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A Review on Zika Virus

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ABSTRACT: The Zika virus has been in the news for quite some time due to the ongoing recent outbreak in Southern America, which started in December 2015. It was declared a public health emergency by the World Health Organization in February 2016 owing to its association with congenital deformities, particularly microcephaly in infants born to infected mothers. The rapid spread of the virus throughout the United States of America and subsequently to Asia has raised serious international concerns. Its spread to countries neighboring India is a serious threat to the Indian population. This review article gives an overview of the virus, its diagnosis, clinical features, and its management.

Zika virus (ZIKA) is a mosquito-borne virus that was first isolated from the Zika forest, in Uganda, in 1947. Since its inception, major and minor outbreaks have been documented in several parts of the world. Aedes spp. mosquitoes are the primary vectors of ZIKA, but the virus can also be transmitted through sexual practices, materno-fetal transmission, and blood transfusion. The clinical presentations of symptomatic ZIKA infections are similar to dengue and chikungunya, including fever, headache, arthralgia, retro-orbital pain, conjunctivitis, and rash. ZIKA often causes mild illness in the majority of cases, but in some instances, it is linked with congenital microcephaly and autoimmune disorders like Guillain–Barre syndrome. The recent Indian ZIKA outbreak suggests that the virus is circulating in the Southeast Asian region and may cause new outbreaks in the future. At present, no specific vaccines or antivirals are available to treat ZIKA, so management and control of ZIKA infections rely mostly on preventive measures.

Keywords: Aedes, arbovirus, Flavivirus, microcephaly, virus, Zika

I. INTRODUCTION

Several emerging and re-emerging infections have taken a heavy toll on public health around the globe.[1] Some of these infections that have been in the news recently include swine influenza, severe acute respiratory syndrome, Middle East respiratory syndrome (MERS), Ebola virus disease, and the Zika virus (ZIKA) infection.[1,2] The situation in resource-limited countries is grave due to growing panic and fear, especially in the absence of clear management guidelines and definitive treatment.[1] Although initially some of these infections have been confined to particular geographical areas such as the MERS-Corona virus infection in the Middle, ZIKA in South America, and Ebola virus disease in Western Africa, the situation may become serious due to rapid globalization, international migration, and relatively easy travel to and from these afflicted countries resulting in the dissemination of these infections to newer countries.[3] The affected cases may travel to other countries where the infection may not have been present and eventually lead to the spread of the pandemic.[3] Most remarkable among all these infections is the infection by ZIKA that has crossed all international borders and has been reported from various corners of the globe.[4]

ZIKA was first identified, almost 70 years ago, in rhesus monkeys during a yellow fever surveillance in the Zika Forest in Uganda (hence its name) and was initially reported in humans in 1952.[3] Seldom was imagined that this virus would become a major international public health concern in the 21st century. Its rapid spread throughout the American continent in 2016 and its potential to cause congenital abnormalities in infants have raised serious concerns. This led to the World Health Organization declaring the ZIKA infection a global health emergency on February 1, 2016.[5]

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About Zika Virus

IKV is one of the re-emerging arboviruses (arthropod-borne) which is transmitted by the Aedes mosquito.[3,4] It is a single-stranded RNA virus belonging to the genus Flavivirus of the Flaviviridae family and has been related to the other Flaviviruses including yellow fever virus, dengue virus (DENV), chikungunya virus, and West Nile virus.[6,7] ZIKA virus has two major geographically different lineages: Asian and African.[6] ZIKA in Africa is maintained in a life cycle (sylvatic transmission) that mainly includes monkeys and apes with humans as occasional hosts, but on the other hand, the Asian lineage of ZIKA includes humans as the main host.[6,8]

Epidemiology

Since its isolation from Uganda, it has been reported to be associated with sporadic human infections in Africa and Asia.[3] The most remarkable details are available from the epidemic that occurred in Yap Island, Micronesia (2007), French Polynesia (2013), and New Caledonia (2014).[3] ZIKA infection in Brazil was confirmed in May 2015 and by January 2016 the ZIKA epidemic had spread to many countries of the Americas, including Bolivia, Brazil, Cape Verde, Colombia, Dominican Republic, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Saint Martin, Samoa, Suriname, and Venezuela.[5,9,10,11]

