REVIEW ARTICLE

Zika Virus: A Review

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ABSTRACT- Zika virus is a mosquito transmitted flavivirus belongs to family *Flaviviridae,* which became the focus of an ongoing pandemic and public health emergency all around the world. Zika virus (ZIKV) has 2 lineages: African and Asian. Mosquito-borne flaviviruses are thought to initially replicate in dendritic cells and then spread to the lymph and therefore the blood stream. Risk for infection through blood transfusion, sexual practices, and perinatal transmission exists. The potential routes of perinatal transmission are all over the delivery, breastfeeding and by close contact between the mother and newborn baby. ZIKV is often misdiagnosed with other infection like Dengue and Chikungunya because of similar clinical manifestation. The association between these conditions with Zika virus infection is still not confirmed and is under assessment. Since ZIKV has neither an effective treatment nor a vaccine is available, therefore the public health authority focuses on preventing infection, particularly in pregnant women and virus transmitted region. Zika infections in adults may result rarely in Guillain-Barre syndrome. World Health Organization and different health officers are working on the development of new projects and mosquito control methods to cope up with infection as there's very less literature present on the pathologic process of the Zika virus to help interpret the clinical disease spectrum and target treatments to minimize or prevent infection. WHO/PAHO encourages the countries to set up and retain Zika virus infection detection, clinical management and community assertion strategies to decrease transmission of the virus. This review describes the current understanding of the epidemiology, transmission, clinical characteristics, and diagnosis of Zika virus infection, as well as the future outlook with regard to this disease.

Key-words- Endocytosis, RNA virus, RNA Zika virus (ZIKV), Viral genome, Viral messenger

INTRODUCTION

The Zika virus belongs to the *Flaviviridae* family and the *Flavivirus* genus, having a non-segmented positive sense Ribonucleic acid (RNA) genome. The virus is about fifty nm in diameter, enveloped and spherical, with an icosahedral like arrangement of surface proteins. Over the past few months, it has rapidly emerged in the Western Hemisphere [1]. This virus is alike to different member viruses of the family Flaviviridae, including yellow fever virus, dengue virus, and West Nile virus that causes symptoms like ill health in conjunction with rashes [2].

ZIKV is transmitted to human beings through the bite of daytime-active *Aedes* mosquitoes; however, infection threat through sexual activity and blood transfusions also exists [3-5]. Phylogenetic analyses of ZIKV suggested two significant lineages, Asian and African, originating from a single ancestor, most likely in Uganda [3]. The possible vectors of *Aedes* species include *Aedes polynesiensis* and *Aedes aegypti*, identified in French Polynesia, and *Aedes hesilli*, identified in Yap [4,6,7]. *A. albopictus*, and *A. aegypti* exist in many states of America, including various parts of the south-central and south-eastern USA and Hawaii [1,4].

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The RNA of the virion is infectious and acts as viral messenger RNA (mRNA) and viral genome. The genome is translated as a polyprotein through a length of 3419 amino acids as well as is processed co and post-translationally by the both host and viral proteases [8]. The ZIKV reproductive cycle begins with the attachment of the virion to the cell membrane of the host via an envelope protein that encourages endocytosis. After endocytosis, the viral membrane fuses with the endosomal membrane, and the single-stranded RNA (ssRNA) is discharged into the cytoplasm of the host cell then, translation begins and a polyprotein is cleaved, which is implicated in the development of all structures along with nonstructural proteins. Replication occurs during the further step, which occurs in the cytoplasmic viral factories of the endoplasmic reticulum (ER), producing double-stranded RNA (dsRNA). This dsRNA undergoes transcription to form additional ssRNAs, which assemble within the ER to form new virions. These virions are then transferred to the Golgi body apparatus and are ultimately discharged into the intracellular spaces, where they cause infection of novel cells [9].

