Janaki Medical College Journal of Medical Sciences (2023); Vol.11 (3):72-79

JMCJMS

Review Article

Zika Virus Infection: An Emerging global Public Health Concern

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ABSTRACT

Zika virus disease is caused by a virus transmitted primarily by day biting *Aedes* mosquitoes. Symptoms are generally mild and include fever, rash, conjunctivitis, muscle and joint pain, malaise or headache, and last for two to seven days. Most people with Zika virus infection do not develop symptoms. Zika virus infection during pregnancy can cause infants to be born with microcephaly and other congenital malformations, known as congenital Zika syndrome, and other complications of pregnancy including preterm birth and miscarriage. In adults and children an increased risk of neurologic complications is associated with Zika virus infection, including Guillain-Barré syndrome, neuropathy and myelitis. Therefore, WHO declared Zika virus infection a public health emergency of global concern. And also, the knowledge and scientific information on Zika virus infection is relatively limited. Hence this comprehensive review on Zika virus infection is undertaken to provide an overview of its transmission, pathogenesis, clinical symptoms, diagnosis, treatment and preventive aspects and to highlight its importance, and impact on public health and further research.

Keywords: *Aedes* mosquitoes, Pregnancy, Public health concern, Zika virus

INTRODUCTION

In May, 2015, the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed Zika virus infection in Brazil [1]. On 1st February, 2016, the WHO declared the Zika virus infection, a public health emergency of International concern. Zika virus can cause birth defects as well as neurological problems [2]. The virus can be transmitted from an infected pregnant woman to her fetus can cause microcephaly and other severe brain anomalies in the

infant. Zika virus infections in adults can result in Guillain–Barré syndrome [3-5]. Clinicians worldwide need to be aware of Zika virus infection owing to International travel and the presence of potentially competent day time biting, urban dwelling mosquito vector *Aedes aegypti*. It can also be spread by the *Aedes albopictus* (Asian tiger) mosquito [6-9]. Hence, this comprehensive review on Zika virus infection is undertaken to provide an overview of its transmission, pathogenesis, clinical symptoms, diagnosis, treatment and preventive aspects and to highlight its importance, and impact on public health and further research.

Epidemiology

The Zika virus (ZIKV) was first isolated in April 1947 from the blood of a Rhesus Macaque monkey that had been placed in a cage in the Zika forest of Uganda, near Lake Victoria, by the scientists of the Yellow Fever Research Institute, during their study on yellow fever. A second isolation from the mosquito *Aedes africanus* followed at the same site in January 1948. When the monkey developed a fever, researchers isolated from its serum a transmissible agent that was first described as Zika virus in 1952. It was later identified in humans in 1953 for the first time in Nigeria [10-12]. Zika virus remained in relative obscurity for nearly 70 years; then, within the span of just one year, Zika virus was introduced into Brazil from the Pacific Islands and spread rapidly throughout Americas [13]

The first major outbreak, with 49 confirmed and 59 probable cases, was reported in 2007 in the Yap Islands caused by a strain of Asian lineage [14,15]. A further outbreak occurred with a closely related Asian lineage strain in French Polynesia in 2013 in which 294 cases were confirmed by RNA detection over a 10 week period [16]. Locally acquired cases (people with no history of travel to known endemic areas within the recognized incubation period) on Easter Island in 2014 marked the first arrival of Zika virus in the Americas [17]. This was followed in May 2015 by confirmation of cases in North-East Brazil, where again the Zika virus sequence belonging to the Asian lineage was found, and the country is experienced the largest epidemic ever recorded with around 1.5 million cases reported by the Brazilian authorities [16]. In October, 2015, Colombia reported first autochthonous transmission of Zika virus outside Brazil, and by March 3, 2016, a total of 51,473 suspected cases of Zika virus had been reported in that country [18]. By March, 2016, the virus had spread to at least 30 countries and territories in the Americas. In 2016, a widespread epidemic of Zika fever occurred in the Americas and the Pacific [7,10,19].

Cases of Zika virus disease globally declined from 2017 onwards; however, Zika virus transmission persists at low levels in several countries in the Americas and in other endemic regions. In addition, the first local mosquito-transmitted Zika virus disease cases were reported in Europe in 2019 and Zika virus outbreak activity was detected in India in 2021. To date, a total of 89 countries and territories have reported evidence of mosquito transmitted Zika virus infection [2]. There is no case of Zika reported from Nepal yet. However, the possibility of viral circulation in Nepal cannot be ruled out due to the presence of its vector. In India, there are reports of seropositive cases who demonstrate anti-Zika antibodies in their serum sample [2,20].

