

**ZIKA VIRUS: AN ALARMING TERROR OF PRESENT DAY**Siddhanadham Arun Satyadev<sup>\*1</sup>, Venkata Raj Kumar Prava<sup>1</sup>, Aparna Koduru<sup>1</sup>, Karishma<sup>2</sup><sup>1</sup>A.U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam.<sup>2</sup>Shri Vishnu College of Pharmaceutical Sciences, Bhimavaram, East Godavari.**\*Corresponding Author: Siddhanadham Arun Satyadev**

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**ABSTRACT**

Zika is an important virus which is discussed the most in recent years. It is creating terror in many parts of the world. It is very important to have a focus on this virus as it is not only infecting adults but also causing birth defects in infants. It is caused by the virus "Zika" which is a flavivirus. It is mainly transmitted through mosquitoes which act as a vector. This virus is transmitted by mosquito *Aedes* species of mosquitoes. This virus is transmitted by similar mosquito which causes chikungunya, and dengue. This virus has potential to cause severe health hazards in both infants and adults. Most common defect caused by this virus is microcephaly in infants. Mostly zika virus transmitted from mother to child. The present review deals with the introduction of zika, its structure, geographical distribution, symptoms and treatment. As zika virus is fast approaching many tropical countries where the vector is widely available. Mostly pregnant women and infants are prone to this virus. Government of India should take proper preventive measures to cease outbreak of zika.

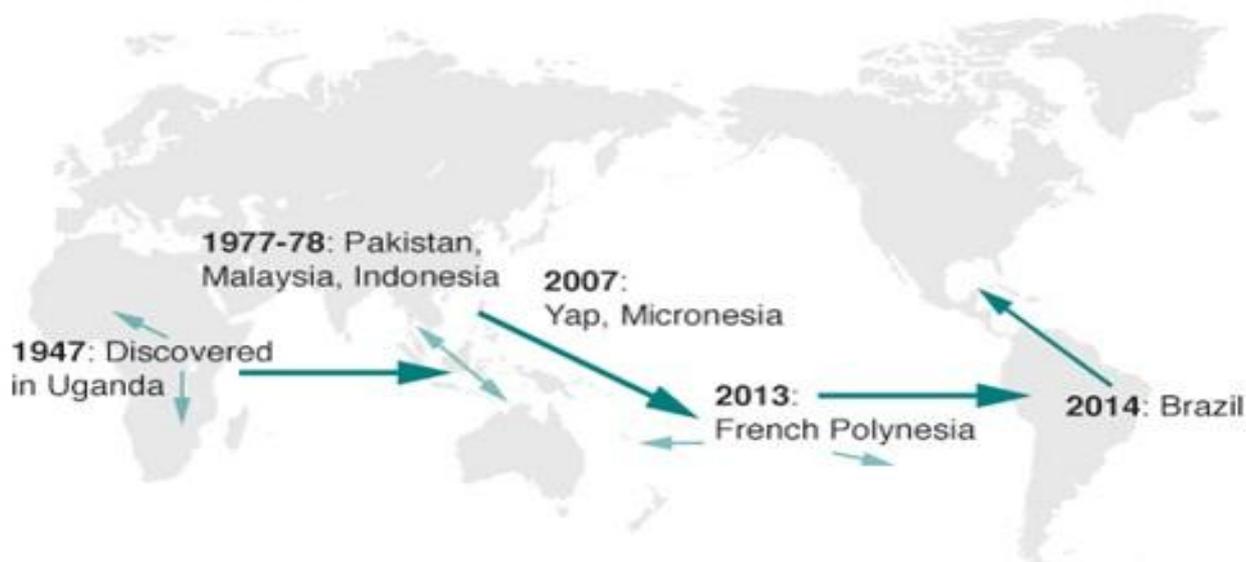
**KEYWORDS:** Zika, flavivirus, *Aedes* species, chikungunya, dengue, microcephaly.**INTRODUCTION**

Zika virus is similar to the virus which causes dengue, chikungunya, yellow fever. Zika or Zika fever is caused by the virus Zika which is transmitted by *Aedes* mosquito. This virus is transmitted from mother to child in case of pregnant ladies. This virus crosses the placental barrier and effects the growth of the infant and causes microcephaly in infants. The common symptoms include fever, rashes, joint pain and conjunctivitis. Zika is not a new virus as it is already affected South Asian countries, Africa, and some of the Pacific islands. This virus is in dormant stage in the amniotic fluid, semen in men. This virus not only transmitted by mosquitoes but this virus also transmitted through sexual contact. This virus can pass through highly lipidic membranes like placental membrane, blood brain barrier, seritoli cell barrier. The deaths due to this virus is rare. There is no vaccine for the prevention of this virus.

