



## Zika Virus Diseases – The New Face of an Ancient Enemy as Global Public Health Emergency (2016): Brief Review and Recent Updates

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### ABSTRACT

Zika virus (ZIKV) disease is caused by a virus transmitted by *Aedes* mosquito. It presents as flu-like symptoms lasting for 5–7 days and shows potential association with neurological and autoimmune complications such as congenital microcephaly and adult paralysis disorder, Guillain–Barré syndrome. Treatment measures are conservative as the disease is self-limiting. ZIKV earlier affected several tropical regions of Africa and Asia from 1951 to 2006. Subsequently, it moved out from these regions to land as outbreaks in Yap Island, French Polynesia, South America, and most recently in Brazil. The WHO declared it as an international public health emergency in 2016 and an extraordinary event with recommendations for improving communications, tightening vigil on ZIKV infections, and improving mosquito control measures. The authors in this article aim to briefly discuss ZIKV infection, its epidemiology, clinical manifestations, management, and prevention.

**Keywords:** *Aedes*, arbovirus, congenital microcephaly, Guillain–Barré syndrome, Zika virus

### INTRODUCTION

Zika virus (ZIKV) infection, caused by ZIKV, is a vector-borne disease that spreads in humans through bites of infected female mosquitoes of the *Aedes* species. The mosquito vector carrying ZIKV has white speckles on its body and legs, is an aggressive biter, and is known to bite during day time with peaks during early afternoon and late afternoon/early evening hours. Two main mosquito species that have been implicated in outbreaks

of Zika virus disease (ZIKVD) are *Aedes aegypti* and *Aedes albopictus*. Other diseases similarly caused by related flaviviruses and having mosquito vectors include dengue, yellow fever, chikungunya, Japanese encephalitis, and West Nile fever. *A. aegypti* is the same mosquito that spreads dengue and chikungunya viruses, rendering it a triple threat mosquito.

### HISTORY AND EPIDEMIOLOGY OF ZIKA VIRUS INFECTION

ZIKV, closely related to the Spondweni serocomplex, was first isolated in 1947 from a monkey (Rhesus 766)

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living in the Zika forest of Uganda near Lake Victoria.<sup>[1]</sup> The scientists while carrying out research on yellow fever accidentally chanced upon the virus. They successfully isolated a transmissible agent from the serum of infected monkey that developed fever and dubbed it as ZIKV after the name of the forest it lived in. A second isolation happened at the same site in January 1948 from an arboreal mosquito *Australopithecus africanus* in Zika forest.<sup>[2]</sup>

Until this period, the virus was not known to cause any recognizable infection in humans. Later in 1952, it was detected for the first time in humans in Uganda and Tanzania, when neutralizing antibodies to ZIKV were found in their sera. It was thereafter discovered that the virus was mosquito-borne and could infect people as well as monkeys. From 1951 to 2006, confirmed ZIKV infection cases were only sporadically reported in humans and were limited to two dozen countries of Africa and parts of Southeast Asia [Table 1]. Accordingly, two lineages of ZIKV: African lineage and Asian lineage were described. ZIKV was identified for only 14 times in humans in this long span of half century.

### ZIKA VIRUS OUTBREAK IN YAP

April 2007 is considered a landmark period as far as spread of ZIKVD is concerned as it was during 2007, the virus popped outside Africa and Asia to affect an entire population on the Pacific island of Yap in the Federated States of Micronesia. The island reported 185 cases of suspected ZIKV infection from April to August 2007 to the Centre for Diseases Control and Prevention (CDC); of which 49 were confirmed by polymerase chain reaction (PCR) and 59 were probable cases as they carried IgM antibodies to ZIKV.<sup>[3]</sup> This outbreak was significant as a huge population was affected, and there were no conceivable monkey carriers seen. Before the Yap outbreak, ZIKVD was believed to primarily infect primates, and only occasionally cross over into humans.<sup>[4]</sup>

### ZIKA VIRUS OUTBREAK IN FRENCH POLYNESIA

The second outbreak surfaced in October 2013 in French Polynesia and extended till April 2014 resulting in over 30,000 patients presenting to health-care facilities for medical consultation.<sup>[4]</sup> The epidemic peaked in the 9<sup>th</sup> week with a decreasing trend seen after

mid-December 2013. Nearly 8,746 suspected cases of ZIKV infection and 383 confirmed cases were identified by the syndromic surveillance sentinel network of French Polynesia. This outbreak was unique as a spike in neurological complications and 42 cases of Guillain-Barré syndrome (GBS) were reported simultaneously. The doctors naturally started correlating these with ZIKV infection. However, a direct association between ZIKV infection and its severe presentation required establishment, as simultaneous prolonged co-circulation of dengue virus was also seen. Death related to infection was not reported.

