

Review Article

Zika Virus: A Clinical Review

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Abstract

Zika virus is a flavivirus related to Dengue virus, yellow fever virus and West Nile virus. It is considered an emerging arbovirus transmitted by mosquito of the genus Aedes. Its first description took place in 1947 in the Zika Forest in Uganda, isolated on Rhesus monkey used as bait to study the yellow fever virus. Clinical picture is characterized as a 'dengue-like' syndrome, with abrupt onset of fever; and an early onset of evanescent rash, often pruritic. Occasionally the disease has been associated with Guillain-Barré syndrome. The diagnosis can be performed by PCR or by IgG and IgM antibodies detection. No specific treatment or vaccine is available for Zika virus disease. Treatment is generally supportive. Control measures are same for dengue and chikungunya based mostly on health education and vector control.

Introduction

Zika virus is an emerging mosquito-borne virus that was first identified in Uganda in 1947 in Africa. It was first confirmed in Brazil in May 2015. It has since been identified in more than 27 countries and territories in the region^{1,2}. Spread to the Americas was predicted because of the abundance of the mosquito vector, *Aedes aegypti*^{3,4,5,6}. Clinicians worldwide need to be aware of Zika virus infection owing to international travel and the presence of another potentially competent mosquito vector (*Aedes albopictus*) in North America and southern Europe. Some Brazilian regions experiencing outbreaks of Zika infection have reported an apparent increase in congenital microcephaly and post-infective neurological syndromes, particularly Guillain-Barré². The association of these conditions with Zika virus infection is currently unproved and is under investigation. On 1 February 2016, the World Health Organization (WHO) declared the recent cluster of microcephaly and other neurological disorders reported in Brazil, following a similar cluster in French Polynesia in 2014, a public health emergency of international

concern⁷. If Zika virus infection is confirmed to cause congenital microcephaly, this could lead to a large international burden of infant neurological morbidity. Zika virus infection should be considered in people presenting with compatible symptoms who have recently returned from countries where outbreaks of the infection are occurring. This review provides up to date information on Zika virus, its evolving epidemiology, how to recognize its clinical presentation, possible complications, and how to confirm the diagnosis.

What is Zika virus?

Zika virus is an arbovirus (arthropod borne virus). It is a member of the Flaviviridae family, genus *Flavivirus*, which includes dengue, yellow fever, and West Nile viruses. Its first isolated in 1947 in the Zika Forest in Uganda, isolated on Rhesus monkey used as bait to study the yellow fever virus⁸. Zika virus is a single stranded RNA virus with two major lineages: Asian and African^{4,9,10}. In Africa, Zika virus is thought to have been largely maintained in a cycle involving transmission between non-human-

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primates (such as monkeys and apes) and mosquitoes, with humans as occasional unintentional hosts^{11,12}. In areas outside Africa, however, humans have probably become the main host³. Few complete Zika virus genome sequences are available, and to date only two are from the current South American epidemic. Phylogenetic analysis of a Suriname Zika virus indicates that it belongs to the Asian genotype. It is most closely related to the strain that was circulating in French Polynesia in 2013, sharing more than 99.7% and 99.9% of nucleotide and amino acid identity, respectively¹³. This finding is consistent with analysis of envelope gene sequences from Brazilian patients^{14,15}. A mutation in the Asian lineage may have led the virus to adapt to the human (as opposed to non-human primate) host¹⁶.

Until recently, Zika virus was less of a research priority than other flaviviruses, as it was not thought to be of public health importance. Limited literature exists on the pathogenesis of the Zika virus to help understand the clinical disease spectrum and to target treatments to minimise or prevent tissue damage^{17,18}. Zika virus replicates readily in skin immune cells, and a large number of receptors are able to mediate entry of the virus into cells¹⁸. Studies on the capability of the virus to replicate in neuronal cells are warranted to further investigate the link with neurological disorders.

Worldwide distribution

Between the first isolation of Zika virus in monkeys in 1947 until 2007, reports of human cases were rare and sporadic^{8,19,20}. Evidence on the extent of human infection was based mainly on serological studies and, in some cases, isolation of the virus¹⁹⁻²⁵. Viral isolation suggested a wide distribution in Africa and South East Asia, although no epidemics were observed. Upon the isolation of the virus in the late 1940s, the first cases of ZIKV infection in humans were identified in Uganda in 1952. Cases were also found in Nigeria in 1953 and mosquitoes of the species *Aedes aegypti* were laboratory infected in 1956 resulting in a 60% successful transmission of the virus in mice. ZIKV-positive patients were still found in serological testing made in Nigeria in the 1960s and also in febrile patients during a YF epidemics that emerged in 1970. Serological and virological evidence of ZIKV infection was found in Sierra Leone, Nigeria, Senegal, Gabon, Ivory Coast and in Central African countries in 1975-1977²²⁻²⁷. The first evidence of ZIKV circulation out of the African continent occurred between 1977 and 1978 when

acutely febrile patients were admitted to an hospital in Indonesia and ZIKV antibodies were found in sera from 30 patients²⁸. Two ZIKV epidemics were reported in the Federated States of Micronesia (in the island of Yap) over the last decade, representing the first outbreak outside Africa and Asia²⁹.

