

## Zika virus fever: beginning of another Zoonotic dilemma?

Murtaza Mustafa<sup>1</sup>, IM. Yusof<sup>2</sup>, AM, Sharifa<sup>3</sup>, EM. Illzam<sup>4</sup>, RK. Muniandy<sup>5</sup>,  
K. Fairrul<sup>6</sup>, H. Firdaus<sup>7</sup>, MK. Nang<sup>8</sup>

<sup>1,2,5-8</sup>Faculty of medicine and Health Sciences, University Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia

<sup>3</sup>Quality Control Unit, Hospital Queen Elizabeth, Kota Kinabalu, Sabah, Malaysia

<sup>4</sup>Clinic Family Planning Association, Kota Kinabalu, Sabah, Malaysia

**Abstract:** In 2016, World Health Organization (WHO) declared a Public Health Emergency due to the recent outbreak of Zika fever in Brazil. Zika virus is a mosquito-borne flavivirus related to dengue virus. Infection can also spread by sexual transmission from infected men. Cases of vertical perinatal transmission have been reported, with multiple problems, including microcephaly, and chorioretinal scarring. Zika virus infections have been associated with Guillain-Barre syndrome (GBS), damaging the peripheral nervous system, which can progress to paralysis. Symptoms of Zika fever are fever, rash, conjunctivitis, muscle and joint pain, and headache, similar to dengue and chikungunya fever. Differential diagnosis of Zika fever should exclude other infection including dengue, chikungunya, leptospirosis, malaria, group A streptococcus, rubella, measles, parvovirus, enterovirus, adenovirus, and alphavirus infection, and other viruses. Pregnant women living in the affected areas, the CDC has recommended testing at first perinatal visit and in the mid-second trimester. At present there is no specific treatment for Zika virus infection, care is only supportive. Use of aspirin and other NSAIDs use is generally avoided as these are associated with hemorrhagic syndrome, especially in children due to the risk of Reye syndrome. The CDC strategies for controlling mosquitoes are useful. Currently there is no available vaccine. To speed new drug development has been proposed by the WHO and NIH.

**Keywords:** Zika virus fever, Clinical manifestation, Microcephaly, Guillain-Barre syndrome

### I. Introduction

Zika fever, Zika virus disease or simply Zika is an infectious disease caused by the Zika virus [1]. The virus that causes the disease was first isolated in Africa in 1947 [2]. First documented outbreak among people occurred in 2007 in the Federated States of Micronesia [3]. As of January 2016, the disease was occurring in twenty regions of Americas [3]. It is also known to occur in Africa, Asia, and the Pacific [1]. Due to recent outbreak that started in Brazil in 2015, the World Health Organization declared it a Public Health Emergency of International concern in February 2016 [4]. Zika fever is mainly spread via bite of mosquitoes of the *Aedes* type [3]. It can also be sexually transmitted and spread by blood transfusion [3]. Mother-to-child transmission during pregnancy can cause microcephaly and other brain malformation in some babies [6]. Infections in adults have been linked to Guillain-Barre syndrome. Symptoms (GBS) [2] Symptoms may include fever, red eyes, joint pain, headache, and maculopapular rash [7]. Diagnosis is by testing the blood, urine, or saliva for the presence of Zika virus RNA when the person is sick [1,3]. No specific treatment, paracetamol (acetaminophen) may help with symptoms [3]. Prevention involves decreasing mosquito bites in areas where the disease occurs and proper use of condoms [3,5], and eliminating mosquito habitats. The paper reviews the clinical manifestations of Zika fever and its association with microcephaly and Guillain-Barre syndrome.

### II. History and Microcephaly

After the initial Zika outbreak in Northeastern Brazil, physicians observed a very large surge of reports of infants born with microcephaly, with 20 times the number of expected cases [8]. Many of these cases have since been confirmed leading WHO officials to project that approximately 2,500 infants will be found to have been born in Brazil with Zika-related microcephaly [9]. On March 10, 2016, a research group from the Faculty of Medicine, University of Ljubljana (Slovenia), led by young researcher Jernej Mlakar, M.D. published an article in the New England Journal of Medicine, connecting the Zika virus to microcephaly [10].

