



## Zika Virus Disease Epidemics

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### Abstract

**Background:** Zika is a mosquito-borne viral disease that produces an illness clinically similar to dengue fever and many other tropical infectious diseases. Currently, there is no vaccine or specific antiviral treatment for Zika virus infection. This study aimed to review the epidemiology of Zika virus infection and to describe the recent epidemics.

**Methods:** We did a review of articles published up to December 2015 on Zika virus diseases epidemics.

**Results and discussion:** Outbreaks of Zika have occurred not only in Africa, Southeast Asia, the Pacific Islands but also in South and Central America. Several travel-related Zika virus infections have been reported in Europe and North America. With the increased reporting of Zika virus transmission in the Americas, countries should create and maintain the capacity to identify and confirm cases of Zika virus infection and effective strategies to reduce the mosquitoes that transmit the disease should be established. In a globalized world, infectious diseases can move faster and easier when vectors such as *Aedes Egypti* mosquito has become naturalized in several parts of the world. Although the natural transmission cycle of zika virus involves mosquitoes, especially *Aedes spp*, perinatal transmission, potential risk for transfusion-transmitted and sexually transmitted zika virus infections has also been demonstrated.

**Conclusion:** Zika virus infection has probably been underdiagnosed and underreported in disease-endemic settings. Laboratory capacity to confirm suspected zika virus infections should be strengthened to differentiate it from other arboviral dengue-like infections. There is also a need for a vaccine and antiviral therapy to fight this disease.

**Keywords:** Zika; Virus; Infections; Epidemics

### Introduction

Zika is a mosquito-borne viral disease caused by Zika virus (ZIKV), a Flavivirus from the Flaviviridae family, that has the name of a forest near Kampala in Uganda, where it was identified in rhesus monkeys in 1947 [1,2]. It was subsequently isolated in humans several years after in 1952 in Uganda and another country in East Africa - Tanzania [1,3]. Genomic comparison showed different sub-clades and the existence of 2 different lineages the African and the Asian lineage [4-6]. The virus is transmitted by mosquitoes, and so far, only *Aedes* mosquitoes are known to be the vector. The *Aedes* species that can carry the virus includes *Aedes apicocoar genteus*, *Aedes africanus*, *Aedes furcifer*, *Aedes luteocephalus*, *Aedes vittatus* and *Aedes aegypti* [7]. Clinical symptoms in patients include fever, transient arthritis or arthralgia with possible joint swelling and maculo-papular rash, conjunctival hyperaemia (red sclerae) or bilateral non-purulent conjunctivitis with non-specific symptoms such as headaches, weakness, and muscle pain. These symptoms appear after an incubation period that lasts between 3 to 12 days [1]. Symptoms are usually mild and infection may go unrecognized or be misdiagnosed as dengue, chikungunya or other arboviral and tropical disease like malaria, and other hemorrhagic viral disease. There are reports of perinatal transmission, most probably transplacental or during delivery [8-10]. Transfusion-derived transmission may occur as reported during the outbreak in French Polynesia, from November 2013 to February 2014 where 3% of blood donors found positive for zika virus by PCR [11]. A possible sexual transmission has been reported in 2011 [12]. The presence of viable virus has also been reported in semen more than two weeks after recovery from an infection [13]. The above-described modes of transmission are uncommon. Diagnosis of zika virus is primarily based on viral RNA detection from clinical specimens. Detection of the virus can only be done on the first 3 to 5 days after onset of clinical symptoms [3,14]. Specific assays have been created for both African and Asian Zika virus strains targeting the NS5

region or the envelope gene [3,14-17]. Currently, there is no vaccine to prevent Zika virus infection [18]. Travelers going to countries where cases of Zika virus infection have been reported are advised to use insect repellents and wear long-sleeved shirts and long pants. The study aimed to review the epidemiology of Zika virus infection and to describe the recent epidemics and reported travel-related infection.

