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Review Article

ZIKA VIRUS: A BRIEF REVIEW

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ABSTRACT

This review highlights the Zika virus which is considered a global concern due to its rapid pandemic potential and effect on humans, and according to its pandemic status, the World Health Organization declared on February 2016 it as a "Public Health Emergency of International Concern." Therefore, we define the epidemiology of Zika virus in addition to its pathogenesis, diagnostic techniques, and treatment.

Keywords: Zika virus, *Aedes* genus, Transmission, Antiviral drugs, Pathogenesis.

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INTRODUCTION

Zika virus was isolated for the 1st time in 1947 from the blood of rhesus monkey in the Zika Forest, Uganda, Zika virus was isolated from many of mosquito species collected during the study of arboviruses in Africa and of fever in Asia. The first outbreak of Zika disease was reported in 2007 on the Western Pacific Island of Yap, followed by a larger outbreak in Polynesia – France in 2013 and 2014, with an estimated 30,000 symptomatic infections [1-6]. According to Zika epidemiology update from the WHO, the infection of virus distributed in 87 countries and territories in these regions: Africa, the Americas, Southeast Asia, and Western Pacific region.

In 2016, Zika infection has peaked in the Americas and reduced during 2017–2018 while in 2018, Ethiopia was the only new country that was added to the infected countries with Zika virus that was transmitted by mosquitos [7].

The WHO has defined and mapped a Zika virus affected countries into four major categories according to country or territory or subnational areas as follows (Fig. 1):

- Countries and territories with current or previous Zika virus transmission (dark blue)
- Countries and territories with established competent vector, but no known cases of Zika virus infection (light blue)
- Countries and territories with no known cases of Zika virus infection and no established competent vector (dark gray)
- Not applicable (light gray).

BIOLOGY AND PATHOGENESIS OF ZIKA VIRUS

Zika virus belongs to *Flaviviridae/Flavivirus* genus. It consists of the lipid-enveloped, positive, single-stranded RNA genome [8], covered by copies of the envelope (E), precursor membrane (prM) and capsid (C) proteins, and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) (Figs. 2 and 3) [2,9,10]. E and M proteins play an important role in viral infection, adhesion, and fusion with the surface of the host cell. NS5 protein is an important protein to produce the negative-strand RNA that is needed for RNA synthesis [11] while NS3 and NS2B are required to form a protease complex that is essential for replication [12]. Other NS proteins contribute to the replication complexes formation that associates with intracellular membranes [13].

The life cycle passes through four basic stages: RNA translation into viral proteins, replication of viral RNA, assembly of viral particles in the endoplasmic reticulum, and virion release from the host cell.

Zika virus has shown similarities with other *Flavivirus* in pathogenesis. When the mosquito bites a human, Zika virus infects different types of cells including skin keratinocytes, dermal fibroblasts, and dendritic cells (DCs) [16]. After cell entry through many receptors such as DC-SIGN, T-cell immunoglobulin, and mucin domain-1, 4, cell surface receptor tyrosine kinases, Zika virus induces interferon response in this cell (Fig. 4). Many studies showed an increase in interferons transcription during 24–48 h after infection [17]. DCs that infected with virus pass to lymph nodes where they induce T-cell proliferation, differentiation, and cytokine production [18].

The infection of dermal fibroblasts and DCs leads to Zika viremia causing fetal viremia in pregnant women [19]. When fetus infection with Zika has happened, the fetal abnormalities such as microcephaly, brain calcifications, cerebral atrophy, and eye abnormalities affecting macular and optic nerve occur (Fig. 5) [2,20-22]. Many of birth defects can be appeared such as open foramen ovale, failure in descending of testes into the scrotum, hearing problems, and difficulties in swallowing [23].

CDC research showed that Guillain-Barré syndrome (GBS) (an autoimmune disease) in adults closely related to Zika where many countries which have Zika outbreaks reported increasing in patients who have GBS. In 2013, the outbreak in French Polynesia showed a strong association between GBS and Zika virus infection [2,9,17,24-28].

ZIKA TRANSMISSION

Mosquito bites

Zika virus transmits by the bite of mosquito species from the *Aedes* genus (such as *Aedes aegypti* and *Aedes albopictus*) which live in tropical and subtropical regions (Fig. 6). The first symptoms develop in a period of 3–12 days depending on the immunity and resistance of the human [2,6,20,28-31].

From mother to child

A pregnant woman can transmit the virus to her fetus during pregnancy through the placenta or at the time of birth causing fetal brain defects which may finally develop into miscarriage. Furthermore, Zika virus was found in the breast milk, but without evidence of its transmission through breast milk and until now there is no information about the long-term effects of the virus on young infants infected after their birth [2,6,20,28-31,33].

