

Zika Virus (ZIKV) Infection: A Review

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Abstract

Zika virus is a mosquito transmitted flavivirus belongs to family *Flaviviridae* which became the focus of an on-going pandemic and public health emergency all around the world. It is often misdiagnosed with other disease like Dengue and Chikungunya because of same clinical manifestation. After outbreak of ZIKV infection in Brazil in 2007, a severe neurological complications, Guillain-Barre syndrome and congenital malformations (microcephaly) suspected to be linked with ZIKV. The association between these conditions with Zika virus infection is still not confirmed and is under examination. Since ZIKV has neither an effective treatment nor a vaccine is available, therefore the public health authority focuses on preventing infection, particularly in pregnant women and virus transmitted region. World Health Organization and other health officials are working on the development of new projects and mosquito control methods to cope up with infection as there is very less literature present on the pathogenesis of the Zika virus to help interpret the clinical disease spectrum and target treatments to lessen or prevent infection. WHO/PAHO encourages the countries to establish and maintain Zika virus infection detection, clinical management and community assurance strategies to reduce transmission of the virus. The future status of ZIKV spreading to other parts of the world is still unknown.

Keywords: Zika virus; Flavivirus; Mosquito; Pregnancy; Transmission; Microcephaly; Africa

Introduction

Zika infection is a mosquito-borne flavivirus from the Spondweni group which was initially recognized in monkeys of Uganda in 1947. It was later diagnosed in people of Uganda as well as Nigeria in 1952 and the United Republic of Tanzania. Later it was recorded in Africa, the Americas, Asia and the Pacific. In July 2015 Brazil reported a relationship between Zika infection and Guillain-Barre disorder [1-4]. Guillain-Barré disorder (GBS) is a quick encounter of muscle weakness damaging the peripheral nervous system caused by the immune system. In October 2015 Brazil reported a relationship between Zika infection disease and microcephaly. Zika virus is considered to have two lineages: the African lineage and the Asian lineage, later has spread recently in the Pacific and the Americas [5].

Relationship with spondweni virus

Zika virus is evolutionary close to **Spondweni virus** (SPOV), with which it forms a branch within the genus flavivirus. It belongs to Family Flaviviridae (arbovirus group B) [6]. It causes Spondweni fever in human. The Spondweni fever is characterized by fever, with chills, headaches, nausea, discomfort and epistaxis. SPOV was first isolated in 1955 from *Mansonia uniformis* mosquitoes gathered from Lake Simbu situated in the Spondweni region of South Africa [7]. It was recently observed in sub-Saharan Africa and Papua New Guinea.

Genomes of virus compose of positive sense ssRNA molecule having two non-coding regions by analogy. It codes for a polypeptide which is divided into the capsid (C), envelope (E), precursor membrane (prM) and non-structural proteins (NS). By genetic recombination, incorporation of fragments of Spondweni virus into coding regions of Zika virus [8] is responsible for the recent outbreak in 2015. This genetic mutation might be responsible for changes in the virulence of the epidemic Zika.

Zika virus: An overview

Zika virus (ZIKV) is an icosahedral, enveloped, single-stranded positive sense RNA virus with non-segmented genome. Virus structure

is 40 nm in diameter, with a lipid envelope coated with dense projections that consist of a membrane and envelope glycoproteins and a dense inner core [9]. The Zika virus RNA is 10,617-nucleotide long. The Zika virus genome encodes for a polyprotein with three structural proteins, capsid, membrane, envelope and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) (Figure 1).

Virions situated on the surface of the cell membrane get entry into the host cells. The mRNA transcription takes place in the cell cytoplasm. When the virus is transmit from mosquito to health person, it results in Zika virus infection. It is quite fatal if the virus gets pass on to foetus from infected mother. The suspected cases of infant born with microcephaly have been reported so far [10,11] (Figure 2).

