REVIEW ARTICLE

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A new global threat for the public safety: Zika virus

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Abstract: *Zika virus, the etiological agent of Zika fever, is transmitted by mosquitoes and has been affecting the South American continent starting with 2015. It was reported in several European countries, carried by the people who returned from Latin America, as reported by the health authorities in those countries. Today, according to the World Health Organization (WHO), the virus suspected to cause serious birth defects in the fetus has also been confirmed in 21 of the 55 countries of South America, but also in other states from Europe and North America. Zika virus is a single stranded positive sense RNA virus belonging to Flavivirus genus (family Flaviviridae) and was first identified in 1947 in Uganda rainforest Zika. The increased number of cases of microcephaly, in children from northern Brazil, suggested a connection with Zika virus, but it has not yet been proven. Also, the virus can be transmitted sexually and through blood or blood products. Diagnosis of the infection is made using Polymerase Chain Reaction (PCR). So far, there is no specific antiviral treatment or vaccine against the infection with Zika virus. The best form of prevention is to avoid mosquito bites. WHO has estimated that the spread of Zika virus, transmitted through mosquito bite, is "a global public health emergency". The priority is to protect pregnant women and to control the mosquitoes.*

Keywords: *Zika virus, Flaviviruses, microcephaly, Aedes aegypti, mosquitoes*

INTRODUCTION

Zika virus, the etiological agent of Zika fever, is transmitted by mosquitoes and has been affecting the South American continent starting 2015. It was reported in several European countries, carried by the people who returned from Latin America, as stated by the health authorities in those countries. Today, according to the World Health Organization (WHO), the virus suspected to cause serious birth defects in the fetus has also been confirmed in several countries from Europe: Great Britain, Italy, Netherlands, Portugal, Denmark and Switzerland.

Zika virus has been reported sporadically in Africa and Asia for several decades. Zika fever outbreaks were reported for the first time in 2007 (Yap island found in the Pacific Ocean), then in 2013 (French Polynesia). In 2015, outbreaks occurred in Africa (Cape Verde Islands) and South America (Brazil and Colombia). From here, Zika virus quickly spread to several countries in South and Central America and was finally reported in 21 countries of the region in early 2016. [1][2][3] On January 28, the World Health Organization announced that 3-4 million people in

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America could be infected with Zika virus in 2016. [4] On February 1, 2016, the WHO has estimated that the spread of Zika virus, transmitted through the bite of *Aedes aegypti* mosquito, is "a global public health emergency".

THE ETIOLOGICAL AGENT

Zika virus is a single stranded positive sense RNA virus belonging to *Flavivirus* genus (family *Flaviviridae*) and was first identified in 1947 in Uganda rainforest Zika. It is the etiological agent of Zika fever, a viral infectious disease transmitted by infected mosquitoes. [1][2][3]

SYMPTOMATOLOGY

The incubation period is 3-12 days after an infected mosquito bite. Most infections caused by Zika virus are asymptomatic (60-80%). Symptoms are usually mild and disappear within 2-7 days without severe complications or death. The main symptoms are rash (macular or a papular exanthema that initially appears on the face and then spreads throughout the body), moderate fever, arthralgia, myalgia, headache, non-purulent conjunctivitis with conjunctival hyperemia. Vertical transmission can occur during labor (in the viremic stage) or transplacentar. The increased number of microcephaly cases in children from northern Brazil suggested a connection with Zika virus, but it has not yet been proven. Also, the virus can be transmitted sexually and through blood or blood products. [1][2][3]

TRANSMISSION

Zika virus is transmitted by mosquitoes and was isolated from species of the genus *Aedes*, such as *A. aegypti* (Figure1), *A. africanus*, *A. apico argenteus*, *A. furcifer*, *A. hensilli*, *A. luciocephalus* and *A. vitattus*. Studies showed that the incubation period in mosquitoes is approximately 10 days.[22] Zika virus can be transmitted through interpersonal sexual contact and can cross the placenta, affecting the unborn fetus. An infected mother (in the viremic stage) can transmit the virus to the newborn at the time of labor. [24][25][26]

The vertebrate hosts of the virus are the monkeys.

