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Zika virus infection, transmission, associated neurological disorders and birth abnormalities: A review of progress in research, priorities and knowledge gaps

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ABSTRACT

On February 1, 2016, the World Health Organization declared that the cluster of microcephaly cases and other neurological disorders constitute public health emergency of international concern. Furthermore, few studies demonstrated that there was an increased evidence of causal relationship of Zika virus (ZIKAV) infection and microcephaly, birth abnormalities and neurological disorders such as Guillain–Barré syndrome. ZIKAV transmission occurs mainly by the bite of infected mosquitos (*Aedes* species), but there are also reports that infections could occur via the placenta, breast milk, saliva, blood transfusion and sex. This article reviews the global efforts, progress in scientific research to understand the pathogenesis of ZIKAV infection & disease, clinical presentations, congenital transmission and autoimmune neurological disorders. The paper further explores the knowledge gaps, future priority research agenda for strategic response including vector control and prevention. We conducted a systematic literature review to synthesise available evidence on ZIKAV infection and its vector and host interaction from electronic databases.

1. Introduction

Zika virus (ZIKAV) is an emerging mosquito-borne flavivirus that was first identified in Uganda in 1947 and later found in humans with increasing outbreaks in Uganda, Yap Island, French Polynesia in 1952, 2007, 2013, respectively, and New Caledonia, Easter Islands and Cook Islands in 2014 [1–4].

From 1 January 2007 to 4 May 2016, ZIKAV outbreaks were reported in a total of 57 countries and territories. In 44 countries these outbreaks were reported for the first time. Four of them (Cook Islands, French Polynesia, Isla de Pascua – Chile, and New Caledonia) reported a ZIKAV outbreak that is now over. Seven countries (Argentina, Chile, France, Italy, New Zealand, Peru and the US) have now documented locally acquired infections without any evidence indicating the presence of the presumptive vectors, probably through sexual transmission [5].

ZIKAV is primarily transmitted by the bite of infected mosquitoes, and the virus has been isolated from a number of *Aedes* mosquito species [6], notably *Aedes aegypti* (*Ae. aegypti*). The *Ae. aegypti* mosquito species are predominantly found in tropical and sub-tropical areas. Another potential transmitter, *Aedes albopictus* (*Ae. albopictus*), is entomologically well recognized in several parts of Europe, particularly in Mediterranean countries. *Aedes polynesiensis* is also incriminated as a possible contributor to ZIKAV transmission in the outbreak of French Polynesia. Other possible ways of ZIKAV transmission are detailed below. However there are several unknown facts and knowledge gaps about the pathogenesis, transmission, complications and treatment of ZIKAV infection.

This article discusses in detail the occurrence of ZIKAV as a public health threat, the progress and gaps in research related to the epidemiology of the virus, pathology, clinical presentations, knowledge, host and vector interaction, vector surveillance, transmission patterns, immunity and immunogenicity, genetic and molecular studies, the development of vaccines, new

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therapeutics and new methods of vector control strategies. The paper reviews the current progress in research and the gaps by elucidating the association of complications of ZIKAV infections, clinical presentations, neurological disorders, and foetal/birth abnormalities such as microcephaly.

We conducted a systematic literature review to synthesise available evidence on ZIKAV infection and its vector and host interactions from electronic data repositories namely from PubMed, Medline, Scopus, JSTOR, of peer reviewed published articles from January 2000 to 2016 including situational reports of World Health Organization (WHO). Publication bias was minimized by searching reports from well recognized international public health agencies and the ZIKAV research database created by the Pan American Health Organization. The search words "Zika", "ZIKAV", and "Zika virus" were used. All authors independently screened and short listed abstracts using the search strategy.

2. ZIKAV epidemiology

2.1. Geographic distribution

ZIKAV was first isolated in 1947 from rhesus monkey in Uganda. The virus was later named after the geographic location, Zika Forest, where it was isolated [7]. The virus was first confirmed as a cause of human disease when three persons became ill in Nigeria in 1953 [8]. Thereafter, ZIKAV was associated with sporadic infections and only 13 cases were documented over the next 57 years [9–11]. It was thus astounding when the first major outbreak of ZIKAV was recognised in the Yap Islands of Micronesia in 2007 with approximately 5000 cases reported among a total population of 6700 [2]. French Polynesia also reported an outbreak of 32000 persons infected in 2013–2014 [4,12–16]. Subsequently, ZIKAV outbreaks occurred on other Pacific islands [4,15,16]. ZIKAV was first reported as causing an outbreak in the Western Hemisphere in 2014 in Chile's Easter Island [17]. The virus was subsequently detected in Brazil in March 2015 [6,18]. ZIKAV had spread to 14 Brazilian states by October 2015 and an estimated 1.3 million cases had occurred [19]. Officials in the Pan American Health Organization on May 2016 estimated as many as 550 million people at risk of ZIKAV infection in the Americas.

