ZIKA VIRUS IN INDIA: EMERGING TRENDS

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ABSTRACT

Zika virus disease is an emerging flavivirus disease in the Indian subcontinent. It is spread primarily by the bite of infected Aedes mosquito. In the recent past, the mutant form of zika virus has resulted in pandemic in the Americas, Africa and the Pacific. India is at high risk of zika virus transmission because of the high rate of international travel and conditions favourable for the growth of mosquito vector. The symptoms of zika virus disease are nonspecific and overlap with the diseases by other flavivirus like dengue and chikungunya. Only a battery of laboratory tests can differentiate among the infection by various flaviviruses. Newer molecules and vaccine are under investigation for treatment of infection by zika virus. Still much research needs to be done to establish the efficacy and safety of these molecules. Also effective implementation of policies by health planners is needed to prevent the spread of virus in India.

KEYWORDS: Zika virus, Flavivirus, Aedes mosquito, Dengue, Chikungunya.

Zika virus disease is an emerging viral disease transmitted primarily through the bite of an infected Aedes mosquito. This mosquito is also known to transmit infections like dengue and chikungunya.[1] Zika virus was first identified in Uganda’s Zika forest in rhesus monkey in 1947.[2] Zika virus disease outbreaks have been recorded in Africa, the Americas, Asia and the Pacific.[1]
Currently, according to the Centers for Disease Control and Prevention (CDC), 58 countries and territories are affected by Zika virus. The original African strain of zika virus went to Asia between 1950 and 2000. It was first found in Pune in 1952 and was benign in nature. Thereafter the newer mutant strain of this virus emerged on a remote Pacific island, (Micronesia) in 2007. The 2013-2014 in French Polynesia involved an independent introduction of the Zika virus from Southeast Asia. This is sometimes called the Asian strain, which went Eastward into the New World and resulted in epidemic in Brazil in May 2015 and then in a pandemic as it swept through 26 countries in the Americas, Cape Verde in Africa and Singapore, where 200 infections were reported within eight days. On February 1, 2016, WHO declared Zika a “Public Health Emergency of International Concern”, requiring a coordinated international response.

Zika virus disease has the potential for further international spread given the wide geographical distribution of the mosquito vector, lack of immunity among population and high rate of international travel. It is believed that an older more benign strain that was detected in Pune in 1952 is likely to be quietly residing within some Indians that has probably laid the genetic ground for quick second coming of the virus.

India is at high risk for the spread of Zika, as it hosts over 67,000 travellers and visitors from areas where there is an active circulation of the virus. The conditions in India are also favourable for the spread and growth of zika virus as there is widespread existence of its vectors: aedes aegypti and aedes albopictus mosquitoes, over-crowding, lack of sanitation and hygiene and suitable climatic conditions all of which can prolong mosquito season. Aedes aegypti and dengue are prevalent wherever there has been a Zika outbreak. India at present is the most affected country with dengue. The reason for the co-existence can be that both viruses are transmitted by Aedes aegypti, or previous dengue infections can also promote increased susceptibility to Zika. Plasma immune to dengue virus showed substantial cross reaction to zika virus. Antibodies to dengue virus are able to bind ZIKV but are unable to neutralize the virus and instead promote antibody dependent enhancement. Hence, immunity to dengue virus results in greater ZIKV replication and disease pathogenesis. Serologically it is difficult to distinguish between dengue and zika virus thus proving their antigenic similarity.

Zika virus is member of family flaviviridae related to dengue, yellow fever, Japanese encephalitis, west nile fever. Zika virus is an enveloped virus, having icosahedral
symmetry and has a non-segmented, single stranded, positive sense RNA genome containing 10,794 nucleotides. The genome has 2 flanking untranslated regions (50 and 30 UTRs) and a single long open reading frame encoding a polyprotein, which is cleaved into capsid (C), precursor of membrane (prM), envelope (E) and 7 non-structural (NS) proteins (50-C-prM-ENS1-NS2A-NS2B-NS3-NS4A-NS4B-NS5-30).\textsuperscript{[14,15]} The E protein is a major virion surface protein that is involved in receptor binding and membrane fusion. Loss of the N154 glycosylation site in the E protein may be associated with adaptation to mosquito vectors and thus facilitate transmission.\textsuperscript{[14]} The recent spread of zika virus may also be associated with NS1 codon adaptation to human housekeeping genes, which could facilitate viral replication and increase viral titres.\textsuperscript{[16]} So mutations in the E and NS1 genes may be the cause of increased virulence of ZIKV.\textsuperscript{[17]}

