Zika virus

Vírus Zika

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Etiological agent

Zika virus is a single-stranded RNA Flavivirus of the *Flaviviridae* family, transmitted by mosquitoes of the genus *Aedes* sp. It was identified in *Rhesus* monkeys in 1947, in the Zika Forest, Uganda, Africa, during jungle yellow fever surveillance. The first report of the disease in humans dates back to 1952 (cited by Campos GS et al.).[1]

Zika virus (ZIKV) was known until the end of the last century as a zoonotic pathogen, with sporadic human cases found in Africa and later also in Southeast Asia. In Africa, it remains in the wild cycle, involving monkeys and several *Aedes* mosquitoes. The Asian lineage spread to a chain of transmission involving humans, mainly through *Aedes aegypti*, in the Pacific Islands and South America.[2]

Epidemiology

In 2007, an outbreak was detected in the Yap Islands, Micronesia.[3] As reported by Musso[4] in an article published in the *Emerging Infectious Diseases* journal, the largest outbreak previously observed occurred in French Polynesia between 2013 and 2014. From there, it spread to other Pacific Islands: New Caledonia, Cook Islands, Easter Island (which belongs to Chile), Vanuatu and Solomon Islands. The source of the Zika virus in French Polynesia remains unknown. It is likely to have been introduced in other Pacific islands, where there is dispersion of *Aedes* sp, carried by infected travelers from French Polynesia. Phylogenetic studies show close correlation between the circulating strain in Brazil and those isolated from patients in French Polynesia. Both belong to the Asian lineage.

Although some authors suggest that Zika virus may have been introduced in Brazil during the FIFA World Cup, held between June and July 2014,[5] no endemic country in the Pacific region participated in the competition. On the other hand, Musso noted that in August 2014 there was a world canoe race, the Va'a World Sprint championship, in the city of Rio de Janeiro. Teams from four countries of the Pacific region, where Zika virus was circulating, French Polynesia, New Caledonia, Cook Islands and Easter Island, participated in this competition. According to Musso, these data, combined with the virus' phylogenetic studies, suggest that the introduction of the virus in Brazil may have occurred during this event.[4]

In May 2015, the Ministry of Health of Brazil confirmed the autochthonous transmission of Zika virus in the northeast region of the country.[2] The first documented outbreak in Brazil and the Americas took place between April and May 2015, in Camaçari, Bahia.[1] Since then, the Ministry of Health requests notification of the confirmed cases using a notification/completion form (Information System of Notification of Diseases – SINAN) to the Brazilian Health Surveillance Agency. For notification of the new disease, the ICD-10 (International Classification of Diseases) code set is A92.8. Also in May 2015, São Paulo's State Department of Health detected a laboratory-confirmed case of disease caused by Zika virus in a patient from the city of Sumaré, in the Campinas area, who did not have a history of travel. Since then, the department warns that the control measures to be adopted are the same used for the control of *Aedes aegypti* and are focused on reducing the vector's density, eliminating potential breeding in urban areas.[6]

Zammarchi et al., in an article published in June 2015, report a laboratory-confirmed case of Zika virus infection in an Italian traveler after his return trip to Salvador, Bahia, Brazil, in March 2015.[7]

On June 10, 2015 the Health Surveillance Coordination (COVISA) of the São Paulo Municipal Government issued a "Statement on the fever caused by Zika virus". It defined what a suspected case is and stated that "the main goal for epidemiological surveillance, at this point, is to

detect the circulation of Zika virus. Laboratory investigation will only be carried out by Instituto Adolfo Lutz after clusters are detected".[8] Until then, the disease caused by Zika virus was considered benign. In this statement of the municipal Department of Health of São Paulo "fever by Zika virus is described as an acute febrile illness, self-limited, lasting 3 to 7 days, usually without severe complications, with no reports of death. Hospitalization rate is potentially low. According to the literature, over 80% of those infected do not develop symptoms".[8]

However, in an article published in March 2014, Oehler et al.[9] described the first case of Guillain-Barré syndrome, diagnosed in November 2013, immediately after Zika virus infection, confirmed by laboratory testing using real-time polymerase chain reaction (RT-PCR) in a patient in French Polynesia. In the same article, the authors report that since the beginning of the Zika virus epidemic in French Polynesia the incidence of Guillain-Barré syndrome has increased about 20 times. They comment that "there is no explanation for the emergence of this complication not previously described, which could be linked to genetic evolution of the virus to a more pathogenic genotype, or a particular susceptibility of the Polynesian people."

In correspondence published in *The Lancet* in July 2015, Musso et al.[10] report that before the epidemic in French Polynesia there was a belief that the Zika virus caused only mild illness. Since this epidemic, severe neurologic complications such as the Guillain-Barré syndrome were detected.