Figure 1: Aedes aegypti (http://www.cdc.gov)

Before the current pandemic, which began in 2007, Zika virus rarely generated collateral infections in humans, even in areas recognized as highly enzootic [7]. In 2009, Brian Foy, a biologist at Colorado State University, reported the sexual transmission of the Zika virus. [13][14]. In 2015, the Zika virus was detected in the amniotic fluid of two pregnant women, indicating that it is possible to cross the placenta and cause infections in newborns. [4][34][4][5][35][36]

DISEASE

Zika virus infection symptoms normally include mild headache, maculopapular rash, fever, malaise, conjunctivitis and arthralgia. [33] The first thoroughly documented cases of Zika virus infections were described in 1964, being characterized by mild headache, progressing through maculopapular rash, fever and back pain. Within two or three days, the initial symptoms remitted, but the rash persisted. Patients with Zika fever are advised to rest and are prescribed fluids and acetaminophen, while aspirin and nonsteroidal anti-inflammatory drugs should be used only after Denga fever was ruled out, in order to reduce the risk of bleeding. [38]

COMPLICATIONS

Microcephaly. In December 2015, it was suspected that an infection of the fetus with Zika virus, transmitted transplacental, may cause microcephaly and brain damage. [5] [34] Consequently, the European Centre for Disease Prevention and Control issued a comprehensive update on the possible association of the Zika virus with congenital microcephaly. [35] (Figure 2)

According to CDC Atlanta (Centers for Disease Control and PreventionUSA), "were reported cases of

microcephaly defects in children of mothers who were infected with the Zika virus during pregnancy."

Figure 2. Comparison between a child with microcephaly (left) and a normal child (http://www.cdc.gov)

Zika viral infections were confirmed in several newborns with microcephaly; the number of microcephaly cases associated to Zika virus infection is unknown. [8][10][34]

On January 17, 2016 the Pan American Health Organization (PAHO), the Regional Office of the WHO, has recommended that its member states "establish and maintain the ability to detect and confirm cases of infection with Zika virus, given the increased number of congenital anomalies, Guillain-Barré syndrome and other neurological or autoimmune syndromes recorded in areas affected by Zika, to prepare healthcare facilities to respond to a possible increasing demand for specialized care for neurological syndromes and to strengthen prenatal care." [28][29]

DIAGNOSTIC

Zika virus is detected through PCR (gene amplification by Polymerase Chain Reaction). [15] [16] Since the viremic stage may be short, the WHO recommends that the RT-PCR testing should be done on the sera collected within 1 to 3 days after symptom onset or on the saliva or urine samples collected during the first 3 to 5 days after onset. [20][21][22][23]. Serological diagnosis can also be used by detection of specific IgM antibodies. Those appear towards the end of the first week of illness. [18]

Serological diagnosis can be difficult, given possible cross-reactions with other flaviviruses, for example the *Dengue* virus, *West Nile* virus or *Yellow Fever* virus. Zika commercial diagnostic tests are available at Euroimmun (www.euroimmun.com).

TREATMENT

Until present time, there is no specific antiviral treatment or vaccine available against Zika virus infection. The best form of prevention is to avoid mosquito bites.

Prophylaxis

The existence of mosquitoes and larval nests is an important risk factor for the infection with Zika virus. Disease prevention consists in decreasing the number of mosquitoes at source (elimination or modification of larval nests) and reducing contacts between these insects and humans. Those traveling to endemic areas should be informed on methods of protection against mosquito bites. These involve avoiding outdoor exposure at dusk and dawn, wearing clothes that cover as much exposed skin, using repellents, nets for beds impregnated with insecticide, accommodation in rooms with air conditioning and mosquito nets. It is also recommended emptying, cleaning and covering all containers that can collect water such as buckets, flower vases and tires in order to eliminate the places where mosquitoes can reproduce. During outbreak, health authorities can proceed to spray insecticide.