**EPIDEMIOLOGY**

- The Zika virus was accidentally isolated from rhesus macaque which is caged in Zika forest in Uganda by Yellow fever research institute.<sup>[1]</sup>
- The same virus is isolated again from the mosquito *A. africanus* in January 1948.<sup>[2]</sup>
- They isolated the same virus from the infected monkey and described Zika virus in 1952.

- It was first identified in the blood sample of a Nigerian in 1968.<sup>[3]</sup>
- From 1951 to 2007 the cases of Zika fever is rare in African and Southeastern countries of Asia.
- In 2007 the outbreak of Zika is found in in the island Yap in Federated national of Micronesia with 185 confirmed cases of zika fever which is characterized by fever, rashes, conjunctivitis.



- In October 2013, French Polynesia reported its first outbreak, which was estimated to affect around 11% of the population. This particular outbreak spread to other Pacific Islands including New Caledonia, Cook Islands, and Easter Island. As most cases of Zika virus infection present with mild illness similar to other circulating arbovirus infections, and there was limited laboratory capacity during this outbreak for the detection of Zika virus, it is likely that many cases of infection were not identified.
- The largest outbreak is in 2015 in Brazil. Brazilian health authorities reported more than 3,500 microcephaly cases between October 2015 and January 2016.
- As of 25 February 2016, 42 countries and territories have reported autochthonous cases of Zika virus.
- On 26 February, a rapid communication published in Eurosurveillance reported a case of Zika virus infection imported in Florence, Italy, from Thailand, which led to a secondary autochthonous case, probably through sexual transmission. The two cases occurred in May 2014 but were retrospectively diagnosed in 2016 on the basis of serological tests (plaque reduction neutralization) performed on stored serum samples.<sup>[4]</sup>
- According to the Ministry of Health, there have been 5 640 cases of microcephaly notified to date in Brazil compared with 5 280 a week earlier. As of 20 February 2016, 583 of these cases were confirmed to have microcephaly and/or other central nervous system findings suggestive of congenital infection. Of the total confirmed cases, 67 fulfilled specific laboratory criteria for Zika virus.
- Across the country, 4 107 suspected cases of microcephaly remain under investigation. The cases have been reported from 1 101 municipalities in 25 Brazilian states.
- Furthermore, countries reporting cases in the past two months can be described as either: experiencing increasing or widespread transmission; or reporting sporadic transmission following recent introduction of the virus.
- Countries or territories with reported confirmed autochthonous cases of Zika virus infection.<sup>[5]</sup>

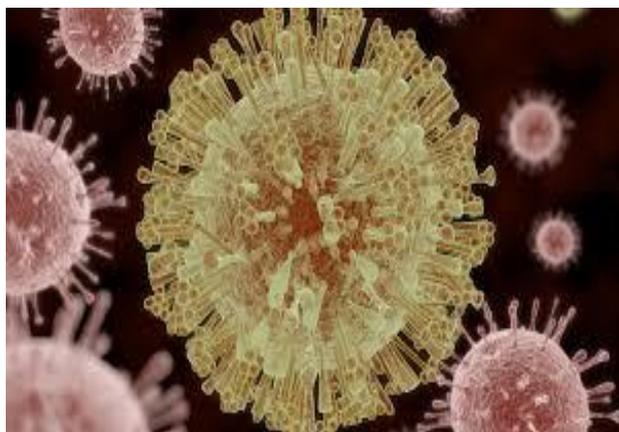
| Country            | Affected in the past 9 months | Affected in the past 2 months                       |
|--------------------|-------------------------------|---|
| American Samoa     | Yes                           | Sporadic transmission following recent introduction |
| Barbados           | Yes                           | Increasing or widespread transmission               |
| Bolivia            | Yes                           | Sporadic transmission following recent introduction |
| Brazil             | Yes                           | Increasing or widespread transmission               |
| Cabo Verde         | Yes                           | Increasing or widespread transmission               |
| Colombia           | Yes                           | Increasing or widespread transmission               |
| Costa Rica         | Yes                           | Sporadic transmission following recent introduction |
| Curaçao            | Yes                           | Sporadic transmission following recent introduction |
| Dominican Republic | Yes                           | Increasing or widespread transmission               |
| Ecuador            | Yes                           | Increasing or widespread transmission               |
| El Salvador        | Yes                           | Increasing or widespread transmission               |
| Fiji               | Yes                           | No  |
| French Guiana      | Yes                           | Increasing or widespread transmission               |

