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MINIREVIEW

Dengue and Zika viruses: lessons learned from the similarities between these *Aedes* mosquito-vectored arboviruses

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The currently spreading arbovirus epidemic is having a severe impact on human health worldwide. The two most common flaviviruses, dengue virus (DENV) and Zika virus (ZIKV), are transmitted through the same viral vector, *Aedes* spp. mosquitoes. Since the discovery of DENV in 1943, this virus has been reported to cause around 390 million human infections per year, approximately 500,000 of which require hospitalization and over 20,000 of which are lethal. The present DENV epidemic is primarily concentrated in Southeast Asia. ZIKV, which was discovered in 1952, is another important arthropod-borne flavivirus. The neurotropic role of ZIKV has been reported in infected newborns with microcephaly and in adults with Guillain-Barre syndrome. Despite DENV and ZIKV sharing the same viral vector, their complex pathogenic natures are poorly understood, and the infections they cause do not have specific treatments or effective vaccines. Therefore, this review will describe what is currently known about the clinical characteristics, pathogenesis mechanisms, and transmission of these two viruses. Better understanding of the interrelationships between DENV and ZIKV will provide a useful perspective for developing an effective strategy for controlling both viruses in the future.

Keywords: Dengue virus, Zika virus, *Aedes* mosquito, arboviruses, flavivirus, microcephaly

Introduction

Since the discovery of dengue virus (DENV) in 1943 (Messina *et al*., 2014), the reported incidence of these infections has increased in tropical and subtropical areas of the world. This virus, which has been characterized in the genus *Flavivirus* and family Flaviviridae, has four serotypes, DENV 1–4. DENV infection is considered to be a global health concern because its endemic area spans over 100 countries. Furthermore, DENV has been estimated to cause more than 390 million infection cases annually, of which about 500,000 individuals suffer severely, while more than 20,000 cases end in dengue-related death (Bhatt *et al*., 2013; Murray *et al*., 2013). Currently, there is no specific treatment for DENV infections, and the licensed vaccine for prevention is still not widely used (Gan, 2014; Thisyakorn and Thisyakorn, 2014). DENV infections can cause dengue fever, which is a self-limiting febrile illness (Guabiraba and Ryffel, 2014). To help clinicians with the proper diagnosis and management of DENV infections, in 1974, the World Health Organization (WHO) implemented the first classification of DENV infectious stages: dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). The classification criteria were revised in 2009 to include dengue without warning signs and dengue with warning signs (Narvaez *et al*., 2011). Hadinegoro suggested that this new classification required further modification (Hadinegoro, 2012). In 2011, the WHO revised its classifications and now grades the disease severity by its clinical manifestations as dengue fever (DF) and dengue hemorrhagic fever (DHF) grades 1 to 4 (WHO, 2011). The severe manifestations of DENV infection have several hallmark characteristics including vascular leakage and severe thrombocytopenia, which can lead to hypovolemic shock and multiorgan failure (Gomes *et al*., 2014). Recently, Mexico was the first country to license a vaccine for DENV. Immunization with this tetravalent vaccine named Dengvaxia® resulted in an approximately 60.8% reduction in the risk of disease development (Sanofi's, 2014; Guy *et al*., 2015; Constenla and Clark, 2016).

Like DENV, Zika virus (ZIKV) belongs to the genus *Flavivirus* and is transmitted via *Aedes* spp. mosquitoes. The first isolation of this once neglected pathogen occurred in 1947 from rhesus macaque monkeys that were caged in the Zika forest, Uganda, but the virus was not called ZIKV until 1952. The first isolation of ZIKV from a human case was in Nigeria in 1954, after which rare cases were found in Africa and Southeast Asia. The most common clinical presentations of infection with this virus includes a flu-like illness, conjunctivitis (red eye), rash, arthralgia, and joint pain (Paixao *et al*., 2016; Savidis *et al*., 2016). In 2007, the first large ZIKV epidemic outside of Africa and Asia occurred. This ZIKV outbreak in Micronesia, which did not cause any deaths or hospitalizations, was confined to Yap's island and consisted of 108 cases, 49 of which were initially characterized by their clinical presentations and later confirmed by reverse-transcriptase PCR testing (Pillet, 2009). Beginning in April 2015,