Vaccination

There are effective vaccines against several *Flaviviruses*. Vaccines against the *Yellow Fever* virus (antiamarilic), *Japanese encephalitis* and *Tick-Borneencephalitis* have been introduced from 1930, while the dengue fever vaccine just became available for use. [37]

According to Anthony Fauci, of the National Institute of Allergy and Infectious Diseases, attempts are made in order to obtain a Zika virus vaccine. [38] Researchers at the Research Center for Vaccines have extensive experience in obtaining vaccines against other viruses such as the Chikungunya and the Dengue fever virus. [38] Nikos Vasilakis, from the Center for Biodefense and Emerging Infectious Diseasesappreciated that getting the vaccine could take up to two years, but an effective vaccine for

public use, approved by regulatory authorities, could be obtained in 10 – 12 years. [38][39][40][41]

EPIDEMIOLOGY

In 1947, scientists researching Yellow Fever revealed the onset of fever in a *Macaccus Rhesus* monkey located in a cage in the Zika Forest (Zika meaning "too high", in the Luganda language), near the Research Institute of Virology East Africa, in Entebbe, Uganda. The researchers have isolated from the monkey's serum a transmissible agent, which was first described in 1952 as the Zika virus [17] and was subsequently isolated in 1954 from a person in Nigeria. Since its discovery until 2007, rare cases of Zika virus infection were recorded in Africa and Southeast Asia. [40] In April 2007, the first outbreak outside Africa and Asia was declared on the island of Yap, in the Federated States of Micronesia; the cases were characterized by skin rash, conjunctivitis and pain, initially associated with Dengue, Chikungunya or Ross River disease. [41] However, the serum samples analyzed from patients in the acute phase of infection confirmed Zika virus infection. There have been 49 confirmed cases and 59 cases were disproved. There was no need for hospitalization and no deaths were reported. [42] Subsequently, outbreaks have appeared in Polynesia, Easter Island, the Cook Islands and New Caledonia. [5]

Starting April 2015, an epidemic broke out in Brazil with Zika virus (Figure 3) and has spread to South and Central America, the Caribbean, having a trend of global spread. In January 2016, CDC issued a level 2 travel alert for people traveling to affected areas (Table 1, Figure 4).

Figure 3: Zika virus epidemic map at 01.22.2016 (www.cdc.gov)

Figure 4: The geographical distribution of the Zika virus(www.cdc.gov)

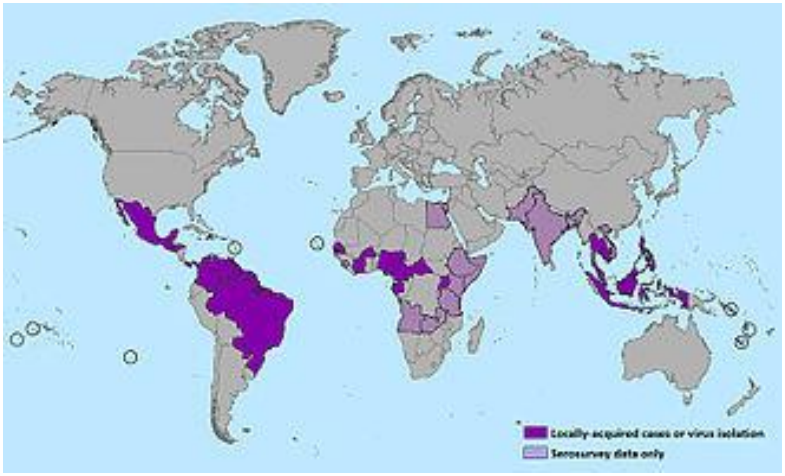

Table 1: Number of cases diagnosed with Zika virus (April 2015-present) (www.cdc.gov)