In October 2015, the Ministry of Health of Colombia reported the first autochthonous case of infection by Zika virus in the Department of Bolivar.[2] In early 2016, there were reports of autochthonous cases of infection by Zika virus in El Salvador, Guatemala, Mexico, Paraguay, Puerto Rico and Venezuela.[11]

The first cases of microcephaly were observed in Pernambuco, Brazil. In October 2015, the Department of Health of Pernambuco received reports from professionals of the state health network of an increased number of cases of children born with microcephaly. An Emergency Operations Committee on Health (COES) was established, consisting of professionals from different institutions: Ministry of Health; Pan American Health Organization (PAHO); Oswaldo Cruz Foundation (Fiocruz); Federal University of Pernambuco; Oswaldo Cruz University Hospital, Barão de Lucena Hospital, Center for Integrated Health Amaury de Medeiros (Cisam), Integrative Medicine Institute Prof. Fernando Figueira (IMIP); Disabled Children Assistance Association (AACD), to discuss cases and plan the actions that should be started. As of October 27, 2015, the State Health Department of Pernambuco (SES-PE) instituted immediate notification of these cases, urging all state services and health professionals to immediately notify the identified cases of microcephaly. In addition to the institution of immediate notification, with support from the Ministry of Health, PAHO and Fiocruz, field epidemiological research was initiated in order to identify possible causes of this change in the pattern of occurrence of microcephaly in the state.[12] On November 10, 2015 a clinical and epidemiological protocol on the management of cases of microcephaly to guide professionals in maternity hospitals and reference units was developed and released by the SES team, the Ministry of Health and professionals from the health facilities involved (infectious disease specialists, pediatricians , neurologists).[12]

On the following day, the Ministry of Health declared that the occurrence, in the State of Pernambuco and other areas in Brazil's Northeast, of cases of babies born with microcephaly possibly related to Zika virus (ZIKV) was a "public health emergency of national importance" (acronym Espin, in Portuguese).[13]

On November 28, 2015, the Ministry of Health of Brazil recognized the relationship between the presence of ZIKV and the occurrence of microcephaly based on:

- Identification of death of malformed newborn infants and suggestive patterns of infection in the state of Rio Grande do Norte.
- Identification of two deaths in different federal units with negative results for other viruses and identification of ZIKV RNA *in viscera*.
- Evidence in the literature that ZIKV is neurotropic and the fact that, after its appearance in Brazil, French Polynesia is identifying similar cases in its territory.
- ZIKV identification in the amniotic fluid of two pregnant women whose fetuses had microcephaly in countryside areas of Paraíba.[14]

In December 2015, the World Health Organization (WHO) issued a warning for this congenital anomaly, as well as for acute neurological syndrome, both possibly associated with ZIKV.[15]

Data released by the ProMED-PORT on January 13, 2016, report that positive results were found for Zika virus in tests (PCR and immunohistochemistry) conducted by the United States CDC (Centers for Disease Control and Prevention), one of the agencies accompanying the investigations of two cases in infants with microcephaly who died after birth and of two fetuses whose mothers had

spontaneous miscarriage in Rio Grande do Norte, based on samples sent from researchers at Federal University of Rio Grande do Norte (UFRN).[16]

Data from the Ministry of Health of Brazil dated January 13, 2016 report that 3,530 recorded cases of microcephaly are being investigated. Suspected cases in newborns have been counted since the beginning of the investigations (on October 22, 2015) until January 9, 2016. 46 deaths of babies with microcephaly possibly related to Zika virus are also being investigated, all in northeastern Brazil. The state of Pernambuco, the first to identify increased occurrence of microcephaly, continues with the highest number of suspected cases (1,236), representing 35% of the total registered across the country. Then, the states of Paraíba (569), Bahia (450), Ceará (192), Rio Grande do Norte (181), Sergipe (155), Alagoas (149), Mato Grosso (129) and Rio de Janeiro (122). So far, 20 Brazilian states have autochthonous circulation of Zika virus. They are: Distrito Federal, Mato Grosso do Sul, Roraima, Amazonas, Pará, Rondônia, Mato Grosso, Tocantins, Maranhão, Piauí, Ceará, Rio Grande do Norte, Paraíba, Pernambuco, Alagoas, Bahia, Espírito Santo, Rio de Janeiro, São Paulo and Paraná.[17]

Clinical symptoms

Infection by Zika virus can be asymptomatic in about 80% of patients.[3] According to the Health Portal of the Ministry of Health of Brazil, only 18% of those infected have clinical symptoms after being bitten by a mosquito.[18] In patients with symptomatic disease, signs and symptoms occur in about four days after the mosquito bite and the most commonly observed are fever, generally low, headache, malaise, arthralgia or arthritis, myalgia, non-purulent conjunctivitis, and pruritic maculopapular rash, which can affect the whole body, even the palm of the hand. Other symptoms less commonly observed include retro orbital pain, swelling and vomiting. Clinical manifestations last around 1-5 days.[1]

Before the epidemic in French Polynesia, this was considered an infection with mild to moderate symptoms without complications. However, after the epidemic, there was an increase in confirmed cases of Zika virus with neurological involvement, i.e. Guillain–Barré syndrome. And more recently, in the epidemic that has taken place in almost all of Brazil, the association of microcephaly in newborns of mothers infected by Zika virus early in pregnancy was confirmed.

