International Journal of Infectious Diseases 48 (2016) 85–90

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Review

Zika virus, vectors, reservoirs, amplifying hosts, and their potential to spread worldwide: what we know and what we should investigate urgently

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ARTICLE INFO

Article history:
Received 24 February 2016
Received in revised form 24 April 2016
Accepted 13 May 2016

Corresponding Editor: Eskild Petersen, Aarhus, Denmark.

Keywords:
Zika virus infection
Vector
Animal
Aedes
Anopheles
Migrants

SUMMARY

Objectives: The widespread epidemic of Zika virus infection in South and Central America and the Caribbean in 2015, along with the increased incidence of microcephaly in fetuses born to mothers infected with Zika virus and the potential for worldwide spread, indicate the need to review the current literature regarding vectors, reservoirs, and amplification hosts.

Vectors: The virus has been isolated in Africa in mosquitoes of the genera *Aedes*, *Anopheles*, and *Mansonia*, and in Southeast Asia and the Pacific area in mosquitoes of the genus *Aedes*. *Aedes albopictus* has invaded several countries in Central Africa and all Mediterranean countries, and continues to spread throughout Central and Northern Europe. The wide distribution of the virus in animal hosts and vectors favors the emergence of recombinants.

Animal hosts: The virus has been isolated in monkeys, and antibodies have been detected in domestic sheep, goats, horses, cows, ducks, rodents, bats, orangutans, and carabaos.

Conclusions: It is a public health imperative to define the domestic and wild animal reservoirs, amplification hosts, and vector capacity of the genera *Aedes*, *Anopheles*, and *Mansonia*. These variables will define the geographic distribution of Zika virus along with the indicated timing and scale of the environmental public health interventions worldwide.

1. Introduction

A widespread epidemic of Zika virus (ZIKV) infection was reported in 2015 in Central and South America and the Caribbean. This epidemic was associated with an increased incidence of microcephaly in fetuses born to mothers infected with ZIKV, with Brazil being the country most affected by both epidemics.[1–4] This rare, devastating, and untreatable complication of the fetus was declared a public health emergency of international concern (PHEIC).[1–4] The neurotropism of the virus was recognized early,[5] and this has been evident in the recent rise in microcephaly incidence in Brazil .[3,4,6] The virus has been found in the amniotic fluid of two pregnant women with fetuses suffering a reduction in the circumference of the head.[6] The virus has also been found in the central nervous system (CNS) of fetuses,[3,4] with negative tests excluding other congenital infections.[6]

Thirty-two countries and territories of the Americas are affected by ZIKV, in addition to Rio de Janeiro, Brazil, where the Olympics and Paralympics are due to be held in August 2016; this poses a threat to international travelers and the local host-country residents .[2] Local transmission has not been observed in Europe yet, and there is a global alert for travelers returning from endemic countries with symptoms consistent with ZIKV infection.

The immediate public health measures feasible at present, in the absence of a vaccine, are interventions relevant to the vector and a better understanding of the wide and unknown range of possible amplification hosts. Two main concerns prompted this exhaustive review of the literature: the historical paradigm of the introduction of yellow fever virus from Africa to the Americas, where it adapted to local sylvatic vectors and primates,[7] and the fact that we do not yet know which could be the competent vectors or amplifying hosts of ZIKV in temperate climate regions, thus hampering any future surveillance and intervention control programs. The range of vectors and animals in which the virus has been detected worldwide was reviewed in order to assess the likelihood of an established circulation of the virus in novel areas.

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http://dx.doi.org/10.1016/j.ijid.2016.05.014

2. Epidemiology

ZIKV is an emerging vector-borne pathogen that was first isolated in 1947 in a sentinel rhesus macaque monkey and again in 1948 from a pooled specimen of *Aedes africanus* mosquitoes from the Zika Forest in Uganda.[5] During the years 1947 through 2007, only serological data, entomological data, and the diagnosis of 14 human cases with viral isolation or serology were reported from Asia and Africa.[8–13] It has been speculated that among those human cases, a few may have represented an unrecognized outbreak. One unrecognized outbreak took place in 1977–1978 in Indonesia.[14,15] The first outbreak outside of Africa and Asia occurred in 2007, on Yap Island in the Federated States of Micronesia, with 49 confirmed cases and 73% of residents aged ≥3 years infected according to IgM seropositivity.[16,17] There are limitations to the seroprevalence studies resulting from the cross-reactive nature of ZIKV with dengue and other flaviviruses. However, IgM antibodies against dengue virus persist for up to 12 weeks, and the specimens for the IgM measurement were collected during a 12-week period from April 1 through July 31, 2007. During this time, the specimens had been collected within 10 days from symptom onset. They tested positive only for ZIKV RNA and not for dengue or other flavivirus RNA.[17]