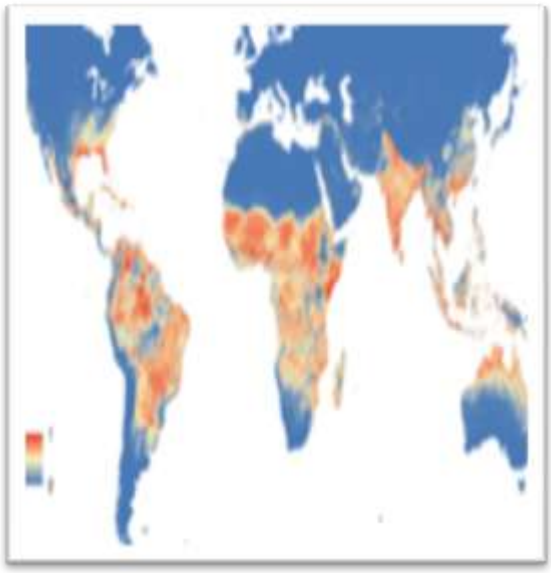
Transmission

ZIKA transmission to humans takes place mostly via the bite of an infected Aedes aegypti mosquito which breeds in fresh standing water and usually bites during the daytime (both indoors and outdoors).[11] Aedes albopictus and other species of Aedes mosquito (A. africanus, A. luteocephalus, A. furcifer, and A. taylori) also have the potential to spread the virus.[12]

Few cases of person-to-person presumptive sexual transmission of ZIKA have been reported in women who had sexual intercourse with their partners suffering from the ZIKA illness.[13,14] Researchers have also confirmed the presence of the ZIKA RNA in semen of the affected male giving the hypothesis of sexual spread of the ZIKA illness.[13]

ZIKA RNA has also been detected in blood, urine, saliva, cerebrospinal fluid (CSF), amniotic fluid, and breast milk.[15,16,17] Maternal to fetal transmission can occur, as the virus can cross the placental barrier resulting in congenital (intrauterine) infection and also intrapartum transmission can occur.[18,19,20] ZIKA transmission through breastfeeding has not yet been described, and thus it is recommended that the affected mothers continue to breastfeed their babies.[21]

1. Mosquito



Global Aedes aegypti predicted distribution. The map depicts the probability of occurrence (blue=none, red=highest occurrence) [22]

Zika is primarily spread by the female Aedes aegypti mosquito, which is active mostly in the daytime. The mosquitos must feed on blood to lay eggs.The virus has also been isolated from several arboreal mosquito species in the genus Aedes, such as A. africanus, A. apicoargenteus, A. furcifer, A. hensilli, A. luteocephalus, and A. vittatus, with an extrinsic incubation period in mosquitoes around 10 days.

The true extent of the vectors is still unknown. Zika has been detected in many more species of Aedes, along with Anopheles constant, Mansonia uniformis, and Culex perfusion, although this alone does not incriminate them as vectors. Detecting the presence of the virus usually requires genetic material to be analyzed in a lab using the technique RT-PCR. A much cheaper and faster method involves shining a light at the head and thorax of the mosquito and detecting chemical compounds characteristic of the virus using near-infrared spectroscopy.

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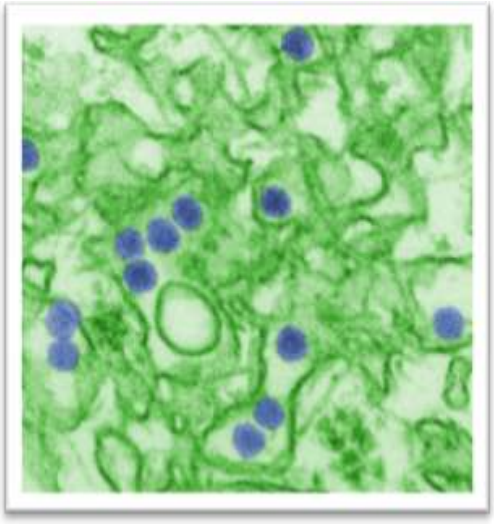
Transmission by A. albopictus, the tiger mosquito, was reported from a 2007 urban outbreak in Gabon, where it had newly invaded the country and become the primary vector for the concomitant chikungunya and dengue virus outbreaks.New outbreaks can occur if a person carrying the virus travels to another region where A. albopictus is common.[22]

The potential societal risk of Zika can be delimited by the distribution of the mosquito species that transmit it. The global distribution of the most cited carrier of Zika, A. aegypti, is expanding due to global trade and travel. A. aegypti distribution is now the most extensive ever recorded – on parts of all continents except Antarctica, including North America and even the European periphery (Madeira, the Netherlands, and the northeastern Black Sea coast). A mosquito population capable of carrying Zika has been found in a Capitol Hill neighborhood of Washington, DC, and genetic evidence suggests they survived at least four consecutive winters in the region. The study authors conclude that mosquitos are adapting for persistence in a northern climate. Zika virus appears to be contagious via mosquitoes for around a week after infection. The virus is thought to be infectious for a longer period after infection (at least 2 weeks) when transmitted via semen.