During this same period, ZIKV outbreaks were also notified in three other islands of Pacific Region: Cook Islands (932 suspected cases and 54 confirmed cases), New Caledonia (1400 confirmed cases), and Easter Island (89 suspected cases and 51 confirmed cases). These outbreaks further confirmed the propensity of the arbovirus to spread beyond its historically affected regions of Africa and South East Asia.<sup>[4]</sup> The virus identified on Easter Island was found to closely resemble the one identified during the French Polynesian outbreak.<sup>[5,6]</sup>

Later in 2015, autochthonous ZIKV infection cases were also seen in Samoa, Solomon Islands, New Caledonia, Fiji, Vanuatu, Tonga, and American Samoa.<sup>[7]</sup>

### ZIKA VIRUS OUTBREAK IN BRAZIL

With the Brazil outbreak, potential for virus spreading to an unaffected distant location was seen. Between February and April 2015, a sudden splurge of cases with skin rashes was reported in Brazil but did not fit into suspected cases of dengue, measles, or rubella. The first report of locally acquired Zika disease was confirmed by Brazil's National Reference Laboratory in May 2015. ZIKV continued to spread and affect as large as 1.5 million people.<sup>[8]</sup> By July 2015, 12 states of Brazil had confirmed ZIKV infection based on laboratory testing. Further spread became dominant after October 2015 when 18 states of Brazil got affected including:

- Northeast - Bahia, Maranhão, Pernambuco, Rio Grande do Norte, Paraíba, Alagoas, Ceará and Piauí
- North - Amazonas, Pará, Rondônia, Roraima and Tocantins
- Midwest - Mato Grosso
- Southeast - Espírito Santo, Rio de Janeiro, and São Paulo
- South - Paraná.

**Table 1: Spread of Zika virus across regions of Africa and Asia from 1951-2006**

| Western Africa  | Central Africa                                  | North Africa | Asia   |
|---|---|--------------|--|
| Nigeria, Sierra Leone, Ivory Coast, Cameroon, and Senegal | Gabon, Uganda, and the Central African Republic | Egypt        | Pakistan, India, Sri Lanka, Indonesia, the Philippines, Laos, Malaysia, Indonesia, Papa New Guinea, Cambodia, and Thailand |

From October 2015 to April 2016, a number of infants born with microcephaly was also unusually high, thus researchers began linking this congenital abnormality with ZIKV.<sup>[9]</sup>

## ZIKA VIRUS DISEASE IN REST OF AMERICAS

September 2015 onward following Zika outbreak in Brazil, infection spreads across more than 22 countries and territories in the Americas [Figure 1]. By early 2016, it had involved countries in South America, Central America, and the Caribbean. Many states including Columbia,<sup>[10]</sup> El Salvador,<sup>[11,12]</sup> Guatemala,<sup>[9]</sup> Mexico,<sup>[13]</sup> Panama,<sup>[12,14]</sup> Paraguay,<sup>[12,15]</sup> Venezuela,<sup>[12,16]</sup> Suriname,<sup>[13]</sup> and Jamaica<sup>[12]</sup> reported ZIKVD.

### Zika virus disease in the united states of america

In the three territories of the USA in 2016, a total of 661 cases were reported, of which 658 were locally acquired and 3 were travel associated. The distribution of cases was 14 in American Samoa, 631 in Puerto Rico, and 16 in the Virgin Islands.<sup>[17]</sup>

### Zika virus disease in Cape Verde in Africa

Beginning October 2015, suspected ZIKVD emerged, and by mid-October 2015, 165 cases were already suspected. The country's first ZIKVD outbreak was confirmed on 21 October 2015. By 6 December 2015, suspected cases of ZIKVD rose to 4744 which further increased to 7081 by mid-January 2016. Neurological complications were however not reported.<sup>[12]</sup>



**Figure 1: Countries in Americas with locally transmitted Zika virus disease**

### Zika virus disease in Chile

Chile announced its first three cases of ZIKVD (confirmed by PCR) in travelers returning from Colombia, Venezuela, and Brazil on February 2, 2016.<sup>[12]</sup>

Three countries, namely, France, Italy, and the United States of America have reported locally acquiring ZIKV through sexual contact in the absence of known mosquito vectors.<sup>[18]</sup>

Beginning 2007 up till 2016, almost seventy countries and territories have shown mosquito-borne ZIKV transmission, of which Cuba and Dominica are the latest to report cases of ZIKV infection on March 14 and 15, 2016, respectively.

## STRUCTURE OF ZIKA VIRUS DISEASE

ZIKV belongs to the family Flaviviridae and genus *Flavivirus*. It is also an arbovirus, a term used predominantly for RNA viruses transmitted by mosquitoes, ticks, or other arthropod vectors. The virus is icosahedral in symmetry attributed to the arrangement of its surface proteins. The virus particle consists of a host-derived lipid bilayer and a positive sense nonsegmented single-stranded RNA genome-10,794 bases long encoding a single polyprotein that is cleaved into three structural proteins and seven nonstructural (NS) proteins. The three structural proteins are capsid or the core protein (C), membrane protein (M)/premembrane protein (prM), and envelope protein (E). The E protein constitutes most of the virion surface and participates in various aspects of replication such as host cell binding and membrane fusion. Glycoprotein E has one glycosylation site that appears as a small protrusion on the viral surface. Loss of glycosylation sites has been noticed in African ZIKV strains that are not commonly reported to cause neurological damage. Glycosylation has been reported in Asian strains causing GBS and microcephaly. The nucleocapsid formed by C protein is approximately 25–30 nm in diameter. The virus itself is spherical and approximately 40–50 nm in diameter with surface projections measuring roughly 5–10 nm.<sup>[19]</sup>