From 2007 through 2013, no new instances of human seropositivity or disease were reported. In 2013, the virus reemerged in French Polynesia, and from 2013 through 2014, it disseminated to the Cook Islands, New Caledonia, Easter Island, and throughout the Pacific.[18] French Polynesia reported 396 epidemiologically confirmed cases and 29 000 suspected cases.[19] The virus has been isolated or has had its nucleic acid extracted by PCR and then sequenced from samples collected in Southeast Asia (e.g., Thailand, Indonesia, Cambodia[20–22]). All strains collected in Asia and the Pacific belong to the Asian lineage and are closely related, indicating that the virus was present in the area for several years but remained undetected, as the clinical manifestations resemble those of other known endemic arboviruses such as dengue virus and chikungunya virus.[20] However, the possibility that the virus has spread to the Pacific and Southeast Asia successively, causing a wave of clinical disease and subsequent detection of the virus, cannot be excluded.[20]

In March 2015, Brazil notified the World Health Organization of an illness compatible with but not suspected to be a ZIKV infection. Soon after, in May 2015, it documented the first confirmed ZIKV transmission in mainland South America, along with the assumption that the virus had been introduced to the country via the Va'a World Sprint Championship canoe race held in Rio de Janeiro in August 2014.[23] Four Pacific countries participated (French Polynesia, New Caledonia, the Cook Islands, and Easter Island). The virus was subsequently transferred from the major cities across the country via the infected Brazilian participants and spectators who returned to their home towns.[24] The strain found in Brazil was phylogenetically closer to the strain in the French Polynesia outbreak of 2013–2014, with both belonging to the Asian lineage. It is estimated that 440 000 to 1.3 million cases had been reported as of December 2015.[23]

3. Virus

ZIKV is an approximately 11-kb single-stranded, positive-sense ribonucleic acid (RNA) virus of the *Flaviviridae* family. It is related to dengue, West Nile, and Yellow fever viruses and is a member of the Spondweni serocomplex, whose transmission cycle consists mainly of vectors from the *Aedes* genus mosquitoes (*A. furcifer*, *A. taylori*, *A. luteocephalus*, and *A. africanus*) and monkeys.[25,26] Phylogenetic analyses have revealed three lineages: two African lineages, i.e., the MR 766 cluster and the Nigerian cluster, and one Asian lineage (Table 1).[16,27,28]

Table 1
Lineages of Zika virus

1. African lineages (two clusters)	2. Asian lineage
a. MR 766 cluster	One Asian genotype
b. Nigerian cluster	

All lineages share a common origin in Uganda early in the 20th century, from where it dispersed west to West Africa via two introductions and east to Southeast Asia and then to the Pacific as follows: (1) a relative of the MR 766 prototype strain was introduced from Uganda to Côte d'Ivoire in 1940 and from there to Senegal in 1985 resulting in the MR 766 lineage; (2) a relative of the Nigerian strain was introduced from Uganda to the Central African Republic and Nigeria around 1935, and from Nigeria to Senegal and Côte d'Ivoire around 1960, forming the Nigerian lineage; and (3) a ZIKV cluster was probably spread from Uganda to Malaysia in 1945, making its way to Micronesia sometime around 1960, where it formed the Asian lineage.[25] However, it is unknown whether to attribute this migration only to human and vector movements, or also to birds carrying the virus along migratory routes.

Regarding the African lineages, the phylogenetic analysis of ZIKV strains collected from 1968 through 2002 in Senegal, Côte d'Ivoire, Burkina Faso, and the Central African Republic indicated that there are more recombinants than in other flaviviruses; however, they all clustered in the two African lineages, the MR 766 cluster and the Nigerian cluster.

4. Transmission

Transmission has been demonstrated to occur mostly via infected female mosquito vectors of the *Aedes* genus (*Culicidae* family). Transmission is mainly urban and sylvatic, with humans serving as primary amplification hosts in areas where there are no non-human primates.[17] The latter constitute the amplification host in a sylvatic cycle.[17] Mosquitoes, as hematophagus arthropods, acquire the virus via a blood meal, and they host it throughout their life-span without being affected. They transmit it to the next amplification host, i.e., their target during the next blood meal.[29] Other routes of transmission are sexual intercourse,[30–33] perinatal transmission from mother to fetus,[34] and blood transfusion.[35] Breast feeding has not been reported as a mode of transmission.

5. Clinical manifestations

The majority of infections are subclinical, estimated to reach 81% of infected individuals. The clinical manifestations mimic those of other arboviral infections, e.g., dengue and the chikungunya endemic in tropical areas (West Africa, Southeast Asia, Pacific area, South America).[2,17,22,36] A macular or papular rash (90%), fever (65%), arthritis or arthralgia (65%), non-purulent conjunctivitis (55%), myalgia (48%), headache (45%), and retro-orbital pain (39%) have been the most commonly reported symptoms,[20] followed by anorexia, vomiting, diarrhea, stomach aches, dizziness, leg pain, lymphadenopathy, and hypotension. No deaths, hospitalizations, or hemorrhagic manifestations have been documented.[17,20] In the Indonesian outbreak among humans in 1977–1978, no rash was reported.[14] In Eastern Nigeria, two patients presented jaundice.[37]

There was early evidence of neurotropism of the virus,[5] which spares all body tissue except for nervous tissue.[38] Intracerebral inoculation of infected human blood in suckling albino Swiss mice was followed by proliferation of the virus in their nervous tissue.[8] ZIKV infection has been associated with Guillain–Barré syndrome (GBS) in Martinique and French Polynesia.[39,40] During the ZIKV outbreak in French Polynesia in 2013–2014, the incidence of GBS