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## The Zika outbreak of the 21st century

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### ABSTRACT

The Zika virus outbreak has captivated the attention of the global audience and information has spread rapidly and wildly through the internet and other media channels. This virus was first identified in 1947, when it was isolated from a sentinel rhesus monkey placed by British scientists working at the Yellow Fever Research Laboratory located in the Zika forest area of Uganda, hence its name, and is transmitted primarily by the mosquito vector, *Aedes aegypti*. The fact that the rhesus macaque is an Asian species being placed in an African forest brings to mind the possibility of rapid adaptation of the virus from an African to Asian species, an issue that has not been considered. Whether such adaptation has played any role in acquiring pathogenicity due to cross species transmission remains to be identified. The first human infection was described in Nigeria in 1954, with only scattered reports of about a dozen human infections identified over a 50-year period. It was not until 2007 that Zika virus raised its ugly head with infections noted in three-quarters of the population on the tiny island of Yap located between the Philippines and Papua New Guinea in the western Pacific Ocean, followed by a major outbreak in French Polynesia in 2013. The virus remained confined to a narrow equatorial band in Africa and Asia until 2014 when it began to spread eastward, first toward Oceania and then to South America. Since then, millions of infected individuals have been identified in Brazil, Colombia, Venezuela, including 25 additional countries in the Americas. While the symptoms associated with Zika virus infection are generally mild, consisting of fever, maculopapular rash, arthralgia and conjunctivitis, there have been reports of more severe reactions that are associated with neurological complications. In pregnant women, fetal neurological complications include brain damage and microcephaly, while in adults there have been several cases of virus-associated Guillain-Barre syndrome. The virus was until recently believed to only be transmitted via mosquitoes. But when the Zika virus was isolated from the semen specimens from a patient in Texas, this provided the basis for the recent report of possible sexual transmission of the Zika virus. Due to the neurological complications, various vectors for infection as well as the rapid spread throughout the globe, it has prompted the World Health Organization to issue a global health emergency. Various governmental organizations have recommended that pregnant women do not travel to countries where the virus is epidemic, and within the countries affected by the virus, recommendations were provided for women of childbearing age to delay pregnancy. The overall public health impact of these above findings highlights the need for a rapid but specific diagnostic test for blood banks worldwide to identify those infected and for the counseling of women who are pregnant or contemplating pregnancy. As of this date, there are neither commercially licensed diagnostic tests nor a vaccine. Because cross-reactivity of the Zika virus with dengue and Chikungunya virus is common, it may pose difficulty in being able to quickly develop such tests and vaccines. So far the most effective public health measures include controlling the mosquito populations via insecticides and preventing humans from direct exposure to mosquitoes.

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### 1. Introduction

The Zika virus has found its way into the public consciousness, as it has recently been associated with brain damage in the offspring of infected pregnant women. The news outlets have

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latched onto this hot item and have been bombarding the public with information that is both legitimate and misleading. The internet age has allowed rapid dissemination of such information, therefore causing rapid reactions or responses by both national and international agencies, regulatory bodies and professional organizations. The story of the impact the Zika virus has played upon humanity is an interesting and unique one, which has led to the government issuing non-traditional recommendations, in an effort to ensure the public's safety and health. Tracing the sequence of events from the discovery of the virus to the current state of affairs provides a useful learning tool that would allow effective responses during unexpected pandemics. Although there are over 325 published articles associated with the Zika virus, the majority coming out of Uganda, there is still little known about the potential of the virus [1].

The Zika virus was identified over 50 years ago in Africa where it is reasoned to have originated. It is known to have spread to various geographic areas of Asia and the Pacific Islands, with the most recent spread eastward to the Americas. Earlier, symptoms associated with infection included a mild response, which included fever and fatigue, until this year when it was reported that pregnant women, primarily Brazilian women, that tested positive with the Zika virus had fetuses born with brain defects. After Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory virus (MERV), the Ebola outbreak, and recurrent re-emergence of measles, influenza, dengue and cholera throughout the globe, the world now has a new enemy to contend with, serving as a reminder that human beings live in a complex relationship with other organisms in an ecosystem that is often unpredictable [2]. The continuous encroachment of otherwise forested and/or remote habitats by humans in search of new space for housing and adventure combined with the ever increasing speed of inter-continental air travel logarithmically increases the likelihood of the jumping of microbial species from its natural habitat to urban locations. This is a reality to be faced by those involved in public health safety and will remain a continuing challenge to health care providers worldwide.

