Review article

Zika Virus Disease: A re-emerging disease with pandemic potential

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ABSTRACT

Emerging and reemerging diseases are increasing in the recent past posing great threat to the human population. Re-emerging communicable diseases are those which are known and reappear after a decline in incidence. The Zika virus, a re-emerging arbovirus, spread by Aedes mosquitoes is causing a panic across continents over the globe. With the information being published every day gives us an alarming insight into how a virus thought to cause a mild disease has reemerged into a novel pathogen with its high potential to cause devastating complications. The clinical presentation of Zika virus disease is nonspecific with mild fever, rash, arthralgia, and conjunctivitis and mimics other arboviral diseases like dengue and chikungunya. The current outbreak of the Zika Virus Disease and its associations with Guillain-Barré syndrome and microcephaly has entranced the human population with a new challenge. The transmission and maintenance of the virus in the human population remains to be elucidated and the best strategy in winning over the current situation is to control or eliminate the vector population. The morbidity and mortality in the hands of such re-emerging viruses with new dimensions is unpredictable and overwhelming. It is therefore important to reanalyze the previous outbreaks and intensify the need to identify the factors responsible for the spread of the vector and the reason behind its increased virulence pattern especially its neurotropic attitude.

KEY WORDS: Zika, Re-emerging, Pandemic potential ,Microcephaly , Guillain-Barre syndrome

INTRODUCTION

Zika virus (ZIKV; genus Flavivirus, family Flaviviridae) is an emerging virus of medical and public health importance.[1] Zika Virus Disease, caused by Zika virus that is spread to people primarily through the bite of an infected Aedes species mosquito, is a re-emerging disease. The disease now has an explosive pandemic potential with outbreaks occurring in Africa, South East Asia, Pacific islands and the America.[2]

There is a growing concern across the globe due to detection and isolation of this viral pathogen being associated with increasing incidence of microcephaly in new born infected fetuses and Guillain-Barre syndrome in adults.[3]

In this article, we review about the recent outbreaks of Zika viruses, pathogenesis of microcephaly and Guillain-Barre syndrome and strategies to prevent and control the diseases.

History and origin

Zika was first isolated in April 1947 from rhesus monkey in the Zika forest of Uganda.[4] (Hence called Zika). Zika virus is transmitted by mosquitoes primarily by female Aedes aegypti and several other Aedes species like A. africans, A. albopictus, etc. First evidence of human infection was identified in Uganda and the United Republic of Tanzania in 1954 in a study demonstrating the presence of neutralizing antibodies to Zika virus in sera.[5] Zika virus which remained obscure and confined to equatorial belt gradually spread from Africa to Asia in 1951-1981.[3]

From its discovery until 2007, there were only 14 confirmed human cases of Zika virus infection from Africa and South East Asia.[6] Since 2007 there are series of outbreaks occurring in most part of the world, alerting for preparedness for the pandemic Zika emergence.

Today cases have been reported from Indonesia, Spain and Europe. It has raised brows against its subtle nature
following the confirmation of its link towards birth defects and GBS in December 2015.

On January 22, 2016, CDC activated its Emergency Operations Center (EOC) to respond to outbreaks of Zika occurring in the Americas and increased reports of birth defects and Guillain-Barre syndrome in areas affected by Zika. On February 1, 2016, the World Health Organization declared a Public Health Emergency of International Concern (PHEIC). On February 8, 2016, CDC elevated its EOC activation to a Level 1, the highest level.

Outbreaks in chronology [6]

1947–First Zika virus isolation in Zika forest in Uganda

1954: The virus is isolated from a young girl in Eastern Nigeria.

1958: Two further Zika virus strains are isolated from Aedes africanus mosquitoes caught in the Zika forest area.

1960s-1980s: Zika is now being detected in mosquitoes and sentinel rhesus monkeys used for field research studies in a narrow band of countries that stretch across equatorial Africa.

1969–1983: The known geographical distribution of Zika expands to equatorial Asia, including India, Indonesia, Malaysia and Pakistan, where the virus is detected in mosquitoes.

2007: Zika spreads from Africa and Asia to cause the first large outbreak in humans on the Pacific island of Yap, in the Federated States of Micronesia.

2008: A US scientist conducting field work in Senegal falls ill with Zika infection upon his return home to Colorado and infects his wife in what is probably the first documented case of sexual transmission of an infection usually transmitted by insects.

