ZIKA VIRUS INFECTION: AN OVERVIEW

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ABSTRACT

Zika virus is a member of the virus family Flaviviridae and the genus Flavivirus. It is spread by daytime-active Aedes mosquitoes, such as A. aegypti and A. albopictus. Zika virus is related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses. Zika virus which was recently in news as it leads to microcephaly birth defect and often causes no or only mild symptoms, similar to a mild form of dengue fever. It is treated by rest and cannot be prevented by medications or vaccines. There has been total death of 152 as of 21 October 2015 in the world. The U.S. Centers for Disease Control and Prevention (CDC) and other governments or health agencies issued travel guidance on affected countries, including the use of enhanced precautions, and guidelines for pregnant women including considering postponing travel. This review focuses on understanding Zika virus, its transmission, structure, symptoms, diagnosis, treatment and prevention.

KEYWORDS: Fever, Flaviviridae, Microcephaly, Pregnancy, Zika.

INTRODUCTION

Zika virus (ZIKV) is a member of the virus family Flaviviridae and the genus Flavivirus. It is spread by daytime-active 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. Zika virus is related to dengue, yellow fever, Japanese encephalitis, Rocky Mountain spotted fever, Kala-azar and West Nile viruses. The infection, known as Zika fever, often causes no or only mild symptoms, similar to a mild form of dengue fever. It is treated by rest. Since the 1950s, it has been known to occur within a narrow equatorial belt from Africa to Asia. The virus spread eastward across the Pacific Ocean between 2013 and 2014 to French Polynesia, New Caledonia, the Cook Islands, and Easter Island and in 2015 to Mexico, Central America, the Caribbean and South America, where the Zika outbreak has reached pandemic levels. As of 2016, the illness cannot be prevented by medications or vaccines. Zika fever in pregnant women is associated with microcephaly but it is unclear whether the virus is the cause. An association with the neurologic conditions, Guillain–Barre syndrome, has been found in adults. In January 2016, the U.S. 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, Ecuador, El Salvador, and Jamaica advised women to postpone getting pregnant until more is known about the risks.

EPIDEMIOLOGY OF ZIKA VIRUS[4]

- The virus was first isolated in 1947 from a rhesus macaque in the Zika Forest of Uganda.
- It was later identified in humans in 1968 for the first time in Nigeria
- The first major outbreak, with 185 confirmed cases, was reported in 2007 in the Yap Islands.
- The first cases confirmed in Brazil were in May 2015 and the country is currently experiencing the largest epidemic ever recorded with 440,000 to 1,300,000 suspected cases reported by the Brazilian health authorities.
- There are 3174 cases and 38 deaths from microcephaly in Brazil as of 21 October 2015.
- There has been total death of 152 as of 21 October 2015 in the world.

HISTORY

TABLE 1: History of Zika Virus

<table>
<thead>
<tr>
<th>Year</th>
<th>Virus isolation in monkeys and mosquitoes:</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1947</td>
<td>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.[5] A second isolation from the mosquito A. africanus followed at the same time.</td>
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site in January 1948. When the monkey developed a fever, researchers isolated from its serum a "filterable transmissible agent" that was named Zika virus in 1948.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1952</td>
<td>First evidence of human infection: Zika virus had been known to infect humans from the results of serological surveys in Uganda and Nigeria. A serosurvey of 84 people of all ages showed 50 had antibodies, with all above 40 years of age being immune.(^{[5]}) Infection was proven by a rise in Zika virus specific serum antibodies. A 1952 research study conducted in India had shown a &quot;significant number&quot; of Indians tested for Zika had exhibited an immune response to the virus, suggesting it had long been widespread within human populations.</td>
</tr>
<tr>
<td>1951-1981</td>
<td>Spread in equatorial Africa and to Asia: From 1951 through 1981, evidence of human infection with Zika virus 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, and Vietnam. From its discovery until 2007, there were only 14 confirmed human cases of Zika virus infection from Africa and Southeast Asia.(^{[6]})</td>
</tr>
<tr>
<td>2007</td>
<td>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 virus. There were 49 confirmed cases, 59 unconfirmed cases, no hospitalizations, and no deaths.(^{[7]})</td>
</tr>
<tr>
<td>2013-2014</td>
<td>Oceania: Between 2013 and 2014, further epidemics occurred in French Polynesia, Easter Island, the Cook Islands, and New Caledonia.(^{[7]})</td>
</tr>
<tr>
<td>2015</td>
<td>American: As of early 2016, a widespread outbreak of Zika virus is 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. In January 2016, the World Health Organization (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 virus outbreak a Public Health Emergency of International Concern. 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.(^{[8]})</td>
</tr>
</tbody>
</table>