## PATHOGENESIS OF ZIKA VIRUS

ZIKV penetrates into host cell by attaching itself to the host cell receptors facilitated by viral envelope proteins which induce endocytosis in the virion. Thereafter, viral membrane fuses with the endosomal membrane of the host and ssRNA is released into host cell. The ssRNA gets translated to a polyprotein and subsequently differentiates into structural and NS proteins. The viral factors responsible for replication of viral genome perform their task, and these factors along with the host endoplasmic reticulum form dsRNA. The

genome is then assembled in the ER of the host cell and then to the Golgi complex. From here, they depart into the intracellular space and continue to infect other host cells. Incubation period (from exposure to appearance of symptoms) of ZIKV is approximately 3–12 days.

## TRANSMISSION OF ZIKA VIRUS

Historically, ZIKV has lived an enzootic (mosquito-monkey-mosquito) cycle involving arboreal mosquitoes and monkey hosts with only occasional transmission to humans. However, over the years, ZIKV gradually adapted to urban cycle (mosquito-human-mosquito) involving human reservoirs and mosquito vectors<sup>[20]</sup> [Figure 2]. Post-2007, it even resulted in several large outbreaks in human population. Suggested routes for its transmission include:

### Mosquitoes

ZIKV is transmitted in humans through bites of infected female mosquitoes belonging to *Aedes* species, primarily *A. aegypti* and *A. albopictus*.<sup>[21]</sup> Other *Aedes* species known to transmit the virus are *A. africanus*, *Aedes vitattus*, *Aedes luteocephalus*, *Aedes furcifer*, *Aedes Hensilii*, and *Aedes apicoargenteus*; human beings serve as amplifier hosts where the virus circulates and multiplies. *Aedes* lives close to human habitations and lays eggs in water lying stagnant in objects such as buckets, bowls, tires, flower pots, vases, and animal dishes. The best suited climatic condition for its breeding is the tropical climate.

### Maternal-fetal intrauterine and perinatal spread

First reported evidence of spread by this route was reported in French Polynesia in 2013–2014 when ZIKV infection was found to be positive by PCR in two mothers and their newborns. Serum for testing was collected within 4 days of birth. Infection was, therefore, suspected to have happened through transplacental

transmission or during delivery.<sup>[22]</sup> Another incidence of intrauterine transmission was diagnosed when viral RNA was detected by reverse transcriptase-PCR (RT-PCR) in amniotic fluid samples of two pregnant women in Brazil, whose fetuses were identified with microcephaly on prenatal ultrasounds.<sup>[23]</sup> Other modes of transmission such as breastfeeding and close contact between mother and newborn also cannot be excluded.<sup>[22]</sup> Although very rare, ZIKV RNA has been reported in samples of breast milk as well as in salivary samples of mother and newborn, no reports have shown vaginal secretions tested for ZIKV.

### Sexual contact

Foy *et al.* in their report have documented the first possible person-to-person transmission by sexual contact.<sup>[24]</sup> According to this report, the patient had acquired possible ZIKV infection while traveling to Southeastern Senegal in 2008. Thereafter, on returning home to Colorado, he presented with common symptoms of ZIKV infection. Four days later, his wife also suffered similar symptoms. History ruled out wife's travel out of the United States, but the history of sexual intercourse with her husband 1 day after his return was present. Transmission by semen was thus suspected. Serologic testing confirmed ZIKV infection in both the patient and his wife, but unfortunately presence of ZIKV in patient's semen was not investigated. In another case in December 2013, during ZIKV outbreak in French Polynesia, a 44-year-old man in Tahiti suffered symptoms of ZIKVD and hematospermia. The patient's serum and blood samples were collected and subjected to real-time RT-PCR testing which showed positive results for ZIKV in semen and negative for ZIKV in blood.<sup>[25]</sup> Recently, more cases of ZIKV infection based on sexual transmission have been reported including two confirmed and four probable cases in February 2016 in women whose only risk factor was sexual contact with symptomatic male partners.<sup>[26]</sup>