Proving that Zika causes these effects is difficult and complex for several reasons [11]. For example, the effects on an infant might not be seen until after mother's initial infection, long after the time when Zika is easily detected in the body [11]. In addition, research is also needed to determine the mechanism by which Zika produces these effects [12]. On February 10, 2016, the World Health Organization declared a recently reported cluster of microcephaly and other neurological disorders a Public Health Emergency of International concern (PHEIC) [13]. On March 10, 2016, the WHO Committee reconfirmed that association between Zika and neurological disorders is of global concern [12].

In March 2016, researchers published a prospective cohort study that found profound impacts in 29 percent of infants of mothers infected with Zika, some of whom were infected late in pregnancy[14].The study did not suffer from some of the difficulties of studying: the study followed women who presented to Rio de Janeiro clinic with fever and rash within the first five days. The women were then tested for Zika using PCR, then the progress of pregnancies were followed using ultrasound [14,15].

In November 2015,the Zika virus was isolated in a newborn baby from northeastern state of Ceara,Brazil,with microcephaly and other congenitaldisorders. It was reported in The Lancet in January 2016,that the Brazilian Ministry of Health had confirmed 134 cases of microcephaly "believed to be associated with Zika virus infection" with an additional 2,165 cases in 549 countries in 20 states remaining under investigation[16].An analysis 574 cases of microcephaly in Brazil during 2015, and the first week of 2016, reported in March 2016,found an association with maternal illness involving rash and fever during the first trimester of pregnancy[17].During this period,12 Brazilian states reported increases of at least 3 standard deviations(SDs) in cases of microcephaly compared with 2000-14,with northeastern states of Bahia, Paraiba and Pernambuco reporting increases of more than 20SDs[17].

In January 2016,a baby was born with microcephaly, the first case in The United States of brain damage linked to virus.The baby and mother tested positive for a Zika virus infection. The mother, who had probably acquired the virus while travelling in Brazil in May 2015 during the early stages of pregnancy, had reported her bout of Zika.She recovered before relocating to Hawaii. Her pregnancy progressed normally, and the baby's condition was not known until birth[18].In March 2016,first solid evidence was reported on how the virus affects the development of the brain. It appears to preferentially kill developing cells[19].the first cases of birth defects linked to Zika in Colombia and Panama were reported in March 2016[20,21]. Ocular disorders in newborns have been linked to Zika virus infection [22].In one study in Pernambuco state in Brazil, about 40 percent of babies with Zika-related microcephaly also had scarring of the retina with spots, or pigment alteration[23].JampolML,and colleagues concluded that clinicians in areas where Zika virus is present should perform ophthalmologic examination on all microcephaly babies[24].

On 20 February 2016,Brazilian scientists announced that they had successfully sequenced the Zika virus genome, and expressed hope that this would help both developing a vaccine and in developing the nature of any link to birth defects[25].In February 2016,rumors that microcephaly is caused by the use of the larvicidepyriproxyfen in drinking water were refuted by scientists[26].Itis important to state that some localities that do not use pyrioxyfen also had reported cases of microcephaly[27].

Researchers also suspected that Zika virus could be transmitted by pregnant woman to her babies(vertical transmission).this remained unproven until February 2016,when a paper by Calvet et al was published, showing not onlywas the Zika genome found in the amniotic fluid but also IgM antibodies against the virus[28].Study by Mlakar and colleagues published in March 2016, found ZIKV in the brain tissues(autopsy tissues) and suggested the brain injuries were probably associated with virus, which also shed a light on the vertical transmission theory[10].

A high rate of autoimmune disease Guillain-Barre syndrome (GBS),noted in the French Polynesia outbreak, has also been found that began in Brazil [29].Laboratory analysis found Zika infections in some patients with GBS in Brazil EL Salvador, Suriname and Venezuela[30].Parra and colleagues reported the results of a prospective study of 68 Colombian patients who had a syndrome consistent with GBS,66 of whom had previously had symptoms of Zika (ZIKV) infection[31].WHO declared on 22 March 2016 that Zika appeared to be "implicated" in GBS infection and that if the pattern was confirmed it would be represent a global health crisis[32].

