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Zika: As an emergent epidemic

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ABSTRACT

Zika virus is a new global threat for 2016 that has been swept to almost all Americas and is now posing serious threats to the entire globe. This deadly virus is playing havoc to unborn lives because of its reported association with upsurge of fetal deformation called microcephaly and neuropathic disorders including Guillain-Barré syndrome. Till today, there is no vaccine prospect, antiviral therapy or licensed medical countermeasures to curb the teratogenic outcomes of this destructive viral infection. Diagnosis, treatment, chronicity and pathogenesis are still vague and unsettled. Therefore, this review article addresses all the aspects related to this disease to mitigate the explosive rise in Zika virus infection.

1. Introduction and epidemiology

Zika virus (ZIKV) is a mosquito-borne RNA virus infection related to yellow fever, dengue and West Nile virus. Zika virus is generally transmitted by bite of an infected *Aedes* species of mosquito. Zika virus poses serious threats to pregnant women [1]. An increased risk of Guillain-Barré syndrome and several other congenital neurological abnormalities associated with Zika virus have also been reported [2]. Zika virus infection is clinically similar to dengue fever and cause acute febrile illness, arthralgia, fever, myalgia, rash, headache and conjunctivitis [3,4]. The diagnosis of Zika virus infection is verified by detection of viral genome using RT-PCR genomic amplification and viral isolation [5].

According to phylogenetic studies, Zika virus emerged in East Africa during early 20th century and later on spread to Southeast Asia. The virus was named after the forest in Uganda from where it was first isolated in rhesus monkey in 1947 [5] and identified in 1952 in human beings. Another study confirmed seven patients with serologic evidence of Zika virus infection in Indonesia [6]. In 2007 a small-scale outbreak was documented in Yap, Federated States of Micronesia [7] followed by a larger outbreak in French Polynesia during 2013 with 28 000 cases reported in the first 4 months [8–10]. Since May 2015, Zika virus infection has been escalated to 1.5 million cases in Northeastern Brazil and now the virus has been transmitted to South and Central America and Caribbean [10–12]. Approximately 440 000–1 300 000 cases of Zika virus in Brazil alone were reported during an outbreak of 2015 [2]. Pan American Health Organization confirmed copious cases of Zika virus infection in French Guiana, Venezuela, Paraguay, Guatemala, Mexico, Honduras, El Salvador, Colombia, Panama and Suriname. Besides America, Atlantic island of Cape Verde reported its first Zika outbreak in October 2015 with 4 744 suspected cases by 6 December 2015 [13].

Currently, more than 4 500 microcephaly cases have been identified [14]. In December 2015, Netherlands confirmed the first domestic case of microcephaly (abnormal small size of head) in a neonate whose mother was back from Surinam followed by 20 more cases all imported from Surinam [15]. The average number of live births in Brazil is around 1 242 975 (2009–2013 data) but a considerable increase in microcephaly was reported in Pernambuco state, Northeast Brazil. Since beginning of 2016, 46 deaths in 20 states and the Federal District has been surveyed and this rate is significantly higher than 2010–2014, during which an average of 163 (standard deviation 16.9) cases of microcephaly were reported nationwide (26 states and 1 Federal District) per year [16].

A research based study applied complement-fixation test reactions to 372 samples of serum (43 from humans, 172 from

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domestic animals, 157 from rodents) collected from Pakistan containing eight viruses belonging to family Togavirida followed by identification of antibodies targeted towards each tested virus. The most elevated over-all prevalence rates were: 7.8% West Nile virus, Japanese 3.2% encephalitis virus and 2.4% Zika virus, followed by 1.6%–1.3% Sindbis virus, Chikungunya virus, Uganda virus and Royal Farm viruses [7,17].

2. Virus structure and genome organization

Zika virus is positive-sense single-stranded RNA virus which belongs to the family Flaviviridae consisting of 11 000 bases approximately. The genome consists of 5′ and 3′ untranslated regions flanking a single open reading frame which encodes only one polyprotein that cleaves into three structural proteins, capsid protein, premembrane/membrane protein, envelope protein, along with seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, 2K, NS4B, and NS5) [18].

A previously done genetic study based on nucleotide sequences derived from the *NS5* gene unfolded three Zika virus lineages: East African, West African and Asian [19,20].

Till today, scientists were familiar with little knowledge regarding the genetic relationships between strains of Zika virus collected from Africa and Asia. Furthermore, the geographical origins of the strains behind human related Zika virus outbreak on Yap Island in Federated States of Micronesia, and that of Cambodia were undetermined. But genomic comparison revealed several sub-clades exhibiting two major geographically distinct lineages of Zika virus *i.e.*, Asian and African. During the past 50 years, the virus has spread in entire Southeast Asia later on, it invaded Yap Island causing human epidemic in 2007, and proved the etiology of a pediatric case of ZIKV infection in Cambodia during 2010 [20].