Research into its ecological niche suggests that Zika may be influenced to a greater degree by changes in precipitation and temperature than dengue, making it more likely to be confined to tropical areas. However, rising global temperatures would allow for the disease vector to expand its range further north, allowing Zika to follow. [22]

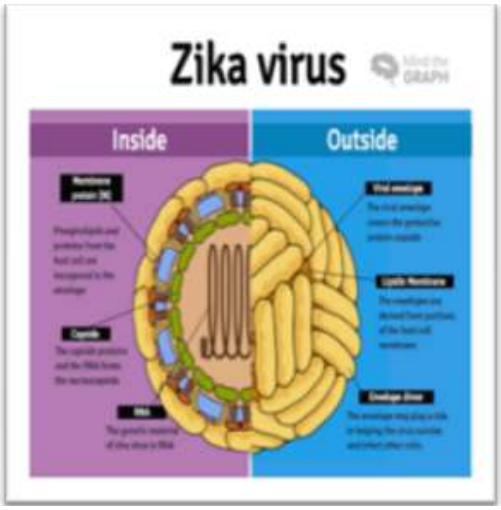
2. Sexual

Zika can be transmitted from men and women to their sexual partners; most known cases involve transmission from symptomatic men to women. As of April 2016, sexual transmission of Zika has been documented in six countries – Argentina, Australia, France, Italy, New Zealand, and the United States – during the 2015 outbreak. ZIKA can persist in semen for several months, with viral RNA detected for up to one year. The virus replicates in the human testis, where it infects several cell types including testicular macrophages, peritubular cells, and germ cells, the spermatozoa precursors. Semen parameters can be altered in patients for several weeks post-symptoms onset, and spermatozoa can be infectious. Since October 2016, the CDC has advised men who have traveled to an area with Zika should use condoms or not have sex for at least six months after their return as the virus is still transmissible even if symptoms never develop.



3. Pregnancy

Zika virus can spread by vertical (or "mother-to-child") transmission, during pregnancy or at delivery. Infection during pregnancy has been linked to changes in the neuronal development of the unborn child. Severe progressions of infection have been linked to the development of microcephaly in the unborn child, while mild infections potentially can lead to neurocognitive disorders later in life. Congenital brain abnormalities other than microcephaly have also been reported after a Zika outbreak. Studies in mice have suggested that maternal immunity to the dengue virus may enhance fetal infection with Zika, worsen the microcephaly phenotype, and/or enhance damage during pregnancy, but it is unknown whether this occurs in humans.



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4. Blood transfusion

As of April 2016, two cases of Zika transmission through blood transfusions have been reported globally, both from Brazil, after which the US Food and Drug Administration (FDA) recommended screening blood donors and deferring high-risk donors for 4 weeks. A potential risk had been suspected based on a blood-donor screening study during the French Polynesian Zika outbreak, in which 2.8% (42) of donors from November 2013 and February 2014 tested positive for Zika RNA and were all asymptomatic at the time of blood donation. Eleven of the positive donors reported symptoms of Zika fever after their donation, but only three of 34 samples grew in culture.[22]

Electron micrograph of Zika virus. Virus particles (digitally colored purple) are 40 nm in diameter, with an outer envelope and a dense inner core.

