

Short Communication

Zika Virus: A Zig Zag Path Ahead for India

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Abstract

Zika virus an arboviral infection, is an important public health problem. Recently, World Health Organization has declared it as 'Public Health Emergency of International Concern'. Zika virus belongs to *Flaviviridae* family, transmitted by *Aedes aegypti* mosquito. Though, it was discovered way back in 1947 from Zika forest in Uganda, but it gained importance in the year 2015 when a possible link with microcephaly was seen in the Brazil outbreak. In India, arboviral infections transmitted by *Aedes* mosquitoes are highly prevalent, hence India may be a fertile ground for the transmission of Zika if introduced in the country due to globalization. At present no vaccine or treatment is available. Thus, research is required to study the pathogenesis of microcephaly in order to develop the therapeutic targets. Efforts should be made to develop a point of care test along with a commitment to contain vector population by adopting vector control measures as it is the best preventive measure available at moment.

Keywords: Zika

Zika Virus (ZIKV) is an arboviral infection transmitted by the bite of infected *Aedes* mosquitoes, commonly *Aedes aegypti* and also by *Aedes albopictus* [1]. The other mosquito species occasionally implicated are *Aedes henselli* and *Aedes polynesiensis*. Recently, World Health Organisation (WHO) has declared an alert related to the pandemic potential of Zika virus [2]. The situation may deteriorate owing to this year's El Nino weather patterns which are expected to increase mosquito populations in many areas [3]. The WHO has already predicted that four million people could be infected with Zika in the Americas in 2016 [4]. On 1st February 2016, the WHO director Margaret Chan declared Zika as "Public Health Emergency of International Concern" [2]. Thus, seriousness of Zika infection can be estimated from the fact that WHO has kept Zika virus under the same category as that of Ebola virus infection. The epicentre of the disease is Brazil and this caused scare and anxiety among the athletes and fans participating in the South America's first Olympics being held at Rio de Janeiro in August 2016 [5]. However so far the WHO has not reported any laboratory

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confirmed cases of Zika virus associated with the Olympics.

The Zika virus was discovered in the Zika forest of Uganda in the year 1947 from a rhesus monkey; this was followed by the detection of human cases in Uganda in 1952 [6,7]. Since its discovery, Zika virus had been of little importance as only 14 cases had been documented prior to the Yap island outbreak [6] and also because its disease severity was quite mild as compared to dengue and chikungunya which were prevalent in those areas. After years of silence, the first outbreak was reported in the Yap island (Federated States of Micronesia in 2007) [8], which was followed by larger epidemic in French Polynesia in South Pacific in 2013 and 2014 [8,9]. This was followed by smaller outbreaks in many islands of Africa, South East Asia and Pacific islands [8]. In May 2015, the Pan American Health Organization (PAHO) issued an alert when ZIKV emerged for the first time in Brazil. The emergence of ZIKV was associated with reports of neurological complications like Guillian Barre Syndrome in French Polynesia and microcephaly in neonates in Brazil [10-12]. It has a widespread pandemic potential as many cases have been documented from different geographical regions. Currently, outbreaks are occurring in many countries of Americas, Oceania/Pacific Islands (American Samoa, Samoa), and Africa (Cape Verde) [13]. The clinical severity varies from mild infection to severe infection presenting as microcephaly in newborns when the disease affects pregnant women. Since October 2015, more than 4,000 cases of microcephaly have been reported in Brazil alone [14]. Currently, no antiviral or vaccine is available for effective management of cases and susceptible population.

India is a fertile ground for Zika virus as the mosquitoes including *Aedes aegypti* are present in abundance as has been documented by a high number of dengue and chikungunya cases being reported in recent years [15-18]. However, Zika is relatively new, and most of the population is not immune, hence the infection may spread at an alarming rate leading to high disease severity. The National Institute of Virology (NIV) study performed way back in 1950s documented that only 33 of the 196 people tested had immunity against Zika virus. Thus, large segment of population seems to be susceptible to Zika infection [19].

Dengue Virus (DENV) and ZIKV, both belong to *Flaviviridae* family and published reports have shown a high degree of antigenic similarity between the two viruses [20,21]. Studies using a panel of Human Monoclonal Antibodies (HMABs) to DENV have reported that antibodies to DENV envelope protein also cross reacted with ZIKV but do not neutralize ZIKV thereby greatly enhancing ZIKV infection by antibody dependent enhancement in vitro [21,22].