2012: Researchers publish findings on the characterization of Zika virus strains collected in Cambodia, Malaysia, Nigeria, Senegal, Thailand and Uganda, and construct phylogenetic trees to assess the relationships. Two geographically distinct lineages of the virus, African and Asian, are identified.

2013–2014: The virus causes outbreaks in four other groups of Pacific islands: French Polynesia, Easter Island, the Cook Islands, and New Caledonia. The results of retrospective investigations are reported to WHO on 24 November 2015 and 27 January 2016. These reports indicate a possible association between Zika virus infection and congenital malformations and severe neurological and autoimmune complications. In particular, an increase in the incidence of Zika infection towards the end of 2013 was followed by a rise in the incidence of Guillain-Barre syndrome.

2015–2016 – Zika is spreading from Brazil to whole of America

Mode of Transmission

Zika virus is primarily transmitted to humans through bites from Aedes mosquitoes, which often live around buildings in urban areas and are usually active during daytime hours (peak biting activity occurs in early mornings and late afternoons). Transmission of ZIKV by artificially fed Ae. aegypti mosquitoes to mice and a monkey in a laboratory was reported in 1956.[7]

Some evidence suggests Zika virus can also be transmitted to humans through blood transfusion, perinatal transmission and sexual transmission. However, these modes are very rare. Zika transmission by sexual intercourse has been reported by Foy et al. [8] and Musso D et al. They also suggested the association of hematospermia with sexually transmitted microorganisms.[9]

Dynamics of Transmission

The epidemiology of ZIKV transmission, with the available data appears to be similar to that of dengue. The ZIKV natural transmission cycle involves mosquitoes, especially Aedes spp is maintained in a zoontic cycle between arboreal Aedes spp. mosquitoes and nonhuman primates in African and Asian forests.

The mosquitoes that carry the virus breed in open ponds/pools of water. The ones that carry Zika tend to bite and infect primates and humans during the day. It is important to understand the seroprevalence, Local transmission and Indigenous (autochthonous) transmission when discussing about the global spread of the virus. [10]Tropical countries not only harbor mosquito species that can transmit the virus, but there is little population immunity to infection.

People, who contract the disease by traveling to countries where Zika virus is circulating, are considered —imported cases; that is, they were bitten by infected mosquitoes during trips to places where the virus is present. In the Pacific Region the epidemiology is distinct due to small populations scattered over thousands of tropical and sub-tropical islands on both sides of the equator in relative geographic isolation, together with (nowadays) significant people’s mobility and thereby exposure to circulating arboviruses through the airline networks of the Asia-Pacific region.

Multiple factors, including economic development and land use, human demographics and behavior, and international travel, commerce, contribute to the global spread of the recently remerged Zika virus. The spread of ZIKV represents an additional challenge for public health systems, particularly because of the risk for concurrent transmission of DENV and CHIKV by the same vectors, Ae. aegypti and Ae. albopictus mosquitoes, which are abundant throughout tropical and subtropical regions.[11]

The viral pathogen

ZIKV is an RNA virus containing 10,794 nucleotides, encoding 3,419 amino acids belongs to the genus Flavivirus,
family Flaviviridae. It is closely related to Spondweni virus. St. Louis encephalitis viruses; yellow fever virus is the prototype of the family, which also includes dengue, Japanese encephalitis, and West Nile viruses. The virus was isolated from the serum of a monkey 9 days after experimental inoculation. ZIKV is killed by potassium permanganate, ether, and temperatures >60°C, but it is not effectively neutralized with 10% ethanol.[11]

More about disease vectors

ZIKV has been isolated from Ae. africanus, Ae. apicoargenteus, Ae. luteocephalus, Ae. aegypti, Ae. vitattus, and Ae. furcifer mosquitoes.[11] Both Ae. aegypti and Ae. albopictus have been implicated in large outbreaks of Zika virus. Ae. aegypti is confined to tropical and subtropical regions, while Ae. albopictus can be found in tropical, subtropical and temperate regions. Ae. albopictus has spread from Asia and become established in areas of the South Pacific, Africa, Europe and the Americas in recent decades.[12] In the South Pacific, Ae. hensilli was implicated in the spread of Zika virus on Yap Island in 2007.[13] While Ae. polynesiensis was suspected to spread Zika virus in French Polynesia in 2013.[6,17] Neither of these endemic species had been recognized as a Zika virus vector before, indicating that as this emerging disease spreads to previously unaffected countries, the potential exists for other endemic Aedes species to play a role in transmission.