Zika virus capsid model, colored by chain

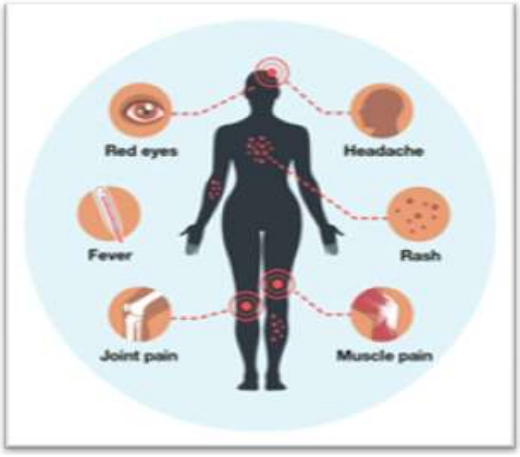
Fig. Zika virus

Virus classification	
(unranked):	Virus
Realm:	Riboviria
Kingdom:	Orthornavirae
Phylum:	Kitrinoviricota
Class:	Flasuviricetes
Order:	Amarillovirales
Family:	Flaviviridae
Genus:	Flavivirus
Species:	**Zika virus**

Zika Symptoms

Many people infected with the Zika virus won't have symptoms or will only have mild symptoms. The most common symptoms of Zika are

- Fever
- Rash
- Headache
- Joint pain
- Red eyes
- Muscle pain



Symptoms can last for several days to a week. People usually don't get sick enough to go to the hospital, and they very rarely die of Zika. Once a person has been infected with Zika, they are likely to be protected from future infections.[23]

Treatment

There is no specific treatment available for Zika virus infection or disease.

People with symptoms such as rash, fever, or joint pain should get plenty of rest, drink fluids, and treat symptoms with antipyretics and/or analgesics. Nonsteroidal anti-inflammatory drugs should be avoided until dengue virus infections are ruled out because of bleeding risk. If symptoms worsen, patients should seek medical care and advice.

Fig:-Infants with Moderate or Severe MicrocItaly Associated with Maternal Zika Virus Infection, as Compared with a Typical Newborn.[24]

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Pregnant women living in areas with Zika transmission or who develop symptoms of Zika virus infection should seek medical attention for laboratory testing, information, counseling, and other clinical care.

Microcephaly

Microcephaly (from Neo-Latin microcephalia, from Ancient Greek μικρός mikros "small" and κεφαλή kephalé "head is a medical condition involving a smaller-than-normal head. Microcephaly may be present at birth or it may develop in the first few years of life. Brain development is often affected; people with this disorder often have an intellectual disability, poor motor function, poor speech, abnormal facial features, seizures, and dwarfism.

The disorder is caused by a disruption to the genetic processes that form the brain early in pregnancy, though the cause is not identified in most cases. Many genetic syndromes can result in microcephaly, including chromosomal and single-gene conditions, though almost always in combination with other symptoms. Mutations that result solely in microcephaly

(primary microcephaly) exist but are less common. External toxins to the embryo, such as alcohol during pregnancy or vertically transmitted infections, can also result in microcephaly. Microcephaly serves as an important neurological indication or warning sign, but no uniformity exists in its definition. It is usually defined as a head circumference (HC) more than two standard deviations below the mean for age and sex. Some academics advocate defining it as a head circumference more than three standard deviations below the mean for age and sex.

There is no specific treatment that returns the head size to normal. In general, life expectancy for individuals with microcephaly is reduced, and the prognosis for normal brain function is poor. Occasional cases develop normal intelligence and grow normally (apart from persistently small head circumference). It is reported that in the United States, microcephaly occurs in 1 in 800-5,000 births.

There are a variety of symptoms that can occur in children. Infants with microcephaly are born with either a normal or reduced head size. Subsequently, the head fails to grow, while the face continues to develop at a normal rate, producing a child with a small head a receding forehead, and a loose, often wrinkled scalp. As the child grows older, the smallness of the skull becomes more obvious, although the entire body also is often underweight and dwarfed.

Severely impaired intellectual development is common, but disturbances in motor functions may not appear until later in life. Affected newborns generally have striking neurological defects and seizures. Development of motor functions and speech may be delayed. Hyperactivity and intellectual disability are common occurrences, although the degree of each varies. Convulsions may also occur. Motor ability varies, ranging from clumsiness in some to spastic quadriplegia in others.

Treatment for Microcephaly

Your baby may not need any treatment with mild microcephaly. Other medical problems caused by microcephaly may need to be treated. Your baby may also need speech, physical, or occupational therapy. These therapies will help your child function at his or her highest level as he or she grows. Life-long treatment will be needed for babies with severe microcephaly. Severe microcephaly may be life-threatening.