Zika Infection: A Global threat to Human Population

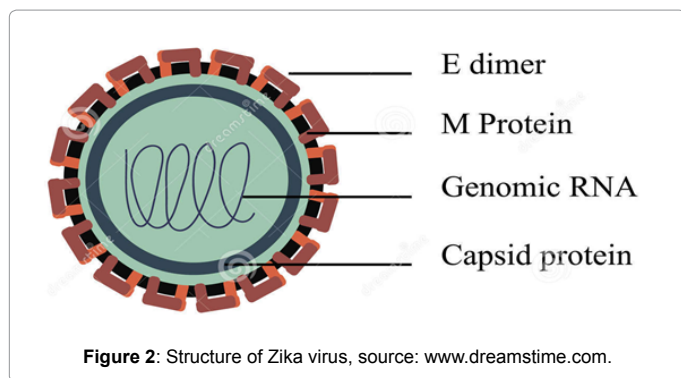
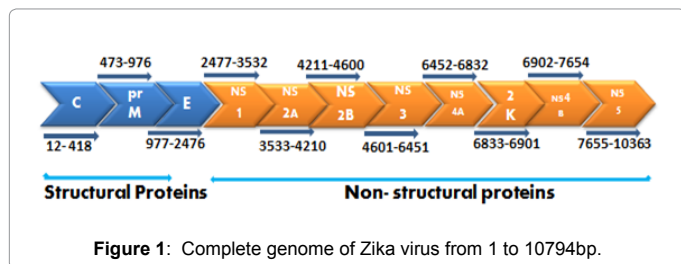
Before November 2015, [12] Zika virus was a quite unknown infectious agent, generating least attention compared to the current year's communicable disease like the MERS coronavirus, influenza and Ebola. The symptoms include a rash, fever, joint pain, red eyes, muscle pain, vomiting, and headaches. Management of ZIKV infected patients is easy as there is no Zika specific therapeutic or vaccine available because of it is mild and treatable symptoms. But now these two factors which have boost the Zika virus to an unusual position of fame. The mildness of the symptoms and low incidence, have allowed this virus to slip below the attention of people [13]. The following are two factors which are responsible for ZIKV infection to become a global issue of discussion.

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Rapid transmission of the virus

In 1947, Scientists isolate the Zika virus in samples taken from a sentinel rhesus monkey in Zika forest, Uganda. First proof of viral infection was reported when a researcher in Uganda who fell ill while working with Zika strains isolated from mosquitoes. This discovered that ZIKV can spread to humans. Later it was reported in few African nations, the Pacific, and components of Asia and Yap Island, Micronesia in 2007. In Oct of 2013, Zika reach French Polynesia and spreading to near islands like Cook Islands and Easter Island. The virus gradually spread to Brazil by May of 2015 [14,15]. Zika virus continues to spread at an extraordinary. Currently it is found in 14 Brazilian states and 10 countries in South and Central America, including Mexico and most recently Panama. Along with Dengue and Chikungunya, which are also transmitted by the *Aedes aegypti* mosquito (Figure 3).

Link with congenital birth defects

French Polynesia and Brazil have reported with many cases of congenital brain and spine malformation, particularly microcephaly [16]. Infants born with microcephaly have a smaller and underdeveloped brain which leads to developmental retardation and can be deadly sometimes. Different types of viral infections cause malformation and has never before been linked to Zika virus.

December 8th 2015, Brazil has had 1,761 cases of microcephaly compared to 59 total reported cases in 2014. A baby born with microcephaly tested positive for Zika virus has died on 28th Nov [17]. This discovery has taken stream of media attention to Zika virus outbreak in Brazil. Also, health care officials have confirmed an increase in disorders of central nervous system (CNS) match with the spreading of Zika virus and most commonly is the neuro-degenerative Guillain-Barre syndrome (GBS). However, out of 42 Brazilian cases of GBS, 62% showed common symptoms with Zika virus infection. So, WHO and other Health Organizations have advised people to study ZIKV infection symptoms and people in pandemic areas particularly pregnant mothers, to take precautions against mosquito bites. The frequent travellers were being warned to limit their travel to affected regions etc [18,19] (Figure 4).

