



Epidemiology, Diagnosis and Preventive Measures of Zika Virus Infection: A Review Update

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Abstract

The relation between ZIKV infection during pregnancy and microcephaly in neonate has been established by the Brazilian Ministry of Health. Therefore, more attention regarding control of *Aedes* mosquito is required. Since it transmits this disease, which has more disastrous consequences than dengue viral infection. Potentially effective methods of prevention that are focused on reducing infections among pregnant women include avoiding unnecessary travel to areas of ongoing Zika virus transmission, avoiding unprotected sexual contact with partners who are at risk for Zika virus infection. According to Institute of Epidemiology Disease Control and Research (IEDCR) there is nothing to panic at this moment for Bangladesh, but they stressed on mosquito control, which is the only tool to prevent and fight off Zika virus. They however, could not mention how the virus came to Bangladesh. May be somebody brought it while travelling. There is good surveillance and testing system to detect the disease in Bangladesh. [Bangladesh Journal of Infectious Diseases 2016;3(1):17-23]

Keywords: ZIKV infection; Zika virus; microcephaly; congenital anomaly; *Aedes* mosquito; pregnancy

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1.0. Introduction

The Zika virus was first isolated from a Rhesus monkey in Zika forest of Uganda in April 1947¹. The name of the virus comes from this Zika

forest². A second isolation was from the mosquito *A. africanus* in 1948³. Human illness caused by Zika virus was first recognized in Nigeria in 1953⁴. From its discovery until 2007, there were only 14 confirmed human cases of Zika infection from

Africa and Southeast Asia⁵. The first outbreak of Zika virus was reported from the Island of Yap, Federated States of Micronesia in April 2007⁶. Further epidemics occurred in French Polynesia, Easter Island, Cook Islands, and New Caledonia Between 2013 and 2014⁷. The outbreak began in April 2015 in Brazil, and has spread to other countries in South America, Central America, Mexico, and other Caribbean⁸. It became the first major infectious disease linked to human birth defects and created such global alarm that in February 2016, the World Health Organization (WHO) would declare A Public Health Emergency of International Concern⁹. This review describes the current understanding of the epidemiology, transmission, clinical characteristics, diagnosis and prevention of Zika virus.

2.0. Virology

The ZIKV is a mosquito-borne flavivirus and is thus related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses. Like other flaviviruses, Zika virus is enveloped and icosahedral and has a nonsegmented, single-stranded, positive-sense RNA genome¹⁰⁻¹². There are two lineages of Zika which are the African lineage and the Asian lineage¹³.

3.0. Epidemiology

3.1. Virus Isolation in Monkey and Mosquitoes: The virus was first isolated in April 1947 from a rhesus macaque monkey that had been placed in a cage in the Zika Forest of Uganda, by the scientists of the Yellow Fever Research Institute¹. A second isolation from the mosquito *A. africanus* followed at the same site in January 1948³.

3.2. First Evidence of Human Infection: Human illness caused by Zika virus was first recognized in Nigeria in 1953, when viral infection was confirmed in three ill persons⁴.

3.3. Spread of Virus: From 1953 through 1983, evidence of human infection with Zika was reported from other African countries, as well as in parts of Asia including India, Indonesia, Malaysia, Philippines, Thailand, Vietnam and Pakistan. The first outbreak of disease caused by Zika infection was reported from the island of Yap (Federated States of Micronesia) in April 2007, resulted in an estimated 5000 infections among the total population of 6700⁶. Subsequently, between 2013 and 2014, further epidemics occurred in French