## 2. History

Several viruses were reported to have been isolated by a team of British and American scientists that were in charge of the Yellow Fever Virus Research Institute housed in Entebbe, Uganda during the late 1930's to late 1940's primarily with the aim of isolating yellow fever viruses (YFV) [3]. In efforts to isolate the YFV, these scientists placed Asian species rhesus macaques (*Macaca mulatta*) in sentinel cages atop forest canopy level platforms in the Zika Forest area located near Entebbe, Uganda, presumably in a location where they could serve as potential hosts for the local mosquito population known to be vectors of the YFV. Blood samples isolated from one of these "sentinel" rhesus macaques (monkey 766) when injected into the brains of Swiss albino mice led to sickness of these mice. Homogenates of brain tissues from these sick mice led to the isolation of several filterable viruses, amongst one that was called the Zika virus 766 because of the forest and the number of the monkey (hence, its name) [4,5]. These viruses were also isolated from mosquito populations from the same location and thus reasoned to be circulating and being kept endemic by virus host interactions between the indigenous monkey species (that include 13 species with the colobus species monkey being predominant) and mosquitoes. The fact that the virus was isolated from "sentinel" Asian rhesus macaques implies that there must have been an adaptation of the virus from the African monkey species to the Asian monkey species (jumping of species). Whether such adaptation was instrumental in further transmission of this virus and whether such adaptation led to increased pathogenicity remains

unknown. It should be noted that sera collected from blood samples of several local individuals residing in the same area during the same time period were found to contain antibodies against the Zika virus presumably suggesting that the virus was already circulating in the human population. However, there were no reports of any disease. What is not clear is the specificity of the antibody test that was utilized at the time since there is considerable cross reactivity among the flaviviruses. It was first isolated from a human in 1969 in Nigeria, though the illness caused by the virus, Zika fever or Zika disease has been known to infect humans since the early 1950s [6]. A time line of the history of the Zika virus is shown in Fig. 1; the countries involved are shown in Table 1.

Early reports of the Zika virus identified very rare cases of human disease. Lanciotti stated in a 2008 review that "Historically, Zika has rarely been associated with human disease" [7]. Early reports of epidemics were reported primarily in the South Pacific and in Southeast Asia. The Yap Island reported 185 cases of probably Zika infection and a seropositivity rate of greater than 74% of the population in 2007.

## 3. Biology of the Zika virus

### 3.1. Classification

The Zika virus belongs to the family Flaviviridae and the genus Flavivirus. Other Flaviviruses include yellow fever, dengue, West Nile and Japanese encephalitis viruses [8,9]. Flaviviruses belong to a group of viruses labeled as "arboviruses", which is a descriptive term that refers to hundreds of RNA viruses which rely on arthropods such as mosquitoes or ticks for transmission. Arboviruses (arthropod borne viruses) cause some of the most devastating diseases in humans and animals worldwide. The families of RNA arboviruses include Bunyaviridae, Flaviviridae, Reoviridae, Rhabdoviridae, and Togoviridae. The arboviruses are acquired orally by their hematogenous vectors in the form of a blood meal of an infected vertebrate host. These viruses are non-pathogenic to the vector but have to be able to survive in a live form in the vector which then transmits via saliva deposition into a new vertebrate host. This cycle is important to remember since the details of how the virus survives in the vector host and whether it replicates in the vector host, and if it replicates, the cell types that it infects in the vector and whether the virus changes in any form in the vector host (such as glycosylation of its envelope for example) are all important issues that influence the ability of the vector to transmit infection including the Zika virus. Evidence for recombination of the virus has already been documented to have potentially occurred by transmission of the virus via a different species of mosquitoes [10]. The Zika virus is closely related to the *Spondweni* virus. There are a total of seven groups of mosquito-borne flaviviruses, according to the International Committee on Taxonomy of Viruses (ICTV). The groups are categorized based on antigenic and genetic considerations. The genus Flavivirus consists of 39 different mosquito-borne viruses [11].

### 3.2. Structure of the Zika virus

The Zika virus is composed of a positive sense, single strand RNA genome. It is an enveloped, icosahedral virus that is a member of the Spondweni clade. The Zika virus is a positive polarity RNA virus with a genomic size of about 11 kb [12]. The single open reading frame sequence of its RNA genome encodes a polyprotein which constitutes the structural architecture of the virus [13]. This polyprotein contains 3 components, including a capsid (105 aa), membrane and pre-membrane portion (187 aa) termed C, M and P, respectively. There is also an envelope protein (E, 505 aa) and an

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