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there was a ZIKV outbreak in Brazil, comprising approximately 500 cases. The epidemic has continued in Brazil, and ZIKV cases have also been reported in the Caribbean as well as in Central and South America. In January 2016, this led the United States Centers for Disease Control to announce a level 2 alert for travel to ZIKV-epidemic areas (Campos *et al.*, 2015; Schmidt, 2016; Teixeira *et al.*, 2016). Worryingly, a recent Brazilian epidemiological study by Teixeira *et al.* (2016) reported that the microcephaly cases that occurred during the 2015 to 2016 period appear to be correlated with ZIKV infections. Currently, the pathogenesis of ZIKV infection is still controversial and there remains no specific treatment or preventative vaccine for it.

Virology

DENV is a single positive-stranded RNA virus with four serotypes (DENV 1–4). Its 10.7-kb genome consists of seven non-structural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) and three structural proteins (C: capsid, prM/M: membrane, and E: envelope). The DENV nucleocapsid, which contains the viral genome and C protein, has a roughly spherical shape. Surrounding the nucleocapsid is a membrane formed by a lipid bilayer embedded with E and M proteins, known as the envelope. Based on studies of the E protein's three-dimensional structure, Rey (2003) suggested that it plays a crucial role in the viral-host cell interaction during viral entry into human cells.

