



## **COMMENTARY**

### **Zika Virus Disease: The New Public Health Emergency of International Concern**

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#### **Abstract**

Zika virus is an emerging mosquito-borne virus that was first identified in Uganda in 1947 in rhesus monkeys. 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. The causal link between Zika and microcephaly has still not been confirmed, but the preliminary evidence for an association is strong. WHO has declared that the recent cluster of microcephaly cases and other neurological disorders reported in Brazil, following a similar cluster in French Polynesia in 2014, constitutes a Public Health Emergency of International Concern. A coordinated international response is needed to improve surveillance, detection of infections, congenital malformations, and neurological complications, to intensify the control of mosquito populations, and to expedite the development of diagnostic tests and vaccines to protect people at risk, especially during pregnancy. Government of India has accordingly formulated Guidelines on Zika Virus Disease following Epidemic in Brazil and other countries of Americas.

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It appears that zika virus infections convey lasting immunity, like chikungunya. However, as zika virus is a member of the Japanese Encephalitis Virus (JEV) serocomplex, there may be some cross-reactivity and potential cross neutralization to other members of the JEV group. The virus itself is going to be very difficult to eradicate and could be endemic. Control efforts, like spraying insecticides and covering standing water, would be of no value inside tropical rainforests. Aggressive urban mosquito abatement programs would help reduce human infections. The only hope for eliminating human disease would rest with the invention of an effective vaccine and mass routine vaccination in the affected countries.

## **Introduction**

Zika virus is an emerging mosquito-borne virus that was first identified in Uganda in 1947 among rhesus monkeys. It was subsequently identified in humans in 1952 in Uganda and the United Republic of Tanzania. Outbreaks of Zika virus disease have been recorded in Africa, the Americas, Asia and the Pacific.<sup>1,2</sup>

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 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.<sup>1</sup>

Zika fever or zika virus infection is an arbovirus infection transmitted by several different species of *Aedes* mosquitoes. Like many flaviviruses including dengue virus, zika virus typically causes fever, rash, headache, arthralgia and myalgia, as well as non-purulent conjunctivitis, but some patients are also asymptomatic. Zika virus appears to be highly neurotropic, and has been linked to human neurological syndromes, including Guillain-Barré syndrome.<sup>3</sup>

Zika fever was believed to have been introduced in Latin America in 2014. The highest microcephaly rates are reported from Brazil's northeastern region and states, although autochthonous transmission of zika fever is occurring in the tropical areas of South America, in addition to Central America and Mexico.<sup>3</sup>

The causal link between zika and microcephaly has still not been confirmed, but the preliminary evidence for an association is pretty strong. Scientists have demonstrated zika virus genomic DNA in the blood and tissues of a baby with microcephaly and in the amniotic fluid of two pregnant women whose fetus were diagnosed with microcephaly through ultrasonography.<sup>3</sup>

As neither treatment nor vaccines are available, prevention is based on personal protection measures similar to the measures that are applied against dengue and chikungunya infections.<sup>4</sup>

According to Morbidity & Mortality Weekly Report of CDC, among a cohort of 35 infants with microcephaly born during August–October 2015 in eight of Brazil's 26 states, the mothers of all 35 had lived in or visited Zika virus-affected areas during pregnancy. 25 (71%) infants had severe microcephaly (head circumference less than 3 standard deviations below the mean for sex and gestational age), 17 (49%) had at least one neurologic abnormality, and among 27 infants who had neuroimaging studies, all had abnormalities.<sup>5</sup>

CDC recently tested samples from two pregnancies that ended in miscarriage and from two infants with microcephaly who died shortly after birth. All four cases were from Brazil and were positive for Zika virus infection, indicating that the infants had become infected during pregnancy. Zika virus was present in the brain of the full term infants, and genetic sequence analyses showed that the virus strain in all four cases was same as the Zika virus strain currently circulating in Brazil. All four mothers reported having experienced a febrile rash illness during their pregnancies.<sup>5</sup>

### **Public Health Emergency of International Concern**

An Emergency Committee convened by World Health Organization, under the International Health Regulations looked in particular at the strong association, in time and place, between infection with the Zika virus and a rise in detected cases of

congenital malformations and neurological complications. A causal relationship between Zika infection during pregnancy and microcephaly is strongly suspected, though not yet scientifically proven. The lack of vaccines and rapid and reliable diagnostic tests, and the absence of population immunity in newly affected countries were further causes of concern.

WHO has declared on 1<sup>st</sup> February 2016 that the recent cluster of microcephaly cases and other neurological disorders reported in Brazil, following a similar cluster in French Polynesia in 2014, constitutes a Public Health Emergency of International Concern(PHEIC).<sup>6</sup>

A coordinated international response is needed to improve surveillance, the detection of infections, congenital malformations, and neurological complications, to intensify the control of mosquito populations, and to expedite the development of diagnostic tests and vaccines to protect people at risk, especially during pregnancy.

