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## Zika Virus: A Review Article

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### Abstract

Zika virus, a flavivirus which is spread by Aedes mosquitoes, was considered as innocent pathogen while restricted to the African and Asian population. However, after reaching the Americas in March 2015, it became a global threat. Alterations in methylation of Zika virus genomic RNA has significant impact on virus production. Zika virus was initially thought to cause asymptomatic or only mild, self-limiting symptoms, but more severe cases and the sequela of Guillain-Barre syndrome have now been recognized. In utero exposure has been observed to result in a congenital syndrome marked by and a range of other brain anomalies. Although vaccine development is an active area of research, there is currently no vaccine of treatment for Zika virus infection. Continued epidemiological monitoring as well as basic research into the biology, pathogenesis (virus-host interaction), and immunology of Zika virus and Zika fever is needed to develop effective counter-measures and vaccines.

**Keywords:** Zika virus, RNA methylation, guillain-barre syndrome, microcephaly, Zika virus vaccines

### Introduction

Zika virus (ZIKV) is an arbovirus belonging to the family Flavivirus. It is spread by daytime-active Aedes mosquitoes, such as *A. aegypti* and *A. albopictus*. Zika virus is related to the dengue, yellow fever, Japanese encephalitis, and West Nile viruses [1]. It is currently one of the most important emerging viruses in the world. In 1947, Zika virus was originally isolated from a febrile sentinel rhesus monkey and from a pool of Aedes africanus mosquitoes in the Zika forest in Uganda during a yellow fever study [2]. It was first detected in humans in the year 1952 using neutralizing antibody testing in sera from East Africa. Zika virus was first isolated from a human in Uganda. Its isolation rate varied by season: peaks in rainy seasons (June to August) and lows in dry seasons (January to February) [8]. Since the 1950s, it has been known to occur within a narrow equatorial belt from Africa to Asia. From 2007 to 2016, the virus spread eastward, across the Pacific Ocean to the Americas, leading to the 2015–16 Zika virus epidemic [4]. Eighteen species of mosquitos were found to be positive for ZIKV during epidemiological sampling in Africa and Asia from 1956 to 2016 and eight were evaluated experimentally for vector competence. The basic reproduction number (R<sub>0</sub>, a measure of transmissibility) of Zika virus was estimated to be between 1.4 and 6.6 [2].

### Genomics of Zika virus

The Zika virus genome is composed of a single-stranded RNA molecule of positive polarity about 10 kb in length. It contains 10,794 nucleotides encoding 3,419 amino acids. Like other flaviviruses, Zika virus is composed of 2 noncoding regions (5' and 3') that flank an open reading frame, which encodes a polyprotein cleaved into the capsid, precursor of membrane, envelope, and 7 nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) [7]. ZIKV genome also contains three conserved sequences (CS 1 to CS 3) that may mediate genome cyclization between 5' and 3' terminal regions of the genome. Notably, the organization of the CS in the 3' end of ZIKV is different from that of other mosquito-borne flaviviruses [7]. Zika virus genomic RNA includes several other mosquito-borne viruses of clinical importance (*e.g.*, DENV, WNV, and yellow fever virus [YFV]) [7]. Its closest relative is Spondweni virus, the only other member of its clade [2]. Besides genomic RNA, it has been described that due to the presence of a “multi-pseudoknot structure” in the genomic RNA that confounds a cellular exonuclease, ZIKV-infection produces subgenomic flaviviral RNAs (sfRNAs) within infected cells that play relevant roles in innate immunity evasion and viral pathogenesis [7].

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### RNA methylation and G-quadruplexes (G4) in the ZIKV genome

Alterations in methylation of Zika virus RNA can have significant impact on virus production [7]. The effects of viral cap methylation have been studied for flaviviruses, and cap methylation was found to be essential for viral RNA stability, translation, and evasion from host antiviral pathogen recognition receptors. By using a methylated 5' cap, viral RNAs mimic cellular RNAs, and in this way the viral RNAs are not recognized as non self by the host. This allows the viral RNAs to be translated by the host's translational machinery [10]. DNA and RNA sequences rich in guanine residues can contain adjacent residues of guanines referred to as G-blocks. When a G-block consists of four or more guanines, they can associate through Hoogsteen base-pairing to form a planar structure referred to as a G-tetra. Recent research has identified 64–78 putative G4 RNA structures in the (+) strand of the ZIKV genome based on bioinformatic analysis. G4 sites in the ZIKV genome might act as binding sites for viral and cellular host factors that contribute to virus replication [10].