Recent results of phylogenetic and molecular clock analyses point towards an introduction of ZIKAV in Brazil as early as May 2013 [20]. However, ZIKAV transmission was only confirmed in the north-eastern states of Brazil in May 2015 [6]. This event was followed by a rapid spread throughout the country, and subsequently to most of the countries in the Americas. In 2016, it was reported that an outbreak of ZIKAV was occurring in the Americas, the Pacific and the Caribbean [21–23].

In December 2014, an outbreak of ZIKAV infection was reported in Haiti rural community [24]. In this outbreak, researchers were able to isolate the virus from three students at different locations in west of Port-au-Prince. The study with phylogenetic analysis suggested that the infection was wide spread in the communities. The viral sequencing showed genetic similarity and relations with ZIKAV from Brazil. Furthermore, the analysis showed the existence of at least three major African sub-lineages and established that the South American epidemic may have begun through the introduction of an initial ZIKAV outbreak in French Polynesia into Easter Island, then to the countries and territories in the Americas [24].

Similarly, in October 2015, the sera of four ZIKAV patients from Suriname were subjected for genomic sequencing and it was identified to be of the Asian genotype as opposed to the African lineage. The Suriname genotype shows over 99% protein and gene homology with the strain isolated from French Polynesia in 2013 [25].

In 2016, numerous countries have reported autochthonous ZIKAV transmission including Aruba, Barbados, Belize, Bolivia, Bonaire, Brazil, Cape Verde, Colombia, Costa Rica, Cuba, Curacao, Dominica, Dominican Republic, Ecuador, El Salvador, Fiji, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Jamaica, Korea, Federated States of Micronesia, Marshall Islands, Martinique, Mexico, New Caledonia, Nicaragua, Panama, Paraguay, Saint Lucia, Saint Martin, Saint Maarten, Saint Vincent and the Grenadines, Samoa, Suriname, Tonga, Trinidad and Tobago, and Venezuela [26–28].

The characterization of ZIKAV strains collected from six African and Asian countries, as published by researchers, showed that there are two geographically distinct lineages of the phylogenetic trees of the virus. The relationships and hence the epidemiological evidence of the Yap Island outbreak may confirm that it originated in South-East Asia [29].

According to the Pan American Health Organization surveillance data, the geographical distribution of ZIKAV has steadily widened since the virus was first detected in the Americas in 2015. Autochthonous ZIKAV transmission (mosquito borne infection) has been reported in 35 countries and territories of the region. In those countries and locations where the presence of competent mosquito vectors like *Ae. aegypti* have been identified, ZIKAV outbreaks and transmission are most likely to occur [1].

2.2. Zika case definitions

The WHO has issued interim case definitions of ZIKAV infections. These definitions identified three categories; *i.e.*, suspected, probable and confirmed ZIKAV cases [30]. A suspected case of ZIKAV is characterized by the presence of rash and/or fever with arthralgia, arthritis, or non-purulent conjunctivitis. A probable case requires these symptoms in conjunction with the presence of anti-Zika immunoglobulin M (IgM) antibodies and an epidemiologic link within two weeks prior to symptom onset to a region with local autochthonous transmission. A confirmed case of ZIKAV disease requires laboratory confirmation of recent ZIKAV infection by either presence of ZIKAV RNA or antigen in serum or other samples (*e.g.* saliva, tissues, urine, whole blood), or IgM antibody against ZIKAV positive and PRNT90 for ZIKAV with titre 20 and ZIKAV PRNT90 titre ratio 4 compared to other flaviviruses, and exclusion of other flaviviruses.

2.3. Methods of ZIKAV transmission

Human to human transmission of ZIKAV predominantly occur from the bite of an infected mosquito of the *Aedes* species [1,31]. ZIKAV RNA has been isolated in blood, semen, urine, saliva, amniotic fluid, breast milk and cerebrospinal fluid [15,27,32–37]. Transmission of ZIKAV has been suggested via other non-vector means such as sex, maternal-foetal transmission and blood transfusions [38–49]. However, no study described transmission of

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