Lack of vaccine, no proper research and common symptoms

The second reason is that there is no vaccine against the Zika virus so far. Efforts to make one have just begun. Producing and testing a vaccine usually takes years and are expensive also. The virus was thought to occur occasionally and there was actually no research done. Very few people were working on Zika virus and were unaware of the severity of the disease and the potential for spreading so rapidly. Much of the funding of research went to infectious disease in reaction to outbreaks [20,21]. People were not really prepared to respond quickly.

In the case of diseases like Zika, which was isolated from remote areas of the world where the population had no resources or facility available, there was not much effort to do research. Until recently, health officials paid slight attention to the Zika virus infection [22].

Another reason is that it often shows common clinical symptoms with that of other viral infection like Dengue, Chikungunya, yellow fever and spondweni viral infection. Virus is circulated in the same regions as Chikungunya, Dengue and compared with those two severe infections; Zika was usually mild and treatable one.

Zika virus infection during pregnancy can result a serious birth defect called microcephaly and also other serious foetal brain defects which became grave health issues recently.

Since, it is impossible to completely prevent mosquito bites to cope up with Zika infections, the CDC and World Health Organisation has encouraged pregnant women to stop going to regions where the virus is being circulated or a women thinking of becoming pregnant to consult doctors before going [23].

Absence of population immunity and lack of rapid and reliable diagnostic tests in those remote areas can also be count as the possible reasons for ZIKV pandemic.

Major possible symptoms

The most common symptoms of Zika virus infection are mild fever, skin rashes, joint pain, conjunctivitis, malaise and headaches which appear between 3-12 days after bite [24]. It might be asymptomatic also, but among affected, the disease is generally mild with symptoms that can last till 7 days. Severe disease requiring hospitalization is rare. Neurological and autoimmune complications have been reported in the recent outbreaks in Polynesia. Other possible manifestation includes: Arthralgia (joint pain) or Myalgia (muscle pain), detection of Zika specific IgM antibodies and nucleic acid in specimen and isolation of Zika virus from a clinical specimen [25,26].

Mode of Transmission

Zika virus is transmitted by *Aedes aegypti*, a day biting mosquito. They are active during day and late morning and evening. These mosquitos also transmit Chikungunya and Dengue and yellow fever through blood and body fluids. Dengue, [27] Chikungunya [28] and Zika virus [29] have all been spreading quickly and outbreaks of Dengue have been reported in the US. When a female *Aedes aegypti* bites a human, she injects virus present in the salivary glands of the infected mosquito into the wound where the anti-coagulants contained in her saliva facilitate feeding. Without knowing, the mosquito also injects the Zika virus into the host [30]. Additional modes of transmission have been identified including Mother-foetal transmission by trans-placental process and during the delivery by infected mother to foetus, Sexual transmission has been also possible from a symptomatic male to a woman as late as 5-6 weeks after onset of the man's symptoms and Blood transfusion and organ transplantation also pose a potential risk of transmission (Figure 5).



Figure 3: Zika virus possible pandemic area, source: geographyexcel.wordpress.com.

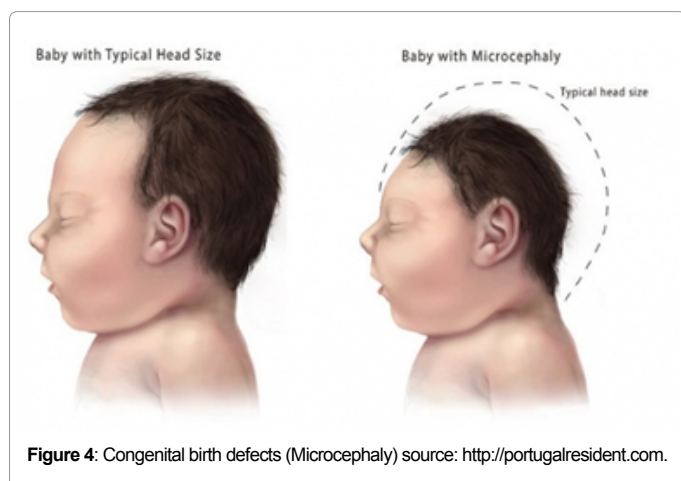


Figure 4: Congenital birth defects (Microcephaly) source: http://portugalresident.com.