### ZIKV symptoms and diagnosis

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, red eyes, joint pain, headache, and a maculopapular rash. Infection during pregnancy causes microcephaly (shortened head than expected) and other brain malformations in some babies. Infection in adults has been linked to Guillain–Barre syndrome (GBS) which is an uncommon sickness of the nervous system in which a person's own immune system damages the nerves, causing muscle weakness, and sometimes, paralysis. Other non-vector modes of Zika virus transmission include sexual contact or blood transfusions [8]. Diagnosis is done by testing the blood, urine, or saliva for the presence of Zika virus RNA when the person is sick [6].

### Virus-Host interaction

Zika virus replicates in the mosquito's midgut epithelial cells and then its salivary gland cells. After 5–10 days, the virus can be found in the mosquito's saliva. A study showed that if the mosquito's saliva is inoculated into human skin, the virus can infect epidermal keratinocytes, skin fibroblasts in the skin and the Langerhans cells. The pathogenesis of the virus is hypothesized to continue with a spread to lymph nodes and the bloodstream. Several entry and adhesion factors (e.g., AXL receptor tyrosine kinase) facilitate infection, which enhances Zika virus replication in skin fibroblasts. Zika virus antigens were found exclusively in the nuclei of infected cells; this finding suggests a location for replication [8]. One study examined the kinetics of Zika virus infectivity in *Aedes aegypti* mosquitoes by using blood-feeding membranes; viral content was high on the day of feeding (inoculation), decreased to undetectable levels through day 10, increased by day 15, and remained high on days 20–60. These findings suggest an incubation period in mosquitoes of  $\approx 10$  days [2].

### ZIKV birth defects

Despite usually causing mild or no symptoms in infected adults, Zika virus displays a different behavior toward fetuses. When infected during gestation, fetuses have their immature neural cells killed by the viruses and consequently have

devastating findings at birth [4]. In the past year the drastic effects of Zika virus infection in new borns include neurological, ophthalmological, audiological and skeletal abnormalities. These findings represent new entities called congenital Zika Syndrome [5]. Intrauterine transmission is supported by the finding of Zika virus RNA by reverse transcription PCR (RT-PCR) in amniotic fluid of 2 mothers with symptoms of Zika virus infection during pregnancy; both delivered babies with microcephaly. ZIKV had also been detected within the brain of a microcephalic fetus and recently, direct evidence has emerged that ZIKV is able to infect and cause the death of neural stem cells. Viral RNA, but not culturable virus, has been detected in breast milk, but transmission by breast feeding has not been reported [5].

### ZIKV drugs, therapeutics and vaccines

More insights into genetic and molecular mechanisms associated with the recent increase in virulence of ZIKV could aid in the design and development of safer and more potent drugs and therapeutics against ZIKV [9]. The introduction of ZIKV into the Americas most probably occurred by a single introduction of an Asian strain of ZIKV between May and December 2013. Remarkably, despite the genetic differences between ZIKV strains, the antigenic relationships between strains support the existence of a single viral serotype which may be of crucial importance for the design of ZIKV vaccines [6]. Some recent therapies have shown promise in inhibiting ZIKV infections and associated disease. These therapies include limiting viral entry into cells, targeting the ZIKV helicase protein, use of nucleoside analogs like 2'-C-methylated nucleosides and 7-deaza-2'-C-methyladenosine to terminate nascent RNA strand formation, and use of antibodies that bind to ZIKV but do not neutralize it [9]. It has been recently reported that passive transfer of human neutralizing antibodies to pregnant mice suppressed ZIKV replication and prevent microcephaly, as did a monoclonal antibody against the Domain III of ZIKV-E protein protected against lethal ZIKV infection in a mice model [5]. In June 2016, the FDA granted the first approval for a human clinical trial for a Zika vaccine [2]. In March 2017, a DNA vaccine was approved for phase 2 clinical trials. This vaccine consisted of a small circular piece of DNA, known as a plasmid which expresses the genes for the Zika virus envelope proteins. As the vaccine does not contain the full sequence of the virus, it cannot cause infection [3].

As of April 2017, both subunit and inactivated vaccines entered clinical trials. Finally, antiparasitics and antimalarials, such as ivermectin, chloroquine, quinacrine, mefloquine, GSK-36796, and pyrimethamine as well as antibiotics like nanchagmycin, daptomycin and kitasmycin have also been shown to reduce ZIKV multiplication [8]. OpenZika, an IBM world community grid project, was used to identify drug molecule docking for various ZIKV structures. This platform allows data to be shared with researchers worldwide to facilitate the speedy discovery of anti-ZIKV drugs [3]. Along with identifying novel drug targets, therapeutics, and vaccines, strengthening of appropriate prevention and control measures, including mosquito control, could help in limiting ZIKV infections, its associated complications, and its potential for further spread [9].

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