In Brazil, Zika virus infection in a patient with HIV/AIDS was reported.[19] The patient developed mild symptoms and recovered without laboratory abnormalities.

The differential diagnosis should be made mainly between dengue and chikungunya, as shown in Table 1, published by the Ministry of Health as part of the "Protocol of Attention to Health and Response to Occurrence of Microcephaly Related to Zika virus Infection".[20]

In addition to the similar symptoms, there are also reports in the literature of concomitant infection with Zika and Dengue viruses. In one of the reported cases, in-

TABLE 1 Comparison of frequency of the main signs and symptoms caused by infection with Dengue, Chikungunya and Zika viruses.[20]

Signs/Symptoms	Dengue	Zika	Chikungunya
Fever (duration)	> 38°C (4 to 7 days)	Afebrile or subfebrile ≤ 38°C (1-2 days subfebrile)	High fever > 38°C (2-3 days)
Skin spots (frequency)	Begins on day 4 in 30-50% of cases	Appears in the first or second day in 90-100% of cases	Appears 2-5 days in 50% of cases
Muscular pain (frequency)	+++/+++	++/+++	+/+++
Joint pain (frequency)	+/+++	++/+++	+++/+++
Intensity of joint pain	Mild	Mild/Moderate	Moderate/Intense
Joint edema	Rare	Frequent and mild	Frequent and moderate to intense
Conjunctivitis	Rare	50-90% of cases	30%
Headache (frequency and intensity)	+++	++	++
Pruritus	Mild	Moderate/Intense	Mild
Lymph node hypertrophy (frequency)	Mild	Intense	Moderate
Blood dyscrasia (frequency)	Moderate	Absent	Mild
Neurologic involvement	Rare	More frequent than Dengue and Chikungunya	Rare (predominantly in newborns)

Source: Carlos Brito – Professor at Universidade Federal de Pernambuco (updated in December/2015).

fection with Zika was concomitant with Dengue 3 virus (DENV 3) and, in the other, Dengue 1 virus (DENV 1). In both cases, occurred in New Caledonia, there was no synergistic effect between the two infections and patients recovered after mild symptoms.[21]

Laboratory testing

The main non-specific laboratory findings are:

- Normal leukocyte count or mild leukopenia.
- Platelet count, normal to slightly decreased.
- Slight increase in aspartate aminotransferase (AST) transaminase; gamma-glutamyl transferase (gama GT); lactic dehydrogenase (DHL) and C-reactive protein.

Etiologic diagnosis:

- Molecular biology: specific laboratory diagnosis is mainly based on detection of viral RNA in samples of blood, urine, spinal fluid or tissue. Since probably the viremia is short-lived, it is recommended to collect samples in the first five days of disease manifestation. Urine can be collected up to eight days after the onset of symptoms. The method used for detection is polymerase chain reaction in real time (RT-PCR). Samples must be stored and transported between -20 and -70° C.
- Serology: enzyme immunoassay (ELISA). In samples positive for IgM, RT-PCR should be performed to confirm the diagnosis.

Instructions for collecting and shipping are available from: http://portalsaude.saude.gov.br/images/pdf/2015/dezembro/09/Microcefalia---Protocolo-de-vigil--ncia-e-resposta---vers--o-1----09dez2015-8h.pdf.

Treatment

Treatment for infection with Zika virus is supportive and there is no specific therapy as well as in other arboviruses.

In symptomatic cases with fever and myalgia, use of analgesics and antipyretics such as acetaminophen and dipyrone is recommended. In case of pruritus, antihistamines may be administered safely.

Similarly to other arboviruses, the use of aspirin is banned due to the risk of bleeding complications.[22]

The care of pregnant women should be intensified during prenatal care due to the possible association of cases of microcephaly in newborns of mothers infected with Zika virus during pregnancy.[20]

Based on the scientific knowledge currently available, breastfeeding is not contraindicated. The Ministry of Health of Brazil[20] and the US Centers for Disease Control and Prevention (CDC)[23] recommend breastfeeding in cases of newborns with microcephaly related to infection by Zika virus.

Studies in French Polynesia failed to identify virus replication in milk samples. Only the presence of virus fragments unable to cause disease was observed.[20]

Prevention and challenges

There is no vaccine available for prevention of Zika virus. The most effective preventive measure is to avoid mosquito bites.