### Materials and Methods

The titles of journal articles in English including the terms “zika” or “zika virus” plus “Europe” and “European”, “Asia”, “America”, “Africa”, “Australia” plus the names of individual countries were searched. Articles published up to December 2015 were included. The search yielded 76 articles. The official websites of the World Health Organization, US Centers for Disease and Control Prevention (CDC), European Centre for Disease Prevention and Control, Pan American Health Organization (PAHO), ProMED-mail were also reviewed for relevant information.

### Results

Outbreaks and transmission of Zika virus have been reported in Africa, the Pacific Islands, Southeast Asia, and in South and Central America.

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## Africa

Epizootic Zika virus has been reported in Zika Forest in Uganda in 1969 following the build-up of non-immune monkeys and in 1970 when biting densities of *Aedes africanus* increased [19,20]. In Nigeria, a study of Zika virus infections was carried out in four communities in Oyo State. Studies between 1971 and 1975 yielded two viral isolations from human cases of mild febrile illness [21]. A survey for haemagglutination-inhibiting arthropod-borne virus antibody was carried out in the Kainji Lake area. Of 267 persons tested, 158 (59%) had flavivirus group HI antibody. The prevalence of antibody to Zika virus antigen was 56% [22,23]. During an epidemic of jaundice in Eastern Nigeria infection with Zika virus was shown to have occurred in three patients. Two of the three patients had evidence of liver damage. Serological studies showed a relationship between jaundice and the presence of zika virus neutralizing bodies in the serum [24]. In 1972, a survey on yellow fever carried out in Sierra-Leone was done. Sera from 899 children aged 0 to 14 years were tested with 12 different antigens by haemagglutination-inhibition and complement fixation tests. Zika virus was identified in most areas while Chikungunya virus was particularly active in the plateau and grassland zones, in the North-East [25]. The first direct evidence of human zika infection in Gabon, and its first occurrence in the Asian tiger mosquito, *Aedes albopictus* was documented in 1975 [26]. Seropositivity toward Zika virus was documented in savannah woodland areas, as well as among monkeys in southeastern Gabon [27]. The serological survey of non-human primates confirmed activity and circulation of other viruses such as Chikungunya virus. Also, transmission of maternal antibodies was established for the following arboviruses: Chikungunya, yellow-fever, Uganda S, Zika and Orungo [28].

High rates of seropositivity toward Zika virus were demonstrated in the southeastern region of Central African Republic in 1979. Serum samples were tested using the haemagglutination inhibition (HI) test and complement fixation test. Only 11% of the population tested had no HI antibodies against the following arboviruses: Zika, Chikungunya, Semliki-forest, Sindbis, Yellow fever, Uganda S, West-Nile, Bunyamwera and Zinga [29]. Zika virus has been identified in two mosquito species: *Aedes (Stegomyia) africanus* and *Aedes (Stegomyia) opok* [30]. A study of the circulation of arboviruses of medical interest in southeastern Senegal was conducted from 1988 to 1991. Specific IgM antibodies were detected in human sera indicating a recent infection within 2 to 5 months. A Zika virus outbreak was reported each year of the study period [31]. Clinical and serologic evidence indicate that 2 American scientists contracted Zika virus infections while working in Senegal in 2008 [13].

Zika virus has been identified in Cote d'Ivoire in the following mosquito species: *Aedes (Stegomyia) aegypti*, *Aedes (Stegomyia) africanus*, *Aedes (Diceromyia) flaviculis*, *Aedes (Mucoides) grahmi*, *Aedes (Diceromyia) furcifer*, *Aedes (Stegomyia) luteocephalus*, *Aedes (Neomelaniconion) taeniarostris*, *Aedes (Aedimorphus) tarsalis*, *Aedes (Aedimorphus) vittatus*, *Eretmapodites inornatus*, *Eretmapodites quinquevittatus* [32].