Sexual contact

It can be passed through sex from a person with Zika to his/her partner, even if the symptoms did not appear in the infected person, many

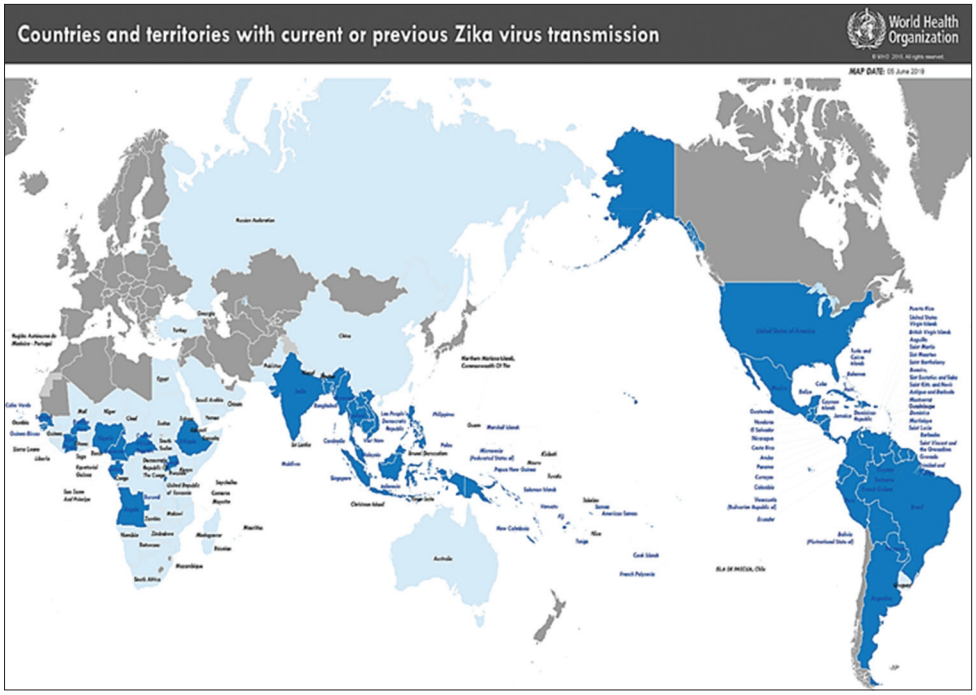

Fig. 1: Map of countries and territories with the current or previous Zika virus transmission

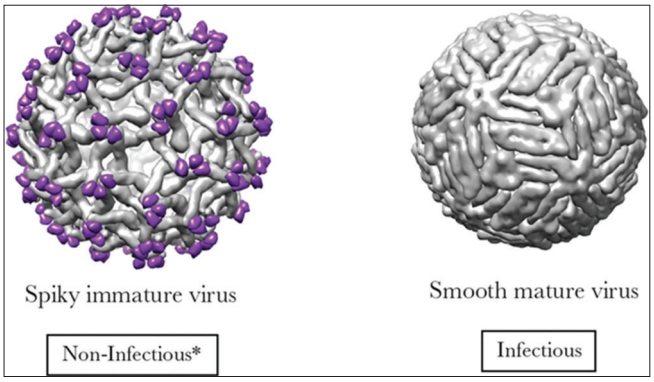

Fig. 2: Structure of Zika virus [14]

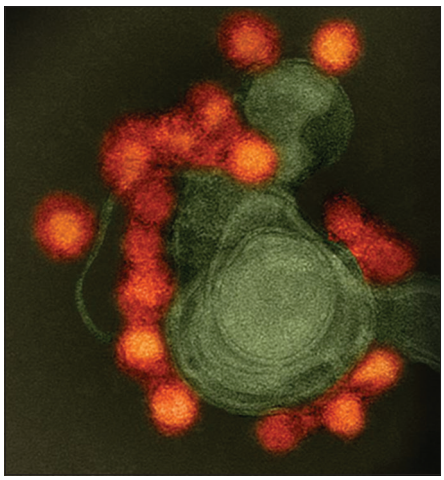

Fig. 3: Electron microscope image of Zika virus, image by Daniel Mietchen/NIAID [15]

studies showed the presence of Zika in the semen and vaginal fluids of patients, and it can remain in semen longer than in other body fluids

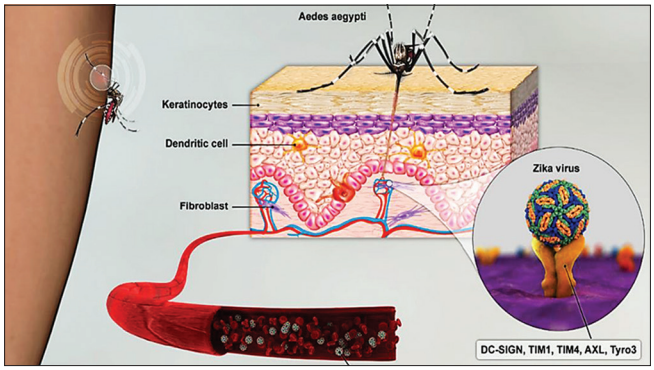

Fig. 4: *Aedes* mosquito introduces Zika viruses into the host [19]

