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Review article

Zika virus: History, epidemiology, transmission, and clinical presentation

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A B S T R A C T

Zika virus (ZIKV), a mosquito-borne positive-stranded RNA virus of the family *Flaviviridae* (genus *Flavivirus*), is now causing an unprecedented large-scale outbreak in the Americas. Historically, ZIKV spread eastward from equatorial Africa and Asia to the Pacific Islands during the late 2000s to early 2010s, invaded the Caribbean and Central and South America in 2015, and reached North America in 2016. Although ZIKV infection generally causes no symptoms or only a mild self-limiting illness, it has recently been linked to a rising number of severe neurological diseases, including microcephaly and Guillain-Barré syndrome. Because of the continuous geographic expansion of both the virus and its mosquito vectors, ZIKV poses a serious threat to public health around the globe. However, there are no vaccines or antiviral therapies available against this pathogen. This review summarizes a fast-growing body of literature on the history, epidemiology, transmission, and clinical presentation of ZIKV and highlights the urgent need for the development of efficient control strategies for this emerging pathogen.

Contents

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1. Classification and nomenclature

Zika virus (ZIKV) belongs to the genus *Flavivirus* in the family *Flaviviridae* (Lindenbach et al., 2007). Currently, the genus comprises 53 virus species (Simmonds et al., 2012), which are transmitted by the bite of mosquitoes (27 species), ticks (12 species), or no known arthropod vector (14 species). Within the *Flavivirus* genus, ZIKV is a mosquito-borne virus that is phylogenetically closely related to other medically important mosquito-borne flaviviruses of global public health significance (Fig. 1), such as Japanese encephalitis (JEV), West Nile (WNV), dengue (DENV), and yellow fever (YFV) viruses (Gubler et al., 2007). These mosquito-borne flaviviruses can be divided into two major classes based on their clinical presentation in humans (Gaunt et al., 2001; Kramer and Ebel, 2003): (1) encephalitic flaviviruses (represented by JEV and WNV), which cause invasive neurological diseases, with birds serving as their natural vertebrate hosts and *Culex* species mosquitoes as their principal vectors (Brinton, 2013; Yun and Lee, 2014); and (2) non-encephalitic or viscerotropic flaviviruses (exemplified by DENV and YFV), which cause lethal hemorrhagic fever, with non-human primates acting as their vertebrate hosts and *Aedes* species mosquitoes as their primary vectors (Monath and Vasconcelos, 2015; Weaver and Barrett, 2004). Of note, DENV has fully adapted to humans and no longer needs animal hosts for viral transmission (Clyde et al., 2006; Mackenzie et al., 2004).

2. History and epidemiology

Discovered in Uganda in 1947, ZIKV was confined for the first 60 years to an equatorial zone across Africa and Asia. Outside this zone, however, it first emerged in Yap Island in 2007, spread eastward to French Polynesia and other Pacific Islands in 2013–2014, reached Latin America in 2015, and disseminated further to North America in 2016. Now, ZIKV is circulating in the Americas, Southeast Asia, and the Pacific Islands.

2.1. Virus discovery and seroprevalence in Africa and Asia prior to the year 2000

ZIKV was first isolated in 1947 from the serum of a sentinel rhesus macaque monkey that was placed in the Zika forest on the Entebbe peninsula, Uganda, during the course of surveillance for YFV (Dick et al., 1952). This isolate, named MR-766, is the African prototype strain of ZIKV. Shortly thereafter, it was also recovered on multiple occasions from *A. africanus* mosquitoes caught in the same area (Dick, 1952; Dick et al., 1952; Haddow et al., 1964; Weinbren and Williams, 1958). Although there was no indication that ZIKV caused disease in the residents of Uganda, the prevalence of antibodies against the virus in their serum was approximately 10–20% (Dick, 1953; Dick et al., 1952). Despite the need for caution because of antibody cross-reactivity with other flaviviruses, a large number of serological studies in the half century since the discovery of ZIKV have revealed a broad but confined geographic distribution of human infection with the virus, across a relatively narrow equatorial belt running from Africa to Asia: Senegal (Monlun et al., 1993), Sierra Leone (Robin and Mouchet, 1975), Nigeria (Adekolu-John and Fagbami, 1983; Fagbami, 1977; Macnamara, 1954), Gabon (Jan et al., 1978; Saluzzo et al., 1982), Central African Republic (Saluzzo et al., 1981), Egypt (Smithburn et al., 1954b), Uganda (Smithburn, 1952), Tanzania

