

ZIKA VIRUS: THE HORRIBLE THREAT

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<p>*For Correspondence: Department of Pharmacy, Prasad Institute of Technology, Panch-hatia, Sadar, Jaunpur-222001</p>	<p>ABSTRACT Zika virus (ZIKV) is a virus of family Flaviviridae. It is transmitted by the bite of Aedes mosquitoes (<i>A. aegypti</i> and <i>A. albopictus</i>). Zika virus causes the dengue, yellow fever, Japanese encephalitis, and West Nile viruses. It was first identified 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 Institute. The evidence of human infection with Zika was reported from other African countries, such as the Central African Republic, Egypt, Gabon, Sierra Leone, Tanzania, and Uganda, as well as in parts of Asia including India, Indonesia, Malaysia, the Philippines, Thailand, Vietnam and Pakistan. There were only 14 confirmed human cases of Zika virus infections from Africa and Southeast Asia till 2007. In January 2016, the WHO said the Zika virus was likely to spread throughout most of the Americas by the end of the year. It is estimated that 1.5 million people have been infected by Zika in Brazil, with over 3,500 cases of microcephaly reported between October 2015 and January 2016. Zika virus is also transmitted from men and women to their sexual partners, transmission through blood transfusions. The Zika virus can also spread from an infected mother to her fetus during pregnancy or at delivery. Bharat Biotech International (India) is working on vaccines for Zika virus currently.</p> <p>Keywords: Zika virus; <i>Aedes</i> mosquitoes; Microcephaly; Dengue; Yellow fever</p>
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INTRODUCTION

Zika virus (ZIKV) is a member of the virus family *Flaviviridae* and the genus *Flavivirus* [2]. It is spread by *Aedes* mosquitoes, such as *A. aegypti* and *A. albopictus*. Its name comes from the Zika Forest of Uganda, where the virus was first isolated in 1947 [3]. Zika virus is related to the dengue, yellow fever, Japanese encephalitis, and West Nile viruses. 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. The infection, known as Zika fever or Zika virus disease, often causes no or only mild symptoms, similar to a very mild form of dengue fever. While there is no specific treatment, paracetamol (acetaminophen) and rest may help with the symptoms [4]. As of 2016, the illness cannot be prevented by medications or vaccines. Zika can also spread from a pregnant woman to her fetus. This can result in microcephaly, severe brain malformations, and other birth defects. Zika infections in adults may result rarely in Guillain–Barré syndrome [7]. 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 travel. Other governments or health agencies also issued similar travel warnings, while Colombia, the Dominican Republic, Puerto Rico, Ecuador, El Salvador, and Jamaica advised women to postpone getting pregnant until more is known about the risks [8].

HISTORY:

Virus Isolation in Monkeys 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, near Lake Victoria, by the scientists of the Yellow Fever Research Institute. A second isolation from the mosquito *A. africanus* followed at the same site in January 1948. When the monkey developed a fever, researchers isolated from its serum a "filterable transmissible agent" that was named Zika in 1948 [12].

First Evidence of Human Infection:

Zika had been known to infect humans from the results of serological surveys in Uganda and Nigeria, published in 1952: Among 84 people of all ages, 50 individuals had antibodies to Zika, and all above 40 years of age were immune. A 1952 research study conducted in India had shown a "significant number" of Indians tested for Zika had exhibited an immune response to the virus, suggesting it had long been widespread within human populations [25]. It was not until 1954 that the isolation of Zika from a human was published. This came as part of a 1952 outbreak investigation of jaundice suspected to be yellow fever. It was found in the blood of a 10-year-old Nigerian female with low-grade fever, headache, and evidence of malaria, but no jaundice, who recovered within three days. Blood was injected into the brain of laboratory mice, followed by up to 15 mice passages. The virus from mouse brains was then tested in neutralization tests using rhesus monkey sera specifically immune to Zika. In contrast, no virus was isolated from the blood of two infected adults with fever, jaundice, and coughs, diffuse joint pains in one and fever, headache, pain behind the eyes and in the joints. Infection was proven by a rise in Zika-specific serum antibodies [24].