For personal protection, repellents containing DEET, picaridin, or IR3535 (whose chemical structure is a beta alanine) provide protection for periods of a few hours, and should be re-applied after excessive sweating. When using sunscreen and insect repellent at the same time, the sunscreen must be passed before, and then repellent. Clothes and curtains can be impregnated with permethrin to repel insects. Air-conditioned rooms, kept with doors and windows closed, can also avoid the presence of insects. *Aedes* sp mosquitoes feed mainly in daytime, without specific biting hours.

For population protection, the measures are the same related to the control of dengue. In addition to the difficulties observed until today to combat the vector, reflected in the high incidence of dengue in different regions of Brazil, there are other worrying factors.

Brazilian researchers found recent Asian epidemic strains of Zika virus that have changes in NS1 and NS4 genes and are more adapted to humans.[24] These authors point out that the pandemic potential of Zika virus is maximized to also be transmitted by *Aedes albopictus*, a mosquito that occurs at high latitudes.

Also, sexual transmission[25] and perinatal infection,[26] although with no epidemiological importance so far, can be alternative transmission routes.[24] As pointed out by Patiño-Barbosa et al.,[25] it would be necessary to combine programs to control vector-borne diseases with integrated strategies for sexually transmitted disease control, until the transmission of Zika virus through sexual contact is confirmed or not.

When reporting an exanthematous illness outbreak associated with Zika virus in Bahia, Cardoso et al.[27] pointed out the increased challenge that the transmission of this virus poses to public health, especially because of the risk of concurrent transmission of Dengue and Chikungunya by the same vectors, *A. aegypti* and *A. albopictus*, which are very common in tropical and subtropical regions. They

suggest that the Brazilian public health authorities establish joint action plans with neighboring countries. Surveillance for case detection must be coupled with laboratory capacity for confirmation of suspected cases.

Zammarchi et al.[7] comment that the identification of two other diseases transmitted by *Aedes* – Zika and Chikungunya – in addition to the already known Dengue, represents a serious threat to the health services in South America. They also warn that due to the high frequency of air travel between Latin America and other regions of the world where the virus does not circulate, but the vectors are present, such as southern Europe and the southern part of the United States, the systems surveillance should be alert to prevent the spread of the disease. Imported cases have been reported in travelers going from Thailand to Germany[28] and Canada;[29] from Indonesia to Australia;[30] from Senegal to the United States;[31] from Bora Bora, in French Polynesia, to Japan;[32] from Tahiti to Norway.[33]

The adaptation of Zika virus to urban and periurban cycles involving *Aedes aegypti* as a vector and man as host, according to Musso et al.,[10] should be a major concern for public health. With more than half the world's population living in areas infested by *Aedes*, there is a great potential for urban epidemics of Zika, Dengue, Chikungunya and yellow fever, and urgent need to develop more effective measures for mosquito control.

In an article published in October 2014, Roth et al.[34] warned that the Pacific region would probably be the initial stage of epidemic waves of infections caused by the three viruses, Dengue, Chikungunya and Zika, since most of the people in this area are immunologically naive, vectors are present, and there is great mobility among people and ease of dissemination represented by air travel. They also noted that the cause of the increased population of transmitting vectors in the region was unknown, but probably due to a combination of socioeconomic, environmental and ecological factors.

According to Fauci and Morens,[35] a pandemic of Zika virus is still in progress, and many important issues, such as teratogenicity, need to be clarified. But it serves as a warning to an important lesson: human interventions that disturb the ecological balance can cause numerous quiescent infectious agents to emerge unexpectedly. Comprehensive and integrated researches aimed to increase our understanding of complex ecosystems in which we interfere are necessary.

The World Health Organization (WHO),[15] in a document published in November 2015, warns that urbanization and globalization are potential risks for outbreaks of infection with Zika virus anywhere in the world where the vector is present or may be established in the future. They recommend the following measures for at-risk countries: strengthen laboratory capacity for confirmation of cases, since the clinical manifestations are similar to those caused by other arboviruses; establish a surveillance system to detect neurological and autoimmune complications and implement social communication strategies to engage the community in reducing vector populations.

The Brazilian public health authorities have been vigilant until now and have responded promptly to detect cases and standardize procedures to address new situations. The Ministry of Health of Brazil published on December 15, 2015, the National Plan to Combat Microcephaly.[20]

As recommended in the editorial published in *The Lancet* in January 2016, now is the time to intensify all efforts to prevent, detect and respond to infection by Zika virus.[11]

The challenges ahead are enormous. In addition to developing effective measures for the control of mosquitoes and the prevention of new cases, the following is required: laboratory training enabling early diagnosis of suspected cases, decentralization of actions in the clinical management and attention to sequelae, which involves a multidisciplinary approach for life. These challenges will require enormous efforts of the entire Brazilian health community.

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