The primary transmission route of Zika is the bite of the infected female Aedes mosquito (Aedes aegypti and Aedes albopictus) as it feeds on the human blood. These mosquitoes are aggressive day time bitters but can bite at night. Other mode of transmission includes sexual intercourse, blood transfusions and perinatal transmission from mother to foetus during gestation or at the time of delivery. There are no reports of virus transmission through breastmilk to the offspring. Mothers are advised to breastfeed babies even in areas with high risk of zika transmission. There are no confirmed cases of ZIKV transmission in health care settings. However, the health care personnels are advised to protect themselves from potential exposure, which includes percutaneous exposure (needle prick or cut with a sharp object), or exposure of non-intact skin (skin that is chapped or abraded) or mucous membranes to any of the following: blood, body fluids, secretions and excretions.\textsuperscript{[18]} There is vertical transmission also — the virus can be passed on from the Aedes aegypti mosquito to its offspring.\textsuperscript{[19]} The virus incubation period is between three and twelve days after the mosquito bites the infected human.\textsuperscript{[20]}

In the past 65 years (till 2012) that Zika has swept through the world, from Africa to Asia to the Americas, it was regarded as benign, with no reported deaths or hospitalisations.\textsuperscript{[21]} With increase in international travel, people travelled across continents and spread the virus. The relatively benign version of the virus causes low grade fever, skin rash, conjunctivitis, muscle and joint pain and headache.\textsuperscript{[22]} The rash is characterised as generalised erythematous maculopapular rash that spreads from face downwards to lower limbs.\textsuperscript{[23]} Less commonly, it can cause high grade fever with chills, sore throat and hypotension.\textsuperscript{[24]} Haematological and
serological functions may get mildly affected.[25] In pregnant female, the newer mutant form of the virus cause congenital zika syndrome which includes swelling of brain and spinal cord, microcephaly and may rarely result in Gullian Barre Syndrome, a temporary paralysis that can sometimes result in choking and death. Zika virus can also cause lifelong vision impairment in babies.[26] Babies born apparently healthy after zika exposure in womb might develop neurological and ophthalmological abnormality later in life and hence need follow up to track progression of these abnormalities.

In one in five cases, the symptoms of zika virus disease overlap with diseases caused by other flaviviruses, such as dengue and chikungunya. Only laboratory tests can differentiate between the viruses, as there is possibility of the cases being clinically diagnosed as dengue or chikungunya fevers could be Zika virus infections. Most of the people usually are asymptomatic and are unlikely to realize that they are infected.[24]

The lab diagnosis of zika virus can be done by various ways like RNA-NAT (Nucleic acid testing), real time RT-PCR assay and serological test.[27] RNA-NAT is done on serum or urine collected in first week after symptom onset. The positive RNA-NAT test confirms zika virus infection and no further tests are needed. However, the negative test does not exclude zika virus infection and further serological testing is needed.[28] Real time RT-PCR assay is another method to differentiate zika from dengue and chikungunya. RT-PCR testing can be done on serum collected within 1 to 3 days of symptom onset or on saliva samples collected during the first 3 to 5 days or on urine samples in first 2 weeks of symptom onset.[29,30] A positive RT-PCR assay along with clinical diagnosis confirms zika infection. In high risk cases like pregnancy further testing is required. Negative tests do not rule out zika infection and hence further testing is required.[31] The serological tests using enzyme linked immunosorbet assay (ELISA) detects zika virus specific IgM and neutralising antibodies that develop towards end of first week of illness and can be detected in human sera and cerebrospinal fluid (CSF). Test become positive by day 4 post onset of symptoms and continues to be positive for 12 or more weeks. Serum samples collected ≥14 days after symptom onset should be tested for anti-Zika virus IgM antibodies. Positive and equivocal results are not definitive for diagnosis of Zika virus infection. False positive results are possible in patients with a history of infection with other flaviviruses. Presumed positive, equivocal, or inconclusive tests must be confirmed by plaque-reduction neutralization testing (PRNT).[27] PRNT is performed by CDC or a CDC-designated confirmatory testing
laboratory using neutralising antibodies that appear 5 days after symptom onset. A four-fold rise in neutralizing antibody titres in the absence of a rise in antibody titre to other flaviviruses is further evidence of recent Zika virus infection.\[28\] Negative results do not preclude the possibility of Zika virus infection, past or present. Other alternate tests to these are virus isolation from samples collected 5 days after symptom onset and “pan flavivirus” amplification technique combined with sequencing data.\[32,33\]