In South West Cameroon (the Fako Division), febrile patients (negative for typhoid fever and malaria) were tested and forty-six sera (58.2%) reacted with members of the genus *Flavivirus* - 30.4% were cross-reactive, 11.4% reacted monotypically with Zika [33].

## Asia

In 1977 and 1978 selected patients with acute fever at the Tegalyoso

Hospital, Klaten, Central Java, Indonesia were studied for evidence of alphavirus and flavivirus infections. Acute and convalescent phase sera from 30 patients were tested for neutralizing antibodies to several flaviviruses and sera from 7 patients demonstrated a fourfold rise in antibody titre from acute to convalescent phase [34]. In Lombok, Indonesia, sera collected from humans, goats, ducks, chickens, cattle, horses, wild birds, bats, and rats were tested by haemagglutination inhibition (HI) for antibodies to certain arboviruses. Neutralization tests showed that dengue virus (DEN-2) and zika virus may have caused some of the infections [35]. Complement-fixation test reactions to eight viruses were studied in 372 serum samples (humans, domestic animals, rodents) from Pakistan. Antibodies to each virus tested were identified. Prevalence rates were 7.8% for West Nile, 3.2% for Japanese encephalitis and 2.4% for Zika virus [36]. In Malaysia, 84 free-ranging orangutans captured for translocation, underwent a complete health evaluation between 1996 and 1998. Serological tests indicated exposure to respiratory syncytial virus (RSV), dengue, coxsackie, and zika virus [37]. In Cambodia, the US Naval Medical Research Unit No. 2 (NAMRU-2) has established a surveillance system for acute fever since 2006 to determine causes of infection among patients who seek health care. In August 2010, a 3-year old boy in Kampong Speu Province, Cambodia was diagnosed using PCR to have zika virus infection. The extent of zika virus is not known and further studies are needed to ascertain zika virus prevalence and distribution in the country [38]. In March 2012, a prospective longitudinal cohort study, which included active surveillance for acute febrile illness, was initiated in Cebu City, Philippines. In the first year of surveillance, 270 acute febrile illnesses were recorded and 267 had samples that showed evidence of dengue, influenza, Japanese encephalitis, chikungunya, and Zika virus infections [39]. In May 2012, a 15-year-old boy with acute fever was diagnosed to have zika virus infection after zika RNA was detected in the patient's serum sample. This was after exclusion of dengue, Japanese encephalitis, and chikungunya using ELISA [15]. In Thailand, seven cases of acute Zika virus infection were confirmed by molecular or serological testing across the country. These cases and previous reports in travelers show that zika virus is endemic in Thailand [40].

## The Pacific islands

In 2007, the first documented Zika virus outbreak was reported from Yap State, Federated States of Micronesia [9]. No further Zika virus transmission was reported in the Pacific until October 2013, when French Polynesia reported the first cases. Thereafter, an explosive outbreak resulted in more than 28,000 cases (approximately 11% of the French Polynesian population) [41-43,15]. The outbreak in Tahiti, Tahaa, Uturoa, Borabora, Taiohae, Tuamotu and Arutua included 74 cases complicated by neurological signs, including 41 with Guillain-Barre syndrome (GBS) [11]. The recent outbreak in Micronesia was initiated by a strain from Southeast Asia - similar to the strain isolated in 1966 in Malaysia [6]. In January 2012, the Pacific experienced a high burden of mosquito-borne disease due to concurrent epidemics of dengue, chikungunya and Zika virus infections. An outbreak (932 suspect and 49 confirmed cases) of Zika virus infection was reported in the Cook Islands [44]. The virus has been circulating in the islands of French Polynesia, New Caledonia and Easter Island. Although the distance between these islands is significant, the virus is being moved by viremic people who travel between them. One can expect further spread to localities where there are populations of vector mosquitoes that can initiate new outbreaks [45]. Indigenous circulation of the virus has been reported in the Americas since 2014. Chilean health authorities confirmed the first case of indigenous zika virus transmission on Easter Island in February 2014 and cases were recorded until June 2014 [41,43-46].

