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Zika: An enormous public health challenge for a miniscule virus

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ABSTRACT

Zika virus (ZIKV) infection has recently affected 4 million people across the globe. The World Health Organization has declared Zika a ''Public Health Emergency of International Concern''. The disease is caused by an arbovirus and transmitted by *Aedes* mosquitoes. Zika has followed a pattern already set in by Dengue and Chikungunya viruses. The virus exists in sylvatic form with spillovers to humans. The present outbreak in Brazil started in May 2015 and spread rapidly to Latin America and the Caribbean. The rapid spread is due to availability of non-immune population. The main concern of Zika is the association with microcephaly in infants and Guillain–Barré (GB) Syndrome. During the current Zika outbreak in Brazil, incidence of microcephaly in infants has shown a 20-fold rise. Increased incidence of GB Syndrome has been noticed during the 2013 outbreak in French Polynesia, and the current outbreak. However, causality has not been proved. It is possible that the ZIKV may enter and get established in India. Surveillance against the disease needs to be scaled up. Research needs to be undertaken regarding the dynamics of Zika spread and the development of vaccines. Inter-sectoral coordination and bottom-up approach along with vector control measures under the ambit of National Vector Borne Disease Control Programme may help fight the virus.

Introduction

When first detected in Brazil in 2015, the Zika virus (ZIKV) created ripples throughout the public health infrastructure of the globe. At that time, not even passing reference had been made about this virus in Indian medical textbooks, leaving the public health worker confused in that contemporary scenario. The disease has affected an estimated 4 million people across the globe, with Brazil being the worst affected. On 1 February 2016, the World Health Organization (WHO) has declared Zika a ''*Public Health Emergency of International Concern*'' due to a possible link of ZIKV infection in pregnancy to microcephaly in infants.[1] The Centers for Disease Control (CDC) then issued an alert to travellers vesting countries that are experiencing an ongoing

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transmission of ZIKV, with the Government of India also issuing a travel advisory on the same.

Epidemiological pattern of ZIKV in the light of other vector-borne diseases

Zika is a vector-borne disease (VBD) caused by an arbovirus of the family Flaviviridae and transmitted by the bite of the day biting tiger mosquito – *Aedes*.[2] Contrary to popular belief, the virus is not a new one but a re-emerging virus, which was first isolated in febrile sentinel rhesus macaques in Uganda in 1947.[3] The first human cases were reported in the 1960s in Africa followed by the South East Asian region.[4] Since then, sporadic cases of ZIKV infection were reported till the first documented outbreak in humans was reported in 2007 in Yap Islands of Micronesia.[5]

The fact that ZIKV was first isolated in rhesus macaques points strongly in favour of a sylvatic origin of the virus. It has essentially followed a pattern already set in by its predecessors – Chikungunya virus (CHIKV) and Dengue virus (DENV), which have both re-emerged to become endemic in major world regions. ZIKV has originated from Latin America, which is host to a number of other viruses such as Oropouche virus and O'nyong'nyong virus. Hence, ZIKV followed by another novel virus spread in the form of a pandemic is a real possibility.

Interestingly, Yellow Fever virus (YFV) too has its roots in Latin America. The non-existence of YFV in Asia is still surrounded in mystery. India is both a conducive and receptive region for YFV as the *Aedes* vector and the animal host are present in abundance to infect a virgin, non-immune Indian population, the only missing link being the YFV. Various hypotheses have been put forth to explain this phenomenon, the most accepted one being the protective vaccine type cross-immunity provided by DENV infection in a hyperendemic population against YFV. Another theory is based on the all or none competitive exclusion principle, wherein only one of the two infections – DENV or YFV – can be present in an area.[6]

Though chances of occurrence of Yellow Fever (YF) in India are low, complacence should not set it in. Importation of YFV is still a possibility with increased air travel. Besides, the global warming effect, rapid and unplanned urbanisation, deforestation and poor waste management may disturb the ecological niche and lead to introduction of the YFV in hitherto uninfected regions. Precedence has already been set by CHIKV, which first emerged in India in the 1960s and then totally disappeared only to reappear again in the last decade, after a long absence. ZIKV too has so far not been reported in India till date, though it has reached as far as China.

Though a valid International Certificate for Yellow Fever Vaccination is required for the travellers entering India from endemic zones, non-observance of strict checking of the vaccination protocol may lead to a possible entry of YFV in our country. In today's age of Chemical, Biological, Radiological and Nuclear (CBRN) warfare, misuse of YFV by terrorists cannot be ruled out. If such an event happens, the damage would be tremendous, as the YF vaccine is not readily available for the Indian masses.