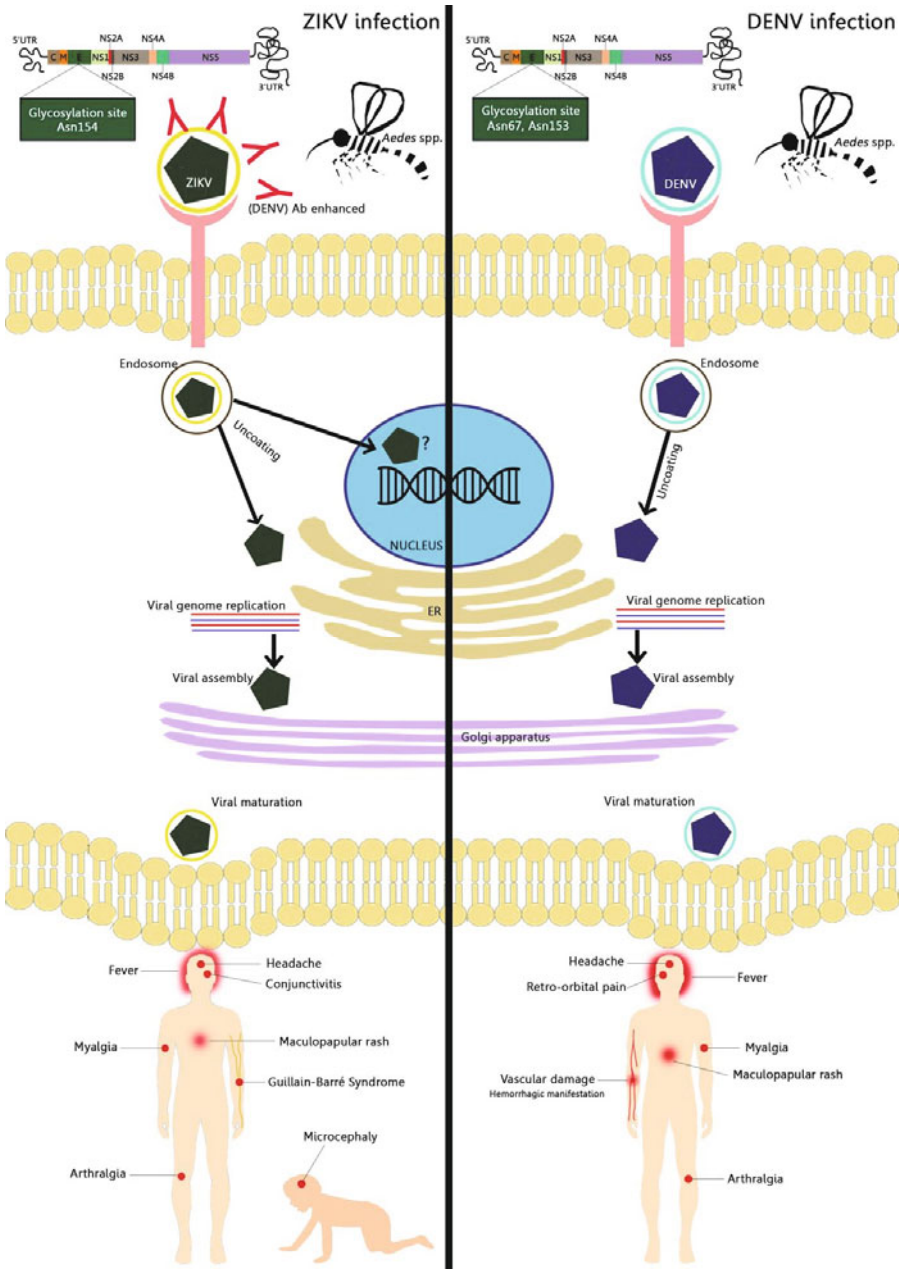

Fig. 1. Comparison of the characteristics and pathogenic profiles of dengue virus (DENV) and Zika virus (ZIKV). Both DENV and ZIKV have an *Aedes* spp. mosquito as a vector for viral transmission. The glycosylation sites of these two viruses differ: Asn^{67} and Asn^{153} are the glycosylation sites for DENV and Asn^{154} is the glycosylation site for ZIKV. The replication process of ZIKV is hypothesized to be the same as that of DENV. However, after virus internalization via endocytosis into target cells triggered by specific receptors on the cell membrane, ZIKV infection can be enhanced by anti-DENV antibodies. The endosome formation process uncoats the virus and releases the viral genome, after which the viral genome replicates in the ER. ZIKV may also replicate in the nucleus, but this idea remains controversial. Following genome replication, viral assembly and maturation occur in the Golgi apparatus in preparation for egress via the exocytosis process to infect additional target cells. The clinical manifestations for each of these two viruses include malaise with specific clinical signs and symptoms. The dominant sign of a ZIKV infection is conjunctivitis, and this infection may result in fetal microcephaly or Guillain-Barre syndrome as a complication. In contrast, DENV infections have hemorrhagic manifestations as the hallmarks of disease severity.

ZIKV, which also has a single positive-stranded RNA genome, has an icosahedral shape. The diameter of ZIKV is approximately 40 nm, and its genome length is approximately 11 kb (Buathong *et al*., 2015; Ellison *et al*., 2016). Like that of DENV, the ZIKV genome encodes three structural proteins (C, prM/M, and E) and seven NS proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). A study by Sirohi *et al.* (2016) using cryo-electron microscopy showed that the resolution of the mature ZIKV structure is about 380 A. Although ZIKV shares structural similarities with other flaviviruses, the ten distinct amino acids surrounding the ZIKV glycosylation site on its E protein were shown to surround the single glycosylation site at Asn^{154}. In contrast, the glycosylation site in DENV occupies two amino acids, Asn^{67} and Asn^{153}. Thus, this unique structure may contribute to the distinct cellular tropism of ZIKV (Sirohi *et al*., 2016).

Mechanisms of infection and virus life cycles

The infectious mechanism and viral replication of ZIKV is currently thought to be similar to those of DENV and other flaviviruses. After an infected mosquito injects its proboscis through the skin of the host for blood feeding, the viral particles released infect target cells such as fibroblasts, keratinocytes, dendritic cells, monocytes, and endothelial cells in the human host. The specific virus ligand, which is located within the E protein, binds to specific receptors on the host plasma membrane to stimulate endocytosis. A viral envelope within the host cell membrane forms an endosome, which is followed by viral uncoating and release of the nucleocapsid thereby promoting viral replication in the endoplasmic reticulum (ER) membrane. After translation, the immature virion, which has a visible spike, buds out from the ER membrane. Thereafter, in the Golgi apparatus, furin protease cleavage of the immature virion produces a mature spike-lacking virion. At this stage, the mature virus particles released by exocytosis can infect other cells. Interestingly, although other *Flavivirus* genus members generally replicate in the cell cytoplasm (Smrati Bajpai, 2016), Backley and Gould (1988) found that the ZIKV antigen can be detected in the nuclei of Vero and BHK- 21 cells (Fig. 1) as well as in mosquito cell nuclei.