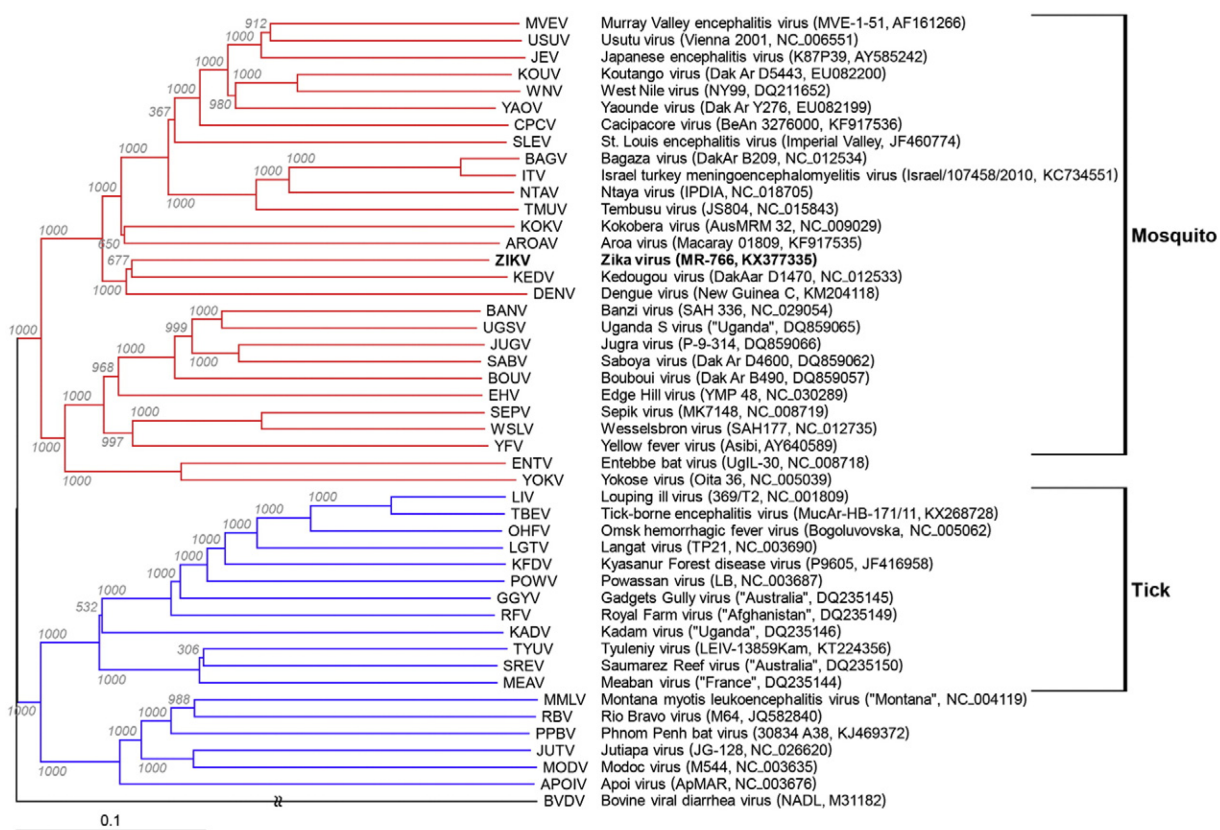

Fig. 1. A rooted phylogenetic tree based on the nucleotide sequence of complete or near-complete genomes of all 46 available flaviviruses (as of November 2016). Multiple sequence alignments were produced by ClustalX (Thompson et al., 1997), and the rooted phylogenetic tree was generated by the neighbor-joining method (Saitou and Nei, 1987). The scale bar represents the genetic distance in nucleotide substitutions per site. Bootstrap values (1000 replications) are shown at each node. The complete genome sequence of the bovine viral diarrhea virus, a member of the genus *Pestivirus* in the family *Flaviviridae*, was used as an outgroup. The virus abbreviations assigned by the International Committee on Taxonomy of Viruses are listed, and the strain names and their GenBank accession numbers are provided in parenthesis. The known or probable vector (mosquito or tick) is indicated on the right side of the tree.