|                                  |     |   |
|----------------------------------|-----|---|
| Guadeloupe                       | Yes | Sporadic transmission following recent introduction |
| Guatemala                        | Yes | Increasing or widespread transmission               |
| Guyana                           | Yes | Sporadic transmission following recent introduction |
| Haiti                            | Yes | Increasing or widespread transmission               |
| Honduras                         | Yes | Increasing or widespread transmission               |
| Jamaica                          | Yes | Sporadic transmission following recent introduction |
| Maldives                         | Yes | No  |
| Martinique                       | Yes | Increasing or widespread transmission               |
| Mexico                           | Yes | Increasing or widespread transmission               |
| New Caledonia (France)           | Yes | No  |
| Nicaragua                        | Yes | Sporadic transmission following recent introduction |
| Panama                           | Yes | Increasing or widespread transmission               |
| Paraguay                         | Yes | Increasing or widespread transmission               |
| Puerto Rico                      | Yes | Increasing or widespread transmission               |
| Saint Martin                     | Yes | Sporadic transmission following recent introduction |
| Samoa                            | Yes | Sporadic transmission following recent introduction |
| Solomon Islands                  | Yes | No  |
| Suriname                         | Yes | Increasing or widespread transmission               |
| Thailand                         | Yes | Sporadic transmission following recent introduction |
| Bolivarian Republic of Venezuela | Yes | Increasing or widespread transmission               |
| Tonga                            | Yes | Sporadic transmission following recent introduction |
| Virgin island (US)               | Yes | Sporadic transmission following recent introduction |

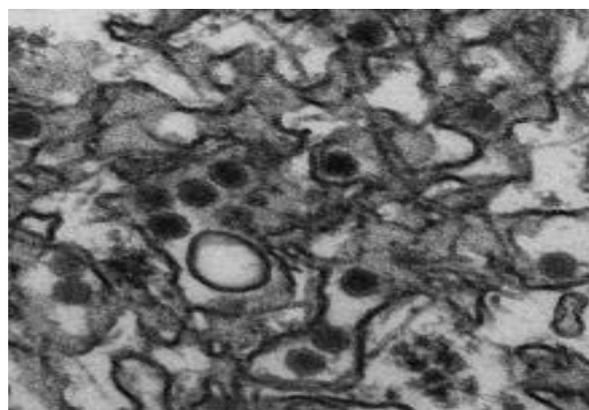
- The classification of countries above is based on: 1) number of reported autochthonous confirmed cases; 2) number of affected areas in the country; 3) duration of the circulation.

#### Structure of zika virus

- Structure of Zika virus follows that of other flaviviruses.
- It contains a nucleocapsid approximately 25-30nm in diameter surrounded by a host membrane derived lipid bilayer that contains envelope proteins E and M.
- The virion is approximately 40nm in diameter with surface projections that measure roughly 5-10 nm.
- The surface proteins are arranged in an icosohedral like symmetry.



Electron microscope image of zika virus.

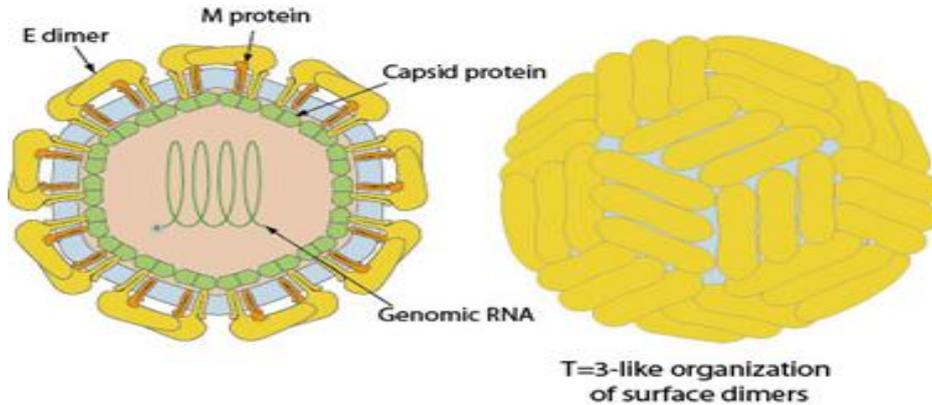


Electron micrograph of Zika virus. Virus particles are 40 nm in diameter, with an outer envelope and a dense inner core (source: CDC).

#### Genomic structure

- Zika virus is a positive sense single stranded RNA molecule 10794 bases long with 2 non coding regions flanking regions known as the 5'NCR and the 3'NCR.<sup>[6]</sup>
- The open reading frame of Zika virus reads as follows: 5'C-prM-E- NS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5-3' and codes for a ployprotein that is subsequently cleaved into capsid©, precursor membrane (prM), envelope (E), and non structural proteins (NS).<sup>[7]</sup>
- The E protein composes the majority of the virion surface and is involved with aspects of replication such as host cell binding and membrane fusion.
- NS1, NS3, and NS5 are large, highly-conserved proteins while the NS2A, NS2B, NS4A, and NS4B proteins are smaller, hydrophobic proteins.

- Located in the 3' NCR are 428 nucleotides that may play a part in translation, RNA packaging, cyclization, genome stabilization, and recognition.
- The 3' NCR forms a loop structure and the 5' NCR allows translation via a methylated nucleotide cap or a genome-linked protein.
- The genome 5' end has a methylated nucleotide cap for canonical cellular translation. The 3' terminal is not polyadenylated but forms a loop like structure.