Current understanding of immunopathogenesis

When a virus-infected mosquito injects its proboscis through the skin of the human host the virus can make contact with its target cells. The host innate immune system then responds as the first line of defense against the virus when pattern recognition receptors (e.g., Toll-like receptors, TLRs) and intracellular helicases sensors (e.g., melanoma differentiation-associated protein 5, MDA5; and retinoic acid-inducible gene 1, RIG-I) recognize the presence of viral RNA. An *in vitro* study found that during DENV endocytosis into acidic endosomes, viral recognition by TLR3 led to the strong activation of downstream interferon α/β responses (Nasirudeen *et al*., 2011). This finding was confirmed by a DENV infection experiment in monkeys, which found that TLR3, 7, and 8 were stimulated during DENV infection, thus illustrating a protective host response to viral infection (Sariol *et al*., 2011). Additionally, it was found that RIG-I and MDA5 are usually stimulated by DENV infection, and this also led to interferon β induction (Nasirudeen *et al*., 2011).

The interferon α and β cytokine system is important for inhibiting DENV infection. The target host cells respond to the paracrine interferon released from other infected cells and to autocrine interferon. The resulting signaling through the interferon α/β receptor is mediated via the STAT1/2 signaling pathway. To avoid such inhibition, DENV has developed strategies that interfere with the interferon α/β pathways. For example, the NS2B-NS3 protease cleaves the human mediator of interferon regulatory factor 3 activator (MITA or STING), which is part of the interferon induction pathway, to downregulate the antiviral responses triggered by DENV infection (Aguirre *et al*., 2012). In the case of DENV infection of Fcγ receptor-bearing cells in the presence of non-neutralizing antibodies, the resulting antibody-dependent enhancement (ADE) of infection can inhibit the RIG-I and MDA5 signaling cascades leading to the suppression of interferon α/β and a general failure of host antiviral responses (Halstead *et al*., 2010).

During a primary DENV infection, neutralizing antibodies directly recognize virion-specific epitopes that are not present on recombinant E monomers (de Alwis *et al*., 2012). The dominant DENV epitopes that are responsible for highly potent, serotype-specific humoral immunity seem to be located in the hinge region of the E protein (de Alwis *et al*., 2012; Teoh *et al*., 2012). Nevertheless, most human anti-DENV antibodies are cross-reactive between serotypes and are directed against the prM/M protein or the E protein fusion loop (de Alwis *et al*., 2011; Smith *et al*., 2012). A study by Modhiran *et al.* (2015) reported that the NS1 antigen plays a crucial role in inducing the increase in vascular permeability that leads to plasma leakage and the development of disease severity via TLR4. Thus, the NS1 antigen can also be called a viral toxin. While a primary DENV infection confers durable, if not life-long, protection against re-infection by a homologous DENV serotype, a secondary DENV infection with another DENV serotype, which occurs mostly in DENV endemic areas, has an increased risk of causing severe disease. Severe cases of secondary DENV infection are quite rare, with around 0.5–1% of infections progressing to DHF and DSS, but the exact mechanism responsible for this progression remains unclear. Several studies have hypothesized that secondary DENV infections occur via the ADE pathway: if the antibodies resulting from a primary DENV infection fall below the threshold of antibody neutralization to a heterologous DENV serotype, these antibodies can promote DENV entry into cells expressing Fcγ receptors. Thus, low-affinity or poorly neutralizing cross-reactive antibodies against DENV structural proteins that were generated during a primary DENV infection can facilitate ADE *in vivo* during a secondary DENV infection, resulting in an increased viral burden and a more severe disease. Additionally, whether a DENV infection progresses to DHF and DSS will depend on the immune characteristics of the infected individual. The strain-specific virulence of the virus is also an important factor for disease progression. Therefore, in terms of the factors deter-

mining whether a DENV infection progresses to DHF and DSS, it seems likely that the process will be multifactorial, but divisible into two main elements: host factors and viral factors. Dominant host factors are likely to be related to an individual's immune status and genetic makeup, while viral factors are likely to be related to the strain and serotype properties of the virus.