Though, not even single case has been reported from India but as a precautionary measure, Government of India has issued general preventive guidelines in public interest [23]. Moreover, India also has a large pool of pregnant women that are susceptible to Zika infection, which can subsequently lead to the development of microcephaly among new-borns as observed in Brazil. As per Open Government Data (OGD) Platform India, more than 20 million pregnant women were enrolled for complete three antenatal check-ups during the year

2010-2011 in India [24]. Thus, the total number of pregnant women in India are even more than the figure quoted above, and once Zika virus enters the Indian subcontinent, it may cause panic among these pregnant women [17]. An important concern here will be that once the Zika is introduced into the Indian subcontinent, further spread may also occur by non-vector borne transmission. The semen has been shown to harbour high amount of Zika virus RNA and both male to female and female to male transmission has been reported. Apart from this, blood borne transmission has also been reported in endemic areas [25,26]. Screening of blood would be necessary to prevent transfusion transmitted infection. Though no FDA licenced tests are available for ZIKV, testing is available through two Investigational New Drug (IND) applications for blood collected in Puerto Rico and Mainland United States [26].

The past few years have been the era of viruses, and many new viruses have emerged and re-emerged including Severe Acute Respiratory Syndrome *Coronavirus* (SARS-CoV), Middle East Respiratory Syndrome *Coronavirus* (MERS-CoV), chikungunya, Avian influenza, Pandemic influenza (H1N1), and recently the Ebola virus [27]. It is pertinent to note that all these are RNA viruses, which are more prone to genetic mutations as compared to DNA viruses. Most of these diseases are zoonotic in origin due to increased human and animal interface [27].

Moreover, due to globalization, there has been a tremendous increase in the international travel. Thus, chances of spreading the infection from one geographical area to a distant location are very high [28]. India has been put on high alert after 13 Indians residing in Singapore were confirmed to have Zika virus infection. Hence, screening is necessary at international airport terminals as was performed during the Ebola outbreak. Also aircraft disinfection as per WHO recommendations would be pertinent in this regards as the transport of infected mosquitoes to the non-endemic area may lead to the spread of infection as demonstrated by numerous cases of "airport malaria" from Europe, North America and elsewhere [29,30].

It is still not clear if multiple arboviruses can be transmitted by a single mosquito. Since many arboviruses are endemic at a given geographical location, the theoretical possibility of the same cannot be ruled out. Though, dual infection with dengue and chikungunya has been documented in the past but it is not clear whether it is caused by a single mosquito infected with both viruses or by two different mosquitoes [31,32]. Moreover, laboratory experiments did not detect dual infection of *A. aegypti* with dengue and chikungunya from the same pool or from individual mosquitoes. It is known that both viruses have different incubation period in the mosquitoes and the one with shorter incubation period is at advantage of being transmitted with higher frequency [33]. However, dual infection with dengue and Zika virus have been reported in 2 patients in the New Caledonia outbreak in the year 2014 [34].

Therefore, the path ahead is not easy, and the scientific community is struggling to find the answers to the following:

- 1) What is the pathogenesis of the microcephaly induced by the Zika virus? Though a definitive link has been seen in some cases, the question to be answered remains is whether all these cases are caused by Zika or is it just a coincidence? An effective animal model may assist in understanding the pathogenesis of the virus. Till date there are three papers which mark an important turning point in Zika virus pathogenesis and enable in vivo testing and evaluation of candidate vaccines and therapeutics. Female immuno-deficient mice lacking the IFN α /B receptor (A129) and congenic control mice (129SV/EV) for ZIKV infection have been used for studying pathogenesis of Zika virus. While Dowall et al., [35] utilized type-1 interferon receptor deficient mice (A129) and showed that these mice are susceptible to Zika. Lazear et al., [36] showed that knockout mice lacking components of the antiviral response developed neurological disease and succumbed to ZIKV infection. Rossi et al., [37] demonstrated that the A129 mice model can also recapitulate the disease with exaggerated signs.
- 2) What is the pathogenesis of Guillain Barre (GBS) Syndrome? In the French Polynesia outbreak and Brazil, there was an increased number of cases of GBS observed in the Zika virus season and also neutralising antibodies to Zika virus were identified. The AXL receptor has been identified as a candidate Zika virus entry receptor in neural stem cells [38]. However, the exact pathogenesis is not clear.
- 3) The development of diagnostic tests: as of now the definitive evidence is only by real time PCR which needs sophisticated set up [39-41]. Considering the alarming figures ahead, point of care tests need to be developed. Also, since the virus is closely related to dengue virus, it may be useful to have an NS1 antigen based assay for early diagnosis which could be possibly be done in a routine laboratory or could be performed as a point of care test in the form of rapid card test [42,43]. Studies are required to develop and evaluate the serological markers of acute Zika infection as cross-reactive antibodies may yield false positive results.
- 4) Vaccine development: The National Institute for Allergy and Infectious Diseases (NIAID) is currently pursuing at least two approaches for a Zika vaccine [44]. First, a DNA based vaccine, and the other a live vaccine is being tried based on highly immunogenic approaches similar to those used for the closely related dengue virus. It might be possible to just swap Zika DNA, or a whole Zika virus, into the experimental vaccines since it is so similar. Bharat Biotech in India has become the first company to file patent for Zika vaccine, which will be tested in animal models and could provide affordable vaccine as has been done earlier by developing indigenous oral Rotavirus Vaccine (Rotavac) [45,46]. In a recent preclinical study, ZIKV purified inactivated virus vaccine candidate was found to give robust protection against the virus in rhesus monkeys; the vaccine may soon advance to human trials [47].
- 5) Vector control: Millions of people die/suffer every year from the mosquito-borne diseases such as malaria, dengue, chikungunya, and yellow fever. Now the danger of Zika virus is hovering around creating a global alert. Currently, various methods are being used for the vector (mosquito) control strategies, and these include chemical control (indoor residual spray, chemical larvicides, aerosol space spray, malathion fogging during outbreaks), biological control (use of larvivorous fish in ornamental tanks, fountains, use of biocides), personal prophylactic measures (use of mosquito repellent creams, liquids, coils, mats, screening of houses with wire mesh, insecticide treated bednets, and wearing of clothes that cover maximum surface area of body), community participation for detection of mosquito breeding sites for its elimination, environmental management and source reduction methods (filling of the breeding places, proper covering of stored water) [23,48]. All these methods have been implicated for the past many years; however, every year millions of cases of malaria, dengue, chikungunya,

and yellow fever are reported from different parts of the world. The scientific community is also testing the novel approaches of vector control such as use of Genetically Modified (GM) males of *Aedes* mosquitoes [49]. Such mosquitoes carry a gene that hinders the development of their progeny and the second generation dies before they can reproduce. Field trials in Cayman Island and Brazil reported a reduction of mosquitoes up to 96% and 92% respectively [49]. However, it requires a large number of mosquitoes to be released into small area and eliminating one particular species of mosquitoes may have deleterious consequences in near future as it may lead to disturbance in food chain. Mosquitoes, and their larvae are an important source of food for birds, bats, fishes and frogs. This may also lead to emergence of some new vector, which may have the strong potential of transmitting even more deadly diseases [49]. Thus, every action needs close monitoring to prevent any adverse consequences.

- 6) Molecular characterisation of the virus: to identify any mutations that has facilitated the spread. In the past mutation in the envelope protein region (E1-A226V) of chikungunya virus led to adaptation to *A. albopictus* mosquitoes that caused an epidemic in a region lacking the typical vector [50]. The next generation whole genome sequencing could provide answers to such queries [51].

Recognizing that human health, animal health and environment health are linked inseparably, One Health concept has been launched to promote, improve and defend the health and well being of all the species by enhancing cooperation and collaboration between physicians, veterinarians, other scientific and health and environment professionals and by promoting management to achieve these goals [52,53].

Due to recent Ebola outbreak in West Africa, various health agencies in the form of rapid response teams are in place to deal with the management, and control of outbreaks [54,55]. In India, due to recent viral outbreaks, rapid response teams along with staff of Integrated Disease Surveillance Programme (IDSP) are active [56], which could speed up the process of managing the Zika outbreak. Still, we require rapid action research teams that can focus on different biological aspects of Zika viral infection related to molecular epidemiology, pathogenesis, development of antivirals and vaccines. Therefore, we all must join our hands to cross the zig zag path of Zika virus infection.

Conflict of Interest: None

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