Review Article

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Zika virus: Current concerns in India

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With confirmation of Zika virus (ZIKV) presence in India, screening of a large number of febrile illness samples yielded only four positive cases. In this review, we address the current concern with context to India. The possible reasons for low level of Zika prevalence in India have been discussed, by extracting some probable explanations from previous experience of chikungunya virus-vector model/studies. In the current context, it is hypothesized that Indian mosquito strains have lower susceptibility gradient/ threshold for ZIKV. The very low positivity in the humans also indicates low levels of mosquito-human-mosquito transmission cycle. There is also a need to look for the existence of any such animal cycle/ sylvatic involvement in India. The recently detected four cases in India show local transmission of ZIKV suggesting that ZIKV might have been present in India since long time. The earlier vector-virus relationship studies with chikungunya suggested that in due course of time, ZIKV might become a major public health concern in the future.

Key words *Aedes* - chikungunya virus - mosquito - vector - Zika virus

Introduction

Since 2013, with the first reported Zika virus (ZIKV) outbreak in the Marquesas Islands[1] and its subsequent spread to Brazil in May 2015[2], health agencies in India have been on alert and kept a watch on the Zika situation in India. There was anticipation that a ZIKV outbreak in India was possible due to the ubiquitous presence of the vector, *Aedes aegypti* mosquitoes and the susceptible host. On May 15, 2017, the Ministry of Health and Family Welfare, Government of India, reported three laboratory-confirmed cases of ZIKV disease from Bapunagar area, Ahmedabad, Gujarat, India[3]. The cases were confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) test[4]. Before this declaration, India was in WHO category-4 (virus may be present but no notified cases documented), but with these three confirmed cases, India has shifted to WHO category-2. Our previous review on Zika[5] provided the epidemiological background and algorithms to handle the ZIKV outbreaks in India. With recent confirmation of one more Zika case from Chennai in India[6], and after screening of a large number of febrile illness samples, yielded only four positive cases. The present review addresses the current concerns with context to Zika virus disease in India and why it has not been detected in a large number of individuals and what may be the risks involved in the future.

As evident from the present cases, Zika may not be a recent introduction in India. In 1954, National Institute of Virology (NIV), Pune (then Virus Research

Centre), had tested samples from Bharuch district, which showed ZIKV antibody detection in 16.8 per cent of the samples[7]. However, due to high cross-reactivity of ZIKV with dengue virus (DENV) and other flaviviruses, it was difficult to confirm Zika virus infection in India based on serology. Three cases identified in Gujarat and one in Chennai did not reveal any travel history to ZIKV endemic region, suggesting that the ZIKV is not a recent introduction into the country and it may have been present as a vector-borne entity albeit in a silent, low key ecological niche. In the context of ZIKV epidemiology, there are still some major concerns in the affected countries *viz.*, travel-related ZIKV introductions, specific symptoms, risks, prevention and clinical management of the individuals, clinical aspects of the affected pregnant women and associated microcephaly. The primary spread of ZIKV infections is through the bite of *Aedes* mosquitoes such as *Ae. aegypti* and *Ae. albopictus*. In the case of vector-borne infection outbreaks, it is essential that the vector population should have a high proportion of susceptible mosquitoes that are competent to pick up and transmit the virus at a minimum infection threshold (pick-up infection at low level of viraemia in peripheral blood)[8].

In India, more than 35,000 serum samples of febrile illness have been tested which yielded only four cases, suggesting a very low level of transmission of the virus within the community. In addition, about 18,000 mosquitoes were tested; this included about 500 mosquitoes from the Bapunagar area in Ahmedabad, Gujarat, India, where two of the Zika cases were reported; however, virus could not be detected[8]. Despite the presence of the agent, susceptible host and ideal tropical climate, the prevalence is lower in India as compared to Brazil[9]. Earlier studies have shown that in nature, mosquito populations have varying proportions of individuals that differ in their susceptibility to the pathogen they transmit. This phenomenon has been observed in the case of malaria with *Anopheles culicifacies* in India[10] as well as for chikungunya virus (CHIKV)[11] in the case of *Ae. aegypti*. The study suggested that susceptibility of *Aedes* to CHIKV is a quantitative trait[12]. Thus, a high vector potential in a mosquito population is an important factor for causing outbreaks. However, effective transmission not only requires the presence of a higher per cent of susceptible mosquitoes in a population that feed preferably on human blood and have low threshold to pick up infection, but it also requires that the virus strain should be capable of infecting a variety of tissues in the mosquitoes and replicate profusely. Finally, viral pathogen needs to bypass all the refractoriness offered by mosquito body's immune responses, thereby infecting a human case.

Although there have been a few Zika cases reported in India, there has been no isolation of virus yet. The present scenario suggests that (*i*) this virus is distinct from the both African as well as pathogenic Asian strains; thus, it does not replicate profusely as the African and Asian prototype strains are known to do, and (*ii*) this is also the reason that there is low susceptibility in mosquitoes and they do not pick up and transmit the infection easily. The current phylogeny data of virus from the clinical sample also suggest that the virus is little different from both known clades (Asian and African)[13].