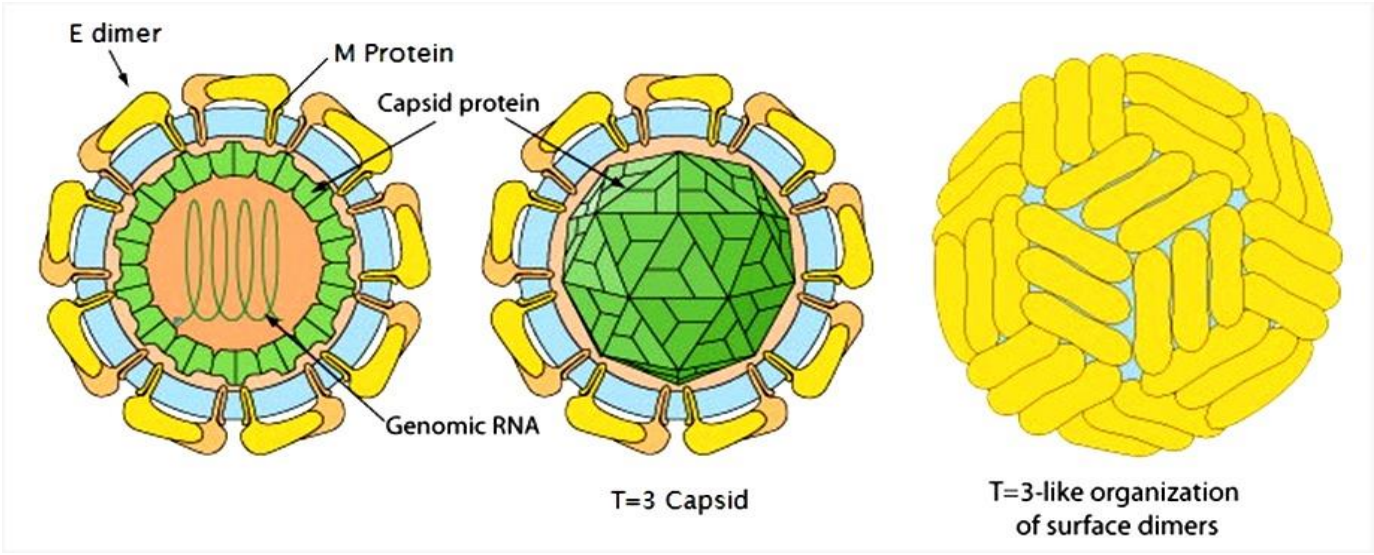

Fig. 1: Structure of Zika virus
Source: http://laboratoryinfo.com/wp-content/uploads/2016/01/zika-virus.jpg

Table 1: Genome structures of ZIKV strains

S. No.	Gene or genomic region	Length	
		African MR 766 prototype strain[a] [10]	**French Polynesia H/PF/2013[b] [11]**
1.	5= NCR	106 nt[c]	107 nt
2.	Capsid	122 aa[d]	105 aa
3.	PrM	178 aa	187 aa
4.	Envelope	500 aa	505 aa
5.	NS1	342 aa	352 aa
6.	NS2A	226 aa	217 aa
7.	NS2B	130 aa	139 aa
8.	NS3	617 aa	619 aa
9.	NS4A	127 aa	127 aa
10.	NS4B	252 aa	255 aa
11.	NS5	902 aa	904 aa
12.	3' NCR	428 nt	428 nt
13.	Complete genome	10,794 nt	10,617 nt

[a]Data collected from Kuno G & Chang [10], [b]Data collected from Baronti *et al.* [11]
[c]nt, nucleotides; [d]aa, amino acids

Classification and Phylogeny of ZIKV

ZIKV is sited in to the clade X mosquito-borne *Flavivirus* cluster, along with SPOV [12]. These outcome, based on incomplete sequencing of the gene for nonstructural protein 5 (NS5), were established by sequencing the complete coding region of the NS5-encoding gene [13]. The full genome of ZIKV (ZIKV MR 766 prototype strain) was completely sequenced for the initially in 2007 [14]. The full sequences of other ZIKV strains from Cambodia, Brazil the Central African Republic, Malaysia, Puerto Rico, Senegal, Nigeria, French Polynesia, Yap State, Thailand, and Guatemala are available in GenBank (http://www.ncbi.nlm.nih.gov/GenBank/) [13,15-17]. The genome structures of the ZIKV MR 766 prototype strain and the French Polynesian H/PF/2013 strain are detailed in Table 2. ZIKV, similar to another flaviviruses, is a single-stranded (ss), positive-sense RNA virus with a genome of 10,794kb [14,18] with two flanking non-coding regions (5= NCR and 3= NCR). The open reading frame (ORF) encodes a polyprotein with 3 structural proteins, *i.e.* capsid (C), pre-membrane (PrM), and envelope (E), and 7 nonstructural proteins, NS1, NS2A, NS2B, NS3, NS4A, NS4B, & NS5 [14].