### **III. Prevalence**

In April 1947,as part of studies sponsored by the Rockefeller Foundation into Yellow fever,6 caged rhesus monkeys were placed in the canopy of the Zika forest of Uganda[33].On April 18 one of the monkeys(no.776) developed fever and blood samples revealed the first know case of Zika fever[34].Population surveys at the time in Uganda found a 6.1% prevalence[35].The first human cases were reported in Nigeria in 1954 [36].A few outbreaks have been reported in tropical Africa and some areas in Southeast Asia[37].There have been no documented cases of Zika virus in Indian subcontinent. Surveys have found antibodies to Zika in health people in India which could indicate past exposure, though it could also be due to cross-reaction with other flaviviruses [38].

By using phylogenetic analysis of Asian strains, it was estimated that Zika virus had moved to Southeast Asia by 1945[35].In1977-1978,Zika virus infection was described as a cause of fever in Indonesia[39].Before 2007,there were only 13 reported natural infections with Zika virus,all with mild, self-limiting febrile illness[40].The first major outbreak with 185 confirmed cases, was reported in 2007 in Yap Islands of the Federated States of Micronesia[41].A total of 108 cases were confirmed by PCR or serology and 72 additional cases were suspected. The most common symptoms were rash,arthralgia,andconjunctivitis, and no

deaths were reported. The mosquito *Aedes hensilli*, was the predominant species identified in Yap during outbreak, was probably the main vector [39]. While the way of introduction of virus on Yap Island remain uncertain, it is likely to have happened through introduction of infected mosquitoes or a human infected with a strain related to those in Southeast Asia [39].

In 2013-2014, several outbreaks of Zika were reported in French Polynesia, New Caledonia, Easter Island and Cook Islands. The source of the virus was thought to be an independent introduction of the virus from Southeast Asia, unrelated to Yap Islands outbreak [39, rpt]. Genetic analyses of Zika virus strains suggest that Zika first entered the Americas between May and December 2013 [42]. It was first detected in the Western Hemisphere in February 2014, and rapidly spread throughout South and Central America reaching Mexico in November 2015 [39]. In 2016 it established local transmission in Florida and Texas [43]. The first death in the United States due to Zika occurred in February 2016.

In May 2015, Brazil officially reported its first 16 cases of illness [44]. The Zika cases were reported in 14 states of the country. Mosquito-borne Zikavirus is suspected to be the cause of 2,400 cases of microcephaly and 29 infants deaths in Brazil in 2015 [45]. Before the Zika outbreak only an average of 150 to 200 cases per year were reported in Brazil [46]. The state of Pernambuco the reported rates of microcephaly in 2015 are 77 times higher than in the previous 5 years [46]. A model using data from a Zika outbreak in French Polynesia estimated the risk of microcephaly in children born to mothers who acquired Zika virus in the first trimester to be 1% [47]. On 24 January 2016, the WHO warned that virus is likely to spread to nearly all countries of the Americas, since its vector, the mosquito *Aedes Aegypti*, is found in all countries in the region, except for Canada and continental Chile [48]. In February 2016, WHO declared the outbreak a Public Health Emergency of International Concern as evidence grew that Zika is a cause of birth defects and neurological problems [16]. In April 2016, WHO stated there is a scientific consensus, based on preliminary evidence, that Zika is a cause of microcephaly in infants and Guillain-Barre syndrome in adults [49].

In 2016 imported or locally transmitted Zika was reported in all countries of Asia except Brunei, Hong Kong, Myanmar and Nepal [50]. Serological surveys have indicated that Zika virus is endemic in most areas of Asia, though at low level [50]. While there is sharp rise in number of cases of Zika in Singapore after 2016 Summer Olympics in Brazil, genetic analysis revealed that the strains were more closely related to strains from Thailand than from those causing epidemic in the Americas [51].

#### **IV. Etiology, Transmission and Pathogenesis**

Zika virus is a mosquito-borne flavivirus closely related to dengue virus. While mosquitoes are the vector, the reservoir species remains unknown, though serological evidence has found in West African monkeys and rodents [40]. Transmission is via bite of mosquitoes from *Aedes* genus, primarily *Aedes Aegypti* in tropical regions. It is also been isolated from

*Ae. africanus*, *Ae. apicoargentus*, *Ae. luteocephalus* [52], *Ae. Albopicticus* [53], *Ae. vittatus* and *Ae. furcifer* [40]. During the 2007 outbreak on Yap Island in the South Pacific, *Aedes hensilli* was vector, while *Aedes polynesiensis* spread the virus in French Polynesia in 2013 [54].