## Latin America

In May 2015, Brazilian health authorities confirmed autochthonous transmission of Zika virus in the northeastern part of the country. Cases of Zika virus infection had been reported in 14 states: São Paulo, Rio de Janeiro Alagoas, Rio Grande do Norte, Roraima, Piauí, Pernambuco, Bahia, Ceará, Mato Grosso, Maranhão, Paraná, Paraíba, and Pará [47,48]. In October 2015, the Brazil International Health Regulations (IHR) notified detection of an unusual increase in the number of microcephaly cases in both public and private medical facilities in Pernambuco state in the Northeastern part of Brazil. In November 2015, 1,248 cases (99.7 out of 100,000 live births) of microcephaly were recorded while in 2000 the prevalence in newborns was only 5.5 cases out of 100,000 live births [48]. Given the temporal correlation of these microcephaly cases with the outbreak of Zika virus infection, the Brazilian health authorities hypothesize that infection may be associated with these abnormalities if mothers are infected during the 1<sup>st</sup> or 2<sup>nd</sup> trimester of pregnancy [49,50]. In Colombia, 9 laboratory-confirmed cases of Zika virus infections were identified out of 98 samples from the Bolívar department in October 2015 [51]. Since the first cases, a cumulative total of 7,516 confirmed and suspected cases have been reported. Zika virus infection cases have been detected in 150 municipalities in Colombia, of which 72 (48.01%) were located in the Central Region [48].

## Travel-related Zika

A 27-year-old Belgian tourist coming from Tahiti was diagnosed with Zika virus infection after traveling to Easter Island, where the presence of the disease was detected [52]. In 2013, a German traveler acquired Zika virus infection in Thailand (including visits to Phuket, Krabi, Ko Jum, and Ko Lanta). This was the 1st laboratory confirmed case of Zika virus reported in Germany. In September 2014, a 45-year-old woman was seen in an outpatient clinic in Heidelberg, Germany for fever and maculopapular rash covering her trunk, arms, and legs. She was diagnosed with Zika virus and had returned from a vacation to peninsular Malaysia and Sabah, Malaysian Borneo [53]. In December 2013, a previously healthy 31-year-old woman from Norway was admitted to the Oslo University Hospital, Norway and diagnosed with Zika virus infection after returning from a vacation to Tahiti, where she mainly stayed in the capital, Papeete [54]. The first two cases of laboratory confirmed Zika virus infections was imported to Italy from French Polynesia. Both patients presented with fever, conjunctivitis, myalgia, malaise, ankle edema, arthralgia, and axillary and inguinal lymphadenopathy. One patient presented with leukopenia with relative monocytosis and thrombocytopenia. The diagnosis was based on ZIKV seroconversion for both cases and RNA detection in one patient from acute serum sample [55,56]. In Canada, a woman who traveled to Thailand came to a local emergency department with a low grade fever and papular rash. This is the first documentation of Zika virus in Canada [57]. In December, 2013, a Japanese man in his mid-20s presented with fever, headache, and arthralgia and one day of rash after visiting Bora Bora in French Polynesia. In January 2014, a previously healthy Japanese woman in her early 30s presented with retro-orbital pain, slight fever (self-reported), rash, and itches. She had travelled to Bora Bora mid-December 2013 for sightseeing [58]. In Australia, in 2013, a traveler with fever and rash acquired Zika virus infection in Indonesia [59] and in 2014, another traveler acquired Zika virus infection in the Cook Islands. This is the first known imported case of Zika virus infection into northern Queensland and the second reported case diagnosed within Australia [60].