Country	Confirmed cases	Update
Australia	2	2 Feb 2016
Barbados	3	20 Jan 2016
Bolivia	1	20 Jan 2016
Brazilia	est. 1,5 mil	30 Jan 2016
Canada	4	30 Jan 2016
Chile	3	2 Feb 2016
Colombia	est. 20.000	30 Jan 2016
Curaçao	1	31 Jan 2016
Dominican Republic	8	27 Jan 2016
Ecuador	6	20 Jan 2016
El Salvador	est. 2.500	31 Jan 2016
French Guiana	2	8 Jan 2016
Guadeloupe	1	21 Jan 2016
Guatemala	1	27 Nov 2015
Guyana	1	21 Jan 2016
Haiti	5	21 Dec 2015
Honduras	3.649	1 Feb 2016
Jamaica	1	30 Jan 2016
Martinique	2	8 Jan 2016
Mexico]	18	31 Jan 2016
Nicaragua	3	31 Jan 2016
Panama]	50	28 Jan 2016
Paraguay	6	3 Dec 2015
Puerto Rico	22	26 Jan 2016
Saint Martin]	1	21 Jan 2016
Suriname	3	24 Jan 2016
United States	40	2 Feb 2016
Venezuela	3.700	28 Jan 2016
Total	**Est. 1.5 mil**	**up to 30.01.2016**

IMPLICATIONS FOR THE PUBLIC HEALTH

The WHO recommends that women planning to become pregnant should consult their physician before traveling to regions affected by the disease. [9][44] Governments and health agencies in the European Union, including UK and Ireland, as well as those in New Zealand, Canada, Colombia, Ecuador, El Salvador and Jamaica have issued similar travel warnings. Specific plans and measures were announced by authorities in Rio de Janeiro, Brazil, to prevent the spread of the Zika virus during the Olympic Games, taking place in this city, in 2016. [11][45][46]

According to CDC, Brazilian health authorities have reported more than 3,500 cases of microcephaly between October 2015 and January 2016. Some affected infants had a severe type of microcephaly, while others died.

These manifestations may be associated with Zika infection, occurred during pregnancy. Several studies are planned to assess the risks of the Zika virus infection during pregnancy. [45] In the worst affected regions in Brazil, about 1% of newborns are at risk for microcephaly. [46]

COMMENT

In humans, Zika virus causes an infectious disease called Zika fever, characterized by fever, headache, maculopapular rash, malaise, conjunctivitis, arthralgia etc.

The WHO has warned that the spread of Zika virus, transmitted by mosquitoes, is ''a global public health emergency'' and can be correlated with an increased number of newborns with congenital malformation recorded in Brazil last year.

WHO warns that Zika virus, transmitted mainly by mosquitoes, "explosively" spreads in South America, where in 2016 could be millions of cases. The priority is to protect pregnant women and to control the mosquito populations.

Medical experts are concerned about the very rapid transmission, over long distances of the virus with devastating consequences. From the confirmation of the presence of Zika virus, in May 2015, the virus has spread so far in 23 countries, including Brazil, Bolivia, Paraguay, Mexico, Venezuela and the epidemic continues to spread.

CONCLUSIONS

The World Health Organization has warned that the spread of Zika virus, transmitted by mosquitoes, is a

”global public health emergency”, which can be correlated with the increased number of newborns with congenital malformation recorded in Brazil last year and that the virus "explosively" spreads in South America, where in 2016 could be millions of cases.

Experts are concerned about the very rapid transmission, over long distances of the virus; the consequences can be devastating, and the priority is to protect pregnant women and to control the mosquito populations.

National health authorities are requested to take necessary measures for the prevention, diagnosis and treatment of Zika fever cases and to isolate import cases, in order to impede the spread of the disease.

Also, scientific research is needed in order to obtain an effective vaccine against Zika virus.

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