Figure 1: Areas with Current or Past Evidence of Zika\(^{[9]}\)
TRANSMISSION AND RISKS\textsuperscript{12,13}

Zika virus is transmitted to people primarily through the bite of an infected Aedes species mosquito (A. aegypti and A. albopictus). These are the same mosquitoes that spread dengue and chikungunya viruses.
These mosquitoes typically lay eggs in and near standing water in things like buckets, bowls, animal dishes, flower pots and vases. They prefer to bite people, and live indoors and outdoors near people.

Mosquitoes that spread chikungunya, dengue, and Zika are aggressive daytime biters. They can also bite at night.

Mosquitoes become infected when they feed on a person already infected with the virus. Infected mosquitoes can then spread the virus to other people through bites.

**From mother to child**

- A mother already infected with Zika virus near the time of delivery can pass on the virus to her newborn around the time of birth.
- A pregnant woman can pass Zika virus to her fetus during pregnancy. We are studying the adverse pregnancy and infant outcomes associated with Zika virus infection during pregnancy.
- To date, there are no reports of infants getting Zika virus through breastfeeding. Because of the benefits of breastfeeding, mothers are encouraged to breastfeed even in areas where Zika virus is found.

**Through sexual contact**

- Zika virus can be spread by a man to his sex partners.
- In known cases of likely sexual transmission, the men had Zika symptoms, but the virus can be transmitted before, during, and after symptoms develop.
- In one case, the virus was spread a few days before symptoms developed.
- The virus is present in semen longer than in blood.

**Through blood transfusion**

- As of February, 1, 2016, there have not been any confirmed blood transfusion transmission cases in the United States.
- There have been multiple reports of blood transfusion transmission cases in Brazil. These reports are currently being investigated.
- During the French Polynesian outbreak, 2.8% of blood donors tested positive for Zika and in previous outbreaks, the virus has been found in blood donors.
RISKS

- Anyone who lives in or travels to an area where Zika virus is found and has not already been infected with Zika virus can get it from mosquito bites. Once a person has been infected, he or she is likely to be protected from future infections.

Figure 4: Transmission cycle of ZIKA Virus

STRUCTURE OF ZIKA VIRUS[14,15]

- The virion is approximately 40 nm in diameter with surface projection that measures roughly 5-10 nm.
- Nucleocapsid is 25-30 nm in diameter surrounded by a host-membrane derived lipid bilayer.
- Enveloped
- Icosahedral
- Contains envelope proteins E and M

Figure 5: Structure of Zika Virus
GENOME OF ZIKA VIRUS\textsuperscript{[15,16]}

- Non-segmented, single-stranded, positive-sense RNA genome
- 10794 bases long with two non-coding regions flanking regions known as the 5′ NCR and the 3′ NCR.

![Flavivirus genome](image)

\textbf{Figure 6: Genome of Zika Virus}

PATHOGENESIS OF ZIKA VIRUS\textsuperscript{[17]}

- Incubation period in mosquitoes is about 10 days.
- The vertebrate hosts of the virus are primarily monkeys and humans.
- 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.
- Flaviviruses generally replicate in the cytoplasm, but Zika virus antigens have been found in infected cell nuclei.
- Infection with the virus appears to be linked to the development of unusually small heads and brain damage in newborns (microcephaly).
- The most dangerous time is thought to be during the first trimester of Pregnancy—when some women do not realize they are pregnant. Experts do not know how the virus enters the placenta and damages the growing brain of the fetus.

