

## Zika Virus Disease

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### ABSTRACT

*In its initial outbreaks, Zika virus disease emerged as a threat to the populations concerned. This review covers the history of the disease, global burden, transmission, surveillance and future policy implications.*

### Background

Zika virus disease is a self-limiting disease caused by Zika virus, an emerging arthropod-borne virus or arbovirus that belongs to the *Flavivirus* genus and the *Flaviviridae* family of viruses [1]. The virus was first identified in the year 1947 in a rhesus monkey within the Zika forest in Uganda during the course of a routine yellow fever surveillance and later isolated in the *Aedes Africanus* mosquito a year later within the same region [2]. The first report of human infection with the virus was made in the year 1952 and up until 2007 only 14 cases had been documented [3], a possible reason as to why the disease was of less concern to the human population despite the presence of the virus in Africa and Asia [3]. However, with no targeted surveillance on the virus during that period, it is possible that multiple human infections existed but were undetected.

The first major outbreak of the disease outside Africa and Asia occurred in the year 2007 in the Yap Island, Micronesia [4]. In this outbreak, Zika virus infection was confirmed in 49 cases and 73% of the 6892 inhabitants of the island who were older than 3 years were suspected cases [4,5].

The second major epidemic occurred further eastward from the first outbreak, this was in the French Polynesia in the year 2013 where more than 400 cases were confirmed [3,4]. The higher magnitude of this outbreak was partly attributable to a higher density of competent mosquito vectors and low level of pre-existing immunity to the disease within the affected region [4]. Subsequent outbreaks in the years 2013 – 2014 were reported in other islands within the South Pacific region that included the Cook Islands, the Easter Island and New Caledonia [3].

The largest epidemic of the disease occurred in the years 2015-2016 in Brazil, with an estimated 1,500,000 suspected cases [4,5]. This later spread to other regions in the Americas.

Currently, the World Health Organisation (WHO) has categorised countries according to their status of Zika virus transmission into categories 1, 2, 3 and 4 [6]. Category 1 countries are areas with new introduction of the virus since 2015 or areas where the virus has been reintroduced, with on-going transmission, these include countries such as Angola, Argentina and the Marshall Islands. Category 2 countries are areas with evidence of virus circulation before 2015 or areas with on-going transmission that's no longer in the re-introduction phase, these include countries such as Burkina Faso, Brazil, Bangladesh and Cambodia. Category 3 countries are areas with interrupted transmission with potential for future transmission, they include the Cayman Island and American Samoa. Category 4 countries are areas with established competent vectors but no documented infection; these include Benin, Uruguay, Myanmar and Australia [6].

### Burden of Disease

Zika virus disease is generally self-limiting with mild symptoms of fever, rash, arthralgia, arthritis and conjunctivitis [4]. However, its suspected complications of microcephaly in congenital infections and Guillain-Barre Syndrome are of great concern with pregnant women and all adults, respectively [7,8].

GBS, an autoimmune condition that results in muscle paralysis and possible death, was initially associated with Zika virus during the French Polynesia outbreak where an increase in its incidence was noted [9].

Microcephaly, a congenital condition characterised by abnormal brain development and reduced brain tissue, is the greatest concern with Zika virus infection amongst pregnant women [4]. Its link with the virus was first noted during the outbreak in Brazil in 2015 where similarly, an increase in the incidence of microcephaly was observed in a temporal and geographic association with Zika virus infection [10].

### Identification of Disease

The diagnosis of Zika virus infection can be either clinical or laboratory and often includes ruling out infection with other flaviviruses such as Dengue and Chikungunya that have similar presentations [11].

Laboratory diagnosis of Zika virus infection can be achieved through samples of blood, urine, breast milk, vaginal secretion, cerebrospinal fluid, saliva, semen and amniotic fluid [11]. These samples can be analysed through reverse transcriptase polymerase chain reaction (RT-PCR), serology or viral isolation, the choice of which depends on the sample available, the technical capability of the laboratory involved and the goal of the analysis [12].

RT-PCR is the most reliable and definitive diagnostic method but must be performed within the first 7 days as viremia is transient. Serological tests can be used to identify virus specific antibodies for as long as 2 months after infection but this must be confirmed with a plaque reduction neutralization test (PRNT) that is more antibody specific or by using paired acute and convalescent sera, both strategies aim to rule out cross-reactivity with other flaviviruses [11].