Diagnosis of ZIKV Infection

Management and Precautions

Presently, there are no prevention methods for this virus causing disease. There are no anti-viral medications or vaccination available although your own immune system is the best soldier for this virus. But one can certainly take precautions [31-33].

From mosquito bites

Shielding against mosquito bites is a key measure to avoid Zika virus infection. Furthermore, minimising interaction with mosquitoes through repellents, screened windows and long-sleeved clothing will minimise the likelihood of viral infection [34]. Children and elder people should be taken care especially. People from the affected areas and travellers should take precautions. If any pregnant women get infected she should be taken to hospital immediately for check-up. Since the virus is transmissible it can affect her baby too. It is critical to cover, vacant or clean potential mosquito breeding sites in and around

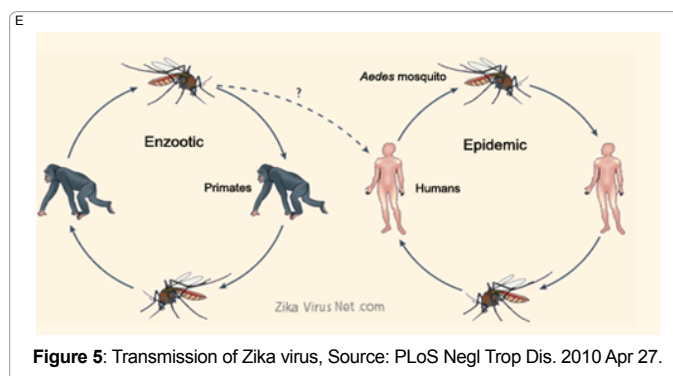


Figure 5: Transmission of Zika virus, Source: PLoS Negl Trop Dis. 2010 Apr 27.

houses. As mosquitoes breed and reproduce in stagnant water bodies, one has to ensure that water collection devices are covered or empty or sprinkled with pesticides which were necessary for reduction of mosquito populations [35] (Figure 6).

Through sexual transmission

Information on Sexual transmission of Zika virus infection has been confirmed by many lab reports. To reduce the risk of sexual transmission and pregnancy complications due to Zika virus contamination, one should practice safe sex (including using condoms) or abstain from sexual activity throughout the pregnancy if the partner is infected with Zika virus. People living in areas affected by Zika virus should take best precautions. In addition, people returning from areas where local transmission of Zika virus occurs should adopt safer sexual practices or abstain from sex for at least 8 weeks after their return, even if they don't display any symptoms.

ZIKV Recent Epidemic Status

The recent 2015 ZIKV outbreak, Brazil and Panama have reported microcephaly. Colombia is probing few cases of microcephaly with possible link to Zika virus. In other countries and territories, there



Figure 6: A female Aedes aegypti mosquito, Source: <https://sentinelblog.com>.

is not enough evidence of link of disease with congenital birth defects. The WHO team are presently in Cabo Verde to find the country's initial reported case of microcephaly. Just after the outbreak, Brazil reported 20 times increase in the number of babies born to infected pregnant mother with microcephaly [36,37]. A total of 4500 cases of microcephaly have been reported by early 2016 by Ministry of health, Brazil.

The virus is presently circulating in 38 countries and territories. It is unknown that the virus can or will spread to other parts of the world and might cause a similar pattern of inborn foetal malformations and neurological disorders [38]. If this goes beyond Latin America and the Caribbean, the world will face a serious public health catastrophe.

