



OUTBREAK OF ZIKA VIRUS DISEASE AND ITS COMPLICATIONS

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SUMMARY

Zika virus (ZIKV) is an arbovirus from *Flaviviridae* family, genus *Flavivirus*. Like most of the viruses which belong to the *Flavivirus* genus, it replicates in and is transmitted by mosquitoes. Unlike other arbovirus infections including dengue and chikungunya, Zika virus causes a relatively mild disease. The most common symptoms of ZIKV are mild fever, arthralgia, myalgia, headache, asthenia, abdominal pain, oedema, lymphadenopathy, retro-orbital pain, conjunctivitis, and cutaneous maculopapular rash, which last for several days to a week. Although 80% of the cases with ZIKV are asymptomatic, severe complications such as microcephalia and GBS may be observed. This explains why ZIKV is more dangerous than it was thought to be and why it rapidly evolves in unexpected challenge for the international and national public health authorities.

Keywords: Zika virus, Pregnancy, Microcephaly, Guillain-Barré syndrome

INTRODUCTION

An increasing number of emerging infectious diseases has been seen in the early beginning of the 21st century. Some of the most outstanding examples are the severe acute respiratory syndrome in China, chikungunya, avian influenza, Middle East respiratory syndrome coronavirus, Ebola virus disease and recently Zika virus disease. The first isolation of Zika virus was in 1947 from a sentinel rhesus monkey in the Zika forest of Uganda. Human has been recognized as possible host in 1952, and since the 60s occasional cases in human population of Africa and of southeast Asia have been rarely reported [1]. The first registered epidemic outbreak was in Yap Island of Micronesia in 2007. The infection was also reported in French Polynesia and Easter Island and has finally reaches the South and Central America and the Caribbean [2]. Between 1 January 2007 and 3 March 2016, a total of 55 countries have reported local transmission of Zika virus [3]. Due to the rapid spread of the Zika virus in Latin American and Caribbean countries, on February 1st 2016 WHO announced that the ZIKV outbreak constitutes a 'Public Health Emergency of International Concern'. The term 'public health emergency of international concern (PHEIC)' is defined in the International Health Regulations as „an extraordinary event that poses a public health risk to other States through the international spread of disease and to potentially require a coordinated international response“ [4].

The Zika Virus

Zika virus (ZIKV) is an arbovirus from *Flaviviridae* family, genus *Flavivirus*. Like most of the viruses which belong to the *Flavivirus* genus, it replicates in and is transmitted by mosquitoes. ZIKV has a single-stranded RNA with a positive-polarity of approximately 11 kb. [5] The viral RNA includes a complete open reading frame sequence, encoding for a polyprotein with three structural components (capsid [C], premembrane [prM] or membrane [M], and envelope [E]) and seven non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5) [6].

The E protein mediates the interaction of ZIKV with receptors on mosquito (or mammalian) cells, then the virus enters cells and produces viral proteins and RNA, followed by the generation of progeny virions. The infected female mosquito may inject virions into the skin of a human, where ZIKV causes infection of dermal and epidermal cells. Finally the virus spreads to the lymph nodes to initiate an immune reaction together with its replication and viremia. The ability of ZIKV to cross the placenta of pregnant women and to affect the fetus is widely discussed and if confirmed, it would make the virus very unique from other arboviruses, which are never reported to reach the embryo [7].

TRANSMISSION

Since its discovery, ZIKV has been isolated from monkeys, mosquitoes, and sick persons. Despite the fact that the reservoir has not yet been surely identified, some authors suggest that primates are the most likely reservoir of infection. The mosquito species which can transmit the virus to human are *Aedes aegypti* and *Aedes albopictus* mosquitoes. They are found throughout Americas, including parts of the United States, and can also transmit dengue and chikungunya infections [8]. These mosquitoes are daytime biters and prefer to lay their eggs in domestic water-holding containers [9]. Importantly, Zika virus infection can spread through the intrauterine route (resulting in congenital infection), during the birth [10], through sexual transmission [11], [12] or via blood transfusion [13]. Organ or tissue transplantation are also theoretically possible mechanisms of infection transmission. ZIKV RNA has been found in breast milk but till now transmission through breastfeeding has not been confirmed [8].