The Committee found no public health justification for restrictions on travel or trade to prevent the spread of Zika virus.

At present, the most important protective measures are the control of mosquito populations and the prevention of mosquito bites in at-risk individuals, especially pregnant women.

WHO has issued the following Temporary Recommendations under IHR (2005).

### **Microcephaly and neurologic disorders**

- Surveillance for microcephaly and GBS should be standardized and enhanced.
- Research into the etiology of new clusters of microcephaly and neurologic disorders should be intensified.

The Committee highlighted the importance of aggressive measures to reduce infection with Zika virus, particularly among pregnant women and women of childbearing age.

As a precautionary measure, the Committee made the following additional recommendations:

## **Zika virus transmission**

- Surveillance for Zika virus infection should be enhanced, with the dissemination of standard case definitions and diagnostics to at-risk areas.
- The development of new diagnostics for Zika virus infection should be prioritized.
- Risk communications should be enhanced in countries with Zika virus transmission.
- Vector control measures and appropriate personal protective measures should be aggressively promoted and implemented.
- Attention should be given to ensure women of childbearing age and particularly pregnant women to have the necessary information and materials for reducing risk of exposure.
- Pregnant women who have been exposed to Zika virus should be counselled and followed for birth outcomes.

## **Longer- term measures**

- Appropriate research and development efforts should be intensified for Zika virus vaccines, therapeutics and diagnostics.
- In areas of known Zika virus transmission health services should be prepared for potential increases in neurological syndromes and/or congenital malformations.

## **Travel measures**

- There should be no restrictions on travel or trade with countries, areas and/or territories with Zika virus transmission.

- Travellers to areas with Zika virus transmission should be provided with up to date advice on potential risks and appropriate measures to reduce the possibility of exposure to mosquito bites.
- Standard WHO recommendations regarding disinsection of aircraft and airports should be implemented.

## **Data sharing**

- National authorities should ensure the rapid and timely reporting and sharing of information of public health importance relevant to this PHEIC.

## **Government of India Guidelines on Zika Virus Disease.<sup>7</sup>**

As of now, the disease has not been reported in India. However, the mosquito that transmits Zika virus, namely *Aedes aegypti*, that also transmits dengue virus, is widely prevalent in India.

A majority of those infected with Zika virus disease either remain asymptomatic (upto 80%) or show mild symptoms of fever, rash, conjunctivitis, body ache, joint pains. Zika virus infection should be suspected in patients reporting with acute onset of fever, maculo-papular rash and arthralgia, among those individuals who travelled to areas with ongoing transmission during the two weeks preceding the onset of illness. Severe forms of disease requiring hospitalization are uncommon and fatalities are rare.

There is no vaccine or drug available to prevent/ treat Zika virus disease at present.

In the light of the current disease trend, and its possible association with adverse pregnancy outcomes, the Directorate General of Health Services, Ministry of Health and Family Welfare advises on the following:

### **1. Enhanced Surveillance**

#### **1.1. Community based Surveillance**

- Integrated Disease Surveillance Programme (IDSP) through its community and hospital based data gathering mechanism would track clustering of acute febrile

illness and seek primary case, if any, among those who travelled to areas with ongoing transmission in the 2 weeks preceding the onset of illness.

- IDSP would also advise its State and District level units to look for clustering of cases of microcephaly among newborns and reporting of Gullian Barre Syndrome.
- The Maternal and Child Health Division (under NHM) would also advise its field units to look for clustering of cases of microcephaly among newborns.

### **1.2 International Airports/ Ports**

- All the International Airports /Ports will display billboards/ signage providing information to travelers on Zika virus disease and to report to Custom authorities if they are returning from affected countries and suffering from febrile illness.
- The Airport / Port Health Organization (APHO / PHO) would have quarantine / isolation facility in identified Airports.
- Directorate General of Civil Aviation, Ministry of Civil Aviation will be asked to instruct all international airlines to follow the recommended aircraft disinsection guidelines
- The APHOs shall circulate guidelines for aircraft disinsection (as per International Health Regulations) to all the international airlines and monitor appropriate vector control measures in airport premises and in the defined perimeter.
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### **1.3 Rapid Response Teams**

- Rapid Response Teams (RRTs) shall be activated at Central and State surveillance units. Each team would comprise an epidemiologist / public health specialist,

microbiologist and a medical / paediatric specialist and other experts ( entomologist etc) to travel at short notice to investigate suspected outbreak.

- National Centre for Disease Control (NCDC), Delhi would be the nodal agency for investigation of outbreak in any part of the country.

#### **1.4 Laboratory Diagnosis**

- NCDC, Delhi and National Institute of Virology (NIV), Pune have the capacity to provide laboratory diagnosis of Zika virus disease in acute febrile stage. Ten additional laboratories would be strengthened by ICMR to expand the scope of laboratory diagnosis.