Polynesia, Easter Island (2014), Cook Islands (2014), and New Caledonia (in 2014). It is estimated to have involved 32,000 persons who underwent evaluation for suspected Zika virus infection although most of the illness appeared similar to those seen in Yap¹². Zika virus was first identified in the Americas in March 2015 in Bahia, Brazil. The outbreak then began to spread to other countries in South America, Mexico, and Caribbean¹⁴. In December 2015, the Brazil Ministry of Health estimated that up to 1.3 million suspected cases had occurred¹⁵. In October 2015, Colombia reported the first autochthonous (local) transmission of Zika virus outside Brazil¹⁶ and by March 3, 2016, a total of 51,473 suspected cases of Zika virus had been reported in that country¹⁷. By March 2016, the virus had spread to at least 33 countries and territories in the Americas^{15,17}. According to WHO report between 1 January 2007 and 25 February 2016, a total of 52 countries and territories have reported autochthonous transmission of Zika virus and from 1 October 2015 to 13 February 2016 Colombia reported 37011 cases including 1612 laboratory confirmed of Zika infection.

4.0. Bangladesh Situation

On 22 March 2016 Reuters reported that Zika was isolated from blood sample of an elderly 67 years man in Chittagong as a part of retrospective study done in Institute of Epidemiology, Disease control and Research (IEDCR), Dhaka Bangladesh¹⁸. After WHO's emergency call on Zika virus, the government in February decided to test again old samples stored at IEDCR that had earlier tested negative for dengue and chikungunya virus. IEDCR had tested 101 samples randomly selected from 1070 samples they had earlier collected from their surveillance sites—two Dhaka, one Khulna and the other in Chittagong. According to GULF NEWS, BANGLADESH (June 16,2016), IEDCR authorities test blood samples from a further 159 people who were neighbours or had close contact with the patient, and find no sign of virus.

5.0. Transmission

5.1. Mosquito-borne Transmission: In urban and suburban environment, Zika virus is transmitted in human-mosquito-human transmission¹⁹. The virus has also been isolated from a number of arboreal mosquito species in the *Aedes* genus, such as *A. africanus*, *A. apicoargenteus*, *A. furcifer*, *A. hensilli*, *A. luteocephalus* and *A. vittatus*²⁰.