- This secondary structure leads to the formation of subgenomic flavivirus RNA (sfRNA) through genomic RNA degradation by host XRN1. sfRNA is essential for the pathogenicity, and it may also play a role in inhibiting host RIG-I antiviral activity shown by dengue virus (flavivirus).<sup>[8]</sup>

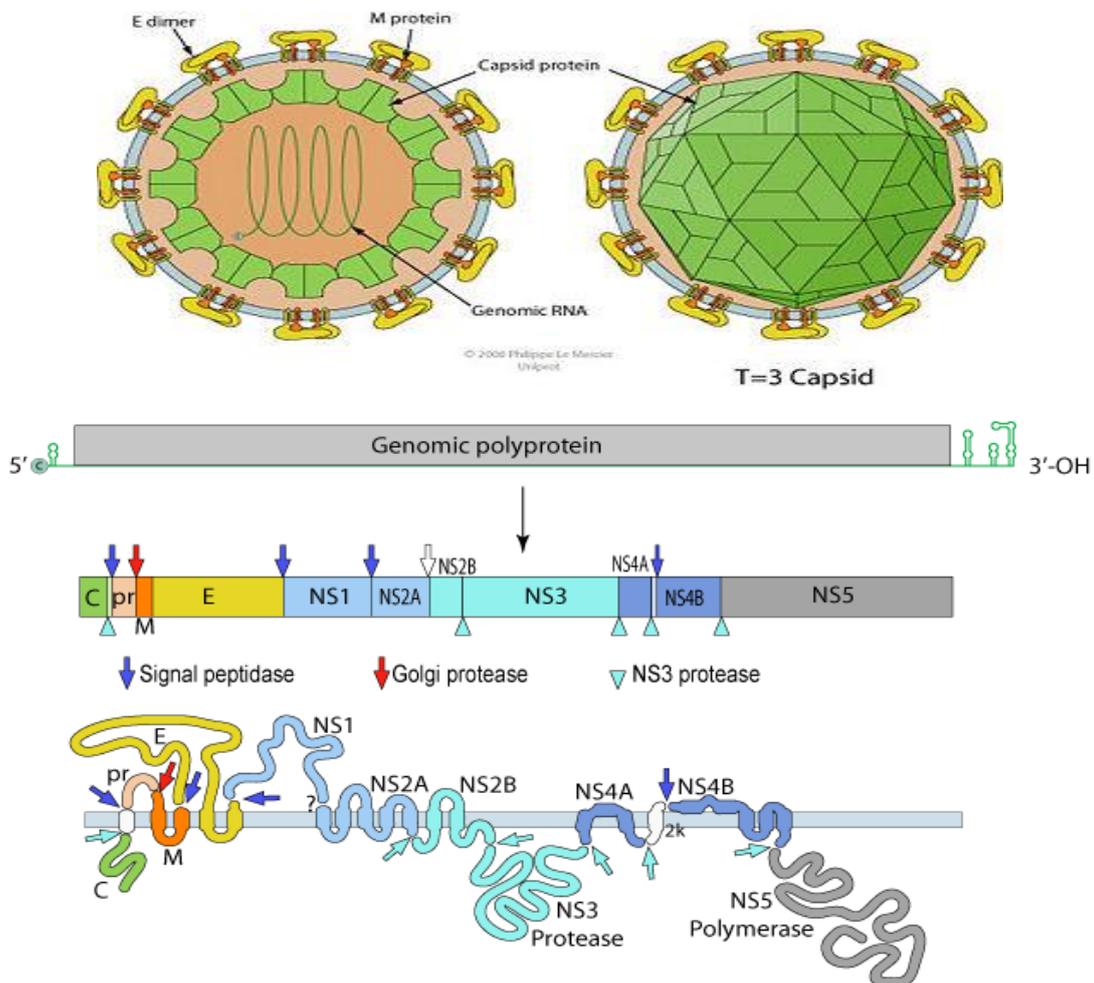
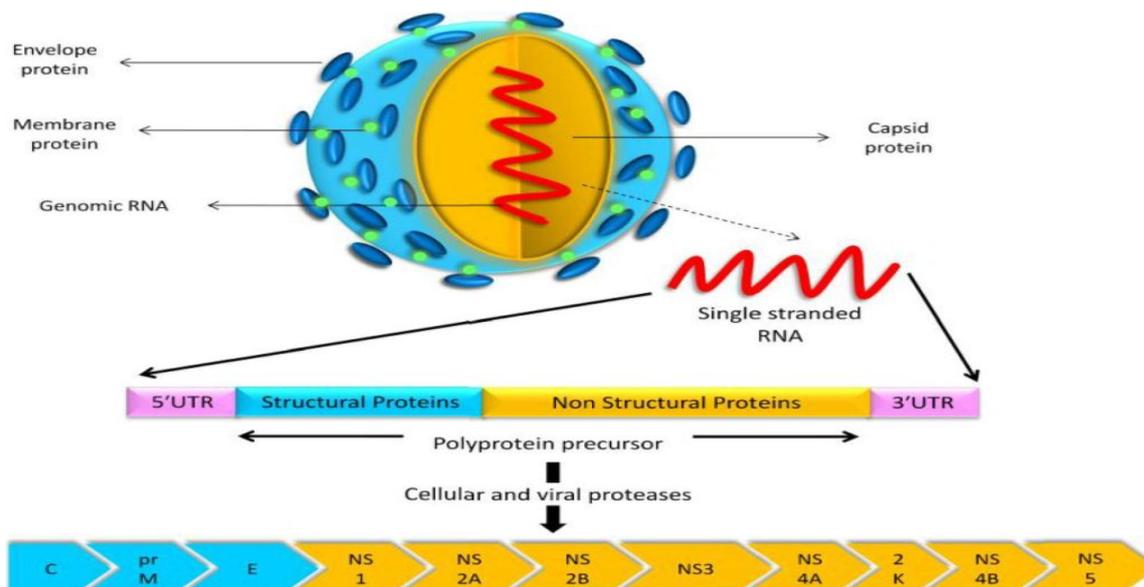