Researchers have identified two classes of compounds effective against Zika: one is antiviral and the other prevents Zika-related brain cell death.\[34\] The compounds include emricasan (neuroprotective drug), niclosamide, sofosbuvir and nine cyclin-dependent kinase (CDK9) inhibitor (antiviral). CDK usually is involved in regulation of cellular processes as well as normal brain development, but the Zika virus can negatively affect this process.

Emricasan is a pan-caspase inhibitor and inhibits natural process that causes programmed cell death.\[35\] It is in phase II clinical trial for hepatic cirrhosis, portal hypertension and non alcoholic steatohepatitis.\[36\] It inhibits zika virus induced increase in caspase 3 activity and prevents death of immature brain cells caused by zika and hence has the potential to protect against microcephaly. This could enable its use in pregnant women infected with zika virus.\[37\]

Niclosamide, a category B drug, is originally an antihelminthic drug that is used for tapeworm infestation.\[35\] It also inhibits ZIKV replication. Niclosamide is not much absorbed from the digestive tract into the blood therefore it remains to be seen how the medication will reach the virus in the rest of the body.\[38\] Sofosbuvir is a nucleotide analog that is an RdRp (NS5B protein) inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of HCV infection. This drug was proposed for zika virus treatment after showing that it reduced viral NS1 staining in human neuroepithelial stem cells.\[39\] The study showed that when Sofosbuvir was orally administered (33 mg/kg/day) for 7 days to ZIKV infected mice, greater overall survival rates against ZIKV-induced death was recorded as compared with vehicle treated mice.\[40\]

The nine CDK inhibitors stop the virus replication. It is found that emricasan, when combined with one of the CDK inhibitors, prevented both cell death and virus replication.\[34\] The CDK inhibitors may also be useful in treating non-pregnant patients who face an increased risk of Guillain-Barre syndrome and other conditions sparked by Zika infection.
The researchers cautioned, however, that the use of emricasan and niclosamide during pregnancy for Zika infection will need to be evaluated in pre-clinical toxicology studies and clinical trials.\[41\]

Researchers have tested these drugs in mice, but much work needs to be done before they will be available to humans. Currently no treatment is available to combat the effects of the virus. Most of the patients respond to symptomatic treatment which includes plenty of rest, fluids to prevent dehydration and medicines such as acetaminophen to reduce fever and pain. Aspirin and other non-steroidal anti-inflammatory drugs can be used only once dengue is ruled out as there is risk of bleeding/hemorrhage in such patients.\[42\]

WHO experts have suggested researchers to develop inactivated vaccines and other non live vaccines which are safe to use in pregnant women and women of child bearing age. In June 2016, FDA granted first clearance for a Zika vaccine (GLS-5700), an intradermal product. It is currently in phase I study in 40 healthy subjects.\[43\]

The best way to control ZIKV is to take measures to prevent the spread of disease by mosquitoes by using mosquito nets, registered mosquito repellants as they are also safe for pregnant and lactating women, using physical methods of contraception to prevent sexual transmission of Zika, wearing long sleeved shirts and pants during the spread of infection, use of physical barriers such as screens, throwing away standing water in pots, utensils, buckets, tyres and cover open water tanks as aedes aegypti mosquitoes breeds in standing water. Children, sick and elderly may not be able to protect themselves and hence should be given special attention. Individuals, especially the pregnant women or women planning pregnancy should avoid travelling to the affected countries. Persons having febrile illness within two weeks of return from an affected country should report to the nearest health facility so that suitable measures to combat the spread of virus can be taken.\[44\]

In November 2016, the WHO declared that the Zika virus was no longer a global emergency while noting that the virus still represents a highly significant and a long term problem.\[45\] As we were finalizing this article, three cases of Zika virus infection that are confirmed by WHO, have been reported from Ahmedabad in India.\[46\] It is an urgent wake-up call for health care planners and policy-makers to invest in preventing further transmission of virus. The researchers are required to accelerate their search for newer vaccines and drugs that could be helpful in zika virus outbreaks in future.
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