In 2007 an outbreak caused by a strain of Asian lineage occurred on the island of Yap, an island state of the Federated States of Micronesia^{3,4}. Estimated cases affected in this and subsequent outbreaks to date are probably imprecise, given the incomplete laboratory confirmation and the similarities in clinical presentation of Zika virus with other arbovirus infections present throughout the tropics. In Yap, 49 confirmed and 59 probable cases (defined according to strict serological criteria or RNA detection by reverse transcription-polymerase chain reaction) were identified over a four month period³. On the basis of one serological test, an estimated 73% of the island's population were infected over three years. A further outbreak occurred with a closely related Asian lineage strain in French Polynesia in 2013 in which 294 cases were confirmed by RNA detection over a 10 week period^{26,27}. Locally acquired cases (people with no history of travel to known endemic areas within the recognised incubation period) on Easter Island in 2014 marked the first arrival of Zika virus in the Americas²⁸. This was followed in May 2015 by confirmation of cases in north east Brazil, where again the Zika virus sequence belonging to the Asian lineage was found²⁹. The countries where the presence of the infection in seroepidemiological studies and the disease's native transmission were already reported are shown in following figure.

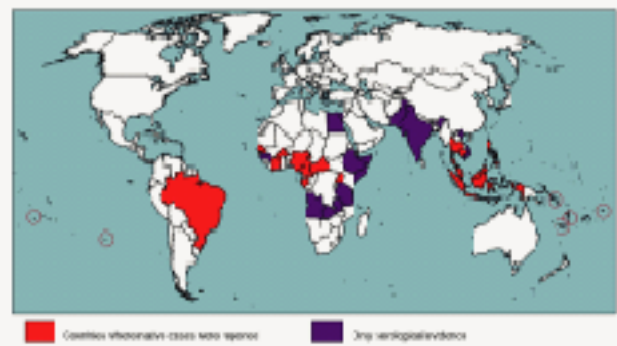


Figure 1 - Countries with an evidence of native transmission or with positive results in seroepidemiological studies. Source: CDC, May 2015; adapted by Acta Médica Portuguesa, December 2015.

Transmission

The key Zika virus vector is thought to be the daytime biting (indoors and outdoors), urban dwelling *Aedes aegypti* mosquito. Evidence to support this comes from detection of the virus in wild *A. aegypti* and by experimental transmission in rhesus monkeys³⁰⁻³². Following laboratory feeding of *Aedes albopictus* mosquitoes with Zika virus infected blood, the virus has been demonstrated in mosquito saliva, suggesting these mosquitoes may also transmit the virus^{33,34}. Presumptive sexual transmission has been reported in two cases^{35,36}. Isolation of virus in semen 17 days after a clinical diagnosis of acute infection supports potential sexual transmission, as does the detection of Zika virus RNA in semen 62 days after the onset of symptoms^{37,38}. Zika virus was detected in approximately 3% of asymptomatic blood donors during the French Polynesian outbreak,³⁹ suggesting that transmission might be possible through infected blood and blood products. Evidence implies transplacental transmission and perinatal transmission during delivery, with Zika virus RNA being found in amniotic fluid¹⁵ and in paired blood samples taken from newborn infants and mothers⁴⁰. There is currently no evidence to support transmission via contact with saliva, urine, or respiratory droplets.

Clinical Presentation

Zika virus infections seem either to be subclinical (possibly in as many as 80% of infections) or to cause a mild illness after an incubation period of three to 12 days. Symptoms, which last for approximately two to seven days include fever, conjunctivitis, arthralgia, myalgia, and widespread rash, which may be itchy. Headache, retro-orbital pain, peripheral oedema, and gastrointestinal disturbance have also been observed^{3,41}. Only one study has examined the proportion of infections that produce symptoms. A serological survey during the Yap outbreak found that only 19% of participants with IgM antibodies against Zika virus reported rash, joint pains, or conjunctivitis that were probably attributable to Zika virus infection. Whether the remaining infected participants experienced any other symptoms was not reported³. The proportion of infected people who experience no symptoms is not known. Observation of Zika viraemia in 31 French Polynesian blood donors who reported no symptoms, during or after blood donation, suggests that asymptomatic infection does occur³⁹. Shock and haemorrhage occur with other flaviviruses such as

dengue, but they have not been documented in Zika virus infection. Severe acute illness seems to be rare. Fewer than 10 possible Zika related deaths have been reported in adults, and an additional three deaths from Guillain-Barré syndrome have occurred in individuals who had symptoms of Zika infection⁴². The Pan American Health Organization of WHO has issued a provisional case definition for suspected acute Zika virus infection, intended for use in countries with ongoing local transmission (see box 4)⁴².