Complications

ZIKA infection has been associated with various complications, including congenital microcephaly, Guillain–Barré syndrome, and even fetal losses in women infected during pregnancy. [25, 26]

Congenital (intrauterine) infection: ZIKA infection in pregnant mothers can occur in any trimester and is reported to cause microcephaly in infants with many confirmed reports coming from Brazil showing the association of the virus infection with microcephaly in the newborn and even infant death (mostly if the infection is acquired during the first trimester).[25,27] The cases of muscular atrophy have also been observed in children with microcephaly born after the onset of the ZIKA outbreak in Brazil.[27]

ZIKA infection acquired during pregnancy is associated with poor outcomes for the fetus, which include central nervous system injury, placental insufficiency, in vitro fetal growth restriction (with or without microcephaly), and also fetal death.[28]

Neurological complications: Few cases have been reported showing the association of ZIKA infection with the Guillain–Barré syndrome.[26,29] About 90% of the patients had reported having symptoms of ZIKA infection about 6 days before neurological symptoms.[26] The

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other neurological manifestations include the reports of acute myelitis and meningoencephalitis associated with the detection of ZIKA in the CSF.[30,31]

Moreover, there is a report of ankle edema, axillary and/or inguinal lymphadenopathy, leukopenia with monocytosis, and thrombocytopenia from the cases of ZIKA infection in travelers from Italy.[32]

Diagnosis

The ZIKA infection should be suspected in patients having clinical symptomology of acute viremia during an ongoing epidemic in an area of the prevalence of Aedes mosquito or a history of recent travel to a ZIKA endemic area or if the person has had unprotected sexual contact with an infected partner.

The diagnosis of ZIKA infection is established by serum reverse transcription polymerase chain reaction (RT-PCR) for detection of ZIKA RNA or ZIKA serology (IgM antibodies).[33,34]

Serum RT-PCR is positive if done in the acute phase of the viremia, i.e., the first 3–7 days of the onset of illness.[34] The specific antibodies against ZIKA in serum (IgM antibodies) are detectable after 4 days of symptom onset, but its diagnostic value is limited due to cross-reactivity with other Flaviviruses (DENV and chikungunya virus). In ZIKA infection, the serum titers of the IgM antibody are ≥4-fold greater than DENV antibody titers, thus helping in the diagnosis.[32,34]

The medical literature has studies suggesting that the ZIKA RNA can be detected in the urine and the saliva of the patients for a longer duration than the serum by the RT-PCR method.[34]

Prenatal fetal evaluation of the pregnant females suspected or confirmed to have a ZIKA infection (also exposed to ZIKA) is done by regular fetal ultrasound examination, which can detect abnormalities as early as 18–20 weeks of gestation but is also operator-dependent.[34] The main ultrasound findings pointing toward fetal ZIKA infection are microcephaly (head circumference more than two standard deviations below the mean for gestational age), intracranial calcifications (cerebellum, intraocular, brain), hydranencephaly, ventricular dilatation, brain atrophy, anhydramnios, hydrops fetalis, and intrauterine growth retardation.[34]

Management

There is no specific treatment option available for ZIKA infection.[1,3,4] The course of the disease is mostly self-limiting and the management is primarily bed rest and supportive care, including increased intake of fluids to prevent dehydration and administration of acetaminophen for relief of fever and pain.[33,34] There is no vaccine or antiviral therapy available presently for ZIKA.[33,34] The preventive measures involve the control of the vector (Aedes mosquito) growth and its elimination and prevention of mosquito bites. The sexual mode of transmission can be avoided by the use of barrier methods (condoms) or abstinence from sexual intercourse.

Mosquito bites can be prevented by wearing a long-sleeved shirt and pants, use of insect repellent, and being indoors as much as possible (with air conditioning, window/door screens, and/or mosquito nets).[35]

Aedes mosquitoes breed in stagnant water, thus found in abundance in places of ongoing construction (making it a disease more prominent in urban areas). Moreover, these mosquitoes are commonly found in tropical and sub-tropical areas, making Asian countries (including the Indian subcontinent) an endemic zone for the growth of Aedes. Environmental control measures include the identification and elimination of the potential breeding sites of water stagnation.[35]

