What should we know about the Zika virus?

DOI: 10.7365 / JHPOR.2015.2.10

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Keywords:

microcephaly, Zika virus, ZIKV

Abstract

Zika virus (ZIKV) is a vector-borne arbovirus of the Flaviviridae family, which also includes dengue, West Nile, yellow fever and Japanese encephalitis viruses. It is transmitted by daytime-active Aedes mosquitoes.

Similarly to other flavivirus infections, Zika virus disease, or Zika fever is usually asymptomatic, and only in 20% of cases non-specific symptoms such as mild fever, rash, conjunctivitis, and arthralgia, may develop.

In 2015, an epidemic of ZIKV infection was reported in South and Central America and the Carribbean. It caused major concern because of a possible association between maternal infection and adverse fetal outcomes, such as congenital microcephaly as well as a possible association with Guillain-Barré syndrome.

Currently, no vaccine or medication exists to prevent or treat Zika virus infection.

On February 1st 2016, World Health Organization (WHO) declared current Zika virus outbreak to be a Public Health Emergency of International Concern.

Introduction

Zika virus was first identified in 1948 in the Zika forest of Uganda in rhesus monkeys and, subsequently, in humans in 1952- in Uganda and in the United Republic of Tanzania. Since then, cases of the Zika virus disease, mostly among monkeys, have been reported in Africa and Asia[1]. The virus has affected humans occasionally, causing mild symptoms such as rash, fever, joint pain and conjunctivits, lasting up to a week. Infection is asymptomatic in approximately 80% of cases. Zika virus disease is generally a vector-borne disease, but sexual transmission and congenital cases have also been reported[2].

Epidemiology

First outbreak was documented in 2007 in the Yap Islands, an island chain in the Federated States of Micronesia. In total, there were 185 suspected cases of the Zika virus fever, out of which 49 were confirmed and 59 were described as „probable cases". Patients typically presented with rash, conjunctivitis, subjective fever, arthralgia, and arthritis. No deaths, hospitalizations, or neurological complications were reported during this outbreak[3]. Up until then, there had been only 14 documented cases of the virus affecting humans. It is also worth noting, that this outbreak demonstrated the transmission of the Zika virus outside of Asia and Africa[4].

Between 2013 and 2014, 4 large outbreaks were reported, also in Pacific Islands. The biggest one (in French Polynesia) affecting 383 individuals was thoroughly investigated. Retrospective data reported in January 2016 indicated a possible association between ZIKV infection and congenital malformations, as well as neurological (Guillain-Barré syndrome, meningoencephalitis) and autoimmune (thrombocytopenic purpura, leucopenia) complications. Since that area was also affected by a dengue outbreak at the time, the connection remained unproven. Nevertheless, those findings challenged the notion that the Zika infection caused only mild illness.

In March 2015 Brazil notified WHO about an illness characterized by skin rash in northeastern states. There were nearly 7000 cases and 425 blood samples were tested for dengue, out of which 13% were positive. At this point, Zika infection was not suspected and no tests for Zika were carried out.

In May 2015 Brazil's National Reference Laboratory confirmed, by PCR (polymerase chain reaction), Zika virus circulation in the country. This was the first report of locally acquired Zika disease in the Americas. Following that, Pan American Health Organization (PAHO) and WHO issued an epidemiological alert to ZIKV infection[5].

As of February 1, 2016, active transmission of Zika virus has been reported in 28 countries and territories mostly in the Americas-including Brazil, Colombia, Venezuela, Mexico, Haiti, and Barbados- but also in Africa (Cape Verde) and Oceania (American Samoa, Samoa)[4].

There are 2 main reasons for the rapid spread of the virus in the Americas: immunologically naive population and the widespread presence of Aedes mosquitoes. PAHO reports that the vector can be found in the region from southern USA to northern Argentina, an area encompassing 500 million people. 440 000–1 300 000 suspected cases of Zika infection occurred in Brazil alone in 2015, as the Brazil Ministry of Health estimates, and according to WHO's prognosis there will be 3-4 million cases in next 12 months in the Americas, including asymptomatic ones[4].

Diagnosis

WHO has developed so-called „interim case definitions", in order to provide global standarization for classification and reporting Zika virus cases[6]. They include 3 types of cases: a suspected case, a probable case, and a confirmed case of ZIKV infection.

Suspected case

A person presenting with rash and/or fever and at least one of the following signs or symptoms:

- arthralgia; or
- arthritis; or
- conjunctivitis (non-purulent/hyperaemic).

Probable case

A suspected case with presence of IgM antibody against Zika virus (with no evidence of infection with other flaviviruses) and an epidemiological link (contact with a confirmed case, or a history of residing in or travelling to an area with local transmission of Zika virus within two weeks prior to onset of symptoms).

Confirmed case

A person with laboratory confirmation of recent Zika virus infection:

- presence of Zika virus RNA or antigen in serum or other samples (e.g. saliva, tissues, urine, whole blood); or
- IgM antibody against Zika virus positive and PRNT90 for Zika virus with titre ≥20 and Zika virus PRNT90 titre ratio ≥ 4 compared to other flaviviruses; and exclusion of other flaviviruses [6]

ZIKV and pregnancy

The major concern in the present outbreak is caused by an apparent link between the virus and microcephaly.

In October and November 2015 the Ministry of Health in Brazil began reporting a sudden increase of microcephaly in the state of Pernambuco and in three other northeast states. Since then, as of February 2, 2016, officials had investigated 1113 of 4783 suspected cases of microcephaly, and confirmed 404 of them. Zika infection was diagnosed in 17 cases.