Phylogenetic analysis was shown that Zika virus can be divided into distinct African and Asian lineages; equally emerged from East Africa during the late 1800s or early 1900s [19]. The Asian lineage originated during the virus's migration from Africa to Southeast Asia, where it was initial detected in Malaysia. From there, Zika virus spread to the Pacific Islands, separately to Yap and French Polynesia, and then to New Caledonia, Cook Islands, Easter Island, and the Americas [19].

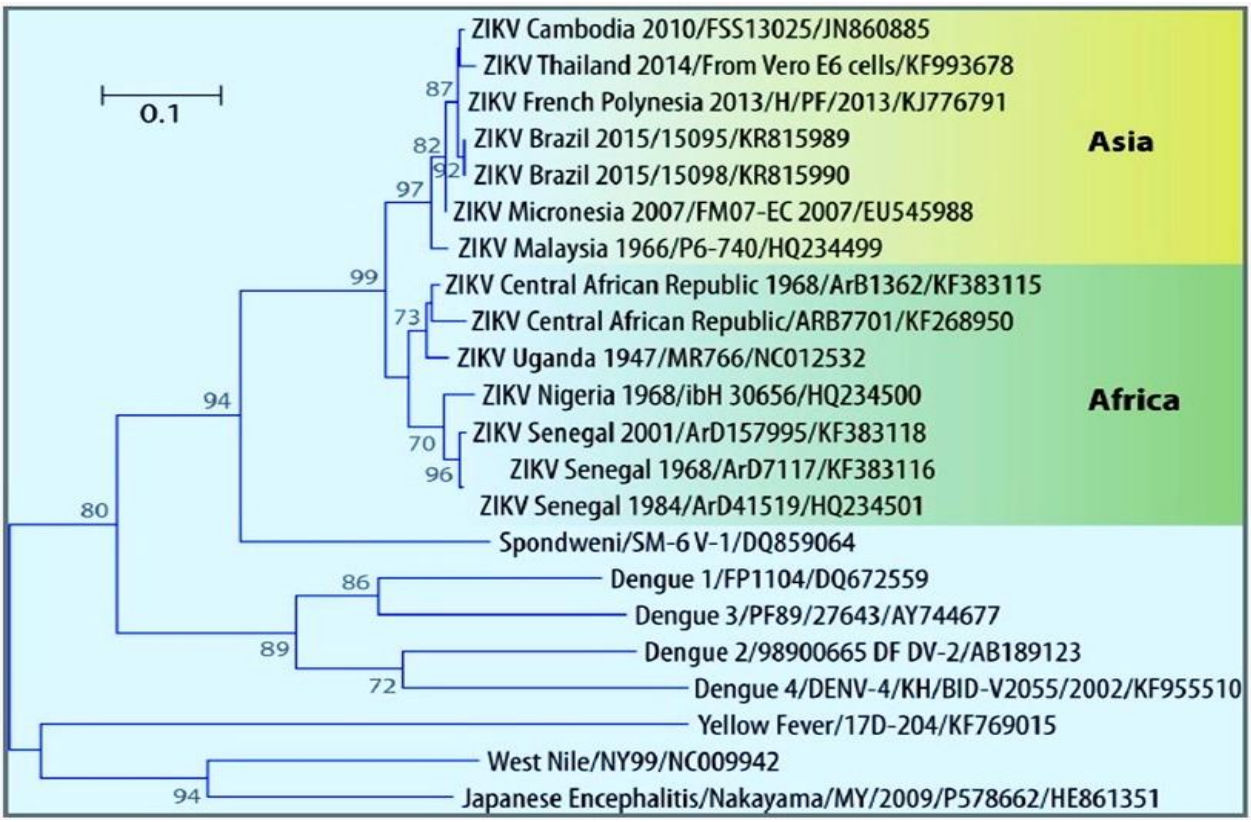

Fig. 2: Phylogenetic tree of ZIKV showing the African and Asian lineages, including the strains that recently emerged in the Pacific and Brazil [20]

Virology and Pathogenesis - Zika virus is a positive sense single-stranded RNA (ssRNA) virus belonging in the family of *Flaviviridae*, which includes numerous other mosquito borne viruses of medical importance (e.g. WNV, DENV, & yellow fever virus [YFV]) [21]. Its neighboring relative is Spondweni virus, another member of its clade [21-22]. The Zika virus genome contains 10,794 nt encoding 3,419 aa [22]. Like other flaviviruses, Zika virus is composed of 2 non-coding regions (5′ and 3′) that flank an open reading frame [22], which encodes a polyprotein cleaved into the capsid, precursor of membrane, envelope, and 7 nonstructural proteins [22].