The pathogenesis of infection with ZIKV is complex and not well understood, and more information is needed to confirm the current hypotheses about the mechanisms used by it to establish an infection. The correlation between ZIKV and microcephaly in fetuses and Guillain-Barre syndrome (GBS) in human adults suggest that ZIKV may have a neural cell tropism (Cao-Lormeau *et al.*, 2016; Mysorekar and Diamond, 2016). Roze *et al.* (2016) reported that ZIKV was detected in the urine of two GBS patients in Martinique, thereby supporting the association between ZIKV infection and GBS in adults. Other studies have proposed that the pathogenesis of ZIKV may affect the process of fetal neurogenesis or that of Wallerian degeneration in adults (Dang *et al.*, 2016; Mlakar *et al.*, 2016). Additionally, a case report stated that ZIKV RNA was detectable in semen from a patient within 93 days after the onset of ZIKV infection (Mansuy *et al.*, 2016), but the horizontal transmission of ZIKV hypothesized in this case is controversial. An *in vivo* study on microcephaly that was conducted by inoculating ZIKV into the brain of a Swiss mouse via the intracerebral route showed that ZIKV has a tropism for neurons, and this study demonstrated that the resulting pathology that occurred mainly in the central nervous system led to motor weakness and paralysis (Dowall *et al.*, 2016). Another *in vivo* study on ZIKV reported that Cowdry type A inclusion bodies, which are important signs of neuronal degeneration, appear in the spinal cord and brain following a ZIKV infection (Panchaud *et al.*, 2016).

A study on human fetuses infected with ZIKV *in utero* found several fetal defects, including diffusion of astrogliosis, activation of microglia, and damage extending to the brain stem and spinal cord, with Wallerian degeneration of the descending corticospinal tracts (Lazear and Diamond, 2016).

To learn more about how ZIKV affects pregnancy, a study by Yockey *et al.* (2016) investigated the susceptibility of the vagina to ZIKV infection and replication and the subsequent effect of infection on the fetus in mice. They found that the mouse vaginas were susceptible to ZIKV infection, and this led to fetal growth restriction, fetal brain infection, and abortion. A study by Calvet *et al.* (2016) confirmed that ZIKV can cross the placental barrier to affect the fetus. Furthermore, postmortem studies and autopsies of fetuses and infants with microcephaly found an overlapping wide spectrum of microscopic neuropathologic abnormalities and brain damage, with the direct viral effects of ZIKV confined to the brain (Schwartz, 2016). In agreement with these findings, a study by Martines *et al.* (2016) that investigated ZIKV pathology in three fatal microcephaly cases, reported that the detection of ZIKV antigen in glia cells and neuron cells was associated with microcalcification in all three cases. Fatima *et al.* (2016) and Linden *et al.* (2016) conducted retrospective studies on computed tomography and magnetic resonance imaging radiological findings in microcephaly cases in Brazil presumed to be related to ZIKV congenital infections. They found that most children presumed to have congenital ZIKV infections had severe cerebral damage and evidence of brain calcification in the junction between the cortical and sub-cortical white matter, and this was associated with cortical development malformation. Moreover, they observed frontal lobes with a simplified gyral pattern and a predominance of pachygyria or polymicrogyria, arthrogryposis, cisterna magna enlargement, corpus callosum hypoplasia, ventriculomegaly, delayed myelination, and hypoplasia of the cerebellum and brainstem in these children (de Fatima Vasco Aragao *et al.*, 2016; van der Linden *et al.*, 2016). Although there is no vaccine or any specific therapies for treating ZIKV infections, Barrows *et al.* (2016) found over 20 compounds that inhibited ZIKV infection using an *in vitro* assay to screen FDA-approved drugs for their ZIKV infection-blocking abilities. Their findings might serve as a platform for generating or developing an anti-flavivirus drug.

Clinical presentation

ZIKV infections exhibit several clinical presentations in people, ranging from no signs or symptoms to an influenza-like viral illness that appears similar in its early stages to illnesses caused by infections with other flaviviruses, such as DENV (Saiz *et al.*, 2016). A small proportion of ZIKV-infected individuals develop a clinically apparent febrile illness, and a few rare cases require hospitalization. The clinical presentation of a ZIKV infection occurs on average within three to seven days of being bitten by an infected mosquito (Slavov *et al.*, 2016). The general signs and symptoms of a ZIKV infection consist of headache, arthralgia, myalgia, conjunctivitis, vomiting, fatigue, and/or maculopapular rash (Hayes, 2009). ZIKV infections are generally considered to be self-limiting (Aliota *et al.*, 2016). However, such infections can also have disease complications, such as those reported during the ZIKV epidemic in French Polynesia, which have been correlated with neurological disorders, including an increased incidence of GBS. It has also been reported that a diffuse demyelinating disorder consistent with GBS is temporally associated with ZIKV infections (Cao-Lormeau *et al.*, 2016; Jouannic *et al.*, 2016).