Zika virus also can spread by sexual transmission from infected men to their partners [55]. Zika virus has been isolated from semen samples, with one person 100,000 times more virus in semen than blood or urine, two weeks after being infected [56]. It is unclear why levels in semen can be higher than other body fluids, and it is also unclear how long infectious virus can remain in semen. There have also been cases of men with no symptoms of Zika virus infection transmitting the disease [57]. The CDC has recommended that all men who have travelled to affected areas should wait at least 6 months before having trying to have conception, regardless of if they were ill [58]. To date there have been no reported sexual transmission from women to their sexual partners [55]. Oral, anal or vaginal sex can spread the disease [59].

Cases of vertical perinatal transmission have been reported [35, rpt]. CDC recommends that women with Zika fever should wait for 8 weeks after they start having symptoms before attempting to conceive [60]. There have been no reported cases of transmission from breastfeeding, but infectious virus has been found in breast milk [61]. Like other flaviviruses it could potentially be transmitted by blood transfusion and several affected countries have developed strategies to screen blood donors [16]. The U.S. FDA has recommended universal screening of blood products for Zika [62]. The virus is detected in 3% of asymptomatic blood donors in French Polynesia [63].

While the pathogenesis-pathophysiology of Zika-induced microcephaly is not fully known, it is reported to involve infection of primary neural stem cells of fetal brain, known as neural progenitor cells [64]. The main roles of brain stem cells are to proliferate until the correct number is achieved, and then to produce neurons through the process of neurogenesis [65]. Zika proteins NS4A and NS4B have also been known to directly suppress neurogenesis [65, rpt]. Infection of brain stem cells can cause cell death, which reduces the production of future neurons and leads to smaller brain [66]. Zika also appears to have an equal tropism for cells of the developing eye, leading to high rates of eye abnormalities as well [64].

### **V. Clinical Manifestations.**

Most people who are infected have no or few symptoms[67]. Otherwise the most common signs and symptoms of Zika fever are fever, rash, conjunctivitis, muscle and joint pain, and headache, which are similar to signs of dengue and chikungunya fever[68]. The time from a mosquito bite to developing symptoms is not yet known, but is probably a few days to a week[69]. The disease lasts for several days to a week and is usually mild enough that people do not have to go to hospital[1,16]. Due to being in the same family as dengue, there has been concern that it could cause similar bleeding disorders. However that has only been documented in one case, with blood seen in the semen, also known as hematosperma [70]

**Guillain-Barre' syndrome (GBS):** Zika virus infections have been strongly associated with GBS, which is an onset of muscle weakness caused by the immune system damaging the peripheral nervous system, and which can progress to paralysis[71]. While both GBS and Zika infection can simultaneously occur in the same individual, it is difficult to definitely identify Zika virus as the cause of GBS[72]. Several countries affected by Zika outbreaks have reported increases in the rate of new cases of GBS. During 2013-2014 outbreak French Polynesia there were 42 reported cases of GBS over a 3-month period, compared to between 3 and 10 annually prior to the outbreak [73].

**Microcephaly:** The disease can spread from mother to child in the womb and can cause multiple problems, most notably microcephaly, in the baby. The full range of birth defects caused by infection during pregnancy is not known, but they appear to be common, with large scale abnormalities seen in up to 42% of live births [14]. The most common observed associations have been abnormalities with brain and eye development such as microcephaly and chorioretinal scarring[74]. Less commonly there have been systemic abnormalities such as hydrops fetalis where there is abnormal accumulation of fluid in fetus[75]. These abnormalities can lead to intellectual problems, seizures, vision problems, hearing problems, problems feeding and slow development[76]. Whether the stage of pregnancy at which the mother becomes infected affects the risk to the fetus is not well understood, nor is whether other risk factors affect outcomes[6]. One group has estimated the risk of a baby developing microcephaly at about 1% when the mother is infected during the first trimester, with risk of developing microcephaly uncertain beyond the first trimester[34]. Affected babies might appear normal but actually have brain abnormalities; infection in newborns could also lead to brain damage[77].