THE DIFFERENCE BETWEEN ZIKA, DENGUE AND CHIKUNGUNYA\textsuperscript{[18]}

All of these viruses cause similar symptoms, but certain symptoms suggest one disease or another. Most Zika patients have skin rashes; most dengue patients have a higher fever and more severe muscle pain; most chikungunya patients have a higher fever and more intense joint pain in the hands, feet, knees, and back.
POTENTIAL COMPLICATIONS OF ZIKA VIRUS DISEASE\cite{19,20}

During large outbreaks in French Polynesia and Brazil in 2013 and 2015 respectively, national health authorities reported potential neurological and auto-immune complications of Zika virus disease. Recently in Brazil, local health authorities have observed an increase in Guillain-Barre syndrome which coincided with Zika virus infections in the general public, as well as an increase in babies born with microcephaly in northeast Brazil. Agencies investigating the Zika outbreaks are finding an increasing body of evidence about the link between Zika virus and microcephaly. However, more investigation is needed to better understand the relationship between microcephaly in babies and the Zika virus. Other potential causes are also being investigated.

SIGNS AND SYMPTOMS\cite{21,22}

Signs and Symptoms are similar to Kala-azar fever and other Flaviviruses such as dengue fever or the alpha virus that causes chikungunya but are milder in form and usually last two to seven days. It is estimated that 80% of cases are asymptomatic. The main clinical symptoms in symptomatic patients are low-grade fever, conjunctivitis, transient joint pain (mainly in the smaller joints of the hands and feet) and maculopapular rash that often starts on the face and then spreads throughout the body.

The most common symptoms are

- Mild to severe fever.
- Non-purulent conjunctivitis.
- Joint pains.
- Headache.
- Myalgia.
- Oedema.
- Weakness.
- Rash.

Person may also experience

- Vomiting.
- Diarrhea.
- Loss of appetite.
- Abdominal pain.
Person at risk for more severe symptoms

- Infants
- The elderly
- Women in an advanced stage of pregnancy
- Persons with underlying medical conditions such as diabetes, heart diseases, hypertension and sickle cell disease.

ZIKA VIRUS AND PREGNANCY\textsuperscript{[23,24]}

Zika, which has been spreading quickly in the Americas, has been linked with a rise in a birth defect called microcephaly that causes babies to be born with abnormally small heads. The link between Zika and microcephaly is still being investigated, but authorities are warning pregnant women to avoid traveling to countries most affected by the virus, and women living in some of these countries to try to delay getting pregnancy.
Symptoms of Microcephaly\textsuperscript{[25,26]}
- Seizures
- Backward-sloping forehead
- Hyperactivity
- Facial distortions
- Delays in speech and movement
- Dwarfism
- Coordination difficulties
- Small head size

Pregnant women can be infected with Zika virus
- The primary way that pregnant women get Zika virus is through the bite of an infected mosquito.
- Zika virus can be spread by a man to his sex partners.

A pregnant woman can pass Zika virus to her fetus
- Zika virus can be passed from a pregnant woman to her fetus during pregnancy or at delivery.

FUTURE PREGNANCIES
Based on the available evidence, Zika virus infection in a woman who is not pregnant would not pose a risk for birth defects in future pregnancies after the virus has cleared from her blood. From similar infections, once a person has been infected with Zika virus, he or she is likely to be protected from a future Zika infection.

DIAGNOSTIC TEST\textsuperscript{[27,28]}
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 areas. The methods currently available to test for Zika antibodies cross-react with dengue antibodies. An IgM-positive results in a dengue or Zika ELISA test can only be considered indicative of a recent flavivirus infection. Plaque-reduction neutralization tests can be performed and may be specific. The Zika virus can be identified by RT-PCR in acutely ill patients.