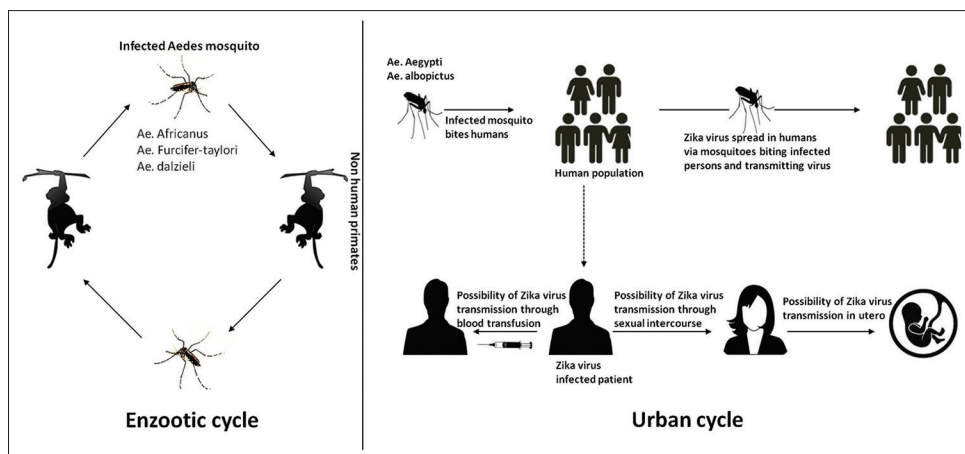


Figure 2: Enzootic and epidemic (urban) cycle of Zika virus



Zika possibly can also be transmitted during blood transfusion as majority blood donors are asymptomatic. Reports of French Polynesia outbreak showed PCR testing of 1505 asymptomatic blood donors as positive for ZIKV. These results cautioned authorities toward the risk of Zika fever in transfusion patients.<sup>[27]</sup> Furthermore, Brazilian officials reported two transfusion-linked Zika cases with great certainty in March 2015.<sup>[28]</sup> Since considering the presence of ZIKV in approximately 3% of asymptomatic donors during 2013–2014 outbreak, some screening before blood donation is highly suggested. Self-deferral from donation until 28 days after travel to affected areas has been recommended as an effective measure for reducing the risk of transfusion-related transmission of ZIKV.<sup>[28]</sup>

ZIKV may also infect donors before organ transplant. The viral infection is usually asymptomatic; however, the type of organs infected with ZIKV and for how long the infectious virus might be present in these organs is not known. Hence, it is important for the transplant community to be cautious about the risk of ZIKV infections.

A report in literature also suggests ZIKV transmission through laboratory exposure.<sup>[29]</sup>

## CLINICAL PRESENTATION OF ZIKA VIRUS

ZIKV infection presents as an influenza-like syndrome. Clinically, disease presentation is mild and may even go unnoticed. One in five people infected with ZIKV may, however, turn symptomatic. Fever usually is mild or low grade ranging from 37.5°C to 39°C. Clinical complaints in symptomatic cases include headache, retrobulbar pain, arthralgia, i.e., painful joints specially joints of hands and feet, nonpurulent conjunctivitis, edema, sore throat, cough, vomiting, myalgia, back pain, cutaneous maculopapular rashes, sweating, and lymphadenopathies lasting from 2 to 7 days. Rare symptoms include loss of appetite, diarrhea, abdominal pain, constipation, aphthous ulceration, and pruritus. Since all symptoms are nonspecific, misdiagnosis is common with other bacterial or viral infections caused by arboviruses such as dengue and chikungunya, especially in endemic areas. Fortunately, most people have low hospitalization rates and fully recover without severe complications. Neurological, ophthalmological, and congenital complications are some worrying features associated with this infection. Till date, fatalities reported with ZIKV are extremely rare.<sup>[20]</sup>

## ZIKA VIRUS AND GUILLAIN-BARRÉ SYNDROME

GBS is an autoimmune disease characterized by body's immune system acting against its own peripheral

nerves and damaging the myelin insulation resulting in rapid onset of muscle weakness and even paralysis. It is rare with an incidence of only 1–2:100,000 per year. More recently, association between ZIKV infection and neurological manifestations/GBS is proposed but is largely under investigation.

The first report of GBS seen immediately in a patient having suffered from ZIKV infection was from French Polynesia.<sup>[30]</sup> Thereafter, as the Polynesian outbreak progressed, 74 cases presented with neurological symptoms or autoimmune disorders. Of these, 42 cases were diagnosed as GBS.<sup>[31]</sup> Increased incidence of GBS was linked to ZIKV infection but was not confirmatory due to concomitant dengue outbreak during the same period. Later in Brazil, 121 cases of neurological manifestations were notified from the Northeastern state of Bahia. All the 121 cases had a history of rash illness between January and July 2015 and possible ZIKV infection. Forty-nine cases were confirmed to have GBS.<sup>[32]</sup> According to media reports of December 1, 2015, Sergipe state reported 28 cases of GBS associated to ZIKV infection.<sup>[33]</sup> Similarly, a large number of cases approximately 327 cases with neurological syndrome and having the previous history of ZIKV symptoms were also detected in Colombia. Of these, approximately 277 cases of GBS (66.6%) and similar neurological conditions such as ascending polyneuropathy were seen from December 2015 up till epidemiological week 13 of 2016.<sup>[34]</sup>

## ZIKA VIRUS AND PREGNANCY

Transmission of ZIKV from a pregnant mother to fetus can likely happen during pregnancy and/or delivery. Maternal infections when occurring during first 12 weeks of pregnancy (first trimester) are known to produce complications involving multiple organs in a fetus.<sup>[35]</sup>

Evidence is strong to support a link between ZIKV infection and adverse fetal outcomes, but till date, there is little available data to definitively confirm this association. Slovenia has reported a case which highly supports a causal link between ZIKV infection and fetal brain damage.<sup>[36]</sup> An expectant mother living in Brazil reported suffering from fever and rash toward the end of her first trimester of pregnancy. Ultrasound performed at 14 and 20 weeks revealed normal growth and anatomy of fetus, but at 32 weeks, ultrasound revealed growth restriction, microcephaly, and intracranial as well as placental calcifications. The patient terminated her pregnancy. Thereafter, an autopsy was conducted and fetal brain tissue studied. RT-PCR revealed a complete ZIKV genome sequence and electron microscopy revealed particles consistent with ZIKV.<sup>[36]</sup>