### Transmission: The role of the agent, vector, host and the environment

The transmission of Zika virus can occur through either a vector or a non-vector transmission route [4]. The main hosts for the virus are humans and non-human primates such as apes, monkeys and orang-utans [13]. However, anti-zika antibodies have also been detected in domestic animals such as goats, sheep, horses and ducks and the role of these animals as amplification hosts or reservoirs for human infection is not well understood [13].

### Vector transmission

Vector transmission of Zika virus occurs through the mosquito vector and is the predominant route for both human and non-human infection [4]. It can occur through two distinct cycles, a sylvatic or enzootic cycle in non-human primates and an urban-suburban cycle in the human population [4].

The viability of this transmission route depends greatly on the host's competence, which influences the host's ability to attain sufficient viremia for subsequent mosquito infection, the specific mosquito's vector competence, which influences the intrinsic ability of the vector to transmit the virus and the mosquito's vectorial capacity, which is the vector's ability to transmit the virus in a given location at a specified time [14]. The mosquito's vector competence is influenced by genetic variations in the virus, genetic

variations in the mosquito vector itself as well as its population density within a particular environment [4].

The predominant human vectors are the *Aedes* genus of mosquitoes, specifically the *A. aegypti* and *A. albopictus*. However, the *A. polynesiensis* and *A. hensilli*, more abundant in South East Asia, were also implicated in the French Polynesia and Yap Island outbreaks, respectively [14]. *A. aegypti* has a high vectorial capacity as it often lives in close association with humans and tends to bite multiple humans in a single blood meal [14].

The main vectors in non-humans are the *Aedes* subgenera *stegomyia* and *diceromyia* [14]. The virus has also been identified in other mosquito species such as *Anopheles coustani*, *Mansonia uniformis* and *Culex perfuscus*, however the former two have low vector competence and are hence unlikely to transmit the virus whereas the latter has a low vectorial capacity and its viral transmission is also unlikely [14].

The sylvatic cycle exists within non-human primates such as apes and monkeys in the wild and transmission is through the forest dwelling species of mosquitoes, the *Aedes* subgenera *stegomyia* and *diceromyia* [4]. This cycle exists predominantly within tropical Africa, possibly as a result of a more favourable host and vector competence [15].

The urban-suburban cycle, thought to cause and sustain epidemics, exists within the human population in urban areas. Humans serve as the carriers and source of the virus for the uninfected mosquito vector that predominantly bites during the day [16]. In this cycle, the virus undergoes an intrinsic period of incubation for 4-5 days once inoculated into the human host after a blood meal, during which viral replication occurs in the skin dendritic cells, facilitating the transmission of the virus to the bloodstream via the regional lymph nodes [17]. A subsequent extrinsic period of incubation for 8-12 days occurs in the mosquito vector once the virus is picked up during a blood meal from an infective host, disseminating to the vector's saliva for subsequent infection of other susceptible and competent hosts [5].

The distribution of the vector and hence disease pattern globally is influenced by prevailing environmental conditions [18]. The mosquito vectors described above exist predominantly within the warm and humid tropical and sub-tropical regions, explaining a corresponding zone of disease transmission globally across Africa, South East Asia, South Pacific, South America and parts of North America [19]. However, *A. albopictus*, a more invasive vector that can survive in temperate regions in both rural and urban areas, poses a great threat in extending the range of Zika virus transmission to temperate areas in North America and Europe, this being further compounded by the consequence of global warming [5].

Increase in temperature and humidity has a positive influence on the mosquito vector's survival, resulting in its abundance and enhanced competence [20]. Temperature increase further shortens the extrinsic incubation period in mosquitoes enhancing viral

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replication and is similarly associated with higher feeding by the mosquito that enhances viral transmission [21].

### Non-vector transmission

The non-vector transmission of Zika virus can occur through mother-to-child transmission, sexual transmission, blood transfusion or direct transmission [4].

The vertical transmission of Zika virus from an infected woman to her unborn foetus can occur during all trimesters of pregnancy. The virus has the ability to cross the placental barrier and infect foetal neuronal tissue as evidenced by the detection of viral RNA and antigens in foetal brain tissue as well as in the amniotic fluid [12]. Transmission in the early trimesters of pregnancy poses a significant risk of microcephaly to the foetus, several reports of which marked the Latin America outbreak in 2015 and subsequent cases being reported in North America and South East Asia [10]. Viral RNA has also been detected in breast milk [22], although transmission from mother to child during breast-feeding is still uncertain.