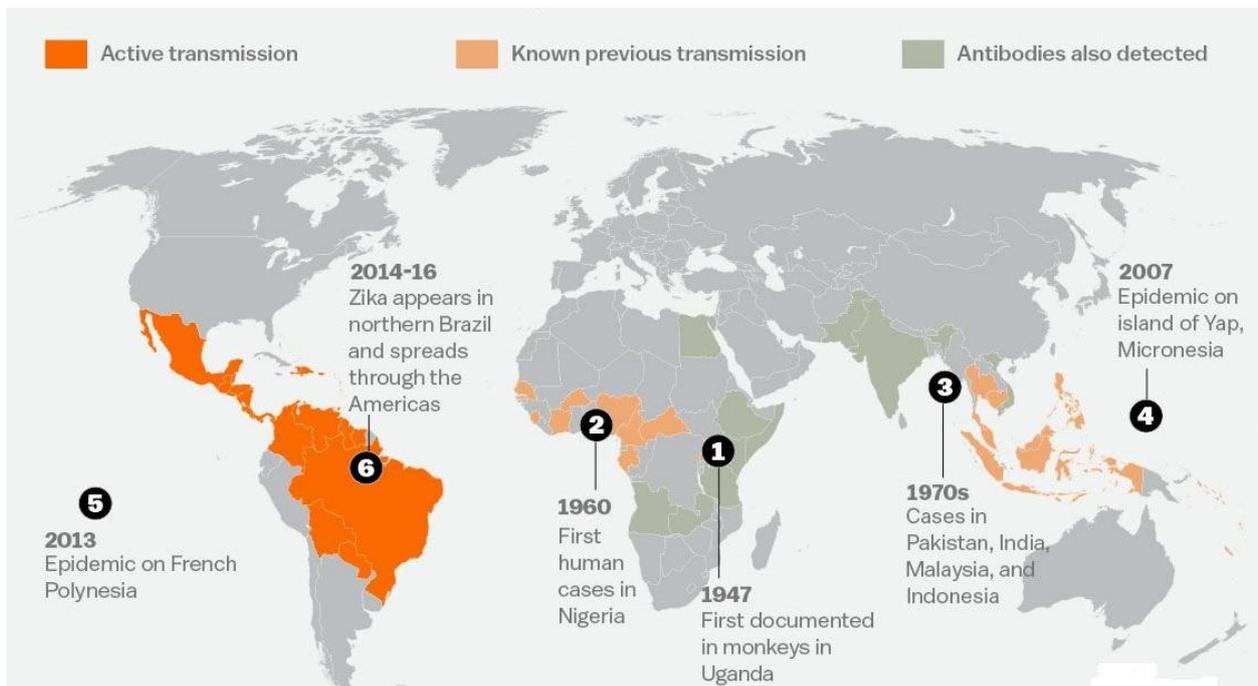


Figure I: Spread of Zika Virus in Globe (WHO & Lancaster University, February 1, 2015)

5.2. Sexual Transmission: Zikavirus can be transmitted from a human to his sex partners²¹. Sexual transmission of Zika has been documented in six countries—Argentina, Chile, France, Italy, New Zealand and United States during the 2015 outbreak¹⁷.

5.3. Vertical transmission: The Zika virus can spread from an infected mother to her fetus during pregnancy or at the time of delivery²². Transmission through breast milk has not been documented, although the breast milk of a woman contained infective Zika viral particles in high titer who became symptomatic with Zika virus infection on the day of delivery²³.

5.4. Through blood transfusion: As of April 2016, two cases of Zika transmission through blood transfusions have been reported from Brazil and French Polynesia²⁴.

6.0. Pathogenesis

Zika replicates in the mosquito’s midgut epithelial cells and then in salivary gland cells. After 5-10 days, ZIKV can be found in the mosquito’s saliva, which can then infect humans. If the mosquito’s saliva is inoculated into human skin, the virus can infect epidermal keratinocytes, skin fibroblasts in the skin and Langerhans cells¹⁰.

7.0. Clinical Features

7.1. Asymptomatic: It is estimated that 80% of Zika virus infections occur without symptoms²⁵.

7.2. Acute Febrile Illness: Zika fever (also known as Zika virus disease) is an illness caused

by the Zika virus. Most cases have no symptoms, but when present they are usually mild and can resemble dengue fever. Symptoms may include fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache²⁶. Symptoms generally last less than 7 days²⁷.

8.0. Neurologic Complications

Infections due to Zika virus in adult has been linked to Guillian-Barre syndrome²⁸. In July 2015 scientists in Brazil reported an association between Zika virus infection and Guillian-Barre syndrome. Besides, Zika virus infection can affect the central nervous system. There are reports of 20 fold increase in the incidence of Guillian-Barre syndrome in Micronesia and Polynesia during the outbreak of ZIKV²⁹. According to WHO report during 2015 and 2016, eight countries and territories have reported an increased incidence of Guillian –Barre syndrome and /or laboratory confirmation of Zika virus.

9.0. Adverse Fetal Outcomes

Microcephaly: By September 2015, investigators in Brazil noted an increase in the number of infants born with micrephaly in the same areas in which Zika virus was first reported³⁰. In November of 2015, the Ministry of Health (MOH) of Brazil issued a bulletin confirming the relationship between Zika virus infection and the microcephaly outbreak in the northeastern region³¹. Center for Disease Control and

Prevention (CDC), USA guidance has recommended that microcephaly be defined as an occipitofrontal circumference below the third percentile for gestational age and sex³². According to information reported by Brazilian live births information system (SINASC), from 2010 to 2014 there were around 150 cases reported per year in the country, and currently, suspected cases totaled 4783³³.

10.0. Laboratory Diagnosis

Infection with Zika virus may be suspected based on symptoms and recent history of travel (e.g. residence in or travel to an area with active Zika virus transmission). A diagnosis of Zika virus infection can only be confirmed through laboratory tests on blood or other body fluids such as urine, saliva or semen²⁸. Current testing recommendation as of March 11, 2016, there are two testing methods available for detection of Zika virus³⁴:

10.1. Detection of Zika virus genetic material by RT-PCR: The detection of viral nucleic acid in sample provides a definitive diagnosis. However, in most instance viremia is transient, and diagnosis by RT-PCR has been most successful within 1 week after the onset of clinical illness. The major limitation of this test is the short duration after the start of Zika virus associated illness during which it is positive.