Structure of Virus

Zika virus is an Arbovirus (Ar=arthropod; bo=borne), a member of Flaviviridae family genus *Flavivirus,* which includes dengue, chikungunya, yellow fever and West Nile viruses. Zika virus is enveloped, with ssRNA (+ve sense). The genome contains 10,794 nucleotides encoding 3,419 amino acids. The virion is approximately 40 nm in diameter with surface projections on envelope, that measure 5-10 nm. The nucleocapsid is 25-30 nm in diameter with icosahedral symmetry. Envelope contains envelope proteins E and M. The genome of Zika virus is single-stranded RNA which has 10,794 nucleotides encoding 3419 amino acids and contains two flanking untranslated regions (3' and 5' untranslated regions) and a single open reading frame encoding a polyprotein that cleaves into three structural proteins, capsid protein (C), precursor of membrane protein (prM), envelope protein (E) along with 7 non-structural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) [20-22].

There are two major lineages of ZIKV, the African lineage and the Asian lineage. In Africa, Zika virus is thought to have largely maintained in a cycle involving transmission between non-human primates (such as monkeys and apes) and mosquitoes, with humans as occasional unintentional hosts. In

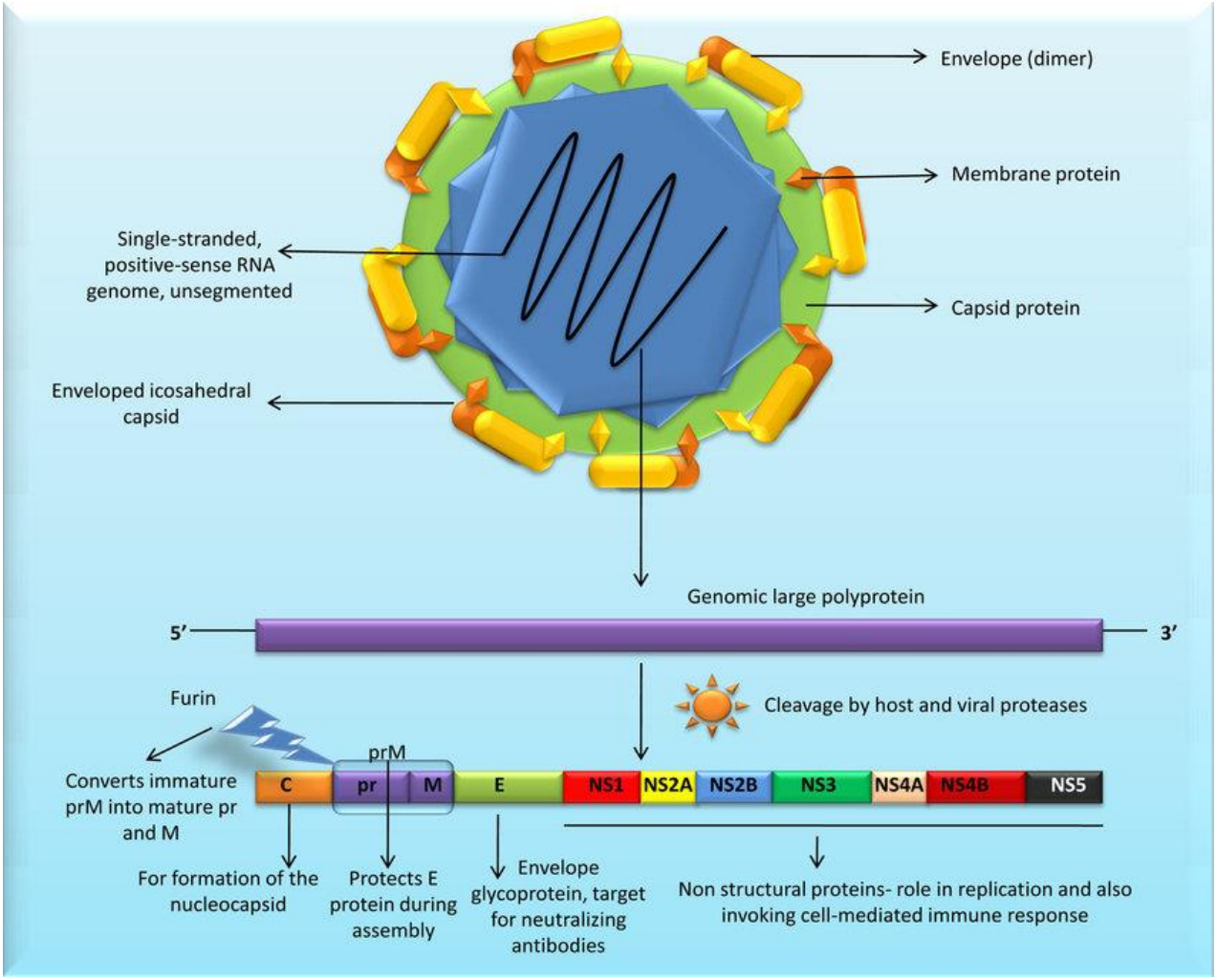

Figure 1: Zika virus structure [20]

areas outside Africa, however, humans have probably become the main host. A mutation in the Asian lineage may have led the virus to adapt to the human (as opposed to non-human primate) host [15,23].

Transmission

ZIKV can migrate between humans through sexual intercourse and it can also cross the placenta, from mother to fetus during pregnancy (transplacental transmission), affecting unborn fetus [24]. A mother already infected with Zika virus near the time of delivery can pass on the virus to her new-born around the time of birth (perinatal transmission), but this is rare. To date, there are no reports of infants getting ZIKV through breastfeeding. Transmission of the virus through blood transfusion has been reported [25]. ZIKV is transmitted by day time actve mosquitoes and has been isolated from a number of species in the genus Aedes, such as *Aedes aegypti*, *Aedes albopictus*, and arboreal mosquitoes such as *Aedes africanus*, *Aedes apicoargenteus*, *Aedes furcifer*, *Aedes hensilli*, *Aedes luteocephalus*, *Aedes taylori*, and *Aedes vittatus*. Studies show that the extrinsic incubation period in mosquitoes is about 10 days. These are the same mosquitoes that transmit dengue fever, chikungunya, and yellow fever [7-9].

Pathogenesis

