁵. Serological surveys in Africa and Asia indicate a most likely silent Zika viral circulation with detection of specific antibodies in various animal species (large mammals such as orangutans, zebra, elephants, water buffaloes) and rodents². The knowledge of geographical distribution of Zika virus is based on results of sero-surveys, viral isolation in mosquitoes and humans, reports of travel-associated cases and very few published outbreaks. Before 2007, the areas with reported Zika viral circulation included tropical Africa and Southeast Asia⁴.

The first outbreak outside of Africa and Asia occurred on the island of Yap in the Federated States of Micronesia in 2007, characterized by rash, conjunctivitis, and arthralgia, which was initially thought to be dengue, Chikungunya, or Ross River disease⁶. However, serum samples from patients in the acute phase of illness contained RNA of Zika virus. There were 49 confirmed cases, 59 unconfirmed cases, no hospitalizations, and no deaths⁷. Between 2013 and 2015, several significant outbreaks were notified on islands and archipelagos from the Pacific region including a large outbreak in French Polynesia. In 2015, Zika virus emerged in South America with widespread outbreaks reported in Brazil and Columbia³.

Recent situation

Since April 2015, a large, ongoing outbreak of Zika virus that began in Brazil has spread too much of South and Central America (except Canada and Chile) and the Caribbean. In January 2016, the CDC issued a level 2 travel alert for people traveling to regions and certain countries where Zika virus transmission is ongoing⁸. The agency also suggested that women thinking about becoming pregnant should consult with their physicians before traveling⁹. Governments or health agencies of the

United Kingdom, Ireland, New Zealand, Canada and the European Union soon issued similar travel warnings¹⁰. In Colombia, Minister of Health and Social Protection Alejandro Gaviria Uribe recommended to avoid pregnancy for eight months, while the countries of Ecuador, El Salvador, and Jamaica have issued similar warnings^{11,12}. Plans were announced by the authorities in Rio de Janeiro, Brazil, to try to prevent the spread of the Zika virus during the 2016 Summer Olympic Games in that city¹². According to the CDC, Brazilian health authorities reported more than 404 confirmed cases of microcephaly between October 2015 and January 2016. Seventeen of those cases have a confirmed link to the Zika virus by real time PCR in the laboratory. Fifteen babies have died from the condition, with five linked to Zika. An additional 56 deaths are under investigation. Even one-third babies with a birth defect linked to the Zika virus also display eye abnormalities that could affect their vision. The World Health Organization (WHO) has declared the microcephaly condition, linked to the mosquito-borne virus, a global public health emergency¹³.

The full spectrum of outcomes that might be associated with infection during pregnancy and the factors that might increase risk to the fetus are not yet fully understood. More studies are planned to learn more about the risks of Zika virus infection during pregnancy¹⁴. In the worst affected region of Brazil approximately 1 percent of newborns are suspected of microcephaly¹⁵. On 4 February 2016, Spain has confirmed that a pregnant woman has been diagnosed with the Zika virus in her 28 weeks of pregnancy- the first such case in Europe. Ultrasonography has been done on in next week of this women, showed different fetal abnormalities with microcephaly. The health ministry said the woman had recently returned from Colombia, where it is believed she was infected¹⁶. Recently the Health department of Australia has confirmed two cases of Zika virus in Australia from passengers travelling from the Caribbean back to Sydney¹⁷. In Indonesia, the Eijkman Institute for Molecular Biology said, one Zika virus positive case is found from 103 dengue negative specimen who has no travelling history in Zika affected countries¹⁸.

Zika virus and Bangladesh

Although Zika virus is not found in Bangladesh and neighboring countries but many sporadic cases of microcephaly are found during deliveries which are maximum under-reported. Even many cases of fever with maculopapular rash in outdoor department at tertiary level hospital but we do the tests against dengue only. It may be caused by Zika virus. It is almost alarming for us because the vector *Aedes* mosquito are available in Bangladesh and it is also responsible for spreading dengue fever throughout the Indian sub-continent region, especially in Bangladesh¹⁹. So, though it is spreading throughout the Americas recently, it could reach Bangladesh anytime. Concerns have grown even stronger in Bangladesh after news media in Thailand and Taiwan this week reported cases of the virus infection among locals. Both places are popular destinations for Bangladeshi travelers, increasing the risk of the virus also spreading here²⁰. However, very recently the director of IEDCR (Institute of Epidemiology, Disease Control and Research) told the daily star, risk of zika virus infection in Bangladesh is low because this virus spread through *Aedes* mosquito and the mosquito's peak reproduction time here is during the rainy season, not now²⁰.

Virology

Along with other viruses in Flavivirus family, Zika virus is enveloped and icosahedral with a non segmented, single stranded, positive-sense RNA genome^{1,1}. The pathogenesis of the virus is hypothesized to start with an infection of dendritic cells near the site of inoculation, followed by a spread to lymph nodes and the bloodstream²¹. Flaviviruses generally replicate in the cytoplasm, but Zika virus antigens have been found in infected cell nuclei²². Recent preliminary findings from sequences in the public domain uncovered a possible change in nonstructural protein 1 codon usage that may increase the viral replication rate in humans²³.