Zika virus and congenital microcephaly also show possible association. A reduced head circumference of about

27–28 cm has been noted in infants affected by ZIKVD compared to 34–37 cm normal head circumference for a newborn. On November 11, 2015, Brazil reported a public health emergency in response to an unexpected splurge in neonatal microcephalic cases in Pernambuco state. Coinciding with ZIKV outbreak, a possible link between ZIKV infection during pregnancy and fetal microcephaly was proposed. After this declaration, five other countries including Colombia, Martinique, Panama, United States, and Slovenia similarly reported ZIKVD-associated congenital abnormalities. Maximum cases (approximately 98% confirmed cases) of congenital syndrome (microcephaly and/or nervous system malformations) have been reported from Brazil. Of these, 92%–94% confirmed cases have been reported from Northeast Brazil which are significantly more than 4%–6% of cases reported from Southeast Brazil.

On November 17, 2015, Flavivirus Laboratory of Oswaldo Cruz Institute notified ZIKV genome in samples of two patients of Paraíba state, whose fetuses were confirmed to have microcephaly on ultrasound examination. Affected mothers reported suffering from symptoms of ZIKVD at 18–19 weeks of gestation. Viral genetic material (RNA) was detected in their amniotic fluid samples using quantitative real-time PCR.<sup>[23,37]</sup> A sharp rise of 17 cases of central nervous system malformations concomitant with ZIKV outbreaks was also notified in fetuses and infants of the French Polynesian Islands on November 28, 2015<sup>[8]</sup> On November 28, 2015, Ministry of Health, Brazil, reported finding ZIKV genome in blood and tissue samples of a microcephalic infant from the state of Pará. The infant expired within 5 min of birth.<sup>[38]</sup> Lately, there is growing evidence from cohort, observational, and case–control studies toward ZIKV causing microcephaly, CBS, and other neurologic disorders. Future tasks in this regard include quantifying the risk of neurologic disorders and investigating biological mechanisms leading to neurologic involvement following ZIKV infection.

Congenital ocular abnormalities have also been linked to ZIKV infection. de Paula Freitas *et al.* have published ophthalmologic findings of 29 microcephalic infants in Brazil with presumed intrauterine ZIKV infection. Out of 29 mothers, 23 declared suspecting ZIKV-related symptoms during pregnancy, with most (18) mothers suffering during first trimester. Ocular abnormalities were detected in 34% of examined infants. Most common findings observed were focal pigment mottling of the retina and chorioretinal atrophy (64.7%) followed by optic nerve abnormalities (47.1%).<sup>[39]</sup> Another report in 2016 similarly reported severe ocular malformations in three microcephalic infants. Their mothers had no ocular lesions. Gross macular pigment mottling and foveal reflex loss were seen in all three infants while well-defined macular neuroretinal atrophy was seen in one child.<sup>[40]</sup>

On February 1, 2016, the WHO issued a high level of alert declaring ZIKV infection an international public health emergency. This was the fourth time when the WHO declared any disease a global health emergency. First time, it was in 2009, H1N1 influenza epidemic when about 200 million people were infected. Second time in May 2014 when paralyzing form of polio resurfaced in Syria and Pakistan. Third time was in August 2014 when Ebola virus epidemic emerged in West Africa. The WHO was however widely criticized for its delay in sounding alarm during Ebola virus outbreak that had culminated in widespread human involvement and large financial losses. This time, WHO was quick to confer the designation of public health emergency for ZIKVD after having learned bitter lessons from its slower response in the management of Ebola virus outbreak. Faster response enabled redirecting national and local funds timely, attract international donors, and improve preparedness at a global level to combat ZIKV outbreak.

Differential diagnosis includes dengue, chikungunya, rickettsia, parvovirus, rubella, measles, adenovirus, enterovirus, leptospirosis, malaria, and Group A streptococcal infections.

## DIAGNOSIS

Nucleic acid detection by RT-PCR, targeting the NS protein 5 genomic region, is a preferred means of diagnosis. Standard RT-PCR and quantitative RT-PCR are rapid, specific, and sensitive methods for early detection. They are helpful in detecting viral RNA in serum samples that have been collected within 1<sup>st</sup> week of symptom onset. PCR can also detect virus in urine samples possibly for a longer duration than in serum. Viral isolation is maximally done for research purposes and is not usually utilized as a diagnostic tool. For virus isolation, serum is collected during initial 1–3 days while saliva/urine are collected during first 3–5 days of symptom onset. Serological tests such as immunofluorescence assays and enzyme-linked immunosorbent assays are employed to detect anti-Zika IgM and IgG antibodies but become positive only after 4 days; hence, serum should be collected only on or after 4 days. Serologic assays may not be very confirmatory as the virus can cross react with antibodies against other similar flaviviruses. Plaque reduction neutralization assay has a specificity improved over immunoassays but may still yield cross-reactive results when secondary *Flavivirus* infections are present.<sup>[41]</sup>

## TREATMENT

There are no specific vaccines or antiviral drugs available for ZIKV. The mainstay of treatment is directed toward supportive care for pain, fever, and itching including bed

rest and lot of fluid intake to prevent dehydration. Aspirin or other nonsteroidal anti-inflammatory drugs should not be prescribed until dengue is ruled out.