Spread in Equatorial Africa and Asia:

From 1951 through 1983, evidence of human infection with Zika was reported from other African countries, such as the Central African Republic, Egypt, Gabon, Sierra Leone, Tanzania, and Uganda, as well as in parts of Asia including India, Indonesia, Malaysia, the Philippines, Thailand, Vietnam and Pakistan. From its discovery until 2007, there were only 14 confirmed human cases of Zika infection from Africa and Southeast Asia [26].

Micronesia:

In April 2007, the first outbreak outside of Africa and Asia occurred on the island of Yap in the Federated States of Micronesia, characterized by rash, conjunctivitis, and arthralgia, which was initially thought to be dengue, chikungunya, or Ross River disease. Serum samples from patients in the acute phase of illness contained RNA of Zika. There were 49 confirmed cases, 59 unconfirmed cases, no hospitalizations, and no deaths [27].

Oceania:

Between 2013 and 2014, further epidemics occurred in French Polynesia, Easter Island, the Cook Islands, and New Caledonia [10].

Other Cases:

On 22 March 2016 Reuters reported that Zika was isolated from a 2014 blood sample of an elderly man in Chittagong in Bangladesh as part of a retrospective study [28].

Americas:

As of early 2016, a widespread outbreak of Zika was ongoing, primarily in the Americas. The outbreak began in April 2015 in Brazil, and has spread to other countries in South America, Central America, Mexico, and the Caribbean. The Zika virus reached Singapore and Malaysia in Aug 2016. In January 2016, the WHO said the virus was likely to spread throughout most of the Americas by the

end of the year; and in February 2016, the WHO declared the cluster of microcephaly and Guillain-Barré syndrome cases reported in Brazil – strongly suspected to be associated with the Zika outbreak – a Public Health Emergency of International Concern. It is estimated that 1.5 million people have been infected by Zika in Brazil, with over 3,500 cases of microcephaly reported between October 2015 and January 2016 [29]. A number of countries have issued travel warnings, and the outbreak is expected to significantly impact the tourism industry. Several countries have taken the unusual step of advising their citizens to delay pregnancy until more is known about the virus and its impact on fetal development [14]. With the 2016 Summer Olympic Games hosted in Rio de Janeiro, health officials worldwide have voiced concerns over a potential crisis, both in Brazil and when international athletes and tourists, who may be unknowingly infected, return home and possibly spread the virus. Some researchers speculate that only one or two tourists may be infected during the three week period, or approximately 3.2 infections per 100,000 tourists [30].

TRANSMISSION:

The vertebrate hosts of the virus were primarily monkeys in a so-called enzootic mosquito-monkey-mosquito cycle, with only occasional transmission to humans. Before the current pandemic began in 2007, Zika "rarely caused recognized 'spillover' infections in humans, even in highly enzootic areas". Infrequently, however, other arboviruses have become established as a human disease and spread in a mosquito-human-mosquito cycle, like the yellow fever virus and the dengue fever virus (both flaviviruses), and the chikungunya virus (a togavirus). Though the reason for the pandemic is unknown, dengue, a related arbovirus that infects the same species of mosquito vectors, is known in particular to be intensified by urbanization and globalization. Zika is primarily spread by *Aedes aegypti* mosquitoes [31], and can also be transmitted through sexual contact [13] or blood transfusions [32]. The basic reproduction number (R_0 , a measure of transmissibility) of Zika virus has been estimated in between 1.4 - 6.6 [14]. In 2015, news reports drew attention to the rapid spread of Zika in Latin America and the Caribbean. At that time, the Pan American Health Organisation published a list of countries and territories that experienced "local Zika virus transmission" comprising Barbados, Bolivia, Brazil, Colombia, the Dominican Republic, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, and Venezuela. By August 2016, more than 50 countries (list and map) had experienced active (local) transmission of Zika virus [15]. Zika is primarily spread by the female *Aedes aegypti* mosquito, which is active mostly in the daytime, although researchers have found the virus in common *Culex* house mosquitoes as well [31]. The mosquitoes must feed on blood in order to lay eggs. 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*, with an extrinsic incubation period in mosquitoes of about 10 days [12]. The true extent of the vectors is still unknown. Zika has been detected in many more species of *Aedes*, along with *Anopheles coustani*, *Mansonia uniformis*, and *Culex perfuscus*, although this alone does not incriminate them as a vector. Transmission by *A. albopictus*, the tiger mosquito, was reported from a 2007 urban outbreak in Gabon where it had newly invaded the country and become the primary vector for the concomitant chikungunya and dengue virus outbreaks. There is concern for autochthonous infections in urban areas of European countries infested by *A. albopictus* because the first two cases of laboratory confirmed Zika infections imported into Italy were reported from viremic travelers returning from French Polynesia. The potential societal risk of Zika can be delimited by the distribution of the mosquito species that transmit it. The global distribution of the most cited carrier of Zika, *A. aegypti*, is expanding due to global trade and travel. *A. aegypti* distribution is now the most extensive ever recorded across all continents including North America and even the European

periphery (Madeira, the Netherlands, and the northeastern Black Sea coast). A mosquito population capable of carrying Zika has been found in a Capitol Hill neighborhood of Washington, D. C., and genetic evidence suggests they survived at least four consecutive winters in the region. The study authors conclude that mosquitoes are adapting for persistence in a northern climate. The Zika virus appears to be contagious via mosquitoes for around a week after infection. The virus is thought to be infectious for a longer period of time after infection (at least 2 weeks) when transmitted via semen [16, 17]. Research into its ecological niche suggests that Zika may be influenced to a greater degree by changes in precipitation and temperature than Dengue, making it more likely to be confined to tropical areas. However, rising global temperatures would allow for the disease vector to expand their range further north, allowing Zika to follow [18].

Sexual:

Zika can be transmitted from men and women to their sexual partners [13]. As of April 2016 sexual transmission of Zika has been documented in six countries – Argentina, Chile, France, Italy, New Zealand and the United States – during the 2015 outbreak. In 2014, Zika capable of growth in lab culture was found in the semen of a man at least two weeks (and possibly up to 10 weeks) after he fell ill with Zika fever. In 2011 a study found that a US biologist who had been bitten many times while studying mosquitoes in Senegal developed symptoms six days after returning home in August 2008, but not before having unprotected intercourse with his wife, who had not been outside the US since 2008. Both husband and wife were confirmed to have Zika antibodies, raising awareness of the possibility of sexual transmission. In early February 2016, the Dallas County Health and Human Services department reported that a man from Texas who had not travelled abroad had been infected after his male monogamous sexual partner had anal penetrative sex with him one day before and one day after onset of symptoms. As of February 2016, fourteen additional cases of possible sexual transmission have been under investigation, but it remained unknown whether women can transmit Zika to their sexual partners. At that time, the understanding of the "incidence and duration of shedding in the male genital urinary tract was limited to one case report." Therefore, the CDC interim guideline recommended against testing men for purposes of assessing the risk of sexual transmission [19]. In March 2016, the CDC updated its recommendations about length of precautions for couples, and advised that heterosexual couples with men who have confirmed Zika fever or symptoms of Zika should consider using condoms or not having penetrative sex (i.e., vaginal intercourse, anal intercourse, or fellatio) for at least 6 months after symptoms begin. This includes men who live in—and men who traveled to—areas with Zika. The couples with men who traveled to an area with Zika, but did not develop symptoms of Zika, should consider using condoms or not having sex for at least 8 weeks after their return in order to minimize risk. Couples with men who live in an area with Zika, but have not developed symptoms, might consider using condoms or not having sex while there is active Zika transmission in the area [20].