In contrast, DENV infections have an incubation period of 4–8 days (Rajapakse *et al.*, 2012). This infection can produce a wide spectrum of clinical presentations, and a large proportion of infections are asymptomatic (Chastel, 2012). Symptomatic cases can have a self-limiting course of infection ending in recovery. However, a small proportion of cases progress to a severe disease form, characterized by plasma leakage, multi-organ failure, and profound shock (Srichaikul and Nimmannitya, 2000; Aye *et al.*, 2014). The clinical presentation of infection with DENV is differentiated into the three phases described below (Hadinegoro, 2012).

Febrile phase

In the febrile phase, the patient suddenly develops a high fever (commonly ≥38.5°C) accompanied by headache, myalgia, joint pain and gastrointestinal symptoms, and a transient macular rash may also be present. This phase occurs during the peak of viremia (Yacoub *et al.*, 2014). Some patients may

also exhibit symptoms similar to those usually found in mild hemorrhagic illnesses, such as measles-like rash, and some petechiae can occur (Dietz *et al.*, 1992; Chen and Wilson, 2010; Tantawichien, 2015).

Critical phase

The critical phase is a 2–3 day period around defervescence (Yacoub *et al.*, 2014); this typically occurs in a small proportion of cases and is evidenced by hypoproteinemia (Balasubramanian *et al.*, 2006), hemoconcentration (Balasubramanian *et al.*, 2004), and pleural effusions. Ascites may also occur during this period (Srikiatkhachorn *et al.*, 2007). In this phase, awareness of the clinically significant indicators of severity is crucial. For example, plasma leakage can lead to a depletion of fluid circulation and decrease the blood supply to vital organs, which may further develop into multi-organ failure, myocarditis, or encephalopathy (Kalayanarooj, 2011).

Recovery phase

The recovery phase, lasting 2–3 days, is the final phase of the clinical course of the disease, during which the clinically significant signs and symptoms resolve and normalize (Yacoub *et al.*, 2014). Leaked fluid is reabsorbed into the circulation, and a maculopapular rash with severe itching and slow heart rate may appear for the second time. During this period, it is important to be vigilant for evidence of fluid overload. Following the recovery phase, fatigue may last for weeks (Ranjit and Kissoon, 2011; Whitehorn and Simmons, 2011).

The interrelationship between DENV and ZIKV

A study by Dejnirattisai *et al.* (2016) which focused on the interrelationship between DENV and ZIKV infections, found that anti-DENV antibodies could enhance ZIKV infection via the ADE phenomenon. Moreover, the DENV and ZIKV co-infections were found in two patients from Caledonia in 2014. However, this study did not find a synergistic effect for these two viral infections (Dupont-Rouzeyrol *et al.*, 2015).

ZIKV vaccine from a DENV platform and future perspectives (Comments and opinions of the authors)

Given the similarities of the viral characteristics and genomes of DENV and ZIKV, DENV could be used as a platform for developing a ZIKV vaccine. This could involve replacing the prM and E genes in the yellow fever 17D backbone (YF17D model) with the DENV prM and E genes to develop a DENV vaccine. Similarly, the YF17D model might also be a useful tool for developing a ZIKV vaccine. However, it is important to bear in mind the potential effects of the dissimilarities among these viruses, such as their differing glycosylation sites, which may be responsible for their distinct viral tropisms and immunomodulation during viral replication. Notably, because DENV and ZIKV infections have similar clinical presentations, it is possible to misdiagnose them. Although several epidemiologists have suggested that ZIKV infections are strongly linked with microcephaly and GBS, further studies are required to determine the mechanisms responsible for these correlations. Furthermore, the viability of ZIKV in semen within 93 days after onset of fever as a possible transmission route needs to be confirmed in other patients. Lastly, to develop appropriate therapeutic strategies and successful vaccines against ZIKV infections, further evaluation of the occurrence of ADE from anti-DENV antibodies, which has