Diagram of typical genome structure of a flavivirus.



### Genomic structure of zika virus

#### Replication of zika virus in human cells

The replication of zika virus is similar to the replication of other flavivirus.

- First the virion attaches to the host receptors in the cell membrane which mediates the internalization into the host cell by clathrin-mediated endocytosis or by apoptotic mimicry.
- Next virus membrane fusions with the host endosomal membrane. Then RNA genome is released into the cytoplasm of the host cell.
- The positive sense ssRNA genome is translated into a polyprotein that is cleaved to form all structural and non-structural proteins.
- Replication takes place at the intracellular compartments of endoplasmic reticulum in cytoplasmic viral factories resulting in formation of dsRNA genome which is synthesised from ssRNA.
- The dsRNA genome is transcribed or replicated thereby providing viral mRNAs or new ssRNA (+) genomes.
- Assembly of virus then occurs in the endoplasmic reticulum then the new virion buds via the host ESCRT complexes at the endoplasmic reticulum, and is transported to golgi apparatus.
- The prM protein is cleaved in the Golgi complex, thereby maturing the virion which is a fusion component.
- Then these virions are excreted into the intracellular space by exocytosis where these new virions can infect new host cells.<sup>[8]</sup>

#### Signs and symptoms of zika fever

- About 1 in 5 people infected with Zika will get sick. For people who get sick, the illness is usually mild. For this reason, many people might not realize they have been infected.

- The incubation period of Zika virus is approximately three to 12 days after the bite of an infected mosquito.

[incubation period: the time from exposure to symptoms]  
[maculopapular rash: redness of skin or mucous membranes/confluent bumps]

- The symptoms are similar to other arbovirus infections such as dengue and include fever, Maculopapular rash, conjunctivitis, muscle and joint pain, malaise and headache.<sup>[9]</sup>

[arbovirus:group of viruses that are transmitted through arthropod vectors]

- These symptoms are usually mild and last for 2-7 days.
- During large outbreaks in French Polynesia and Brazil in 2013 and 2015 respectively, national health authorities reported potential neurological and autoimmune complications of Zika virus disease.
- Recently in Brazil, local health authorities have observed an increase in Zika virus infections in general public as well as an increase in babies born with microcephaly in northeast Brazil.
- [microcephaly: abnormal smallness of head, a congenital condition associated with incomplete brain development.]



Symptoms of zika fever



Conjunctivitis due to zika fever



Rashes due to zika fever

### Microcephaly

Microcephaly is a birth defect where a baby's head is smaller than expected when compared to babies of the same sex and age. Babies with microcephaly often have smaller brains that might not have developed properly. During second trimester of pregnancy, a baby's head grows because the baby's brain grows. Microcephaly can occur because a baby's brain has not developed properly during pregnancy or has stopped growing after birth, which results in a smaller head size. Microcephaly can be an isolated condition, meaning that it can occur with no other major birth defects, or it can occur in combination with other major birth defects.<sup>[10]</sup>



Baby with Microcephaly

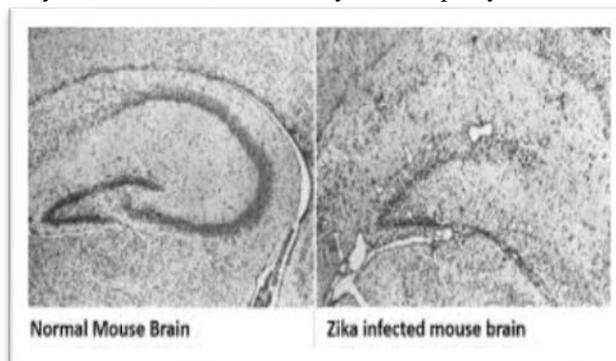
### Risk Factors

The causes of microcephaly in most babies are unknown. Some babies have microcephaly because of some mutations in their genes. Other causes of microcephaly can include the following exposures during pregnancy.