Zika virus's molecular evolution studies is based on viral strains collected from four different countries in West Africa duration of 1947-2007, identified numerous sites within Zika viral genome, were under well strong negative selection pressure. This result suggested that frequent purging of deleterious polymorphisms in functionally essential genes and the possibility of recombination, which present rarely amongst flaviviruses [23]. The implications of this result require further estimation with respect to viral spread, zoonotic maintenance, and epidemiologic potential.

After mosquito inoculation of a human host, cellular entry likely resembles that of other flaviviruses, whereby the virus enters skin cells through cellular receptors, enabling migration to the lymph nodes and bloodstream. Few studies have investigated the pathogenesis of Zika virus infection. One study showed that human skin fibroblasts, keratinocytes, and immature dendritic cells allow entry of Zika virus [24]. Several entry and adhesion factors (e.g. AXL receptor tyrosine kinase) facilitate infection, and cellular autophagy, needed for flaviviral replication, enhances Zika virus replication in skin fibroblasts [24]. After cellular entry, flaviviruses typically replicate within endoplasmic reticulum-derived vesicles. However, Zika virus antigens were found exclusively in the nuclei of infected cells; this finding suggests a location for replication that differs from that of other flaviviruses and merits further investigation [25].

Vectors and Transmission- A vector of arboviruses may be defined as an arthropod that transfers the virus from one vertebrate to other vertebrate by the bite [26]. The most ordinary approach of biological transmission is infection during a viremic blood meal and injection of infectious saliva during blood feeding (horizontal transmission). Non-vector arbovirus transmission has been reported to occur straight between vertebrates [27,28], from mother to child [29-34], nosocomially [35–37], by transfusion [38–41], via bone marrow [42] or organ transplantation, and sexually.