Table 1. Comparison of DENV and ZIKV

Characteristic	DENV	ZIKV	References
Viral shape	Spherical	Spherical	Kuhn *et al.* (2002), Saiz *et al.* (2016), Waddell and Greig (2016)
Viral genome	+ssRNA	+ssRNA	Gebhard *et al.* (2011), Faye *et al.* (2014), Sim and Hibberd (2016), van Hemert and Berkhout (2016)
Genus	*Flavivirus*	*Flavivirus*	Kuhn *et al.* (2002), Faye *et al.* (2014), Rolfe *et al.* (2016)
Glycosylation site	E protein	E protein	Mondotte *et al.* (2007), Christian *et al.* (2013), Kostyuchenko *et al.* (2016)
Glycosylation position	$Asn^{67, 153}$	Asn^{154}	Mondotte *et al.* (2007), Faye *et al.* (2014), Sirohi *et al.* (2016)
Encoded genome	3 structural proteins with 7 non-structural proteins	3 structural proteins with 7 non-structural proteins	Chao *et al.* (2005), Bollati *et al.* (2010), Wikan *et al.* (2016)
Vector	*Aedes* spp. mosquito	*Aedes* spp. mosquito	Marchette *et al.* (1969), Howard (2016)
Epidemiology	Endemic area	Outbreak and case reported	Duffy *et al.* (2009), Toan *et al.* (2015)
Disease pathology	Hemorrhagic virus	Neurotropic virus	Tantawichien (2015), Carod-Artal (2016), Massey and Robertson (2016)
Disease severity	- Plasma leakage - Multi-organ failure	- Microcephaly* - GBS*	Srikiatkhachorn *et al.* (2007), Srikiatkhachorn (2009), Povoa *et al.* (2014), Araujo *et al.* (2016), Butler (2016), Cao-Lormeau *et al.* (2016), Millichap (2016), Oliveira Melo *et al.* (2016)
Treatment	Supportive	Supportive	Singhi *et al.* (2007), Sikka *et al.* (2016)
Vaccine	Dengvaxia® with 60.8% efficacy		Sanofi's (2014), Scott (2016), Sikka *et al.* (2016)
Prevention	- Mosquito control - Vaccine	-Mosquito control	Ooi *et al.* (2006), Benelli and Mehlhorn (2016), Teixeira *et al.* (2016)
Therapeutic and prevention development	- Vaccine development - Monoclonal antibody		Puttikhunt *et al.* (2003), Zanluca *et al.* (2014), Flingai *et al.* (2015)

* This information is speculative and requires further confirmation.
+ssRNA, positive single stranded RNA; E, envelope; spp., species; GBS, Guillain-Barre syndrome

been shown to enhance ZIKV replication, is required.

Concluding remarks

DENV and ZIKV both belong to the *Flavivirus* genus and share the same *Aedes* spp. mosquito vector for their transmission. Over half of the world's tropical and subtropical regions fall within the DENV endemic area, and its wide impact on the affected countries has led to this virus being well-studied. In contrast, less attention was paid to ZIKV until the 2007 ZIKV outbreak on Yap Island led to an increase in ZIKV research aimed at determining the disease pathogenesis and developing preventative measures and therapies against it. In 2015, the outbreak of ZIKV infections that occurred in Brazil indicated that this infection is correlated with microcephaly in fetuses. The first vaccine for DENV has been approved in some hyperendemic countries, but the efficacy of the approved vaccine is controversial. That no vaccine against ZIKV exists is partly attributable to the current lack of understanding of the complexity of ZIKV infection. Although ZIKV and DENV have many things in common, several studies have found important dissimilarities between ZIKV and other flaviviruses, such as the presence of ZIKV antigen in the nuclei of host cells and different glycosylation sites, which may affect host cell tropism and clinical features during viral infection. Moreover, antibodies against DENV have been evidenced to enhance ZIKV infection, while ZIKV antigen was detected in semen within 93 days after the onset of a ZIKV infection. The pathogeneses of these two viruses are not well understood, and additional studies are required if we are to develop effective antiviral strategies and vaccines to prevent and control them. Because DENV and ZIKV share many features (Table 1), the platform used for DENV studies could possibly be applied to the study of ZIKV pathology.

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Conflict of Interest

The authors declare that they have no conflicts of interest in regard to this work.

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