- Certain infections, such as rubella, toxoplasmosis, or cytomegalovirus.
- Severe malnutrition, meaning a lack of nutrients or not getting enough food
- Exposure to harmful substances, such as alcohol, certain drugs, or toxic chemicals

CDC (Centers of Disease Control and Prevention) continues to study birth defects, such as microcephaly, and how to prevent them. If you are pregnant or thinking about becoming pregnant, talk with your doctor about ways to increase your chances of having a healthy baby.<sup>[11]</sup>

Baby infected with zika virus by microcephaly



Comparison between a Mouse infected by zika virus and normal brain of normal mouse.

### Other problems with microcephaly

Microcephaly is not a common disorder. Babies with microcephaly can have a range of other problems, depending on the severity of their microcephaly. Microcephaly may have relation with the following problems:

- Seizures
- Developmental delay, such as problems with speech or other developmental milestones (like sitting, standing, and walking)
- Intellectual disability (decreased ability to learn and function in daily life)
- Problems with movement and balance
- Feeding problems, such as difficulty swallowing
- Hearing loss
- Vision problems

These problems can range from mild to severe and are often lifelong. In some cases, these problems can be life-threatening. Because it is difficult to predict at birth what problems a baby will have from microcephaly.<sup>[11]</sup>

### Diagnosis

Zika virus is diagnosed through PCR (polymerase chain reaction) and virus isolation from blood samples.<sup>[12]</sup>

- PCR test is used to detect the viral RNA as well as it also detect zika virus antibody (IgM) in serum. IgM for zika virus is typically detectable after 3-5 days of infection.
- Diagnosis by serology can be difficult as the virus can cross-react with other flaviviruses such as dengue, West Nile and yellow fever.
- This cross-reactive result is more common in patients who were infected by flavivirus previously than patients with primary zika virus infection.

- For better diagnosis results, serum sample should be analyzed as early as possible with a second test 2 to 3 weeks after the first test.

#### During Pregnancy

- During pregnancy, sometimes microcephaly can be diagnosed during an ultrasound scan (which creates pictures of the body).
- To see microcephaly during pregnancy, the ultrasound test should be done late in the 2nd trimester or early in the third trimester.

#### After Child Birth

- To diagnose microcephaly after birth, a healthcare provider has to measure the distance around a newborn baby's head, also called the head circumference, during the physical examination. The healthcare providers then have to compare those measurements with population standards by sex and age.
- Head circumference charts for newborns, infants, and children up to age 20 years in the United States can be found on standard CDC's growth charts website.
- CDC recommends that health care providers to use the WHO growth charts to monitor growth for infants and children ages 0 to 2 years of age in the U.S.
- Often, healthcare providers should take the head circumference measurement when the newborn baby is at least 24 hours old.
- This helps make sure that compression due to delivery through the birth canal has resolved.
- If the healthcare provider suspects the baby has microcephaly, he or she can request one or more tests to help confirm the diagnosis.
- For example, special tests like a CT scan or an MRI can provide critical information on the structure of the baby's brain that can help determine if the newborn baby had an infection during pregnancy.

#### Guillain-Barré Syndrome (GBS)

Guillain-Barré syndrome (GBS) is a rare disorder where a person's own immune system damages the nerve cells, causing muscle weakness and sometimes, paralysis. These symptoms can last for a few weeks or several months. While most people fully recover from GBS, some people have permanent damage and in rare cases, people have died.<sup>[13]</sup>

Zika virus is proved to cause GBS. The Brazil Ministry of Health is reporting an increased number of people affected with GBS.

GBS was reported during the 2014 outbreak in French Polynesia and the Americas since 2015. A similar increase along with an unusual increase of congenital microcephaly was observed in some regions in north eastern Brazil in 2015.

#### Transmission

- Zika virus is transmitted to people by mosquitoes. It has been isolated from *Aedes aegypti* mosquitoes and experimental infections show that this species is capable of transmitting Zika virus.
- Other *Aedes* mosquito species (notably *Ae. africanus*, *Ae. albopictus*, *Ae. polynesiensis*, *Ae. unilineatus*, *Ae. vittatus* and *Ae. hensilli*) are considered as potential vectors of Zika virus. These species bite during the day.<sup>[14]</sup>
- *Aedes* genus, mainly *Aedes aegypti* mosquitoes are mainly present in tropical regions. This is the same mosquito that transmits dengue, chikungunya and yellow fever.



