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Review

Zika virus in Asia

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SUMMARY

Zika virus (ZIKV) is an emerging mosquito-borne virus that was first isolated from a sentinel rhesus monkey in the Zika Forest in Uganda in 1947. In Asia, the virus was isolated in Malaysia from *Aedes aegypti* mosquitoes in 1966, and the first human infections were reported in 1977 in Central Java, Indonesia. In this review, all reported cases of ZIKV infection in Asia as of September 1, 2016 are summarized and some of the hypotheses that could currently explain the apparently low incidence of Zika cases in Asia are explored.

1. Introduction

Zika virus (ZIKV) is an emerging mosquito-borne virus and member of the family *Flaviviridae*, which includes dengue virus (DENV), West Nile virus (WNV), Japanese encephalitis virus (JEV), and yellow fever virus (YFV) (Figure 1). The closest relative to ZIKV is Spondweni virus. ZIKV was first isolated from a sentinel rhesus monkey in the Zika Forest in Uganda in 1947 and from *Aedes africanus* mosquitoes in 1948.[1] ZIKV is transmitted by Aedes mosquitoes, with humans representing the amplifying host. A sylvatic cycle of transmission also exists and involves non-human primates and arboreal zoophilic Aedes mosquitoes from African and Asian forests.[2] ZIKV has also been isolated from *Culex* species mosquitoes, but their susceptibility to the virus seems low.[3]

The first human infection was recorded in Nigeria in 1954, where the virus was detected in a 10-year-old Nigerian female.[4,5] In Asia, the virus was isolated in Malaysia in 1966 from *Aedes aegypti* mosquitoes,[6] and the first human infections were reported in 1977 in Central Java, Indonesia.[7] Prior to the outbreak in Yap State (part of the Federated States of Micronesia) in 2007, where an estimated 75% of the residents were infected, only 14 human cases had been confirmed.[8,9] During 2013, an epidemic in French Polynesia affected approximately 28 000 people, and the possible association between ZIKV infection and Guillain–Barré syndrome was suggested for the first time.[9] As of August 31, 2016, 72 countries and territories had observed local ZIKV transmission.[10] In the Americas alone, over 500 000 locally acquired cases had been reported up to September 1, 2016; however the real number of infections is probably closer to several million, based on almost 2000 microcephaly and/or central nervous system malformation cases, which are suggestive of congenital ZIKV infection or potentially associated with ZIKV infection.[10,11]

2. The challenges of Zika diagnosis and detection by surveillance systems

In general, the clinical picture of natural human ZIKV infection is of a short duration, self-limiting, mild febrile illness that is accompanied by a maculopapular rash.[12] The most common clinical features reported during ZIKV infection are fever, rash, arthritis and/or arthralgia and/or myalgia, conjunctivitis, and fatigue.[13] Although it is difficult to clinically differentiate ZIKV infections from other arboviral diseases like dengue and chikungunya, symptoms such as oedema of the extremities, conjunctivitis, and the absence of leukopenia/thrombocytopenia are more common with Zika.[14]

To date, the literature describing the performances of Zika diagnostic tests remains relatively limited. The routine diagnosis of ZIKV infection can be determined by either direct methods, i.e., isolation and detection of viral genome by RT-PCR in blood, saliva, urine, and other body fluids (cerebrospinal fluid, amniotic fluid, semen, vaginal fluid, breast milk, pharyngeal secretions), or by indirect methods based on the identification of Zika antibodies in the blood.[2,15,16] Although a confirmation of the diagnosis is easily achieved with the direct diagnostic methods, the cross-reactivity between viruses of the *Flaviviridae* family makes the serological