In humans ZIKV causes an illness known as Zika fever, Zika, or Zika disease. Limited literature exists on the pathogenesis of the Zika virus to help understand the clinical disease spectrum and to target treatments to minimize or prevent tissue damage. Zika virus replicates readily in skin immune cells, and a large number of receptors are able to mediate entry of the virus into cells. Studies on the capability of the virus to replicate in neuronal cells are warranted to further investigate the link with neuronal disorders. Flaviviruses generally replicate in the cytoplasm, but Zika virus antigens have been found in infected cell nuclei. Zika virus affects people travelled to affected tropical areas and have bitten by an infected mosquito. During 2014-2016, these areas included the Pacific Islands, South East Asia, Central and South American countries. It is estimated that only about one in five people carrying the virus actually develop symptoms from Zika virus infection [20,26-28].

Clinical Symptoms

Zika virus infections seem either to be subclinical (possibly in as many as 80% of infections) or to cause a mild illness after an incubation period of three to 12 days. Symptoms, which last for approximately two to seven days include fever [27], conjunctivitis (pink eye) [27,28], arthralgia [26], myalgia [27], and widespread skin rash (exanthema) [27,28], which may be itchy. Headache, retro-orbital pain, peripheral edema, and gastrointestinal disturbance (vomiting) have also been identified [26-28].

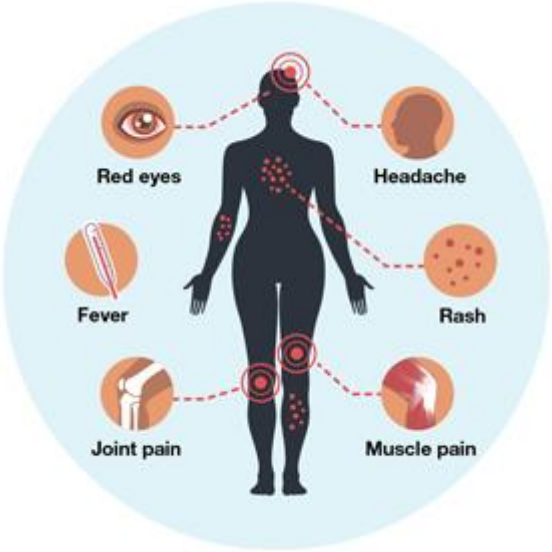

Figure 2: Clinical symptoms of Zika virus infection [31]

Complications

Guillain-Barré syndrome, an autoimmune disease, is a rare, rapid-onset form of paralysis, is often triggered by Zika virus infection. The first case of Zika virus infection complicated by Guillain-Barré syndrome was reported from French Polynesia in March 2014, and others have occurred in Brazil. Death is rare [5,16]. Brazil has reported an increase in birth defects in babies born during the recent Zika virus epidemic, specifically fetal microcephaly (small head), intracranial calcifications (Calcium deposits in the brain) [29,30]. Zika virus RNA has been identified in the amniotic fluid of mothers whose fetuses had cerebral abnormalities detected by ultrasonography, and viral antigen and RNA have been identified in the brain tissue and placentas of children who were born with microcephaly and died soon after birth. From November 2015 to February 2016, 5280 suspected cases of microcephaly and/or central nervous system malformation, including 108 deaths, were reported by Brazil [4,29,30].