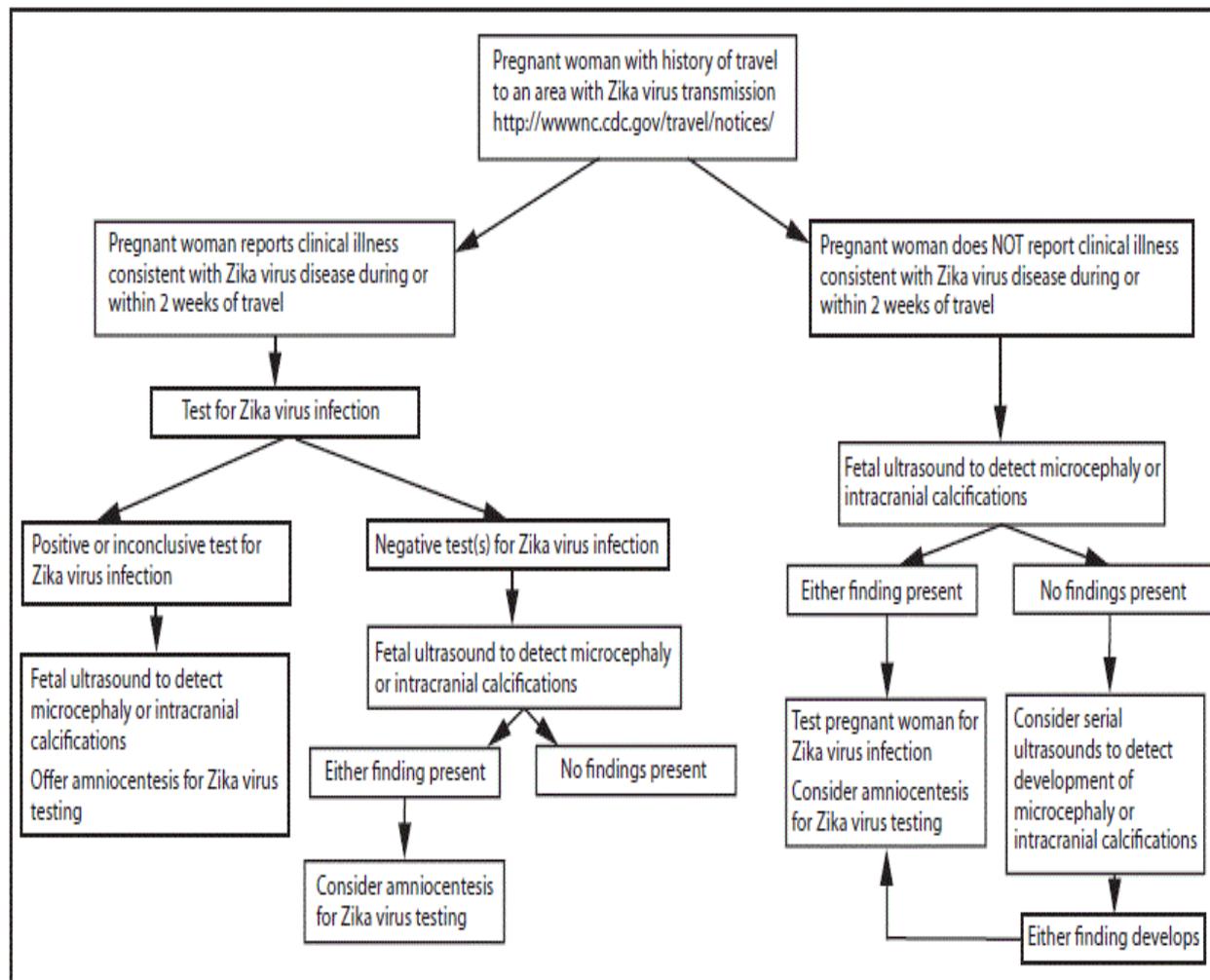
*Aedes aegypti*—a mosquito vector of Zika virus

- Zika virus is mainly transmitted by daytime-active mosquitoes and has been isolated from a number of species in the genus *A. edes*, such as *A. aegypti*, and arboreal mosquitoes such as *A. africanus*, *A. apicoargenteus*, *A. furcifer*, *A. hensilli*, *A. luteocephalus* and *A. vittatus*. Studies show that the extrinsic incubation period in mosquitoes is about 10 days.
- Zika virus can transmit from person to person through sexual contact and it can also cross the placenta, affecting an unborn fetus.
- 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, but it is rare.
- Additional modes of transmission have been identified. Perinatal transmission can occur most probably by trans-placental transmission or during delivery when the mother is infected.<sup>[15]</sup>
- Sexual transmission was reported in a few instances.<sup>[16]</sup>
- The vertebrate hosts of the virus are primarily monkeys and humans. Before the current pandemic, which began in 2007, Zika virus "rarely caused recognized 'spillover' infections in humans, even in highly enzootic areas".
- Travelling to Zika virus infected countries<sup>[17]</sup>
- There is a potential risk of Zika virus transmission from a blood transfusion.
- In 2015, Zika virus RNA was detected in the amniotic fluid of two fetuses, indicating that it had crossed the placenta and could cause a mother-to-child infection.<sup>[18]</sup>

### Treatment

There is currently no vaccine available.<sup>[19]</sup>

- Zika virus disease is usually relatively 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 advice.
- Do not take aspirin or other non-steroidal anti-inflammatory drugs.
- If you are taking medicine for another medical condition, talk to your healthcare provider before taking additional medication.