Reasons for evolution and spread

Though the ZIKV was detected decades ago, it had been an innocuous virus, and limited to a narrow geographical region in Africa and Asia. Akin to Dengue and Chikungunya viruses, enzootic ZIKV had been maintaining itself in sylvatic cycles in forest canopies in non-human primates (NHPs). The infection has been maintained by transmission through local vectors such as *Aedes africanus*, *Aedes luteocephalus* and *Aedes aegypti*, with infrequent spillovers resulting in jumping the human barrier.[7] Once the virus gained entry in the urban and suburban setting, it has been transmitted between humans through *Aedes* mosquitoes, mainly *A. aegypti* and potentially *Aedes albopictus*. Since 2014, the virus has spread eastwards to engulf South and Central Americas and also the Caribbean.

The first case of ZIKV transmission in the ongoing outbreak was reported in Brazil in May 2015. Since then, the virus has spread quickly worldwide, with transmission being reported in many countries in South and Central America and the Caribbean, as well as in countries outside this region. This rapid spread is mainly due to the virgin population who have had no prior exposure to the virus, and thereby having no immunity against it. Besides, the vector mosquito *Aedes* is found in abundance in the region, making it the perfect recipe for propagation of ZIKV.

The re-emergence of DENV, CHIKV and now ZIKV, all having *Aedes* as the common vector host, has been linked to human activities including deforestation, building rapid unplanned settlements and poor waste management systems. These activities have upset the ecologic niches occupied by arboviruses including ZIKV, resulting in spillover of the virus. However, the exact reason for jumping the human barrier is not known. RNA viruses have nearly 100-fold higher mutation rates *vis-a-vis* DNA viral genomes.[8] As ZIKV is an RNA virus, it is speculated that continuing mutations and genetic recombination coupled with natural selection may have led to emergence of a novel ZIKV strain capable of infecting humans.

Causes of concern

ZIKV infections in themselves are not a cause of worry. The main concern is the possible association of the infection with two dreaded complications – microcephaly in infants and of Guillain–Barré (GB) Syndrome.

During the current Zika outbreak in Brazil, incidence of cases of microcephaly in infants has shown a 20-fold rise in 2015 *vis-a-vis* 2014, suggesting a possible association with the ongoing outbreak. By the end of January 2016, 4783 cases (99.7 per 100,000 live births) of suspected microcephaly were reported in Brazil, including 76 with a fatal outcome.[9] Similarly, during the ZIKV outbreak in French Polynesia in 2013, 17 cases of foetal CNS malformations were reported. Four of these women were tested and had detectable antibodies to flavivirus.[10] However, no increase in cases of microcephaly has been reported from other countries affected by ZIKV.

It cannot be concluded with certainty that this association is causal as per Hill's criteria, or if hitherto unknown complex

supplementary ecological factors are involved. Temporal association is there, as cases of microcephaly have increased in Brazil within 9 months of the outbreak. Besides, it has been confirmed that transpacental transmission of ZIKV crosses the placental barrier, as the complete genome of ZIKV has been isolated directly from the amniotic fluid of a pregnant woman in a recent study.[11]

Public health authorities worldwide have acted in a knee-jerk fashion and advised women in the child-bearing age group to postpone travel to Zika-affected regions and to even to delay pregnancy for women staying in affected regions. As per the CDC, there is no concrete evidence showing that pregnant women are at increased risk of ZIKV infection, or the infection is more severe during pregnancy, as is the case with Hepatitis E virus.

During the 2013 outbreak of Zika in French Polynesia, 73 cases of GB Syndrome were reported.[10] Besides, cases of GB Syndrome have been reported from Brazil, El Salvador, Venezuela and Martinique in the current outbreak. 62% and 54% of the GB Syndrome cases gave history of symptoms suggestive of Zika before onset of neurological symptoms in Brazil and El Salvador, respectively.[12] However, this potential temporal and spatial association requires to be proved. The underlying pathophysiology of GB Syndrome following ZIKV infection is not clear. Though immunological catastrophe following ZIKV infection leading to GB Syndrome cannot be ruled out, it has been suggested that ZIKV infection super-imposed on a prior DENV infection in the same individual may be responsible for development of GB Syndrome, as DENV infection has also been found to be associated with GB Syndrome.[12]

Challenges and remedies

India is a potential hotbed for spread of ZIKV, as the *Aedes* vector breeds here in plenty and a large susceptible, non-immune population is available. In today's age of air travel, the disease may spread rapidly to India through viraemic travellers, as happened in the case of SARS, which spread from Hotel Metropole in Hong Kong to the entire globe within 72 h.[13] ZIKV has already been imported from Latin America to China and is now knocking on the public health set-up of ours. Once the virus enters India, there is high probability of it getting established and embedded in the community, a pattern that has already been set by DENV.

ZIKV infection follows the typical iceberg phenomenon of disease wherein almost 80% of the cases of ZIKV infection are inapparent.[5] In addition, as majority of the remaining 20% are mild, the disease outbreak may pass off under-diagnosed and therefore, under-reported. Or else, it may be diagnosed only as a case of any other viral fever. It is also plausible that antibody tests for Zika may be false positive in individuals with prior infection to closely related viruses such as DENV.