Substantial evidence now indicates that Zika virus can be transmitted from the mother to fetus, particularly in the first trimester of pregnancy. The pregnant mothers with suspected Zika virus infection, or recently travelled to an infected zone, should see their doctor and undergo testing for Zika virus infection. CDC recommends serial ultrasound examination to monitor fetal growth and anatomy and referral to a maternal fetal medicine or infectious disease specialist with expertise in pregnancy management. Amniocentesis may be considered after 15 weeks of gestation [29,30].

CDC recommends both molecular and serologic testing of infants who are being evaluated for evidence of Zika virus infection. Paediatric health care providers should work closely with obstetric providers to identify infants whose mothers were potentially infected with Zika virus during pregnancy (based on travel to or residence to an area with Zika virus transmission) and review fetal ultrasounds and maternal testing for Zika virus infection [31].

The Pan American Health Organization of WHO has issued a provisional case definition for suspected acute Zika virus infection, intended for use in countries with ongoing local transmission: Rash or increase in body temperature (>37.2^0 C), with any of the following not explained by other conditions such as arthralgia or myalgia, non-purulent conjunctivitis, conjunctival hyperemia, headache, and malaise [28,31,33].

Diagnosis

Diagnosis is guided by history (countries of travel, sexual contacts, and contact with other cases of infection) and examination. The symptoms and clinical signs do not have sufficient positive or negative predictive value, and therefore laboratory testing is needed for reliable diagnosis. Definitive diagnosis is based on detection of Zika virus RNA in blood (serum or EDTA treated plasma) by RT-PCR.

In acute phase, IgM-ELISA is used to detect specific IgM antibody in serum samples against Zika virus. After the acute phase, diagnosis by antibody detection is compromised by considerable cross reactivity with antibodies to other flaviviruses. No commercial tests for Zika virus available. Zika virus testing is performed at CDC. Recently, in India, National Institute of Virology (NIV) developed a diagnostic test kit [20,34,35].

Treatment

Treatment and management of congenital Zika virus infection is supportive, symptomatic, and should address specific medical and neurodevelopmental issues for the infant's particular needs. Investigations are ongoing to better understand what services will be most effective for these children as they grow. Mothers are encouraged to breastfeed even in areas where Zika virus is found, as available evidence indicates the benefits of breastfeeding outweigh any theoretical risks associated with Zika virus transmission through breast milk [26,34,36].

Prevention

No specific antiviral treatment or vaccine against Zika virus is available. The only way to prevent congenital Zika virus infection is to prevent maternal infection, either by avoiding areas where Zika virus transmission is ongoing or avoiding mosquito bites. People should make every effort to eradicate mosquitoes from their living and working environment, and to avoid being bitten by mosquitoes. Emptying standing water from containers around house that can become breeding grounds for mosquitoes, wearing long-sleeved shirts, using mosquito repellents, and condom use sexual intercourse are but some of the many efforts that individuals can undertake [10,36-39].

Conclusion

ZIKV disease is a newly emerging infectious disease with a serious global public health problem, with limited surveillance measures. Its risk is more when infection occurs during pregnancy due to the potential to cause fetal abnormalities. At present, enough epidemiological and clinical data is not available. Diagnostic test kits for Zika virus are limited in number and availability. There is a need to develop anti-viral therapy and vaccine. Research is required for understanding the mechanism of pathogenesis, management, and prevention of this emerging pathogen. Surveillance is limited globally.

ACKNOWLEDGEMENT

We are thankful to Department of microbiology, UCMS, Bhairahwa for evincing keen interest and helping us.

Conflict of interest

None

Funding

N/A

Author's Contribution: *Preparation and planning of review study design, collection of literature, writing the article-**RRK;** Planning review study design, collection of literature-**AP,SB,SK**; Planning review study design, writing the article-**LP.** All author read the manuscript and agreed to publish.*

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