10.2. Detection of antibodies against Zika virus (serology): This test looks for the human body's reaction against the virus in the form of antibodies. IgM antibodies can be detected by ELISA or immunofluorescence assays in serum specimens from day five after the onset of symptoms. However, there are no commercial kits for serological diagnosis of ZIKV³¹. The major advantage of a serology test is that it remains positive for several months or longer after infection. The major limitations are that it is slow to perform and prone to cross-react with other viruses related to Zika virus. A positive result may, in fact, represent a previous exposure to another virus or past vaccination (e.g. to Yellow fever). This makes the result difficult to interpret. Reliable testing regimens for the diagnosis of prenatal and antenatal Zika virus infection have not been established. Amniotic fluid has tested positive by RT-PCR in instance of congenital Zika virus infection. However, the sensitivity of RT-PCR in this context is unknown^{35,36}. At the time of delivery, cord blood can be tested by RT-PCR and MAC-ELISA, but the sensitivities of these tests for detecting prenatal Zika virus

infection are unknown. RT-PCR and immunohistochemical testing have been useful in establishing Zika virus infection in tissues of fetal losses and full-term infants who died shortly after birth³⁶.

11.0. Treatment

Treatment for uncomplicated Zika virus infection focuses on symptoms. As with the other mosquito-borne flaviviruses, Zika virus disease is usually mild and requires no specific treatment. People sick with Zika virus should get plenty of rest, drink enough fluids, and treat pain and fever with common medicines. If symptoms worsen, they should seek medical care and advice²⁸.

12.0. Prevention

As no vaccine exists against Zika virus, following prevention and control measures can be taken³² like avoiding mosquito bites, reducing sexual transmission and controlling the mosquito vector. Potentially effective methods of prevention that are focused on reducing infections among pregnant women include i) avoiding unnecessary travel to areas of ongoing Zika virus transmission, ii) avoiding unprotected sexual contact with partners who are at risk for Zika virus infection, iii) and using mosquito repellent treatment for clothing, bed nets, window screens and air conditioning. To reduce the risk of sexual transmission and potential pregnancy complications related to Zika virus infection, the sexual partners of pregnant women, living or returning from areas where local transmission of Zika virus occurs should practice safer sex (including using condoms) or abstain from sex at least 8 weeks after their return, even if they don't have symptoms. If men experience Zika virus symptoms they should adopt safer sexual practices or consider abstinence for at least 6 months.

12.1. Vaccine development

The NIH Vaccine Research Center (U.S) began work towards developing a vaccine for Zika virus per January 2016 report³⁷. In early February 2016, Bharat Biotech International (India) reported, that it was working on vaccines for Zika. They are using two approaches: 1) "recombinant", involving genetic engineering and 2) "inactivated", where the virus is incapable of reproducing itself but can still trigger an immune response^{38,39}. As of March 2016, 18 companies

and institutions were developing vaccines against Zika, but none had yet reached clinical trials⁴⁰.