3. Potential transmission of Zika virus

Zika virus has the potential to attack any area where the *Aedes* mosquito vector is present [5,21]. Zika virus has been isolated from *Aedes furcifer*, *Aedes africanus*, *Aedes apicoargenteus*, *Aedes luteocephalus*, *Aedes vittatus*, and *Aedes aegypti* (*Ae. aegypti*) mosquitoes [22–25]. It has been reported that *Aedes hensilii* was the most frequently found mosquito species present on Yap island during the Zika virus epidemic of 2007 [7]. Zika virus infection was transmitted by *Ae. aegypti* during the recent outbreak of Brazil [2]. Epidemiological studies in Uganda had suggested that *Aedes africanus* was a vector of Zika virus [26,27].

Studies indicate that the usual mosquito vectors in Asia are *Ae. aegypti* and *Aedes albopictus (Ae. albopictus)* [20]. *Ae. albopictus* is considered as invasive mosquito because of its transportation to other continents through commerce [28]. In Brazil, *Ae. albopictus* was present in 59% of municipalities in 2014 [29] and spread to 24 of 27 states [30]. This vector is able to adapt to both urban and sylvatic habitats, including bromeliads [31] perforated bamboo internodes [32], and tree holes (also with *Ae. aegypti* and *Aedes vittatus*) [33], and is a suspected link for yellow fever virus between preserved and modified environments in the south and southeast regions of Brazil [34]. *Ae. albopictus* species feed on wide range of hosts because it is endophagic and exophagic, as compared to *Ae. aegypti* that usually feeds on humans.

Transmission of Zika virus by blood transfusion has been confirmed during the recent outbreak of Zika virus that invaded 7 Brazilian States [35].

In 2013, French Polynesia faced the largest reported outbreak of Zika virus infection. To escape the Zika virus transmission by blood transfusion, specific nucleic acid testing of blood donors was performed which indicated that 3% (42 out of 1 505) blood donors were positive for Zika virus by PCR from November, 2013 to February, 2014. Therefore, blood safety authorities were recommended to get alert in order curb the risk of Zika virus infection through blood transfusion [36]. During a Zika virus outbreak in French Polynesia, Zika virus was identified and isolated from the semen of a patient in Tahiti when he underwent treatment for hematospermia. This observation supports the fact that Zika virus can also be transmitted by sexual intercourse [4]. In 2008, another evidence of Zika virus infection by sexual intercourse had also been reported in a patient in southeastern Senegal [37]. Zika virus can attack pregnant ladies in all three trimesters [38]. Vertical, maternal fetal transmission or perinatal transmission of Zika virus has also been reported. The possible routes of transmission were breastfeeding, close contact between mother and newborn and transplacental during delivery [9] (Figure 1).

4. Pathogenesis of ZIKV

Very little information is known about the pathogenesis of Zika virus but flaviviruses transmitted by mosquitos replicate in dendritic cells near the site of inoculation and later on lead to blood stream and lymph nodes [39]. It is generally considered that *flaviviral* replication occurs in cellular cytoplasm but another study demonstrated that Zika virus antigens might be found in infected cell nuclei [40]. Till today, infectious Zika virus has identified in blood of humans as early as the day of onset of disease but nucleic acid of virus was confirmed as late as 11 d after onset of illness [41]. Human skin is an important portal for the entry of Zika virus and act as major contributor in the induction of antiviral immune responses. It has been reported that immature dendritic cells, epidermal keratinocytes and dermal fibroblasts were responsible for Zika virus outbreak occurred in French Polynesia. There are number of adhesion factors like DC-SIGN (known as CD209), Tyro3, AXL and, to a lesser extent, TIM-1 which support Zika virus entry, with a dominant role attributed to TAM receptor AXL. The use of neutralizing antibody and specific RNA silencing confirmed Zika virus permissiveness of human skin fibroblasts. Zika virus triggered the transcription of Toll-like receptor 3, retinoic acid-inducible gene 1, Melanoma Differentiation-Associated protein and various interferon stimulated genes like MX1, OAS2, and ISG15 characterized by strongly boosted gene expression of beta interferon. Zika virus was sensitive to the antiviral reactions of both type I and type II interferons. The infection of skin fibroblasts lead to production of autophagosomes that were linked with increased replication of virus influenced by a chemical inducer of autophagy *i.e.*, Torin 1, and the specific autophagy inhibitor 3-methyladenine [42].

5. Clinical manifestation of ZIKV

It has been documented that majority (about 73%) of Zika virus infections are asymptomatic [7]. In case of symptomatic