This ZIKV is capable of causing large outbreaks as recently seen in Brazil[2]; it may be possible that in due course of time, mutations might render mosquitoes more susceptible and that might result in outbreak-like situation. In the recent past, a similar situation has been observed in India with CHIKV. During the late years of 1990-1999, it was suggested that this virus disappeared from India[14]. However, in India, during 2000, a CHIK virus strain was isolated from mosquitoes from Yawat town, Maharashtra state[11]. Further, during the virus isolation, several passages in mosquitoes by intrathoracic inoculation were required following 2-3 passages in mice finally to isolate this virus strain. Chikungunya appeared in an epidemic form in the Indian Ocean in 2004; the molecular clock studies on the CHIKV showed that the epidemic strain originated from the Yawat strain and the approximate time calculated was 9-11 yr[12]. The phylogenetic analysis showed that the progenitor of the 2005-2007 outbreak existed around 9-11 yr ago and might have originated from Uganda[15]. This epidemic strain was highly susceptible for both humans as well as *Aedes* mosquitoes.

On the phylogeny of partial sequence of non-structural gene of ZIKV, virus strain found in India falls in the third distinct clades between African and Asian clade[13]. Similar phylogeny was noted earlier for CHIKV in India during the 1960s[12]. One of the postulates stated that the CHIKV was maintained in nature at low level due to misdiagnosis with DENV infection, and nearly three and a half decades later from its first epidemic in 1965 till 1973 and then, CHIKV resurfaced as major epidemic in 2005[15]. The

cause for this sudden outbreak after decades is not fully understood; however, a probable explanation can be better adaptability of vector to get infected by the virus and its effective transmission. Lesson learnt from CHIKV can also help explain the current low prevalence of ZIKV in India and future prediction. Like CHIKV, when ZIKV will show higher affinity to effectively attach to the virus-specific receptors in the gut of mosquito, it will have the potential to cause outbreaks[16]. Besides this, there is one more factor that needs careful consideration keeping in view the DENV and CHIKV, where in human, the level of viraemia is high and duration is longer, whereas in the case of ZIKV in human, it is lower and of shorter duration[17].

In the current context, it is hypothesized that Indian mosquito strains have lower susceptibility gradient/threshold for ZIKV, and considering other associated factors, it is probably maintained at a very low level. The very low positivity in the humans also indicates that the low-level mosquito-human-mosquito cycle may not be enough for its sustenance in nature, and therefore, there is a need to look for possibility of existence of animal/vertebrate cycle that probably does not have close human-animal interface. Thus, there is also a need to look for existence of any such animal cycle involvement in India. There is also the possibility of existence of transovarial transmission with very low minimum filial infection rates.

It is difficult to confirm Zika infection (out of acute phase of 4-5 days) by serology, due to a very high cross-reactivity with DENV. In such a situation, performing serology is not advised where high false positivity will create panic. At present, only a few commercial serology kits are available. It is difficult to ascertain whether there will be congenital disabilities in children born to ZIKV-infected women or with history of infection. It is so far not feasible to screen all asymptomatic pregnant women by molecular tests. Now, that the presence of ZIKV in the country is confirmed, microcephaly may be made a notifiable disease in the country so as to indirectly estimate the burden caused by ZIKV.

Research is required to understand the ZIKV natural cycle in India and several questions need to be addressed *viz*., (*i*) how is the virus maintained in nature (vector biology)?, (*ii*) what is the threshold titre of ZIKV for mosquito population in India?, (*iii*) the population genetic studies on different vector populations with reference to the ZIKV susceptibility/refractivity need to be done, (*iv*) what is the spectrum of pregnancy outcome in ZIKV infected pregnant females?, (*v*) are there any other vertebrate hosts prevalent in India?, and (*vi*) what is the effect of interaction of other flaviviruses on ZIKV transmission? The virus has lived a ubiquitous life for decades in tropical and equatorial zone and has also not shown any dramatic evolutionary mutations, but the vector biology and pathogenesis of the ZIKV need to be better understood. It will be ideal to make Zika and microcephaly screening mandatory amongst pregnant women and initiate surveillance network in collaboration with hospitals and laboratories across the country, which will help us know the burden of ZIKV in India. The four ZIKV cases are only 'tip of the iceberg' and many subclinical cases may be present; hence, an efficient surveillance network needs to be initiated, but in a country like India, such ventures are cost-intensive and require political commitment.

The environment in India is conducive for ZIKV because of preponderance of the *Ae. aegypti* mosquitoes. Though these mosquitoes breed throughout the year in and around the houses in potable water sources, the density is extremely high during monsoon since more number of breeding sites becomes available. High humidity and optimal temperature support their survival for many days; thus, they get opportunity to lay eggs every 3-4 days and have multiple blood meals. The most effective and long-term preventive and control measure for *Ae. aegypti* as recommended by the authorities is 'source reduction involving community participation'[18]. In India, it is difficult to achieve this due to perineal water shortage and other constraints of the community. The concept of prevention of the disease by the use of repellents, bednet use, standing water treatment tablets, *etc.* have also been suggested.

In summary, the four cases of ZIKV infection detected in India showed ZIKV local transmission and were not associated with travel history. This also suggested that ZIKV might be present in India since long time. The earlier vector-virus relationship studies with CHIKV suggested that in due course of time ZIKV might become a major public health concern in the future. ZIKV still does not have priority as other flaviviruses such as DENV and CHIKV in India. Thus, to estimate the extent of ZIKV impact in India, a long-term rigorous surveillance network is needed with an active participation of the concerned public health authorities at the local, regional, State and the central level.

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