13.0. Public Health Emergency

Public health emergency committee of WHO declares Zika virus is a global public health emergency⁹. As many as 1.3 million persons have been affected in Brazil alone and 55 countries or territories have been reported local transmission of the virus during 2016. Because of the ease of air travel and international trade, further spread into regions where the virus is not endemic is likely, and transmission is probable in locations with competent mosquito vectors. In January 2016, the United States Centers for Disease Control and Prevention (CDC) issued travel guidance on affected countries, including the use of enhanced precautions, and guidelines for pregnant women including considering postponing travel⁴¹. A robust, multifaceted response is underway that involves public health authorities, government agencies, the biomedical industry, medical practitioners, and researchers. Preventive measures specially vector control are a current priority. The relation between ZIKV infection during pregnancy and microcephaly in neonates is established. Pregnant woman should be concerned about exposure to endemic areas, and if possible, avoid remaining in such locations. The MOH of Brazil endorses instructing fertile women, who wish to have a child, about current situation of microcephaly⁴². A group of Scientist working with lab-grown cells may have found a clue to how the Zika virus could cause abnormally small heads in the children of woman who contract virus early in pregnancy. During early pregnancy, stem cells divide rapidly and travel to various areas, building the architecture of a healthy brain. The researcher hypothesis is that the virus invades some of these cells, killing some and preventing others from dividing. This impairs the construction of the cortex. This disruption in the building plan leaves the brain malformed and under developed. An underdeveloped brain leads to a smaller than normal head⁴³. It is important for healthcare professionals to inform the population in general about the disease. Moreover, it is particularly important to make an early diagnosis of microcephaly and recognize possible brain dysfunctions to guide the patient to a health care unit that can implement early brain stimulation measures. It is known that the brain of microcephalic patients is proportionally smaller, thus about 90% of the cases are associated with some degree of intellectual disability³¹. Therefore any suspected case of microcephaly caused by

ZIKV should be immediately notified to health authorities.

14.0. Travelers and Zika Virus treat

Travelers with active symptoms persist less than 10 days, before seeking medical attention, the best test is Zika virus PCR, although serology may also be performed on the precise timing of symptoms. Pregnant travellers with history of active symptoms compatible with Zika virus that started more than 10 days ago, the Zika virus PCR will likely to be negative. Serology for Zika virus would be the most appropriate test with this condition. At this time, based on our existing knowledge, pregnant women who developed active symptoms of Zika virus are expected to be most at risk for impact on their fetus. As a result, test should be offered and consideration to be given to consult with an infectious diseases specialist or maternal-fetal medicine specialist. For all asymptomatic travellers, routine testing is not recommended because interpreting the meaning of a negative Zika virus test is difficult. For example, depending on the timing of the test, antibodies may not yet have developed in the traveller, making the test result false negative. The use of barrier methods (such as condoms) for 6 months to prevent potential Zika virus transmission following return from travel is currently the safest approach. For pregnant travellers with a history of travel to an area at risk for Zika virus but with no history of symptoms, this scenario is the most difficult to navigate in terms of testing. It is estimated that approximately 75-80% of individual who are infected by the Zika virus never develop symptoms. However, the degree of risk to the fetus following asymptomatic infection in the pregnancy is still unknown³⁴. As of April 2016, two cases of Zika transmission through blood transfusions have been reported from Brazil and French Polynesia²⁴. A potential risk had been suspected based on a blood donor screening study during the French Polynesia Zika outbreak, in which 2.8% of donors from November 2013 and February 2014 tested positive for Zika RNA and were all asymptomatic at the time of blood donation⁴⁴. Blood safety authorities need to be vigilant and should consider deferral of blood donors returning from areas with an outbreak of Zika virus. In areas endemic for *Aedes* species, a preparedness plan to respond to future outbreaks of Zika virus infection should include emergency plans to sustain blood supply. The most effective plan to combat this outbreak of microcephaly is prevention. The most effective *A. aegypti* mosquito vector control relies on an

integrated approach that involves elimination of mosquito breeding sites, application of larvicides and application of insecticide to kill adult mosquitoes. However, each of these approaches has substantial limitations. Communities are mobilized to reduce *A. aegypti* breeding sites.

15.0. Conclusion

The underlying reasons for the emergence of Zika virus in the past decade are unknown. Recent global increases in the incidence and spread of dengue, chikungunya and now Zika virus—all with *A. aegypti* as the primary vector—suggest common underlying mechanisms for their emergence, such as globalization and urbanization. Other possible explanations include viral mutations affecting transmission or virulence and viral introduction to previously unexposed populations leading to epidemic spread. Further research will be required to determine whether the recently observed associations with adverse birth outcomes and Guillain-Barre syndrome simply affect an increased incidence of infection or whether they result from a change in viral virulence.

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