Pregnancy:

The Zika virus can spread from an infected mother to her fetus during pregnancy or at delivery [21].

Blood Transfusion:

As of April 2016, two cases of Zika transmission through blood transfusions have been reported globally, both from Brazil, after which the US Food and Drug Administration (FDA) recommended screening blood donors and deferring high-risk donors for 4 weeks. A potential risk had been suspected based on a blood-donor screening study during the French Polynesian Zika outbreak, in which 2.8% (42) of donors from November 2013 and February 2014 tested positive for Zika RNA and

were all asymptomatic at the time of blood donation. Eleven of the positive donors reported symptoms of Zika fever after their donation, but only three of 34 samples grew in culture [33].

PATHOGENESIS:

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, 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 the Langerhans cells. The pathogenesis of the virus is hypothesized to continue with a spread to lymph nodes and the bloodstream.^[11] Flaviviruses generally replicate in the cytoplasm, but Zika antigens have been found in infected cell nuclei.

Zika Fever:

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. Symptoms generally last less than seven days. It has not caused any reported deaths during the initial infection. Infection during pregnancy causes microcephaly and other brain malformations in some babies.^[5,6] Infection in adults has been linked to Guillain–Barré syndrome (GBS). Diagnosis is by testing the blood, urine, or saliva for the presence of Zika virus RNA when the person is sick. Prevention involves decreasing mosquito bites in areas where the disease occurs, and proper use of condoms. Efforts to prevent bites include the use of insect repellent, covering much of the body with clothing, mosquito nets, and getting rid of standing water where mosquitoes reproduce. There is no effective vaccine. Health officials recommended that women in areas affected by the 2015–16 Zika outbreaks consider putting off pregnancy and that pregnant woman not travel to these areas. While there is no specific treatment, paracetamol (acetaminophen) and rest may help with the symptoms. Admission to hospital is rarely necessary^[4].

VACCINE DEVELOPMENT:

Effective vaccines have existed for several viruses of the flaviviridae family, namely yellow fever vaccine, Japanese encephalitis vaccine, and tick-borne encephalitis vaccine, since the 1930s, and dengue fever vaccine since the mid-2010s. World Health Organization (WHO) experts have suggested that the priority should be to develop inactivated vaccines and other non-live vaccines, which are safe to use in pregnant women and those of childbearing age^[22]. The US NIH Vaccine Research Center began work towards developing a vaccine for Zika per a January 2016 report. Bharat Biotech International (India) reported in early February 2016, that it was working on vaccines for Zika using two approaches: "recombinant", involving genetic engineering, and "inactivated", where the virus is incapable of reproducing itself but can still trigger an immune response with animal trials of the inactivated version to commence in late February. As of March 2016, 18 companies and institutions internationally were developing vaccines against Zika, but none had yet reached clinical trials. The first human trial for Zika vaccine, a synthetic DNA vaccine (GLS-5700) developed by Inovio Pharmaceuticals, is approved by FDA in June 2016. Interim results of the Phase 1 study are expected in later 2016. Nikos Vasilakis of the University of Texas Medical Branch (UTMB) predicted that it may take two years to develop a vaccine, but ten to twelve years may be needed before an effective Zika vaccine is approved by regulators for public use. A single dose of two distinct vaccines (DNA-based and inactivated virus vaccines) protected mice against the Zika virus^[23].

CONCLUSION

In this review, we concluded that the Zika virus is the fetal micro-organism. Zika virus mainly affects the pregnant woman and foetus. In foetus it causes a dangerous disease 'microcephaly'. It also affects other normal persons. There is no any treatment or vaccines are available in all over the world, but the symptomatic treatment is preferred by medical practitioners. So finally, it is concluded in this review that precaution is the best treatment from the Zika virus currently.

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