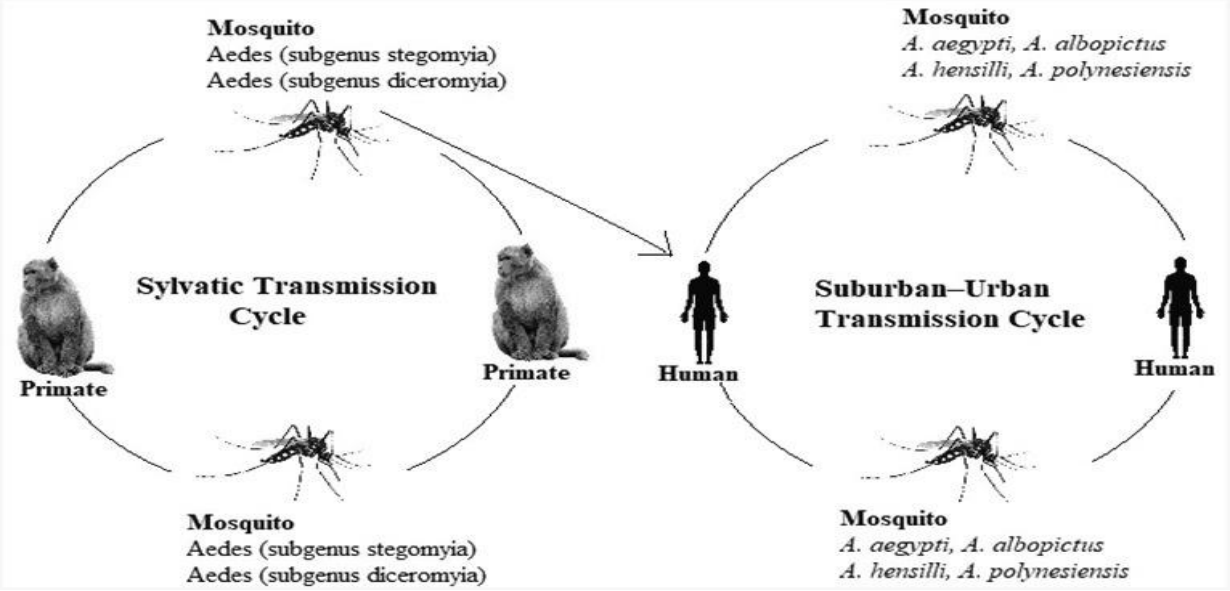

Fig. 3: Zika Virus Transmission Cycle

Health Care Worker Prevention- Health care workers practicing may face distinctive health hazards. Varied infectious risks area unit related to patient contact or handling clinical specimens. varied sorts of health care workers are also at risk: Physicians, nurses, and alternative adjunct clinical employees providing care in international settings, as well as clinics, hospitals, and field locations, Medical students and alternative health care trainees participating in clinical rotations overseas, Other people working in clinics, hospitals, or laboratories, as well as researchers, laboratory technicians, adjunct employees, and public health workers. Risks vary deepending on the duties of the employee, the geographic location, and therefore the practice setting. Increase risks area unit attributable to multiple factors as well as the following-

- Less stringent safety rules or infection management standards
- Limited availability of personal protective equipment (PPE) or safety-engineered devices
- Unfamiliar practice conditions or instrumentation
- Challenging practice conditions that can prevent providers from adhering to standard precautions (such as extremely resource-limited settings, natural disasters, or conflict zones)
- Unfamiliar medical procedures
- High prevalence of transmissible (such as HIV, hepatitis B, hepatitis C or TB)
- Potentially high infectious burden and increased transmission risk from source patients (such as high HIV viral loads in untreated patients)
- Limited resources for evaluation and treatment after exposure to blood-borne pathogens
- Potential to encounter uncommon or emerging infectious diseases that are highly transmissible in health care settings [such as Middle East respiratory syndrome (MERS) or Ebola virus disease]
- Increased psychological stress resulting from practicing in resource-limited settings, isolated areas, and long-term assignments.

Management commitment and employee involvement- Essential to implement effective infection management programs selected personnel should review, update and act on all steerage, as well as normal operational procedures and exposure management plans, and should communicate those policies and practices to any or all employees. Early identification procedures /signage will facilitate to quickly establish suspect cases. Healthcare workers must receive training and education on Zika identification and control. In addition to awareness training, personnel who are at risk should receive training on how properly don and doff their personal protective equipment [44].

Clinical Manifestation- Many people infected with Zika won't have symptoms or will only have mild symptoms. The most common symptoms are fever, rash, headache, joint pain, red eyes, and muscle pain. Symptoms can last for several days to a week. Once a person has been infected with Zika, they are likely to be protected from future infections.

Differential Diagnosis- In the lack of other arbovirus epidemics, diagnosis can be solely made on clinical grounds; however, as mentioned earlier, ZIKV outbreaks are generally linked with other arbovirus epidemics making diagnostic investigations an essential for clarifying the medical presentation [45].

Serological analysis- Detecting IgM in the serum of patients by the ELISA procedure is a valuable process, but unavailable in many laboratories. Moreover, the cross reactivity with antibodies to other arboviruses decreases the specificity of this technique [46-48]. In a recent study, serum samples from twenty-one patients with acute undifferentiated fever in Thailand were examined for immune reactivity against the Zika virus, Japanese encephalitis, Dengue, and Chikungunya envelope antigens. This inversion showed evidence of immunoreactivity against ZIKV envelope, suggesting that the Zika virus outbreak might have transmitted to

Thailand [49]. However, due to the cross reactivity of serological analysis, more specific investigative process (e.g. molecular diagnosis using real time PCR) is necessary.

Molecular diagnosis (RT-PCR)- Molecular diagnosis could be performed by the using of Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) [50]. These diagnostic studies were recommended that serum can give positive test for viral particles and the illness as soon as fever appear, other than when the rash occurs, viremia starts to drop. However, viral nucleic acids remain detectable for about 20–60 days from the onset of symptoms [51,52]. During the French Polynesia epidemic, Kutsuna *et al.* [53] reported positive viral RNA in urine, while serum samples from the same patients were negative. Gourinat *et al.* [48] were reported that the virus could be detected in the infected individual's urine samples of with higher titers after 20 days from the onset of the illness. These result data are consistent with former studies, which recommended prolonged finding of viral RNA of other flaviviruses as dengue virus [54] and West Nile virus [55] in urine samples. These reports emphasize the function of viral detection in urine as a diagnostic technique for Zika viral infection during epidemics.

