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REVIEW

Zika virus: what, where from and where to?

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Summary

The significance of Zika virus as a clinically significant flavivirus has previously been under-recognised, until extensive outbreaks in Yap in 2007, French Polynesia in 2013 and the Americas since 2015. Although Zika virus infection is commonly asymptomatic or mild, emerging evidence suggests a strong link to microcephaly in babies and Guillain–Barré syndrome in adults. This article reviews the epidemiology, geographic distribution, basic virology, transmission, clinical presentation, potential complications, laboratory diagnosis, treatment and prevention of Zika virus infection. Education on mosquito avoidance measures and vector control efforts currently remain key to reducing risk of transmission, whilst further research is underway to develop antiviral therapies and vaccines.

Key words: Zika virus; flavivirus; *Aedes*; microcephaly; Guillain–Barré syndrome.

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INTRODUCTION

Zika virus (ZIKV) is a member of the genus *Flavivirus* of the family *Flaviviridae*. ZIKV was first isolated in a captive rhesus monkey in 1947 which was part of a sentinel surveillance program for sylvatic yellow fever virus (YFV) in the Zika forest of Uganda. The *Flaviviridae* also include dengue virus (DENV), YFV, West Nile virus (WNV) and Japanese encephalitis viruses (JEV).[1,2] MacNamara reported the first human cases of ZIKV infection in Uganda and the United Republic of Tanzania in 1952.[3] In 1964 Simpson cast doubt on the first human case, suggesting this first case was most likely a misdiagnosed Spondweni virus infection.[4]

Before the outbreak in the Federated States of Micronesia (Yap) in 2007, there were only a handful of sporadic human cases reported across Africa and Asia, (including Pakistan, Malaysia and Indonesia), although there was likely underascertainment of cases. Serological studies suggest that ZIKV was present in India in the early 1950s.[5] The movement of ZIKV out of Africa and Asia in recent times has highlighted potential for widespread transmission of disease, facilitated by competent mosquito vectors and susceptible populations.

On 1 February 2016, the World Health Organization (WHO) declared ZIKV as a Public Health Emergency of International Concern following suspected links between ZIKV infection and congenital malformations including microcephaly and neurological conditions such as Guillain–Barré syndrome (GBS). Using Shepard's and Bradford Hill criteria, Rasmussen *et al.* proposed that there is sufficient evidence to infer a causal relationship between ZIKV and microcephaly in the absence of an alternate cause,[6] which has been further supported by laboratory studies of cellular and tissue targets for ZIKV.[7,8] A case-control study of patients with GBS during the ZIKV outbreak in French Polynesia also provides circumstantial evidence of links between GBS and ZIKV infection in adults.[9,10] Education on mosquito avoidance measures and vector control efforts remain key to reducing risk of transmission, particularly as there are no vaccines or antiviral treatments currently available for routine clinical use.

GEOGRAPHIC DISTRIBUTION

Since the description of ZIKV in 1947 there have been small clusters of cases in other African countries in the late 1940s and Asia in the 1970s, with only 14 cases reported in the literature of human ZIKV infection worldwide prior to the Yap outbreak in 2007.[11,12] Following its discovery, serological studies showed that ZIKV is endemic in East and West Africa.[5] Duffy *et al.* reported almost three-quarters of the population of Yap in the Federated States of Micronesia were infected with ZIKV in 2007.[13]

The next outbreak occurred six years later in 2013, with the presence of competent mosquito vectors and susceptible populations leading to a rapid increase in ZIKV infection spreading to Micronesia and Polynesia. In French Polynesia, it was estimated that 11% of the population were infected (although cases were not always laboratory-confirmed) during the outbreak that started in October 2013,[14] with spread to Cook Islands, New Caledonia and Easter Island.[15] Fauci and Morens note that ZIKV epizootics closely followed *Aedes* transmitted epizootics including chikungunya virus (CHIKV).[16]

Aedes aegyptii is a ZIKV competent vector that is present across Latin America. In February 2014, the national authorities of Chile confirmed the first case of autochthonous transmission of ZIKV on Easter Island.[2] Initially cases were identified in north-eastern Brazil, with autochthonous transmission being established by May 2015, marking the beginning of the extensive Brazilian[2] and South American outbreaks. It is unknown when and by what means ZIKV was introduced into South America. Brazil had seen an increase in international passenger arrivals from countries with reported ZIKV outbreaks in the two years prior from 3775 passengers per month in early 2013 to 5754 passengers per month in

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2014,[17] and overall the number of foreign visitors increased by 132% compared to the preceding 12 months over this period.[18] Hypotheses surrounding the introduction of ZIKV include transmission via a viraemic traveller from Polynesia during the 2014 FIFA World Cup in Brazil[19] or the Va'a canoe event held in August 2014 in Rio de Janeiro;[20] Faria *et al.* offered an alternative hypothesis, suggesting introduction during the Confederations Cup soccer tournament in June 2013 or earlier.[17] The delay in the identification of ZIKV as the causative pathogen in the recent outbreak in Brazil may have been due to the misdiagnosis of ZIKV as DENV or CHIKV which can present with similar, albeit less severe symptoms. This may also account for the delay between the hypothesised time points when ZIKV was first introduced and actual recognition of the outbreak.