Box 4: Provisional case definition of suspected acute Zika virus infection. Pan American Health Organization⁴²

- Rash or increase in body temperature (>37.2°C), with any of the following not explained by other conditions:
- Arthralgia or myalgia
- Non-purulent conjunctivitis
- Conjunctival hyperaemia
- Headache

In addition to dengue and chikungunya, other diagnoses that should be considered include HIV seroconversion, measles, scarlet fever, rickettsial infection, leptospirosis, parvovirus, enterovirus, rubella, and secondary syphilis.

Table: Clinical manifestations more frequently associated to dengue, chikungunya and ZIKV infection

Symptom	Deng	Chikungunya	Zika
Fever (Intensity)	+++	++	+
Myalgia	+++	++	+
Rash	+++	++	+
Arthralgia	+++	++	+
Headache	+++	++	+
Conjunctivitis	+++	++	+
Blood dyscrasia	+++	++	+
Shock	+++	++	+
Thrombocytopenia	+++	++	+
Neutropenia	+++	++	+
Lymphopenia	+++	++	+

Laboratory diagnosis

Due to the fact that currently no commercial tests allowing for the serological diagnosis of ZIKV infection are available, ZIKV acute infection may be diagnosed by RT-PCR (reverse transcription polymerase chain reaction) directly from virus RNA in patient's serum, preferably obtained up to the sixth day of disease. However, the virus was identified (by virus genomic amplification) at the 11th day upon symptom onset in-

one patient from the epidemic on the island of Yap⁴³. The virus may also be detected by using molecular techniques in other body fluids like saliva and in urine³⁷. IgM antibodies may be found from the third day of disease onset and IgG antibodies should be looked for in the acute and convalescent serum⁴⁴. The possible cross-reactivity related to previous infections with other flaviviruses can be a problem⁴⁶. The presence of ZIKV epidemics in regions where dengue virus was previously in circulation may represent a diagnostic challenge. Even the use of a plaque reduction neutralization test (PRNT), also used in the epidemic on the island of Yap, is unable to differentiate possible cases of ZIKV infection in patients with previously acquired anti-dengue virus antibodies, even when the anti-ZIKV titres were higher than the heterologous (non-ZIKV).

Nevertheless, different studies have described both qualitative and quantitative assessments regarding the presence of anti-ZIKV antibodies in biological samples where some of the techniques that have been used are non-standardized techniques used in specific laboratory contexts (in-house techniques). Despite the presence of diagnostic tests, its use is still rather limited as no commercial kits are available on the market. Therefore, diagnosis is restricted to public health, training and research institutions. The detection of viral genome through RT-PCR is the most sensitive and specific method for the diagnosis of the ZIKV infection; however, these are not fail-safe methods. Unlike other viruses, the limited circulation of the virus has reduced the knowledge regarding its real genetic diversity and therefore there is a non-zero probability that the primers used in ZIKV genomic amplification may not allow the required amplifications to be obtained (false-negative results in amplification tests).

Treatment

There is currently no vaccine against Zika virus, nor specific antiviral for the treatment of Zika virus. Treatment is symptomatic, although it is not known what agents are optimal for treating the fever, itch, and arthralgia. Minimisation of the chance of mosquito bites is advised by wearing long sleeves and trousers and using mosquito repellents⁴⁶. Specific travel advice is dealt with in the accompanying article^{47,48}.

Control measures

Ae. aegypti is a highly synanthropic mosquito that takes

advantage from peri-domestic environments and may even make its blood meals within human households. Considering that it is one of the ZIKV vectors and that vector control measures based on the use of insecticide agents are difficult due to (i) financial constraints, (ii) logistic issues, (iii) strict regulations regarding the use of insecticide agents and/or (iv) spreading of resistances in vector population, removal of larval breeding sites has a crucial role in the control of this vector. Individual protection measures should also be encouraged, involving the use of insect repellents and window and door screens to keep insects outside. The detection and study of suspected cases, aimed to prevent transmission in more problematic regions should be the priority in health surveillance. Those with an active disease or that recently presented with it are unable to donate blood.

Although no ZIKV-related deaths occurred until now, health professionals should be aware and trained in order to differentiate ZIKV disease from other diseases that simultaneously circulate, namely dengue⁴⁹. Attention to travellers returning from regions with ZIKV transmission should be a priority in ZIKV-free regions. Early recognition may contribute to take measures aimed to prevent disease spreading, considering the spread of *Ae. albopictus* in temperate regions.

Conclusion

ZIKV-related epidemics over the last decade lead to a relevant spreading from Asia and Pacific Ocean to the Americas. It is not yet known whether this flavivirus will establish within these new territories and further studies on its transmission dynamics are needed. Its presence in areas where the transmission of other flaviviruses has been already observed, such as the different serotypes of dengue virus, brings the possibility of an increase in mortality due to issues related to the differential diagnosis and also to the unavailability of commercial diagnostic kits. Despite the apparently benign characteristics of the disease, potentially lethal complications such as GBS emerged as a new issue in the approach to patients presenting in regions with active transmission. Vector control measures should be increased, as well as healthcare actions. In ZIKV-free regions and where there is the circulation of *Aedes* mosquitoes, care should be taken with travellers returning mainly from tropical regions.

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