

Zika Virus Infection: An Emerging Mosquito-Borne Disease Threatening Global Health

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Abstract

Zika virus is an arbovirus of the Flaviviridae family consisting of two strains, Asian and African, and is transmitted mostly by *Aedes* mosquitoes. It was first discovered in a monkey during the 1940s. Until 2007 the virus had not been detected outside Africa and Asia and it was characterized as a mild infection with fast recovery and no fatalities. Its clinical manifestations are similar to dengue fever and chikungunya fever as a fever with rash, myalgia, arthralgia and headache. But since the 2013 outbreak in French Polynesia, neurological complications following the disease were identified. The virus has continued to spread and has extended to Oceania and has now arrived at the American Continent in 2015. Brazil was the first country in the Americas where Zika virus was identified. Since an increase of cases of microcephaly was detected in areas with the highest virus infection rates, Zika virus has been thought to be the cause of this congenital malformation. Laboratory confirmation of Zika virus infection relies mostly on the detection of viral RNA or specific antibodies in blood samples. There are no vaccines or specific medication to prevent or treat this disease. Zika virus infection is present in almost all countries of America and the first imported case has already been detected in Taiwan in January 16, 2016 at Taoyuan International Airport. Zika virus infection is becoming an extra-burden to tropical countries that are already endemic for dengue and chikungunya which share the same mosquito vectors. Unless drastic actions are taken early to control the Zika virus infection, it is likely that the virus will keep spreading and affecting the health of millions of people worldwide.

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Epidemiology

Zika virus is a single stranded ribonucleic acid (RNA) arbovirus belonging to the Flaviviridae family which was first found in Zika Forest located 25 km east of Kampala, Uganda in 1947. This virus was accidentally discovered in a rhesus monkey during a surveillance program that aimed to isolate the yellow fever virus, but found this pathogen instead. In 1952, 7 years after its discovery, the presence of neutralizing antibodies against the virus was verified in human serum taken from people living in Uganda and Tanzania [1]. Nevertheless, by means of phylogenetic studies the emergence of the Zika virus is estimated to be present in nature since 1920 with a confidence interval between 1892–1947, which means the circulation of the virus in the wild was 27 years earlier than its initial discovery date [2]. Additional studies revealed that it possesses two major lineages, Asian and African. The virus is known to cause a disease with clinical manifestations very similar to dengue fever [3].

The first human case of Zika virus infection in a symptomatic patient was detected in Nigeria in 1954. A study done in Nigeria between 1971–1975 revealed that about 40% of 130 blood samples tested had neutralizing antibodies against the virus [4]. Phylogenetic studies showed that both lineages of Zika virus were already circulating for about 50 years in Southeast Asia [5, 6]. It has been suggested that the migration of Zika virus to Asia occurred around 1945 but until the late 1960 it was found in Malaysia [2].

By 2007, only 14 cases of Zika virus infection had been documented worldwide. The 2007 outbreak of Zika virus infection in Yap Island, Federated States of Micronesia marked the first detection of Zika virus infection outside Africa and Asia [7]. Genetic analysis revealed that the outbreak was caused by the Asian lineage strain most likely introduced either by an infected mosquito or human from Southeast Asia [8, 9].

Since its arrival to Micronesia, Zika virus continued to spread to other islands of the South Pacific. The sudden expansion of the virus became a cause of immediate concern to neighboring nations. Since then, it had spread to French Polynesia, New Caledonia, Cook Islands, Easter Island (belonging to the Republic of Chile), and reached the American continent, to Brazil and Colombia [8].

By January 2012, the South Pacific was suffering a high incidence of mosquito-borne disease as a result of the epidemics of dengue, chikungunya and Zika virus. An estimated 120,000 people were infected, but it could be underestimating the actual burden of the disease as a large number of cases were not reported [10].

As of June 2014, countries such as Japan, the United States (Hawaii), Canada, Germany, France, Norway and New Zealand had officially confirmed the presence of the virus [9].

In early 2015 several patients presenting a “dengue-like syndrome” were first detected in Natal, Rio Grande do Norte, Brazil. Patients presented similar clinical manifestations, but laboratory testing revealed that the virus was neither dengue nor chikungunya. Because the symptoms were compatible with Zika virus infection, reverse transcription polymerase chain reaction (RT-PCR) assay was done to detect Zika virus RNA and found Zika virus of Asian lineage [11].