## Discussion

Zika virus outbreaks have occurred in Africa, Southeast Asia, the Pacific Islands, and in South and Central America and several cases in non-endemic countries have been recorded from people who travelled to places where Zika virus outbreaks have been reported. However, since the *Aedes* mosquitoes that spread the virus are found worldwide, there is a potential for Zika virus to spread through countries where the (*Aedes*) vector is found. In 2007, the Yap State, Micronesia, reported the first outbreak of Zika virus outside Africa and Asia [41,46]. Subsequent infections were not reported until 2013 when this virus reappeared in French Polynesia and then disseminated throughout the Pacific [41,42]. In January to February 2014, one case of Zika virus infection was confirmed in Eastern Islands in the Pacific Ocean [61]; then in May 2015, 17 cases were confirmed in three states of Brazil [62]. Infection with the virus has been associated with microcephaly in mothers who have been infected during the 1<sup>st</sup> or 2<sup>nd</sup> trimester of pregnancy. Microcephaly is a congenital neurological condition that presents with an abnormally small head and brain development issues. In November 2015, an autopsy of an affected infant revealed the presence of the virus [60,63]. Because of the increased transmission of Zika virus in the Americas, the Pan American Health Organization/World Health Organization (PAHO/WHO) recommends that its Member States create and maintain the capacity to identify and confirm cases of Zika virus infection, prepare their health services for a potential increase in burden and healthcare costs, and implement an effective and efficient public communications strategy to reduce the mosquitoes that transmit this disease, especially in areas where the vector is present [47]. Zika fever surveillance should be set up based on the existing surveillance system in the different countries for dengue and chikungunya, while taking the differences in clinical presentation into account. Once introduction of the virus is documented, ongoing surveillance should be maintained in order to monitor epidemiological and entomological changes that may affect the transmission of Zika virus and changes detected should be promptly communicated to the national authorities to ensure timely decisions for actions as appropriate [47].

A big challenge in many countries such as the low income countries is the laboratory detection. During the first 5 days after the onset of clinical symptoms, viral RNA can be detected in serum by molecular techniques (RT-PCR). A generic assay against flavivirus followed by genetic sequencing can also be used to establish the specific etiology.

Regarding the case management and the treatment, so far there is no vaccine or specific antiviral treatment for Zika virus. Symptomatic treatment after excluding more severe conditions (i.e. dengue, malaria, and other bacterial infection) is recommended. To replenish fluid lost from sweating and vomiting, patients should be advised to drink plenty of fluids. To prevent infection of other persons, patients should avoid being bitten by *Aedes* mosquitoes during the first week of illness and should stay under a bed net (treated or without insecticide) or in a place with intact window or door screens. Physicians or health care workers who manage patients should use insect repellent and wearing long sleeves and pants to avoid mosquito bites.

It is important to differentiate Zika virus infection from dengue due to severe clinical outcomes in dengue cases. Cases of co-infection, Zika and dengue, may also occur since both viruses share the same vector. Because Zika virus outbreaks could cause additional burdens on all levels of the health care system, it is necessary to develop and implement protocols and well-established plans for the patient screening and treatment [1,47]. Health authorities need to advise travelers heading to any country with documented circulation of Zika, chikungunya,



and dengue to take the necessary measures to protect themselves from mosquito bites [47,64].

## Conclusion

Zika is an emerging infectious disease currently found in parts of tropical Africa, Southeast Asia, the Pacific and the Americas. Zika virus infection in humans produces an illness clinically similar to dengue fever and many other tropical infectious diseases. Thus, zika virus infection has probably been underdiagnosed and underreported in disease-endemic settings. The natural transmission cycle of zika virus involves mosquitoes, especially *Aedes spp*, but perinatal transmission, potential risk for transfusion-transmitted and sexually transmitted zika virus infections has also been demonstrated. Clinicians and travel medicine clinics should include zika virus infection in their differential diagnosis for travelers from those areas. The laboratory capacity to confirm suspected zika virus infections should be strengthened to differentiate zika virus infections from other arboviral dengue-like infections. Strategies for the prevention and control of zika virus infection should include the use of insect repellent and mosquito vector eradication. There is also a need for a vaccine and antiviral therapy to fight this disease.

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