SYMPTOMS AND COMPLICATIONS

Unlike other arbovirus infections including dengue and chikungunya, Zika virus causes a relatively mild disease

[14]. A very few of the infected individuals develop symptoms, while most of the people (80 %) remain asymptomatic [15]. The incubation period for Zika virus disease is unknown, but likely lasts up to 2 weeks [9]. The most common symptoms of ZIKV are mild fever, arthralgia, myalgia, headache, asthenia, abdominal pain, oedema, lymphadenopathy, retro-orbital pain, conjunctivitis, and cutaneous maculopapular rash [6, 16], which last for several days to a week. Severe diseases are uncommon and deaths are extremely rare [9]. Although the disease is self-limiting, cases of neurologic manifestations and the Guillain-Barré syndrome were described in French Polynesia and in Brazil during ZIKV epidemics [17].

Microcephaly is a condition in which baby's head is smaller than expected compared with neonates of similar gestational age and sex [9]. According to the Brazil Ministry of Health a case definition for Zika virus – related microcephaly was defined as neonatal head circumference ≥ 2 SD below the mean for gestational age and sex of the infant at birth [18]. Microcephaly can occur with other major birth defects: seizures, vision or hearing problems, and developmental disabilities including cognitive impairment or cerebral palsy.

During the Zika virus outbreak between October 2013 and April 2014 in French Polynesia, 42 patients were admitted to hospital with Guillain-Barré syndrome (GBS), which represents a 20-fold increase in incidence of GBS in French Polynesia compared with the previous four years. Guillain-Barré syndrome is an acute, immune-mediated polyradiculoneuropathy - the motor function of the patients is usually affected, beginning distally and progressing proximally over up to a 4-week period as well as the presence of generalized weakness, areflexia, and a varying degree of sensory disturbances and involvement of cranial nerves. GBS is found to be between 0.4 and 4.0 cases per 100,000 inhabitants per year [3]. Despite this data, much more epidemiological and experimental research are still ongoing in Brazil and French Polynesia to clarify the relation between Zika virus and the risk of developing GBS and congenital abnormalities such as microcephaly [19].

The first cases of the ZIKV disease in Brazil were reported in April 2015 and since then the virus has rapidly spread throughout the country. During the period from April 2015 to November 2015, 18 of the 27 Brazilian states reported ZIKV cases. After the emergence of ZIKV in Brazil, microcephaly cases have increased 20-fold [20]. For example a total of 5909 cases of microcephaly and/or central nervous system malformation and 139 deaths were reported in

Brazil between 22 October 2015 and 27 February 2016, while approximately 163 microcephaly cases were recorded per year during the period from 2001 to 2014 [3]. Although Brazilian government has made efforts to prevent the mosquito *Aedes aegypti* from breeding, the number of ZIKV cases was significant. A total of 6906 reported cases with microcephaly, other congenital abnormalities of the CNS, or both (of which 4046 are still under investigation) were registered according to the latest epidemiological bulletin issued by the Brazilian Ministry of Health, as of April 2, 2016 [21].

Since October 2015 when the Brazilian ministry of health reported an unusual increase in cases of microcephaly in the north-eastern states of Brazil, possible links between Zika virus infection in pregnancy and microcephaly of the fetus have been under investigation. On 17 November in amniotic fluid samples collected from two pregnant women with foetal microcephaly from the state of Paraíba was found the presence of Zika virus RNA and it was confirmed by RT-PCR. Zika virus genome was also detected in the blood and tissue samples of a baby from the state of Pará who died within five minutes of being born with microcephaly and other congenital anomalies. An unusual increase of at least 17 cases of central nervous system malformations in fetuses and infants coinciding with the Zika outbreaks was reported by the health authorities of French Polynesia on 24 November 2015 [13].

Due to the fact that no vaccine against Zika virus exists, the only prevention of ZIKV disease is to control the mosquito population. The most important is to avoid mosquito bites and this could be achieved by using physical barriers such as window screens, closed doors and windows; and if needed, additional personal protection, such as sleeping under mosquito nets during the day [22, 23] or using insect repellents especially by pregnant and lactating women [18].

CONCLUSION

Although 80% of the cases with ZIKV are asymptomatic, severe complications such as microcephalia and GBS may be observed. The changed geographic distribution reported in the beginning of this century is closely related to the new clinical presentations of the virus – until last year cases of microcephalia were not connected with ZIKV infection, but with the new not immune target population, new complications are observed. This explains why ZIKV is more dangerous than it was thought to be and why it rapidly evolves in unexpected challenge for the international and national public health authorities.

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