Suitable climatic conditions have contributed to the epidemic currently seen in Brazil with Bogoch *et al* reporting estimates of up to 1,300,000 cases of ZIKV infection.[21] A mobile population along with the above-mentioned vector and climatic conditions has seen ZIKV spread further throughout Latin American and the Caribbean, perpetuating the transmission cycle with over 20 countries and territories reporting autochthonous transmission, including recently in Singapore (Table 1, Fig. 1).[21–24]

There have been increasing reports of ZIKV infection cases exported to the United States of America (USA) and Europe.[25] The first case of locally transmitted ZIKV in the USA, in the outbreak in Latin America, was reported in December 2015 in the US territory of Puerto Rico. Since then local transmission has also been reported in continental USA in Miami, Florida, as well as US territories in the Pacific Ocean including United States Virgin Islands and American Samoa.[26] France has previously documented local mosquito-borne transmission by *Aedes albopictus* of other arthropod-borne virus (arboviruses) including DENV and CHIKV, highlighting the potential risk of the establishment of local transmission of ZIKV in France and Southern Europe under the right circumstances.[27]

November 2015 marked the re-emergence of ZIKV in Africa with the outbreak in Cape Verde where previously there had only been sporadic cases. However, the strain identified was the same as circulating in South America, the introduction likely related to tourism as Cape Verde is a popular destination for Brazilians.[5]

Table 1 Region and countries with current autochthonous ZIKV transmission[4]

Region	Countries
Oceania/Pacific Islands	American Samoa, Fiji, Marshall Islands, The Federated States of Micronesia, New Caledonia, Samoa, Tonga
Asia	Philippines, Vietnam, Singapore
South America	Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Suriname, Venezuela
Central America	Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama
The Caribbean	Aruba, Barbados, Bonaire, Cuba, Curacao, Dominica, Dominican Republic, Guadeloupe, Haiti, Jamaica, Martinique, Commonwealth of Puerto Rico, Saint Martin, Saint Vincent and the Grenadines, Trinidad and Tobago, US Virgin Islands
Africa	Cape Verde

TRANSMISSION

Zika virus is an arbovirus originally transmitted via a sylvatic cycle mainly involving the mosquito vector and non-human primates, with humans occasionally a secondary host.[28] ZIKV has been detected in other mammals such as water buffalos, elephants and zebras.[29] The primary mode of transmission of ZIKV is via the bite of an infected *Aedes* mosquito.[30] Ayres detected the presence of ZIKV by reverse transcriptase polymerase chain reaction (RT-PCR) in Senegal in ten species from the genus *Aedes*, as well as *Mansonia uniformis*, *Anopheles coustani*, and *Culex perfuscus*. It is postulated these species contribute to the zoonotic cycle, however ZIKV detection in these species alone is not sufficient evidence that they are significant vectors.[31] Only a subset of *Aedes* mosquitoes are competent transmission vectors including *Ae. aegypti, Ae. albopictus, Ae. polynesiensis* and *Ae. hensilii.*[12,19,30,32–35]

ZIKV ribonucleic acid (RNA) has been isolated from human body fluids including blood, urine, semen, saliva, cerebrospinal fluid, amniotic fluid, breast milk, placenta and brain tissue,[36–41] which may act as a mechanism of non-vector borne transmission. Currently the exact incubation period for ZIKV infection is unclear, but has been suggested to be approximately 7 days (range of 3–10 days).

Perinatal transmission

Perinatal transmission of arboviruses has been reported for DENV,[12–16] CHIKV,[19,20] WNV,[17,18] YFV[21,22] and more recently ZIKV, although the exact mechanisms have yet to be elucidated.[4,14] Trans-placental, during delivery, during breastfeeding and through close contact between mother and newborn baby are all possible modes of perinatal transmission. Transmission via breast milk has been reported in other flaviviruses such as DENV,[42] but no cases of breast milk transmission have been reported to date. Whilst ZIKV RNA has been detected in breast milk,[14] it remains unclear whether transmission can occur during breastfeeding.

Sexual transmission

There is evidence of sexual transmission of ZIKV,[43] with ZIKV RNA being detected in semen[44–46] up to 188 days after the onset of a febrile illness consistent with ZIKV infection.[7] The possibility of sexual transmission of ZIKV was first reported in the wife of an American scientist who returned from Senegal in 2008. The index case and his wife demonstrated symptoms consistent with ZIKV infection 6 and 10 days after the former's return, respectively. Paired acute and convalescent-phase sera collected from the index case and his wife showed serological evidence of ZIKV infection by haemagglutination inhibition, complement fixation and plaque reduction neutralisation assays. Sexual transmission was postulated as the most likely route of transmission as the pair reported unprotected vaginal intercourse in the first few days upon the index case's return, and there was no evidence of infection in other members of the same household who may have been exposed to other bodily fluids such as saliva.[45]

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