On the account of recent medical products, the authority agreed that a reliable, Point of Care Testing (POCT) is the most urgent priority. Currently, more than 30 companies are working on and also have developed advanced new diagnostic tests.

For vaccines, 23 proposals are being worked on by 14 vaccine developers in the US, France, Brazil, India, and Austria. Since the vaccine will be used to protect pregnant women or women of child-bearing age, it must meet an exceedingly high standard of safety. Many experts also tested the potential results of five new tools for mosquito control among which none of them were judged qualified for full-scale implementation.

Some Brazilian health officials were concerned that whether Zika alone is responsible for microcephaly [39], or whether along with Zika some other yet to be determined factors are responsible for birth defects.

As of 4th August 2016, 184 travels related cases, two sexually transmitted cases and one case of mother to foetal transmission have been reported in Canada. On 5th Aug, top athletes were missing from the 2016 Olympics are those who prefer out of the Rio Games, expressing the concerns about the Zika virus (Figure 7).

Drugs and Vaccines Available so far

There has been a lot of research on Zika virus vaccines recently, but hardly any have made it to market. The target population are pregnant women and women of child-bearing age which means it should be safe and effective [40,41]. Only effective DNA vaccines would be favoured more over vaccines made out of live or weakened Zika viruses to assure a safety concerns. The need and racing clinical trials shows a necessity to develop a safe vaccine quickly.

Clinical trials

The best clinical trial models used were mice, rhesus macaques and then human.

Three different investigational Zika virus vaccines used consist of an inactivated virus vaccine, DNA-based vaccine, and adenovirus vector based vaccine. The results propose that each of the three ways holds possibility of designing an effective Zika vaccine.

Efforts with mouse model

Researchers conducted experiments in mice and reported six Zika virus antibodies, out of which four neutralize African, Asian and American strains of the mosquito transmitted virus. The team supported by NIAID developed x-ray crystal images of these four antibodies in complex with Zika protein which could be useful for new vaccine development [42]. Purified inactivated virus vaccine or Plasmid DNA vaccine provides complete safety in mice against ZIKV in a single immunization.

Efforts with rhesus macaques

Researchers supported by NIAID also tested the inactivated Zika virus vaccine in 16 rhesus macaques. They were given two injections for four weeks. After challenged with Zika virus, the animal does not show any detectable virus and showed no other evidence of infection.

In another experiment, the researchers administered two doses of an experimental DNA vaccine, one dose of an adenovirus vector vaccine to three groups of four monkeys each. Monkeys were then exposed to Zika virus for four weeks [43,44]. Both the DNA and adenovirus vector vaccine provided complete protection against infection. Both vaccines provide protection against infection, induced immune responses, and produced no adverse side effects according to the report in *Journal Science*.

Due to large differences in gestational features between mice, rhesus macaques and humans, these studies may require experiments in human which would allow for optimal transfer of antibodies from the mother to the foetus in humans [45].

Efforts with human testing

The NIAID and NIH have begun clinical trial of a vaccine candidate including 80 healthy volunteers from 18 to 35 years old. Vaccine Research Centre (VRC) developed the NIAID Zika virus investigational DNA vaccine for the clinical trials in human. The early stage study will check out the experimental vaccine's safety and ability to provoke an immune response in participants.

Inovio's vaccine uses two new technologies including synthetic pieces of DNA and a new delivery system that uses an electric pulse to open up immune cells so they take up the vaccine better [46,47].

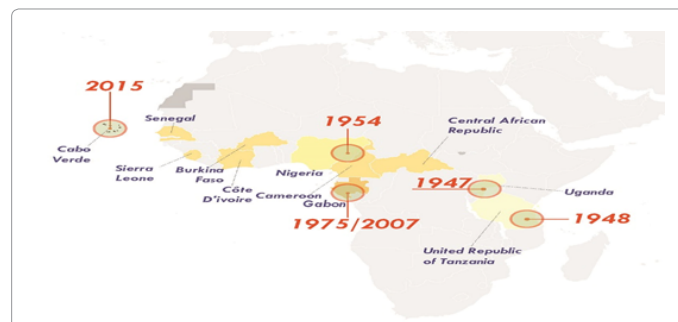


Figure 7: Zika affected countries from 1947-2016, Source: www.WHO International Emergency of Zika virus.