- RT-PCR test would remain the standard test. As of now there is no commercially available test for Zika virus disease. Serological tests are not recommended.

### **2. Risk Communication**

- The States/ UT Administrations would create increased awareness among clinicians including obstetricians, paediatricians and neurologists about Zika virus disease and its possible link with adverse pregnancy outcome (foetal loss, microcephaly etc). There should be enhanced vigilance to take note of travel history to the affected countries in the preceding two weeks.

- The public needs to be reassured that there is no cause for undue concern.

### **3. Vector Control**

- There would be enhanced integrated vector management with stress on vector surveillance (both for adult and larvae), vector management through environmental modification/ manipulation; personal protection, biological and chemical control at household, community and institutional levels. The measures undertaken for control of dengue/ dengue hemorrhagic fever will be further augmented.



#### 4. Travel Advisory

- Non-essential travel to the affected countries to be deferred/ cancelled. Based on available evidence, World Health Organization is not recommending any travel or trade restrictions.
- Pregnant women or women who are trying to become pregnant should defer/ cancel their travel to the affected areas.
- All travelers to the affected countries/ areas should strictly follow individual protective measures, especially during day time, to prevent mosquito bites.
- Persons with co-morbid conditions (diabetes, hypertension, chronic respiratory illness, Immune disorders etc) should seek advice from the nearest health facility, prior to travel to an affected country.
- Travelers having febrile illness within two weeks of return from an affected country should report to the nearest health facility.
- Pregnant women who have travelled to areas with Zika virus transmission should mention about their travel during ante-natal visits in order to be assessed and monitored appropriately.

#### 5. Non-Governmental Organizations

- Ministry of Health &FW / State Health Departments would work closely with Non-Governmental organizations such as Indian / State Medical Associations, Professional bodies etc to sensitize clinicians about Zika virus disease.

### Emergence and Persistence Patterns

It appears that zika virus infections convey lasting immunity, like chikungunya.

However, as zika virus is a member of the

Japanese Encephalitis Virus (JEV) serocomplex, there may be some cross-reactivity and potential cross neutralization to other members of the JEV group. There is conflicting information regarding the potential for zika virus cross-reactivity specifically with dengue virus. Some studies have demonstrated cross-reaction with

dengue virus , while others demonstrated that ELISA for IgM and IgG in zika virus acute and convalescent serum samples do not cross react with dengue virus .

Thus, there is still need for clarification of clinical protection and immunogenic cross reactivity of zika virus, dengue virus, and potentially other JEV group members.<sup>8</sup>

## **Vector Host Range**

Despite the importance of competent vector identification, in only two of the eleven outbreaks of the past decade have the vector(s) been identified: *Ae. albopictus* was incriminated as the primary vector in Gabon and *Ae. hensilli* in the Island of Yap outbreak; *Ae. aegypti* has been implicated in the on-going transmission in the Americas.<sup>8,9</sup>

## **Alternate routes and added complexity**

As dengue and chikungunya viruses are already established in the areas where zika virus is reported and/or has the potential to establish, there is a high likelihood for co-circulation. Arbovirus co-infection in mosquitoes do not often result in dually infectious mosquitoes, though there are few exceptions.

While dengue and chikungunya are primarily transmitted through the bite of infectious mosquitoes, Zika virus has been detected in urine and saliva, and there are case reports of sexual and perinatal transmission.<sup>8,10</sup>

Further, recent surges in microcephaly incidence in Brazil has coincided with the emergence of zika virus. The education infrastructure is likely to have a challenge in the years to come when this comparatively larger population of children with special needs enter the education system. Thus, the social implications of zika virus look to be more long-term and multifaceted than either dengue or chikungunya.<sup>8</sup>

## **Challenges**

The transmission of zika virus presents multiple challenges, especially in the prevention of maternal infection and congenital transmission.

There are also economic implications, including the prospect of taking care of a generation of neurodevastated children in northeastern Brazil, in addition to the possible derailment of the tourist industry in parts of the Caribbean and South America.

The virus itself is going to be very difficult to eradicate and could be endemic. Control efforts, like spraying insecticides and covering standing water, would be of no value inside tropical rainforests like the Amazon. Aggressive urban mosquito abatement programs would help reduce human infections. And in the end, the only hope for eliminating human disease would rest with the invention of an effective vaccine and mass, routine vaccination of hundreds of millions of people across the Western Hemisphere.<sup>11</sup>

The major outcome is microcephaly, which impacts pregnant women. The real problem is that, trying to develop a vaccine that would have to be tested on pregnant women, is a practical and ethical nightmare.<sup>11</sup>

The development of a zika vaccine could be a game-changer. It is not clear if the vaccine will be feasible or can be introduced in a timely manner.<sup>3</sup>

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