### Prevention and control of zika virus

Mosquitoes and their breeding sites are the significant risk factor for Zika virus infection. Prevention and control relies on reducing mosquitoes through source reduction and reducing contact between mosquitoes and people.

- This can be done by using insect repellent;
- Wearing clothes (preferably light-coloured) that cover as much of the body as possible;
- Using physical barriers such as screens, closed doors and windows
- Sleeping under mosquito nets.
- It is important to empty, clean or cover containers that can hold water such as buckets, flower pots or

tyres, so that places where mosquitoes can breed are removed.

- Special attention and help should be given to those who may not be able to protect themselves adequately, such as young children, the sick or elderly.
- During outbreaks, health authorities may advise to spray insecticides which are to be carried out.
- Insecticides recommended by the WHO Pesticide Evaluation Scheme may also be used as larvicides to treat relatively large water containers.



- Avoid travel to areas with an active infestation.
- Travellers should take the basic precautions described above to protect themselves from mosquito bites.
- Reducing mosquito populations and avoiding bites, which occur mainly during the day.
- Eliminating and controlling *Aedes aegypti* mosquito breeding sites reduces the chances that Zika will be transmitted.<sup>[20]</sup>

#### What About India

India is one of the *Aedes aegyptis*'s many homes but the Zika virus itself has not ever been detected in our country so far.

- However, in a study in the 1950s, healthy individuals from six Indian states showed passive immunity to the virus. This means that though their blood contained antibodies against the virus, this was not because they were exposed to the virus. Usually passive immunity is acquired through vaccines, from mother-to-child transmissions or breast milk.
- In the case of India, where the Zika virus is not known to exist, the antibodies probably arose from exposure to similar viruses. One likely candidate for this similar virus is the dengue virus, also carried by the same mosquito and prevalent here.
- Nevertheless, theoretically, Zika can spread anywhere that the mosquito exists. That means India, too. Indians are just as susceptible if they travel to high-risk countries. The best case scenario is that we remain as lucky as we have so far with yellow fever (another *Aedes aegypti* cargo).<sup>[21]</sup>

#### Vaccine Development

- Work has begun towards developing a vaccine for Zika virus, according to Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases.

- Nikos Vasilakis of the Center for Biodefense and Emerging Infectious Diseases predicted that it may take two years to develop a vaccine, but 10 to 12 years may be needed before an effective Zika virus vaccine is approved by regulators for public use.<sup>[22]</sup>

#### Genetically Engineered Solution

- Our first preventive measure is to eradicate mosquitoes by different measures like fumigation and removing the source of stagnant water where the mosquitoes breed.
- Biotech based vector control solution is the use of genetically engineered mosquitoes developed by the British firm Oxitec.
- The modified male *Aedes aegypti* mosquitoes mate with females in the wild population and produce offspring that do not survive to adulthood, essentially making the males sterile.
- Such a mosquito was approved for use in the city of Piracicaba, Brazil last year in the middle of the dengue outbreak and trials showed that they reduced vector populations by as much as 82 percent.
- Oxitec announced that it was expanding its production facilities in Piracicaba in view of a potentially increased demand to combat dengue and Zika.<sup>[23]</sup>
- Though a similar trial was proposed in Florida which also has a high *Aedes* mosquito population, its adoption has been controversial in the United States. The FDA is currently reviewing the application for a trial and it is not known whether the rapid spread of Zika and its potential to quickly move to the US will hasten the process in any way.

#### CONCLUSION

Zika virus is so dangerous as it is infecting the new generation causing neurological diseases like microcephaly and Guillain-Barré syndrome (GBS). It is transmitted by mother to child, by vector like *Aedes* mosquitoes, and it is also transmitted sexually. It is

mainly crossing countries by travelers from one infected country to the other. As it is mainly transmitted by mosquitoes, certain measurements have to be taken by the government and WHO to protect the lives of new generation and to ensure their future. It is causing severe neurological diseases. The preventive measures are to be taken during tour to zika virus infected areas by protecting them day time mosquitoes and pregnant ladies must take care that no mosquitoes are there. The couple who are planning children they should consult healthcare provisionals and should be tested for the presence of zika virus. There is no specific treatment for this virus. There is no vaccination for this virus. The government has to support the research on zika virus.

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