One *in vitro* study has reported a sensitivity of ZIKV toward interferon treatment, which is commonly used against other viral infections.<sup>[42]</sup> Another study for checking inactivation of ZIKV in plasma with amotosalen and ultraviolet A (UVA) illumination showed that photochemical process inactivated ZIKV in plasma and was able to reduce viral RNA loads, thus concluding that amotosalen and UVA light inactivation process appeared suitable in decreasing plasma transfusion-related risk of ZIKV infections.<sup>[43]</sup>

## PREVENTION

Basic preventive measures for ZIKV infection primarily revolve around traditional methods of checking mosquito populations, reducing breeding sites, and avoiding mosquito bites. Besides this, travel to potentially affected areas should be curtailed. Women of child-bearing age are required to exercise extra precautions. Because of the current nonavailability of vaccine or prophylactic medication to prevent ZIKV infection, CDC has issued guidelines which recommend postponing travel for pregnant women in any trimester to areas with ongoing ZIKV infection. If at all she lives or travels there, she should strictly follow measures to avoid mosquito bites. Pregnant women developing influenza-like symptoms suggestive of dengue, chikungunya, and ZIKV within 2 weeks of their return from travel to these areas should be thoroughly investigated. Furthermore, their fetuses or infants should be evaluated for any possible congenital infection.

A collective response is required from several agencies such as health, environmental, and civic to combat ZIKV disease.<sup>[44]</sup> Public health teams must work in unison with community organizations to ensure that precautions and treatment measures are adopted at a broader social level. The United Nations Sustainable Development Goal aims at strengthening the competence of all countries, particularly developing nations for early detection, risk minimization, laboratory testing, and management of national and global health risks.<sup>[45]</sup> Prevention is undoubtedly important as huge financial losses have happened during ZIKV outbreaks. Affected countries have shown concern over ZIKV adversely affecting emerging markets, birth rates, demographics, and tourism. Economic impact by ZIKV epidemic in Latin America and the Caribbean region for 2016 has been estimated at US\$3.5 Billion. In February 2016, World Bank announced US\$150 million for financing anti-Zika efforts in countries struggling to control ZIKV including increasing awareness, identifying high-risk individuals, and rendering improved medical care to pregnant women.

## FUTURE PROSPECTS

Newer tools that seem promising in ZIKV management include vaccines, antiviral drugs, therapeutic antibodies, and biomarkers for severe disease. However, these may not be available for clinical use for next 3–5 years. Currently, several companies nearly thirty are working to develop potential diagnostic tests for ZIKV. Furthermore, in five countries across the world, i.e., the USA, France, Brazil, India, and Austria, 14 vaccine developers are actively involved in 23 projects for developing ZIKV vaccines. By 2016 end, few of these projects are expected to proceed into clinical trials, but still it may be long before a fully tested and licensed vaccine is available to patients.

Genetically modifying mosquitoes to check ZIKV transmission is also a newer suggested measure toward controlling ZIKV spread. Genetic modification is directed toward producing sterile self-limiting male mosquitoes that are capable of transferring the deleterious gene to its offspring resulting in failure to reproduce. This approach may be safer for the surrounding environment as it targets only the concerned vector, but wiping out an entire species could also have deleterious effects on the ecosystem and existing species could be replaced by more threatening species. Oxitem firm released these mosquitoes in April 2015 and found a significant reduction in disease producing larva by the end of the year in the city of Piracicaba, Brazil.

## CONCLUSIONS

ZIKV is drawing global attention due to its rapid spread outside Africa and Asia. Zika is neither contagious nor lethal but has struck the globe in a cruel way from simple flu-like symptoms to serious complications such as congenital microcephaly and GBS. Because of its clinical presentation being similar to other arbovirus diseases and lack of laboratory technology in most potentially endemic areas, the incidence and prevalence of this disease is probably much more than estimated. The WHO already considers ZIKVD an international health emergency requiring a united response. Combined government and individual efforts are required to fight against ZIKV which involves simple measures of controlling mosquito population and preventing mosquito bites, to more comprehensive steps such as issuing travel warnings, heightening surveillance, and accelerating vaccine development.