Transmission

Zika virus is transmitted by daytime-active mosquitoes and has been isolated from a number of species in the genus *Aedes*, such as *A. aegypti*, and arboreal mosquitoes such as *A. africanus*, *A. apicoargenteus*, *A. furcifer*, *A. hensilli*, *A.*

luteocephalus, and *A. vitattus*. Studies show that the extrinsic incubation period in mosquitoes is about 10 days². The vertebrate hosts of the virus are primarily monkeys and humans. Various reports have proved that Zika virus can be transmitted by sexually, blood transfusion and even through breast milk²⁴. In 2015, Zika virus RNA was detected in the amniotic fluid of two fetuses, indicating that it had crossed the placenta and could cause a mother-to-child infection²⁵. On 20 January 2016, scientists from the state of Paraná, Brazil, detected genetic material of Zika virus in the placenta of a woman who had undergone an abortion due to the fetus's microcephaly, which confirmed that the virus is able to pass the placenta²⁶. Very recently one case in Dallas, Texas has been confirmed that Zika virus can be transmitted by sexual contact and The CDC advises men with a pregnant partner to use condoms if they have traveled to an area with active Zika virus transmission. During February 6-22, 2016, two confirmed and four probable cases of Zika virus sexual transmission were reported to CDC by health officials from multiple states. Median patient age was 22.5 years (range = 19-55 years), and several women were pregnant. All cases occurred when the male partner was symptomatic or shortly after symptoms resolved, but further query will be needed that how long Zika virus persist in semen^{27,28}. A Brazilian public health institute said active Zika virus has been detected in saliva and urine. The finding poses new questions for researchers trying to understand how the virus could spread²⁹.

Reservoir

Zika virus is a mosquito-borne Flavivirus closely related to dengue virus. While mosquitoes are the vector, the reservoir species remains unknown, though serological evidence has been found in West African monkeys and rodents^{2,30}.

Clinical Feature and Sequelae

The incubation period ranges between approximately three to 12 days after the bite of an infected mosquito. Most of the infections remain asymptomatic (between 60 to 80%). Disease symptoms are usually mild and the disease is usually characterized by a short-lasting self-limiting febrile illness of 4-7 days duration without severe

complications, with no associated fatalities and a low hospitalization rate. The main symptoms are macular-papular rash, fever, arthralgia, non-purulent conjunctivitis/conjunctival hyperaemia, myalgia and headache. The rash often starts on the face and then spreads throughout the body. Less frequently, retro-orbital pain and gastro-intestinal signs are present².

In a French Polynesian epidemic, 73 cases of Guillain- Barré syndrome (GBS) and other neurologic conditions occurred in a population of 270,000, which may be complications of Zika virus³¹. In December 2015, the European Centre for Disease Prevention and Control issued a comprehensive update on the possible association of Zika virus with congenital microcephaly and GBS^{31,32}. However, further evidence is needed to establish a causal link between these neurological/neuro developmental impairments and infections with Zika virus³¹.

Diagnosis

It is difficult to diagnose Zika virus infection based on clinical signs and symptoms alone due to overlaps with other arboviruses that are endemic to similar areas³¹. Zika virus can be identified by RT-PCR in acutely ill patients. However, the period of viremia can be short and the World Health Organization recommends RT-PCR testing be done on serum collected within 1 to 3 days of symptom onset or on saliva or urine samples collected during the first 3 to 5 days³⁰. Later on, serology through detection of specific IgM and IgG antibodies can be used. IgM can be detectable within 3 days of the onset of illness². Serological cross-reactions can occur with closely related flaviviruses such as dengue virus^{2,33}. Commercial assays for Zika diagnosis are not yet available³¹. The US Centers for Disease Control and Prevention advises that the differential diagnosis of suspected Zika virus infection is broad and includes, in addition to dengue and other viruses of this family³⁰.

Treatment

There is currently no specific treatment for Zika virus infection. Care is supportive with treatment of pain, fever and other symptom³¹. Some authorities

have recommended against using aspirin and other NSAIDs as these have been associated with hemorrhagic syndrome when used for other flaviviruses³².

Zika virus had been relatively little studied until the major outbreak in 2015, and no specific antiviral treatments are available as yet. Advice to pregnant women is to avoid any risk of infection so far as possible, as once infected there is little that can be done beyond supportive treatment. One in vitro study found that Zika virus may be sensitive to interferon treatment, which is commonly used against other viral infections; however these results have not been tested in animals or humans³⁴.