### **VI. Diagnosis**

It is difficult to diagnose Zika virus infections based on clinical signs and symptoms alone due to overlaps with other arboviruses that are endemic to similar areas[16,rpt]. CDC advises that based on the typical clinical features, the differential diagnosis for Zika virus infection is broad. In addition to dengue, other considerations include leptospirosis, malaria, rickettsia, group A streptococcus, rubella, measles, and parvovirus, enterovirus, adenovirus, and alphavirus infection, chikungunya and other viruses[78]. In small case series, routine chemistry and complete blood counts have been normal in most patients. A few have been reported to have leukopenia, thrombocytopenia, and elevated liver transaminases [79].

Zika virus can be identified by reverse transcriptase PCR (RT-PCR) in acutely ill patients. However the period of viremia is short[80]. WHO recommends RT-PCR testing done on serum collected within 1 to 3 days of symptoms or on saliva samples collected during 3-5 days[54]. In paired samples Zika virus was detected more frequently in saliva than serum[79]. Urine samples can be collected and tested up to 14 days after the onset of symptoms, as the virus has been seen to survive longer in the urine than either saliva or serum[81]. The longest period of detectable virus has been 11 days and Zika virus does not appear to establish latency[40]. Later on, serology for the detection of specific IgM and IgG antibodies to Zika virus can be used. IgM antibodies can be detected within 3 days of the onset of illness[40]. Serological cross-reactions with closely related flavivirus such as dengue and West Nile virus as well as vaccines to flavivirus are possible[80].

**Zika virus tests in pregnancy:** CDC recommends screening some pregnant women even if they do not have symptoms of infection. Pregnant women who have travelled to affected areas should be tested between two to and twelve weeks after their return from travel[82]. For women living in affected areas, the CDC has recommended testing at first prenatal visit with a doctor as well as in the mid-second trimester, though this may be adjusted based on local resources and the local burden of Zika virus[81]. Women with positive test results for Zika virus infection should have their fetus monitored by ultrasound every three to four weeks to monitor fetal anatomy and growth[81]. For infants with suspected congenital Zika virus disease, the CDC recommends testing with both serological and molecular assays such as RT-PCR, IgM ELISA and plaque reduction neutralization test (PRNT). RT-PCR of infants serum and urine should be performed in the first two days of life[83]. Other recommended tests are cranial ultrasound hearing evaluation[84] and, eye examination[82].

### **VII. Treatment and Prevention**

There is currently no specific treatment for Zika virus infection. Care is supportive and treatment of pain, fever, and itching[54]. Some authorities have recommended against using aspirin and other NSAIDs as these have been associated with hemorrhagic syndrome when used for other flaviviruses[16]. Additionally, aspirin use is generally avoided in children when possible due to the risk of Reye syndrome [85]. Advice to pregnant women is

to avoid any risk of infection so far as possible, once infected there is little that be done beyond supportive treatment[86].Most of the time Zika fever resolves on its own in 2 to 7 days, but rarely, some people develop Guillain-Barre syndrome[80].The fetus of pregnant women who has Zika fever may die or to be born with congenital central nervous system malformations, like microcephaly[80].

**Prevention:** Virus is spread by mosquitoes, making mosquito avoidance an important element to disease control. The CDC recommends strategies for controlling mosquitoes such as eliminating standing water, repairing septic tanks, and using screens on doors and windows[87].Spraying insecticide is used to kill flying mosquitoes and larvicide can be used in water containers[1].Modern methods for mosquito control such as the use of *Wolbachia* bacteria to reduce mosquitoes resistant to virus,and, the use of sterilized male mosquitoes that breed with wild female mosquitoes to give rise to non-viable offspring's(offspring's that do not survive to the biting stage),[88]Oxitec's genetically modified OX513A mosquito used in Brazil to try to combat mosquito carrying Zika virus[89,90].Because Zika virus can 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 for six months after travel if their partner is pregnant or could potentially pregnant[16].Currently there is no available vaccine. Development of vaccine could take years [80].To speed new drug development has been proposed by the WHO and NIH[91].

### VIII. Conclusions

Diagnosis of Zika virus infection based on clinical manifestations is difficult due to similarities of symptoms with other arboviruses in the endemic areas. Routine blood chemistry and complete blood counts are normal in most patients.Zika virus can be identified by reversetranscriptase PCR(RT-PCR), and byserologic detection of IgM and IgG antibodies. CDC recommends screening of pregnant women and infants with suspected congenital Zika virus disease in the affected areas. No specific treatment only supportive treatment.

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