The Ministry of Health of Brazil confirmed in May 2015 that there was autochthonous transmission of Zika virus in the north-eastern part of the country. This was the first confirmed epidemic of the virus in Brazil and in the American continent [8]. The Pan American Health Organization (PAHO) immediately issued an alert for Zika virus transmission in northeast Brazil. This confirmed the spreading of the disease to a new continent and indicated the virus was following the path of its predecessors, dengue and chikungunya [12].

There are several theories regarding the arrival of the virus to Brazil. Because of the massive mobilization of foreign tourists for the 2014 Football Association International Federation (FIFA) World Cup tournament to Brazil, it was first hypothesized that the virus was brought among the African tourists that arrived in the country. However, the circulating virus strain identified in Brazil was confirmed as the Asian strain of the virus, so it was unlikely that the virus came from Africa. For this reason, another alternative explanation was suggested. Around this time, there was also an international canoe racing event taking place in Brazil. Most countries participating in the canoe event were from Pacific nations whose citizens were more potential candidates for carrying the Asian strain. Other explanations include that the transmission of the virus was the result of the proximity of Brazil to Chile, which confirmed a case of Zika virus from Easter Island presented the Asian strain. Domestic travel within Brazil could be another explanation as it involves a mass movement of locals and foreigners as the cities hosting the football games were in different areas of the country [2, 13].

In November 2015, the first case of Zika virus infection in Central America was reported in El Salvador. Zika virus is now being reported in other countries in Central America. As of February 2, 2016 the PAHO has confirmed the presence of Zika virus in the following American Countries: Barbados, Bolivia, Brazil, Colombia, Dominican Republic, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Puerto Rico, Saint Martin, Suriname, US Virgin Islands, Venezuela [14].

Transmission

This virus was first isolated from *Aedes africanus* mosquitoes, and, in 1956, vector transmission was experimentally proven using *Aedes aegypti* mosquitoes to infect a previously healthy monkey from an infected mouse [6]. Transmission of the virus is by mosquitoes of the *Aedes* genus (sylvatic and domestic transmission) including *Aedes aegypti*. Other species reported include *Aedes polynesiensis* and *Aedes albopictus*. *Aedes hensilli* was identified during the Zika epidemic on Yap Island in 2007, in Micronesia [3].

Zika transmission through sexual intercourse has been suggested by Foy et al. who described a patient who became infected with Zika virus in Senegal during 2008. Afterwards the patient's wife presented with similar symptoms as well, despite the fact that she had not traveled outside the United States during the previous year, but had sexual intercourse with the patient one day after he returned home. Transmission through semen is plausible because the virus can also be isolated from semen days after it can no longer be detected in serum [15].

Perinatal transmission of arbovirus has been reported for both chikungunya and dengue viruses. In November 2013, the first cases of perinatal transmission by Zika virus were suspected in French Polynesia. The newborns presented a rash and other clinical manifestations compatible to Zika virus infection. The first mother presented compatible symptomatology to Zika 2 days before delivery and the second mother presented symptoms 3 days after her caesarean section. In the breast milk samples of both mothers the virus was detected by polymerase chain reaction (PCR) so there was the possibility of transmission by breastfeeding. But this was questionable, because no replicative virus was found in the milk samples and on the second newborn serum was positive for Zika virus one day after initiating breastfeeding. It was concluded that the infection probably occurred by transplacental transmission or during delivery [16].

Blood transfusion transmission of the virus has been suggested. It is theoretically possible as, during the outbreak period, 3% of all asymptomatic blood donors in French Polynesia were found to be positive by PCR for Zika virus [17].

Clinical manifestations

The incubation period is usually 3 to 12 days. Asymptomatic patients are frequent, only 1 of every 4 people infected present symptoms. [3,18]. The typical disease presentation is fever accompanied by some of the following, polyarthralgia, myalgia, maculopapular rash, headache, edema of the extremities, retro-orbital pain and conjunctivitis, a sign most characteristic to Zika virus infection. Unlike dengue or

chikungunya, Zika virus infection does not present hepatomegaly, thrombocytopenia or hemorrhage. These similar clinical manifestations complicate differential diagnosis among viral infections [2].