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## REFERENCES

- Kirya BG. A yellow fever epizootic in Zika forest, Uganda, during 1972: Part I: Virus isolation and sentinel monkeys. *Trans R Soc Trop Med Hyg* 1977;71:254-60.
- Dick GW, Kitchen SF, Haddock AJ. Zika virus. I. Isolations and serological specificity. *Trans R Soc Trop Med Hyg* 1952;46:509-20.
- Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *N Engl J Med* 2009;360:2536-43.
- Roth A, Mercier A, Lepers C, Hoy D, Duituturaga S, Benyon E, et al. Concurrent outbreaks of dengue, chikungunya and Zika virus infections – An unprecedented epidemic wave of mosquito-borne viruses in the Pacific 2012-2014. *Euro Surveill* 2014;19. pii: 20929.
- Cao-Lormeau VM, Roche C, Teissier A, Robin E, Berry AL, Mallet HP, et al. Zika virus, French Polynesia, South Pacific, 2013. *Emerg Infect Dis* 2014;20:1085-6.
- Tognarelli J, Ulloa S, Villagra E, Lagos J, Aguayo C, Fasce R, et al. A report on the outbreak of Zika virus on Easter Island, South Pacific, 2014. *Arch Virol* 2016;161:665-8.
- Craig AT, Butler MT, Pastore R, Paterson B, Durrheim DN. Update on Zika virus transmission in the Pacific Islands, 2007 to February 2016 and failure of acute flaccid paralysis surveillance to signal Zika emergence in this setting [Submitted]. *Bull World Health Organ* 2016. doi:<http://dx.doi.org/10.2471/BLT.16.171892>.
- European Centre for Disease Prevention and Control. Rapid Risk Assessment: Zika Virus Epidemic in the Americas: Potential Association with Microcephaly and Guillain-Barré Syndrome, 10 December, 2015. Stockholm: ECDC; 2015 Available from: <http://ecdc.europa.eu/en/publications/Publications/zika-virus-americas-association-with-microcephaly-rapid-risk-assessment.pdf>. [Last accessed on 2016 May 17].
- Frontline. The Spread of Zika. Available from: <http://www.apps.frontline.org/zika/>. [Last accessed on 2016 May 14].
- Pan American Health Organization - World Health Organization – Regional Office for the Americas. Epidemiological Alert: Zika Virus Infection: 2015 May 7. Washington: PAHO; 2015. Available from: [http://www.paho.org/hq/index.php?option=com\\_docman&task=doc\\_view&Itemid=270&gid=30075&lang=en](http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=30075&lang=en). [Last accessed on 2016 May 14].
- World Health Organization. Disease Outbreak News: Zika Virus Infection. El Salvador: WHO; 2015. Available from: <http://www.who.int/csr/don/27-november-2015-zika-el-salvador/en/>. [Last accessed on 2016 May 17].
- Kindhauser MK, Allen T, Frank V, Santhana RS, Dye C. Zika: The origin and spread of a mosquito-borne virus. *Bull World Health Organ* 2016;94:675-86C.
- World Health Organization. Disease Outbreak News: Zika Virus Infection. Mexico; 3 December, 2015. Available from: <http://www.who.int/csr/don/03-december-2015-zika-mexico/en/>. [Last accessed on 2016 May 14].
- Ministry of Health of the Republic of Panama. Ministry of Health Informed the Panamanian Population on the Zika Virus. Ancon; 3 December, 2015. Available from: <http://www.minsa.gob.pa/noticia/ministerio-de-salud-comunica-la-poblacion-panamena-sobre-el-virus-zika>. [Last accessed on 2016 May 14].
- Ministry of Public Health and Social Welfare Paraguay. Introduction of Zika Virus (ZIKAV) in Paraguay; 30 November, 2015. Available from: <http://www.mspbs.gov.py/v3/wp-content/uploads/2015/12/Alerta-Introduccion-de-virus-Zika.pdf>. [Last accessed on 2016 May 17].
- World Health Organization. Disease Outbreak News: Zika Virus Infection – Venezuela; 3 December, 2015. Available from: <http://www.who.int/csr/don/03-december-2015-zika-venezuela/en/>. [Last accessed on 2016 May 17].
- Centres for Disease Control and Prevention. Zika Virus Disease in the United States; 2015-2016. Available from: <http://www.cdc.gov/zika/geo/united-states.html>. [Last updated on 2016 May 12; Last accessed on 2016 May 14].
- Emergencies: Zika Situation Report; 17 March, 2016. Available from: <http://www.who.int/emergencies/zika-virus/situation-report/17-march-2016/en/>. [Last accessed on 2016 May 17].
- Hulo C, de Castro E, Masson P, Bougueleret L, Bairoch A, Xenarios I, et al. ViralZone: A knowledge resource to understand virus diversity. *Nucleic Acids Res* 2011;39:D576-82.
- Musso D, Nhan TX. Emergence of Zika virus. *Clin Microbiol* 2015;4:222. [DOI: 10.4172/2327-5073.1000222].
- Hayes EB. Zika virus outside Africa. *Emerg Infect Dis* 2009;15:1347-50.
- Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. *Euro Surveill* 2014;19. pii: 20751.
- Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: Tip of the iceberg? *Ultrasound Obstet Gynecol* 2016;47:6-7.
- Foy BD, Kobylinski KC, Chilson Foy JL, Blitvich BJ, Travassos da Rosa A, Haddock AD, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. *Emerg Infect Dis* 2011;17:880-2.
- Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. *Emerg Infect Dis* 2015;21:359-61.
- Hills SL, Russell K, Hennessey M, Williams C, Oster AM, Fischer M, et al. Transmission of Zika virus through sexual contact with travelers to areas of ongoing transmission – Continental United States, 2016. *MMWR Morb Mortal Wkly Rep* 2016;65:215-6.
- Musso D, Nhan T, Robin E, Roche C, Bierlaire D, Zisou K, et al. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. *Euro Surveill* 2014;19. pii: 20761.
- Brazil Confirms Blood-transfusion Zika; PAHO Calls for Global Support. Zika Lisa Schnirring | News Editor | CIDRAP News; 14 February, 2016. Available from: <http://www.cidrap.umn.edu/news-perspective/2016/02/brazil-confirms-blood-transfusion-zika-paho-calls-global-support>. [Last accessed on 2016 May 15].
- Filipe AR, Martins CM, Rocha H. Laboratory infection with Zika virus after vaccination against yellow fever. *Arch Gesamte Virusforsch* 1973;43:315-9.
- Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastere S, Valour F, et al. Zika virus infection complicated by Guillain-Barre syndrome – case report, French Polynesia, December 2013. *Euro Surveill* 2014;19. pii: 20720.
- European Centre for Disease Prevention and Control. Microcephaly in Brazil Potentially Linked to the Zika Virus Epidemic. Stockholm: ECDC; 2015. Available from: [http://www.ecdc.europa.eu/en/publications/\\_layouts/forms/Publication\\_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1407](http://www.ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1407). [Last accessed on 2016 May 15].
- Ministry of Health (Brazil). Public health event related to cases of Zika Fever; 2015. Available from: <http://www.portalsaude.saude.gov.br/index.php/o-ministerio/principal/secretarias/svs/noticias-svs/19139-evento-de-saude-publica-relacionado-aos-casos-de-febre-do-zika>. [Last updated on 2015 Aug 13; Last accessed on 2016 May 15].
- Sergipe registers 28 cases of Guillain-Barré Syndrome; 1 December, 2015. Available from: <http://www.g1.globo.com/se/sergipe/noticia/2015/12/sergipe-registra-28-casos-da-sindrome-guillain-barre.html>. [Last updated on 2015 Dec 07; Last accessed on 2016 May 15].
- Pan American Health Organization – World Health Organization. Zika-Epidemiological Update, 17 March, 2016. Washington: PAHO; 2016. Available from: [http://www.paho.org/hq/index.php?option=com\\_docman&task=doc\\_view&Itemid=270&gid=33768&lang=en](http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=33768&lang=en). [Last accessed on 2016 May 14].
- Silasi M, Cardenas I, Kwon JY, Racicot K, Aldo P, Mor G. Viral infections during pregnancy. *Am J Reprod Immunol* 2015;73:199-213.
- Mlakar J, Korva M, Tul N, Popovic M, Poljšak-Prijatelj M, Mraz J, et al. Zika virus associated with microcephaly. *N Engl J Med* 2016;374:951-8.
- Ministry of Health (Brazil). Microcephaly - Ministry of Health publishes epidemiological bulletin. Brasília: Ministry of Health; 2015. Available from: <http://www.portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/20805-ministerio-da-saude-divulga-boletim-epidemiologico>. [Last updated on 2015 Nov 17; Last accessed on 2016 May 15].
- Pan American Health Organization, Epidemiological Alert: Neurological Syndrome, Congenital Malformations, and Zika Virus Infection. Implications for Public Health in the Americas. Washington, DC: World Health Organization, Pan American Health Organization; 2015. Available from: 2015-dec-1-cha-epi-alert-zika-neuro-syndrome%20(1).pdf. [Last updated on 2015 Dec 1; Last accessed on 2016 Dec 16].
- de Paula Freitas B, de Oliveira Dias JR, Prazeres J, Sacramento GA, Ko AI,