These vaccine candidates were found to be safe and induce an immune response. DNA or gene-based vaccines induce antibodies as well as activate the cell-mediated immune response which ultimately provides strong and durable protection against disease. Initial safety and immunogenicity data from the Phase 1 trial are expected by the end of 2016. If the results show favourable safety profile and immune response, NIAID aims to begin a Phase 2 trial in Zika-endemic areas by early 2017 [48,49].

The U.S. government has announced the vaccine materials and technology are made licensure across the world. There's the Butantan Institute in Brazil which have an exclusive license for the product in Brazil and Merck & Co in the U.S, two companies in India and one in Vietnam are also interested in producing the vaccine [50-52].

Bharat Biotech International Limited in Hyderabad claims that it has patented the Zika vaccine. Using a live Zika virus imported officially, the Hyderabad Company Bharat Biotech Ltd. has developed two candidate vaccines. The Indian Council of Medical Research (ICMR) has also agreed to help them.

Process of Vaccine Delivery

The Inovio Zika product called GLS-5700 is called DNA vaccine. In that vaccine, DNA gets coded to yield the protein that encircles the Zika virus [53]. The site of the injection is damaged with a device that delivers a short electrical pulse that guides the DNA into cells through a process called electroporation. The cells then instruct the immune system to see the Zika virus as a foreign invader which needs to be attacked, producing antibodies to fight against it [54,55]. Inovio's vaccine employs a new drug delivery system that operates an electric pulse to open up immune cells so they take up the vaccine better.

ZIKV Drugs

Several research teams of scientists are in competition to develop a vaccine for the Zika virus [56]. But a group of researchers has found 24 FDA approved drugs that have exhibited some potential to block Zika from infecting human cells in the lab. Few of these drugs which treat cancers infections and depression also showed ability to prevent infection in certain cells bound to fatal defects in pregnant women.

These researchers first screened 774 drugs and eventually limit them to 24 drugs that showed some potential to block Zika from infecting cells [57-59]. The 24 drugs act as model for other scientists to study in animals and eventually human, to see if they are truly powerful against Zika but some of the drugs shows extra side effect risks for pregnant women which need to be considered.

Antibiotic like Duramycin was suggested for ZIKV, which decrease Zika's ability to infect cells. Scientist will continue to work on vaccine development even when drugs that stop Zika infection are identified [60]. A vaccine could prevent the cycle of transmission of virus. There needs to be vaccine development in parallel with drug development.

Conclusion

Zika virus infection is generally caused by the mosquito bites (*Aedes aegypti* and some other species), especially, during the day time. It was only a mild, treatable infection when it was first discovered in 1948. Africa was considered the most affected country followed by south and North America which reported ZIKV cases recently [61,62]. The main reason for ZIKV to become a global emergency is its link with congenital birth defects (i.e. microcephaly) to infected mother and lack of drugs or vaccines available due to very limited research and also an absence of population immunity.

Since, there are no particular drugs or vaccine available in the market for treatment of infection [63-66]. WHO and other health officials advised people to stay home, prevent mosquito breeding and bite, abstain from travelling to Zika prone or affected region and abstain from sexual intercourse even if so. Tremendous information available in the literature suggests extensive work has been done on viral infections for different deadly viruses belonging to Flaviviruses [67], Togaviruses [68], Influenza [69], and Ebola [70] and presently on Zika virus. Such mammoth efforts always keep our hope towards a solution for such adverse situations. Obtaining a combined solution in this direction may aid in proper solution against these viral families. Soon after the human trial of vaccines and drugs by 2017, the drugs and vaccine would be available for masses at affordable cost.

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