How to Treat Pregnant Women with Diagnoses of Zika Virus Disease

No specific antiviral treatment is available for Zika virus disease. Treatment is generally supportive and can include rest, fluids, and use of analgesics and antipyretics³⁵. Fever should be treated with acetaminophen³⁰. Although aspirin and other non-steroidal anti-inflammatory drugs are not typically used in pregnancy, these medications should specifically be avoided until dengue can be ruled out to reduce the risk for hemorrhage³⁵. In a pregnant woman with laboratory evidence of Zika virus in serum or amniotic fluid, serial ultrasounds should be considered to monitor fetal anatomy and growth every 3-4 weeks. Referral to a maternal-fetal medicine or infectious disease specialist with expertise in pregnancy management is recommended³⁶.

Prevention and Control

There is currently no vaccine, but development is a priority of the National Institutes of Health^{31,32}. The virus is spread by mosquitoes, making vector control and avoidance an essential element to disease control. The US Centers for Disease Control recommends some preventive measures: exposed skin should be covered by long-sleeved shirts and long pants, insect repellent should be used, permethrin-treated clothing and gear should be used (such as boots, pants, socks, and tents) and air-conditioned rooms should be required for stay and sleep³¹.

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Zika and Microcephaly

Data suggests that newborn babies of mothers who had a Zika virus infection during the first trimester of pregnancy are at an increased risk of microcephaly³⁷. In December 2015 it was suspected that a trans-placental infection of the fetus may lead to microcephaly and brain damage^{38,39}. The Brazilian Ministry of Health has confirmed the relation between the Zika virus and microcephaly³⁹. Pan American Health Organization (PAHO) reported the identification of Zika virus RNA by reverse transcription-polymerase chain reaction (RT-PCR) in amniotic fluid samples from two pregnant women whose fetuses were found to have microcephaly by prenatal ultrasound, and the identification of Zika virus RNA from multiple body tissues, including the brain, of an infant with microcephaly who died in the immediate neonatal period⁴⁰. Very recently one of the most senior public health officials has also revealed the strongest evidence of mother to fetus transmission of Zika virus. A cohort study was done for evaluation of association between Zika virus and microcephaly, total 37 infants with microcephaly were found, only 35 cases are included in this report. Two infants with microcephaly were excluded from the original cohort of 37 babies: one had autosomal recessive microcephaly and one had cytomegalovirus infection. Overall, 26 (74%) mothers of infants with microcephaly reported a rash during the first (n = 21) or second (5) trimester or residence in or travel during pregnancy to areas where Zika virus is circulating was confirmed for all mothers, including women without a history of rash^{40,41}.

January 2016 CDC travel alert

Because of the "growing evidence of a link between Zika and microcephaly" the Centers for Disease Control and Prevention (CDC) issued a travel alert on 15 January 2016 advising pregnant women to consider postponing travel to the following countries and territories: Brazil, Colombia, El Salvador, French Guiana, Guatemala, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Suriname,

Venezuela, and the Commonwealth of Puerto Rico⁹. The agency also suggested that women thinking about becoming pregnant should consult with their physicians before traveling^{9,42}.

Recommendations for Pregnant Women with History of Travel to an Area of Zika Virus Transmission

Health care providers should ask all pregnant women about recent travel. Women who traveled to an area with ongoing Zika virus transmission during pregnancy should be evaluated for Zika virus infection and tested in accordance with CDC Guidance³⁷.

Zika virus testing of maternal serum includes reverse transcription-polymerase chain reaction (RT-PCR) testing for symptomatic patients with onset of symptoms within the previous week. Immunoglobulin M (IgM) testing should be performed on specimens collected ≥ 74 days after onset of symptoms³⁷. Zika virus RT-PCR testing can be performed on amniotic fluid⁴³. Currently, it is unknown how sensitive or specific this test is for congenital infection. Also, it is unknown if a positive result is predictive of a subsequent fetal abnormality. However, amniocentesis is associated with an overall 0.1% risk of pregnancy loss when performed at less than 24 weeks of gestation⁴⁴. For a live birth with evidence of maternal or fetal Zika virus infection, the following tests are recommended: histopathologic examination of the placenta and umbilical cord; testing of frozen placental tissue and cord tissue for Zika virus RNA; and testing of cord blood for Zika⁴⁵.

January 2016 WHO recommendation

On 17 January 2016 the Pan American Health Organization (PAHO), the regional office of the United Nations' World Health Organization, considering the increased number of cases of congenital anomalies, Guillain-Barré syndrome and other neurological or autoimmune syndromes in Zika-affected areas, recommended that its member states "establish and maintain the capacity to detect and confirm Zika virus cases, prepare healthcare facilities to respond to a possible increase demand of specialized care for neurological syndromes, as well to strengthen antenatal care"⁴⁶.

Conclusion

The main goal currently being addressed with Zika virus is finding ways of treatment and effective vaccines that can be applied to humans especially pregnant women. Although Zika virus infection is not a problem right now for most populations outside America, it has the potential to be alarming from the point of view in global health in the future.

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