- Maia M, et al. Ocular findings in infants with microcephaly associated with presumed Zika virus congenital infection in Salvador, Brazil. *JAMA Ophthalmol* 2016. doi: 10.1001/jamaophthalmol.2016.0267.
40. Ventura CV, Maia M, Bravo-Filho V, Góis AL, Belfort R Jr. Zika virus in Brazil and macular atrophy in a child with microcephaly. *Lancet* 2016;387:228.
  41. Giri D. Zika Virus: Structure, Epidemiology, Pathogenesis, Symptoms, Laboratory Diagnosis and Prevention; 29 January, 2016. <http://www.laboratoryinfo.com/zika-virus-structure-epidemiology-pathogenesis-symptoms-laboratory-diagnosis-and-prevention/#sthash.lzDCCzTs.dpuf>. [Last accessed on 2016 May 16]
  42. Hamel R, Dejarnac O, Wichit S, Ekchariyawat P, Neyret A, Luplertlop N, et al. Biology of Zika virus infection in human skin cells. *J Virol* 2015;89:8880-96.
  43. Aubry M, Richard V, Green J, Brout J, Musso D. Inactivation of Zika virus in plasma with amotosalen and ultraviolet A illumination. *Transfusion* 2016;56:33-40.
  44. Hennessey M, Fischer M, Staples JE. Zika virus spreads to new areas – Region of the Americas, May 2015–January 2016. *MMWR Morb Mortal Wkly Rep* 2016;65:55-8.
  45. Goal 3: Ensure Healthy Lives and Promote Well Being for all at All Ages. Sustainable Development Knowledge Program. Division for Sustainable Development, UN-DESA. Available from: <https://www.sustainabledevelopment.un.org/sdg3>. [Last accessed on 2016 Aug 02].