Although the association is strongly suspected, it still remains to be proven. There are two lines of evidence that support it. First, the increased rate of microcephaly appeared about 6 months after the officials reported virus circulation in Brazil, which indicates a possibility of in utero exposure causing the defect. Second, traces of the virus, or antibodies to it were found in the amniotic fluid, brains or spinal fluid of 15 microcephalic fetuses and newborns[7].

There are some issues associated with reports regarding this outbreak. Up until 2015 it was not mandatory to report microcephaly in Brazil, which according to some adds a bias that overestimates the increase of this defect in the area.

Other than that, there are two different notification systems to report microcephaly in Brazil- SINESC, which existed before the outbreak and is meant for all children born in the country- and Registry of Events in Public Health (RESP), which was created specifically for the outbreak, because SINESC proved to be too complex. Due to conflicting information from the Ministry of Health regarding the use of those two forms, each state created its own interpretation of the guidelines. For example, in the state of Sao Paulo, only cases with possible connection to Zika are reported to the RESP, whereas in the state of Rio de Janeiro all cases of microcephaly are reported to the RESP.

On the other hand, some experts believe the number of potentially Zika-related microcephaly to be underestimated. ZIKV infection has to be confirmed by PCR and currently there are only five laboratories in Brazil that run those for Zika, completing together no more than 100 tests per week. The issue here is that the viral RNA is most likely to be identified in the first few days after first symptoms. Additionally, 80% of patients with Zika are asymptomatic, and as mentioned before, such cases can go unreported in some areas[4].

Other congenital neurological anomalies and an increased frequency of Guillain-Barré syndrome linked to Zika virus have also been reported[8].

CDC (Centers for Disease Control and Prevention) has developed interim guidelines regarding providing health care for pregnant women during this Zika outbreak[9].

Pregnant women who are considering travelling to an area of Zika virus transmission are advised to either postpone it, or to strictly follow steps to avoid mosquito bites. Those steps include: wearing long-sleeved clothing and long pants, using insect repellents, using permethrin-treated clothing and gear, and staying and sleeping in screened-in or air-conditioned rooms. Repellents containing DEET, picaridin, and IR3535 are considered safe for pregnant women, if used correctly.

Pregnant women who have recently travelled to an area with ongoing Zika virus transmission should be evaluated for Zika infection. Testing includes performing reverse transcription polymerase chain reaction (RT-PCR) of maternal serum with onset of symptoms within the previous week. IgM and neutralizing antibody testing should be performed on specimens collected at least 4 days after onset

of symptoms. Zika virus RT-PCR may also be performed on amniotic fluid, however it is unknown how specific and sensitive this test is for congenital infection. In case of asymptomatic pregnant women, CDC advises to perform a fetal ultrasound first; in the absence of intracranial calcifications or microcephaly, it is not advised to perform further laboratory tests, but it is recommended to perform serial ultrasounds throughout the pregnancy.

Pregnant women with Zika virus present in serum or amniotic fluid should undergo a featl ultrasound every 3-4 weeks. CDC recommends that such patients should be referred to a maternal-fetal medicine or infectious disease specialist. As there is no specific antiviral therapy, treatment includes rest, fluids, analgesics and antipyretics[9].

Prevention

ZIKV is transmitted by daytime-active Aedes mosquitoes, such as Aedes aegypti or Aedes albopictus. Lately, ZIKV has been detected in many mosquito species, human beings, and non-human primates. It needs to be stressed that A aegypti cannot be assumed to be the only vector, especially in areas where other mosquito species coexist. Therefore, vector control strategies must be directed at all potential vectors, and identifying those vectors should be considered a priority[10].

As there is no treatment or vaccine available, disease control consists primarily of mosquito control, that relies on either insecticides or breeding sites reduction. However, both approaches prove to be insufficient, considering the rapid spread of mosquito-borne diseases in the recent years. Since 2010, a total of 60 countries have reported resistance to at least one class of insecticide, with a total of 49 of those countries reporting resistance to two or more classes[11]. Although WHO stresses that the elimination of mosquito breeding sites is most effective, the impracticality of such interventions- as larvae of Aedes aegypti have been found in host containers like discarded plastic cups and bottle caps, plates under potted plants, birdbaths, vases in cemeteries, and water bowls for pets- encouraged public health authorities to seek more novel approaches.

One of techniques being developed involves the mass release of male insects that have been sterilized by low doses of radiation. When sterile males mate, the female's eggs are not viable, and the insect population dies out. The sterile insect technique has been successfully used, on a large scale, by the International Atomic Energy Agency and FAO to control agriculturally important insect pests. Main drawback of this method is that radiation treatment can reduce male mating fitness.

Another method is genetic control of Aedes aegypti mosquitos, specifically a strategy called RIDL- the Release of Insects carrying Dominant Lethal genes, which involves introducing a repressible dominant lethal gene into the insects. This gene normally kills the insects, but can be inhibited by a dietery supplement not present in nature (eg, tetracycline), which they are provided with while being captive. Males carrying the gene are released, and their offspring do not survive to the adult stage, since they are not provided with the dietery supplement. Also, males from RIDL lines seem to have equivalent mating fitness to wild males. Some studies show that this method can achieve up to 95% reduction in local moquito population.

An approach that seems to be also promising is the use of endosymbiotic bacteria that prevents arboviruses replicating withing the mosquito. Wolbachia bacteria from Drosophilafruit flies has proven before to prevent dengue transmission in Aedes mosquitoes, as well as other arboviruses such as chikungunya virus and yellow fever virus. It is worth noting that both these methods are species-specific and environmentally-friendly, as opposed to insecticides.[12,13]

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