In the present scenario, surveillance measures against ZIKV should be put in place. Screening and quarantining of travellers arriving on flights from Latin American countries experiencing the ongoing outbreak should be undertaken. Sentinel surveillance of all cases of microcephaly, especially from the periphery, needs to be carried out in ZIKV-affected regions. Since ZIKV spreads through sexual contact, persons who have visited ZIKV-infected areas should be advised to practice safe sex. Blood safety measures should focus on deferring blood donation from individuals visiting ZIKV-infected areas.

Further research involving all stakeholders needs to be undertaken to establish a cause–effect relationship between ZIKV infection and microcephaly. The same will go a long way in further understanding the dynamics of ZIKV spread and the development of protective vaccines. Though advisories may deter women from outside to visit ZIKV-infected regions, women already inhabiting these areas are left in uncertainty. Even if a causal relationship between ZIKV infection and microcephaly is established, there will still be a gap in knowledge of various aspects of the disease, such as the trimester during pregnancy that has the maximum effect on foetus and the risk levels.

No commercial tests are available against ZIKV as of now. Presently, the real-time polymerase chain reaction (RT-PCR) is used, which detects the viral RNA and is positive only during the short period of viraemia.[14] Besides, serological samples of ZIKV infection may cross react with those of other closely related flaviviruses such as DENV and YFV. Dengue is endemic in many parts of the country, and an outbreak of ZIKV infection may lead to a catch-22 situation. Hence, the need of the hour is development of rapid diagnostic tests for ZIKV.

There is no vaccine for ZIKV and no efforts were made in this direction till recently. Flaviviral vaccine platforms may be utilised to develop an effective vaccine against the disease. However, once the vaccine is developed, the main issues will be the clientele to be vaccinated, as the disease has so far appeared locally in certain specific regions. Pre-emptive vaccination will be a costly and non-cost-effective affair. The trials of the potential vaccine will also face ethical issues as the main clientele for the vaccine will be pregnant women and the trial will put both the mother and foetus at risk. Trials on non-pregnant women may not generate the same immune response as those in pregnant women. To respond, we urgently need research on ZIKV and the ecologic, entomologic and host determinants of viral maintenance and emergence.

In Brazil, which is bearing the brunt of ZIKV infection, a law has been promulgated allowing public health officials to access any public or private building to eradicate breeding grounds of mosquitoes, even in the absence of the owner. Such an aggressive approach is also required in India.

National Vector Borne Disease Control Programme (NVBDCP) is the umbrella organisation in India for prevention and control of VBDs. The programme is already doing yeoman service in the public health domain by issuing timely policies and guidelines on VBDs. The need of the hour is to involve all stakeholders including physicians, microbiologists, public health personnel, NGOs and more importantly, the government machinery to identify and fill up the research gaps. Stress should be laid on surveillance of the likely routes of entry for ZIKV in our country. Sentinel surveillance sites for detection of ZIKV infection should be created in India, which as of now are non-existent for other VBDs such as Malaria,

Dengue, Chikungunya and Japanese Encephalitis, resulting in gross under-reporting of cases and deaths due to these diseases. Private hospitals should form an important part of the sentinel surveillance system. Besides, sincere efforts should be made to integrate all public health challenges including VBDs into the National Health Management Information System (NHMIS), which is a part of the Integrated Disease Surveillance Project (IDSP). This would help in timely tracking of clustering of cases of febrile illnesses, microcephaly amongst newborns and cases of GB Syndrome, besides also identifying the likely source of infection. The National Centre for Disease Control (NCDC) is an important link as far as the International Health Regulations (IHR) regarding Zika are concerned. It is the agency that will collaborate with the WHO and the IHR focal points in Zika-affected countries regarding the current international status of the outbreak and newer modalities in control of the outbreak.

We have already learnt lessons from the recent outbreak of Ebola in our country. When the Ebola virus was first imported to India, the general public was as clueless about it as it was about Zika. Notwithstanding, the disease was commendably tackled by tracking movement of travellers and creating a Nodal Centre at Ram Manohar Lohia Hospital, Delhi, having designated Nodal Officers and Nodal Wards with testing and quarantining facilities for suspect cases. Besides, daily community awareness programmes were conducted and medical students and interns too were briefed about the clinical features and management protocol of Ebola-infected patients. A similar contingency planning should be made for future ZIKV outbreaks in the country.

Conclusion

ZIKV outbreaks point to yet another re-emergence of a virus attributable to human activity. Broad-based inter-sectoral coordination holds the key to timely identification of a potential ZIKV outbreak in India. A bottom-up communicative approach at all levels of the public health set-up needs to be in place. Vector surveillance to quantify human risk for transmission of ZIKV should form an integral part of the approach. However, we must not forget the basic golden, time-tested and cost-effective theme of controlling the vector through source reduction, anti-larval and anti-adult measures with active community involvement, which is within our reach.

Causal association between ZIKV infection and microcephaly or GB Syndrome needs to be established or refuted at the earliest, whatever the case may be. Urgent animal model studies and analytical observational studies on humans based on careful selection of cases and controls need to be undertaken for the same.

Conflicts of interest

The authors have none to declare.

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