TREATMENT\textsuperscript{[29]}
- Get plenty of rest.
• Drink fluids to prevent dehydration.
• Take medicine such as acetaminophen or paracetamol to reduce fever and pain.
• Do not take aspirin and other non-steroidal anti-inflammatory drugs (NSAIDS) until dengue can be ruled out to reduce the risk of bleeding.
• If you are taking medicine for another medical condition, talk to your healthcare provider before taking additional medication.

PREVENTION\textsuperscript{[30,31,32]}

The virus is spread by mosquitoes, making mosquito avoidance an important element to disease control.
• Cover exposed skin by wearing long-sleeved shirts and long pants.
• Use an insect repellent containing DEET, picaridin, oil of lemon eucalyptus (OLE), or IR3535.
• Always follow product directions and reapply as directed.
• If you are also using sunscreen, apply sunscreen first, let it dry and then apply insect repellent.
• Follow package directions when applying repellent on children. Avoid applying repellent to their hands, eyes, or mouth.
• Stay and sleep in screened-in or air-conditioned rooms.
• Use a bed net if the area where you are sleeping is exposed to the outdoors.

The recommends strategies for controlling mosquitoes such as eliminating standing water, repairing septic tanks and using screens on doors and windows. Spraying insecticide is used to kill flying mosquitoes and larvicide can be used in water containers. Because Zika virus may be sexually transmitted, men who have gone to an area where Zika fever is occurring should be counseled to either abstain from sex or use condoms if their partner is pregnant; they should consider using condoms even if she is not. Breastfeeding is still recommended by the WHO, even by women who have had Zika fever. There have been no recorded cases of Zika transmission to infants through breastfeeding, though the replicative virus has been detected in breast milk.

VACCINE\textsuperscript{[33]}

There is currently no vaccine but Bharat Biotech, a Hyderabad based company, amidst an Ebola like deje vu moment for the world, has recently announced that they have developed
two vaccines (ZIKAVAC) to fight against Zika Virus one is a recombinant vaccine and another an inactivated vaccine that has reached the stage of pre-clinical testing in animals. Even though the virus is yet to spread in parts of India, it is imperative for the hoi polloï to be aware of its spread, chiefly for two reasons. The first and the more universal reason are because the virus has reached pandemic levels in various parts of Central and South Americas. As recently as last month the U.S. Center for Disease Control and Prevention has issued guidelines concerning pregnant women for future travels in the affected countries. The second reason, being much closer to home, is that the virus belonging to the family Flaviviridae, is related to other pathogenic vector borne flaviviruses like dengue, a disease that is all too common among the lower-middle class and related income groups in India.

**CONCLUSION**

Zika virus is one of the recently known infection which has reported outbreaks in many countries namely America and Africa. The transmission of this virus is usually through mosquitoes hence strategies for controlling mosquitoes such as eliminating standing water, repairing septic tanks, using screens on doors and windows, spraying insecticide should be followed. Further there is also evidence of transmission of Zika virus through sex and to the infants by their mother causing birth defects. Therefore the U.S. Centers for Disease Control and Prevention (CDC) and other governments or health agencies issued travel guidance on affected countries, including the use of enhanced precautions, and guidelines for pregnant women including considering postponing travel. Currently there is no appropriate treatment and vaccine available for this infection thus prevention is the only better remedy to stay away from this infection.

**REFERENCES**

8. Enfissi, Antoine; Codrington, John; Roosblad, Jimmy; Kazanji, Mirdad; Rousset, Dominique,"Zika virus genome from the Americas". Lancet, 2016; 387(10015): 227–8.
20. Centers for Disease Control and Prevention (CDC) - Zika Virus.


28. Microbeonline- Zika virus: Transmission, Pathogenesis, symptoms and laboratory diagnosis,