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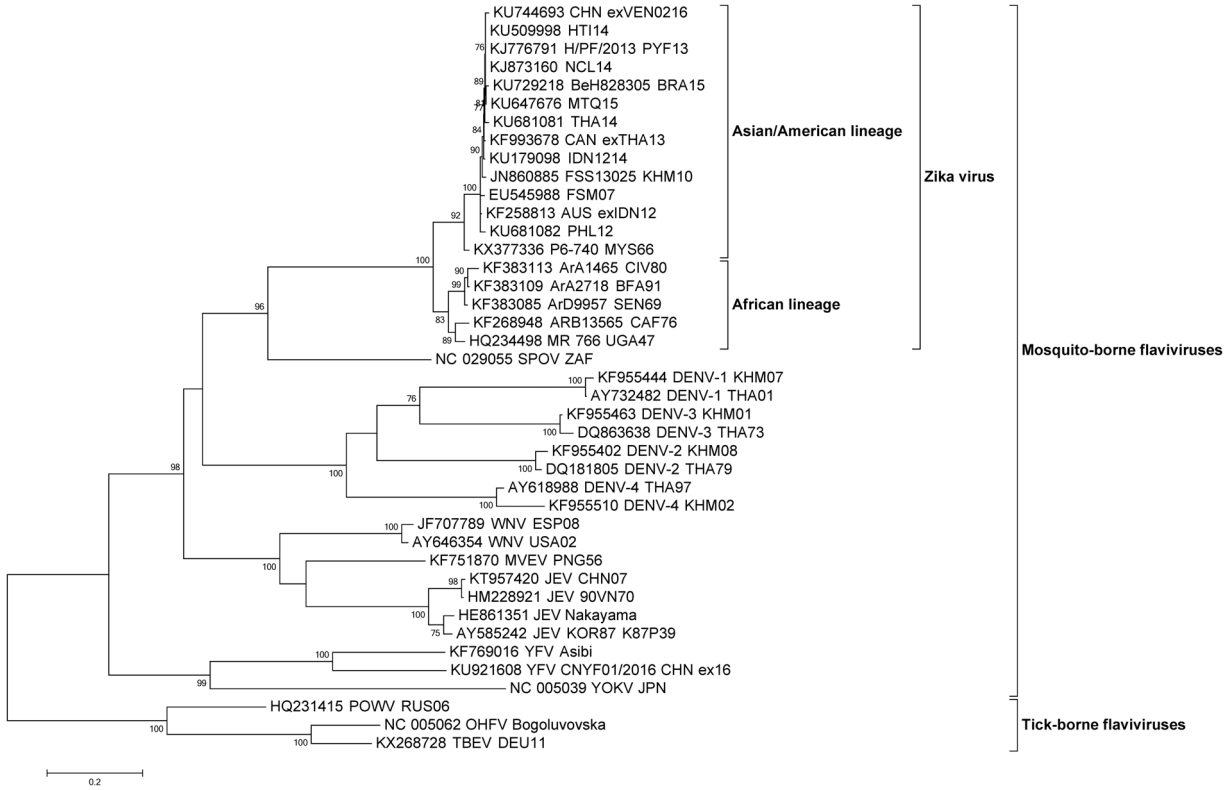

Figure 1. Phylogenetic tree of the NS5 gene of flaviviruses. The alignment includes 41 reference NS5 partial sequences from tick-borne and mosquito-borne flaviviruses available in GenBank. MEGA 6[99] was used to perform multiple sequence alignment and phylogenetic analyses using the maximum likelihood (ML) method and the GTR model with 1000 bootstrap re-sampling.

results very difficult to interpret, especially in those countries where more than one flavivirus circulates. The antibodies against ZIKV are often detected by ELISA and then confirmed by plaque reduction neutralization test (PRNT). Because of the potential for cross-reactivity, antigens from DENV and JEV should be tested in parallel and the results compared to identify the most likely aetiological agent. The Centers for Disease Control and Prevention (CDC) in the USA offer guidelines for the interpretation of serology results (http://www.cdc.gov/zika/pdfs/laboratory-guidance-zika.pdf).

There is a clear lack of a laboratory network with ZIKV diagnostic capacities, and access to standardized reagents remains difficult in many countries.[15,17] Using the existing national arbovirus surveillance systems in Asia to detect the circulation of ZIKV remains extremely challenging for several reasons.[15,17] First, the routine diagnosis of acute ZIKV infection relies essentially on the detection of viral nucleic acid by RT-PCR and the detection of IgM antibodies by IgM antibody capture (MAC)-ELISA. The detection of viral RNA by RT-PCR is often considered as a gold standard and provides a definitive diagnosis; however, this test remains unavailable in most clinical settings due to the associated costs and lack of experienced laboratory personnel. Virus isolation is useful for diagnostic and research purposes but is time-consuming and faces the same technical limitations as molecular assays. A number of ZIKV sero-epidemiological studies have been conducted in Asia; however because of the extensive cross-reactivity of anti-flavivirus antibodies and the large number of flaviviruses circulating in the region, the interpretation of serological results is complicated.[18–21] The antibodies against ZIKV antigen may be reactive to DENV, JEV, and/or YFV antigens to the same level, or with even higher titres in MAC-ELISA and haemagglutination inhibition (HI) assays.[16,22] PRNT can be used to differentiate antibodies of closely related viruses.[23] However, this test is labour-intensive and costly, requires handling of live virus, takes up to a week to perform, requires standardized reagents that are often not available, and is not widely performed. Due to the 'original antigenic sin' phenomenon, even the PRNT cannot reliably provide a diagnosis in patients who have previously been exposed to a heterologous *Flavivirus*,[24] which again poses some interpretational challenges in regions where dengue and/or other flaviviruses are co-circulating and more than 90% of the population may have had previous exposure to at least one of these flaviviruses.[18,25–27] In settings where PRNT is not available, specimens that test positive by ZIKV MAC-ELISA and negative by DENV and/or JEV MAC-ELISA may be interpreted as presumptive recent ZIKV infections (http://www.cdc.gov/zika/pdfs/laboratory-guidance-zika.pdf). However, the diagnostic accuracy of this approach remains to be validated.

Second, most of the surveillance programmes have a syndromic approach and they are often based on the report of hospitalized cases. Since ZIKV infection symptoms are rarely severe, poorly specific, and often misdiagnosed as dengue and chikungunya cases, the prevalence of Zika remains difficult to estimate through such surveillance systems.

3. Epidemiology of Zika in Asia

Tropical countries in Asia are believed to be endemic for many arboviral diseases including DENV, JEV, and chikungunya virus (CHIKV). In contrast to DENV, studies on ZIKV in Asia have been scarce, due to its apparent limited public health importance and the initial belief – prior to knowledge of the neurological