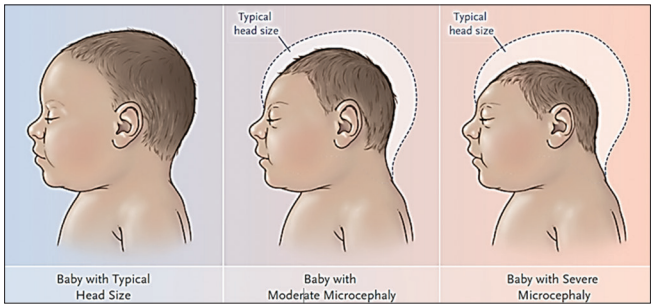

Fig. 5: Infants with microcephaly associated with maternal Zika virus [24]

such as vaginal fluids, urine, saliva, and blood (ZIKV was more detected in saliva than in blood) [2,6,20,27-31,33-35].

Organ transplantation and transfusion of blood

Transmission can be accrued through blood donation from an infected person without testing it [28,23]. According to a study carried out by Musso and Gubler [29,36], they found that 42 of 1505 of those donors were asymptomatic, but using polymerase chain reaction, they found Zika virus in their bodies [2,6,28-31].

Fig. 6: *Aedes* **mosquitoes [32]**

Symptoms

The incubation period for Zika infection extends 3–14 days, most patients show no symptoms. In general, the symptoms of Zika include fever, rash, headache, muscle and joint pain, and conjunctivitis (red eyes), these symptoms usually last for 2–7 days. These symptoms usually did not cause enough risk for the patient to go to the hospital [2,20,24,28,30,37].

Diagnosis

The diagnosis is so difficult because of the similarities of symptoms of Zika with other arboviral diseases and, on the other hand, because the antibodies against Zika continue for many years and cross-react with other similar viruses such as dengue. Thus, the positive result does not give us the right diagnosis whether the infection was an old or new one. In addition, we do not know whether the infection happens to be caused by Zika or dengue infection [6,29,38].

In general, laboratory techniques include molecular methods for the detection of ZIKV RNA in blood and urine and enzyme-linked immunosorbent assays. According to European Centre for Disease Prevention and Control, ZIKV infection is confirmed by the following laboratory criteria: Detection of ZIKV RNA in the specimen, viral isolation from the specimen, and detection of ZIKV-specific immunoglobulin M antibodies and must be confirmed by neutralization test [2,22,29,38-42].

Treatment

Until now, there is no medicine or vaccine for Zika, symptoms are usually treated by taking enough rest, preventing dehydration by drinking a lot of fluids, taking medications such as acetaminophen to reduce fever and pain, while aspirin should not be given until confirmation of dengue fever.

Many researchers are working on the development of a vaccine against Zika taking into account important qualities such as administration of a single dose, its safety during pregnancy. Vaccine strategies including live-attenuated vaccines, DNA vaccines, and vectored vaccines are under investigation [43].

Several studies showed that chloroquine prevents ZIKV infection in human neural progenitor cells (hNCPs) [44] and inhibits autophagy [45]. Hence, chloroquine is a candidate drug to human trials for treatment.

Merimepodib, which is an enzyme, involved in *de novo* synthesis of guanine nucleotides and has antiviral activity against *in vitro* DNA and RNA viruses, especially when it is used in combination with other antivirals like ribavirin. Tong *et al*. [46] explained the ability of merimepodib in inhibiting ZIKV RNA replication and reducing the production of ZIKV in Vero cells [47].

Since the first studies that showed the effect of ZIKV on the hNPCs, several drug candidates have been identified based on their effects on suppress viral replication or improving its consequences on NPCs.

The early studies identified niclosamide as an effective antiviral drug according to its ability in the inhibition of ZIKV replication [48] Other studies showed that the Hippeastrum hydrobromide cleared infection from NPCs in culture, whereas using amodiaquine dihydrochloride dihydrate with Hippeastrum hydrobromide can reverse transcriptional dysregulation [13,49].

Control and recommendations

It's recommended to follow the prevention strategies combined with early detection of infection. Vector controlling plays an important role in limiting the disease including avoiding mosquito bites using mosquito repellent and the removal of identified breeding grounds and the use of bed nets, reducing sexual transmission using male and female condoms, in addition to avoiding travel to infected areas and many recommendations confirm testing the blood which is donated from an infected person [2,24,27,32,50].

CONCLUSION

Studies on ZIKV biology and its pathogenesis role showed the ability of the virus to cause severe complications including placental and congenital infection and nerve damaging. There are many unknown data about that such as ways of host restriction and immune evasion, the neurodevelopmental implications of congenital infection in humans.

It is believed that future of Zika virus is unpredictable but according to its spread which is similar to the spread of chikungunya virus and dengue virus, we suggest that this virus will become a serious global public health problem.

AUTHORS' CONTRIBUTIONS

Both authors have contributed to the preparation of this review and editing of the manuscript.

CONFLICTS OF INTEREST

There are no conflicts of interest.

AUTHORS' FUNDING

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