Treatment strategy- There is no specific treatment or antiviral drug for Zika viral infection [56]. The present management guidance is based on a limited body of facts. Recommendations are the handling of symptoms based on acetaminophen for pain and fever, an antihistaminic for pruritic rash, and drinking of fluids. Treatment with acetylsalicylic acid and nonsteroidal anti-inflammatory drugs are discouraged because of the reported increased risk of hemorrhagic syndrome with other flaviviruses (Secretariat of the Pacific Community, http://www.spc.int/phs/english/publications/informaction/IA27/Zika-outbreak-Yap-2.pdf). In the initial days after onset of symptoms (viremic phase), patient isolation to pass up mosquito bites is recommended to avoid the infection to other people [56].

Prevention- No vaccine exists to prevent ZIKV in these days. Avoid ZIKV by avoiding mosquito bites only. Mosquitoes that spread ZIKV by people bite during the day & night. Mosquitoes that spread ZIKV is also spread dengue and chikungunya viruses. Zika can be passed through sex from a person, who has Zika to his or her sex buddies. Condoms either male or female are able to decrease the chance of getting Zika during sex. Local mosquito-borne Zika virus transmission has been reported in the continental US. The mosquitoes could spread Zika are found throughout the US.

The major vectors concerned with the spread and transmission of dengue, chikungunya, and ZIKV are a broad range of *Aedes* mosquitoes. Therefore, preventive measures begin with strategies intended to keep away from mosquito contact. These strategies include drainage of mosquito breeding sites and use of insecticides and N,N-diethyltoluamide (DEET) or picaridin containing insect repellents. In addition the testing of the nucleic acid of blood donors, avoidance of post-transfusion ZIKV can be performed by microbial pathogen inactivation in blood products [57]. To moment, none vaccines have been made up till now. But it is expected that the ZIKV 3 vaccine would encounter the same problems of arbovirus vaccines owing to the 4 sporadic & unexpected eruptions of epidemics; therefore, vaccinating a large five populations for fear of its outbreak might not be cost-effective [58].

CONCLUSIONS

Zika virus is a flaviviruses, which is transmitted by the bites of mosquitoes (*A. aegypti* and some other species), especially, during the day time. Zika virus can be transmitted by sexual activity, blood transfusions and from mother to child. Africa was considered the most affected country followed by south and North America which reported ZIKV cases recently. Zika infection is a pandemic that is spreading throughout different parts of the world. Research preparedness is required on an immediate basis to improve mosquito control procedures and to develop point-of-care laboratory diagnostics, vaccines and antivirals that are appropriate to be used in pregnant women. The main reason for ZIKV to become a global emergency is its link with congenital birth defects (i.e. microcephaly) to infected mother and lack of drugs or vaccines available due to very limited research and also an absence of population immunity. The most severe disease associated with ZIKV in French Polynesia and Brazil, however, suggests that this virus will become a very serious global public health problem due to lack of any better vaccine against ZIKV infection. Continued vigilance is warranted, along with a concerted effort toward improving our understanding, management, and prevention of this emerging pathogen.

FUTURE PROSPECT

Due to the current explosive rise in Zika virus, there is a dire need to carry out research based study to comprehend this life-threatening disease and develop medical countermeasures. ZIKV illness is a risk, not only to public health, but also to global security and the economy. We need to get serious about tracking Zika in patients, who have traveled in South and Central America and have symptoms. Prevention measures specifically vector control are a current priority. Affordable insurance policy to develop experimental treatments especially vaccines, against potential threats. However, there are virus-specific therapeutic targets, which may lead to the improvement of targeted anti-ZIKV drugs. In terms of treatment, the development of a broad spectrum antiviral drug has been recently recommended because the "One Bug-One Drug" approach is no longer practical. Because of the potential for birth defects, pregnant women to stay out of places where the virus is currently circulating. The association between Zika virus and neurological manifestation require further verification. In addition, the underlying pathological process and identification of the

population whom are at risk of these neurological manifestations should be investigated in the future.

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