So far the cases of ZIKA in India have not been reported, but a study conducted in six states of India in the year 1952–1953 reported the neutralizing antibodies in the sera to certain viruses including ZIKA in the Indians.[36,37] This detection could well be due to cross-reactivity among different flavivirus antibody assays. However, the recent reports from Bangladesh are alarming where the first case of ZIKA infection in a 67-year-old male has been detected.[38] The problem of ZIKA could become grave in Asian countries due to warm and humid conditions which are ideal for mosquito vector breeding.[37] In these resource-strained countries where the per capita income is low and there is a meager contribution from the government's annual health budget, the emergence of ZIKA could only add to the woes.[39,40,41] Moreover, in the absence of clear guidelines, management strategies, and cure, the proper dissemination of healthcare information about ZIKA is imperative, and thus the role of all the stakeholders, including clinicians, healthcare workers, the general public, government agencies,

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NGO's such as the HIFA2015 is very important.[42,43,44]

Zika Virus Epidemic Concerns

The outbreak of ZIKA infection in 2013 in French Polynesia is considered to be the largest and is postulated to have spread to Brazil during the major sports events of 2014, the World Cup Soccer and the Va'a World Sprint Championship canoe race, which were hosted by Brazil.[45] Now with the upcoming Summer Olympics in August 2016 to be again hosted in Brazil, the spread of this virus to a massive scale remains a global concern.[11]

The rapid spread of zoonotic diseases such as ZIKA is due to the urbanization of forest areas for the ever-expanding human population. Moreover, the speed and the ease of transport (airways, roadways, railways, and water travel) not only for humans but also for disease vectors, lead to the rapid and widespread dissemination of the disease.[11]

India carries a potential threat of an outbreak of ZIKA infection, being an endemic country for the vector (Aedes aegypti) and thus realizing the same, the Indian government has issued guidelines for tackling this problem.[46,47

II. SUMMARY

Zika virus was first discovered in 1947 and is named after the Zika Forest in Uganda. In 1952, the first human cases of Zika were detected and since then, outbreaks of Zika have been reported in tropical Africa, Southeast Asia, and the Pacific Islands. Zika outbreaks have probably occurred in many locations. Zika is a mosquito-borne virus, similar to dengue fever, yellow fever, and West Nile virus. The infection is associated with a birth defect called microcephaly, which can affect babies born to people who become infected with Zika while pregnant.The most common symptoms of Zika are fever, rash, headache, joint pain, red eyes, and muscle pain. Zika is spread mostly by the bite of an infected mosquito. Prevent Zika by avoiding mosquito bites. Zika can cause birth defects and is linked to Guillain-Barré syndrome. Zika virus was discovered in East Africa in 1947 by the Rockefeller Foundation during investigations on the ecology of yellow fever. Although it was subsequently shown to have widespread distribution in Africa and Asia, it was not known to cause epidemics until 2007.The best protection from the Zika virus is preventing mosquito bites indoors and outdoors, especially from sunrise to sunset when mosquitos are most active. Such measures include: Using mosquito repellent according to the instructions indicated on the product label. Wearing long-sleeved shirts and long trousers. People are the disease reservoir, meaning mosquitoes get Zika from an infected person during the first week of their symptoms. Mosquitoes can then spread the disease to other people through bites. There are three primary methods of Zika transmission: mosquito bite, mother-to-baby, and sexual transmission.

III. CONCLUSIONS

The recent outbreaks of ZIKA infection in the Americas have brought this emerging arbovirus disease into the limelight as a cause of congenital anomaly (microcephaly) in infants born to infected mothers. The rapid spread of ZIKA is an international cause of concern with the virus reaching the Asian countries, including the neighboring countries of India. The other issue of epidemic control in the future to be addressed is the spreading menace of mosquito-borne diseases due to the inadequate control of the breeding of this vector. Furthermore, there is a need for large-scale animal and human studies from various corners of the globe so that clear management guidelines can be developed against ZIKA. Furthermore, efforts to control the emerging menace due to obscure and new viruses should be given prime importance.

The explosive outbreak in Brazil and the recent Indian outbreak have already highlighted ZIKA's potential for rapid population spread. Public health authorities should make effective policies to prevent non-vector-borne transmissions along with conventional vector control measures. Detailed research using animal models is greatly needed to clearly understand the pathogenesis and association of ZIKA with neurological and autoimmune complexities. Factors such as climate change, increasing urbanization, global travel, and growth in the human population are behind the increase in the geographical range of mosquitoes and leading burden of various arboviral diseases. It is difficult to predict the next Zika epidemic, but with the help of effective surveillance studies integrated with accurate and rapid diagnosis and the development of specific antivirals and vaccines, we could prepare ourselves for better management and control of this emerging infection

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