Sexual transmission of Zika virus has been reported in several cases involving travellers from endemic areas [23,24]. Male to female transmission is the predominant mode and the fact that viral RNA can persist in semen for as long as 188 days from the initial onset of symptoms [25] raises more concern on the magnitude of threat posed by this route of transmission.

Blood transmission of other flaviviruses such as Dengue, Yellow Fever and Chikungunya has been reported [26], making the transmission of Zika virus through blood transfusion also possible.

Direct transmission of Zika virus, an idea supported by the detection of the virus in saliva and nasopharyngeal swabs, is thought to occur through contact with the skin or mucous membranes of an infected host [4,27]. Although, this is not a common route of transmission.

### Surveillance, Prevention and Control

The effective surveillance of Zika virus disease requires a multi-faceted approach that involves vector surveillance, disease surveillance and birth defects surveillance. Data collected from surveillance is instrumental in tracking the spread of Zika virus, addressing the spectrum of outcomes that are linked with Zika during pregnancy, updating recommendations for patient care and enhancing the prevention of Zika virus infection in pregnant women [28].

Vector surveillance and management plays a central role in controlling vector transmission of the disease [16]. On a large scale, mosquito vector surveillance generates data on the location and possible population density of the *Aedes* mosquito vector, this informs the initiation of strategies such as the use of larvicides, use of adulticides and the elimination of identified breeding grounds [30]. At a domestic level, vector control is thought to be the most effective prevention strategy in endemic areas and can be achieved through the use of insect repellents that contain DEET or icaridin, use of window screens, use of bed nets, appropriate dressing to

minimise vector contact, air conditioning and the elimination of household debris that may facilitate mosquito breeding [5].

Disease surveillance involves the identification of cases of Zika virus infection in a given population. Confirmed cases are identified through laboratory testing whereas suspected and probable cases are identified based on the clinical presentation, travel history and proximity to confirmed cases. The Centre for Disease Control and Prevention recommends Zika virus testing for anyone with possible Zika virus exposure and was recently symptomatic of disease, on pregnant women who have a possible exposure and are symptomatic, on asymptomatic pregnant women who have an ongoing exposure and on pregnant women with possible exposure and a fetal ultrasound that is suggestive of congenital Zika virus infection [30].

In addition to the vector control methods, to prevent Zika virus infection in pregnant women it is recommended that they avoid travel to Zika endemic areas and practice abstinence or use of condoms if the partner is symptomatic of disease was a recent traveller to an area of active Zika transmission [5].

Birth defects surveillance is vital in providing information that will facilitate better understanding of the effects of Zika virus infection during pregnancy. This involves surveillance on brain abnormalities such as microcephaly and other defects that result from brain damage, as well as on hearing loss and eye defects [28]. This data is useful in understanding disease patterns and its associated risk factors and as well as the effects of the disease in populations.

### Policies and the future

The declaration of Zika virus as a Public Health Emergency of International Concern (PHEIC) in 2016 by the World Health Organization (WHO), its fourth such declaration, was arguably the first global response to the emerging threat posed by the disease [31]. Although later lifted, this declaration aimed at leading the world towards an urgent yet coordinated response to the infectious disease as recent outbreaks of Zika virus are thought to be the ultimate consequences of poverty, climate change and lack of sufficient research and development [32,33].

With an increasing range of the mosquito vector secondary to the effects of global warming, the transmission of Zika virus infection is expected to spread to areas in N. America and Europe where no previous transmission occurred [32]. This highlights the need for all stakeholders to work collaboratively in formulating policies that will curtail the effects of global warming.

Since the discovery of Zika virus disease, no vaccine or definitive treatment has been developed [34]. However, several vaccine strategies that include live-attenuated vaccines, inactivated vaccines and DNA vaccines are currently under investigation [5], the choice of which is still open to debate as the administration of live attenuated vaccines to pregnant women may pose a risk of infection and transmission to the foetus [34].

Ultimately, the development of a safe and effective vaccine will be the most effective strategy in preventing new infections and transmission of the disease in future, the only way to effectively eliminate the risks associated with the virus in populations.

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