Before the 2013 outbreak of Zika virus infection in French Polynesia, the virus was known to cause a mild disease with a quick recovery and no severe complications. However, during this outbreak it was the first time reports of neurological and auto-immune complications, such as Guillain-Barré syndrome were observed. Other complications mentioned were encephalitis, meningo-encephalitis, paresthesia, facial paralysis, myelitis and immune thrombocytopenic purpura, as well as ophthalmologic and cardiac complications [6,9]. Furthermore, the first 3 deaths by Zika virus were reported in a newborn, a teenager and an adult during the Brazil epidemic [17].

On November 21, 2015, the World Health Organization (WHO) notified the presence of 739 cases of microcephaly in 9 states of north-eastern Brazil, the same region as the Zika virus outbreak in that country. There is still a gap in knowledge regarding the disease pathogenesis, its complications, genetic susceptibility and levels of risk for pregnant women, newborns or patients with co-morbidities [6].

Diagnosis

Clinical diagnosis for Zika virus is unreliable; however, blood testing can be used to distinguish Zika virus infection apart from the other similar diseases [3]. The diagnosis of Zika virus infection relies mostly on the detection of viral RNA in blood samples: RT-PCR and viral isolation for blood samples less than 5 days after the onset of symptoms is the gold standard. The “pan flavivirus” amplification technique combined with sequencing may be used as an alternative [3]. Direct virus detection can be done during the first 3–5 days after the initial symptoms. IgM/IgG antibodies specific to Zika virus can be detected by Elisa and immunofluorescence assays in serum from day 5–6 of illness. IgM antibody response is reported to be specific for Zika virus with minor cross reactivity with other arboviruses [2]. Positive results should always be confirmed by neutralization to document an increase of Zika virus neutralizing antibody titers [6].

One study investigated the diagnostic utility of urine for the detection of Zika virus by real-time RT-PCR. Results suggest that urine might be useful for diagnosis of Zika virus infection because the virus can be detected at higher concentrations and for longer time in urine samples than in blood serum samples. Nevertheless, more research is needed before standardizing it as a definitive method of diagnosis [19].

Treatment and Prevention

There are no specific treatments for the disease. People infected with Zika virus should get plenty of rest and drink enough fluids. Symptomatic treatment can be given to alleviate disease symptoms, but it will not shorten the duration of the disease nor prevent its complications. [1,14]. Acetaminophen is used to reduce fever and ameliorate pain and headaches. Antihistaminic drugs can help in cases of pruritic rash [3].

In Latin America, dengue fever has been endemic as a result of the presence of the *Aedes* mosquito. Furthermore, chikungunya virus reached the Americas from Africa in 2013, an arbovirus that shares the same vector as dengue virus. The arrival of another vector-borne disease raised concerns about the ability of these different nations to implement effective vector control strategies [1].

There is no vaccine or effective medicine that can prevent Zika virus infection. Just like any other vector-borne disease, prevention is an important part of the disease control and eradication. The elimination of breeding sites and protection against mosquito bites is essential such as wearing long-sleeved clothes, using mosquito repellent and using mosquito nets when sleep. Deltamethrin is the best aerosol insecticide [1, 3, 14].

Due to the association between Zika virus infection and an increase of microcephaly cases, many countries who have high presence of Zika virus like Brazil, Colombia and Ecuador, are recommending women to postpone getting pregnant during the epidemic in hopes of avoiding more children born with this malformation. Pregnant women as well as people residing in countries where there is no infection of the virus are recommended to abstain from travelling to endemic areas [14, 20].

Conclusions

Zika virus transmitted by mosquitos of the genus *Aedes*, but rare cases of sexual and perinatal transmission have been reported. Neurological complications and deaths after infection is possible, and it is believed that infection in pregnant women can lead to microcephaly in the newborns. Serological testing is the definitive diagnostic tool. Just like dengue and chikungunya, the disease has no specific treatment and there is no medication that can cure nor prevent the disease onset. Yet, vector control is the only effective method to diminish disease incidence and propagation in addition, to prevention of mosquito bites.

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