a) Ae. aegypti is closely associated with human environments and can breed in indoor (flower vases, concrete water tanks in bathrooms), and artificial outdoor (vehicle tyres, water storage vessels, discarded containers) environments.

b) Ae. albopictus thrives in a wider range of water-filled breeding sites than Ae. aegypti, including coconut husks, cocoa pods, bamboo stumps, tree holes and rock pools, in addition to artificial containers such as vehicle tyres and plant pot saucers. This diversity of habitats explains the abundance of Ae. albopictus in rural as well as peri-urban areas and shady city parks.

c) Ae. hensilli breeds in coconut shells, tins, plastic containers, vehicle tyres, tree holes, canoes and metal drums.

d) Ae. polynesiensis breeds in tree holes, coconut shells and crab holes

Clinical symptoms:
The main symptoms of ZIKV disease include:

a) low-grade fever (<38.5°C)

b) transient arthritis/arthralgia with possible joint swelling mainly in the smaller joints of the hands and feet

c) maculo-papular rash often spreading from the face to the body

d) conjunctival hyperemia or bilateral non-purulent conjunctivitis
e) general non-specific symptoms such as myalgia, asthenia and headaches.

The outbreak on Yap Island was characterized by rash, conjunctivitis, and arthralgia. [13, 14] Other less frequent manifestations included myalgia, headache, retro orbital pain, edema, and vomiting. [14]

The incubation period ranges from 3 to 12 days. [15] The disease symptoms are usually mild and last for 2 to 7 days. Infection may go unrecognized or be misdiagnosed as dengue, chikungunya or other viral infections presenting with fever and rash. Asymptomatic infections are common – as described with flaviviral infections such as dengue and West Nile fever – and only one in four people infected with ZIKV are believed to develop symptoms. [16] Association with neurological complications such as Guillain-Barré syndrome has been suspected during the French Polynesia outbreak and remains under investigation. [16] Most people recover fully without severe complications, and hospitalization rates are low. To date, there have been no reported deaths associated with ZIKV infection.

Prenatal or perinatal complications of ZIKV infections have not been described in the literature. There is some evidence that perinatal transmission can occur, most probably transplacental or during the delivery of a viraemic mother. [8] ZIKV transfusion-derived transmission is theoretically possible as 3% of asymptomatic blood donors were found positive for ZIKV by PCR during the ZIKV outbreak in French Polynesia, from November 2013 to February 2014. [17] The presence of a viable virus was detected in semen more than two weeks after recovery from an illness consistent with ZIKV infection. Possible cases of sexual transmission of ZIKV have been reported. [9] However, the three modes of transmission described above have been rarely reported prior to the current ongoing disease outbreak.[18]

Pathogenesis- microcephaly

Although flaviviral replication is thought to occur in cellular cytoplasm, it replicates initially in dendritic cells near the site of inoculation then spreads to lymph nodes and the bloodstream. The research conducted by the Flavivirus Laboratory at the Oswaldo Cruz Foundation (IOC-Fiocruz) showed that Zika virus is able to cross the placental barrier and reach the amniotic fluid, which involves the fetus during pregnancy. This happens because Zika is a neurotropic virus, which means it tends to strike the host’s nervous system by crossing the blood brain barrier and can lead to microcephaly still in the placental environment. [4]

These research findings were complemented by Bell and Colleagues in 1972. According to them the virus infected both neurons and glia producing intracytoplasmic inclusions, which they called it —virus factories. These factories originated from the endoplasmic reticulum and associated with other organelles. Interactions between virus and endoplasmic reticulum induce autophagy. In reference to microcephaly abnormal function of centrosomes i.e amplification of centrosome number has been revealed to be one of the inducers of this condition. [19]

In neural brain development an increase in centrosomes in mice resulted in a delay of mitosis ,an increase in apoptosis, improper neural stem orientation, premature neuronal differentiation and decrease in progenitor cells. The overall
Pathogenesis of Gullian-Barre syndrome-

The pathophysiological mechanism of Zika-related G-B syndrome is unknown. It could be of immunological origin as described with other infectious agents. The antibodies produced by Zika infection cross react with peripheral nervous components and cause destruction leading to paralysis. [21]

Infectious ZIKV has been detected in human blood as early as the day of illness onset; viral nucleic acid has been detected as late as 11 days after onset it is present in the blood for a very limited period of time, measured in a week to at most 10 days. Detected in semen for 62 days after a person is infected, adding to evidence of the virus’s presence in fetal brain tissue, placenta and amniotic fluid. In individual patients, the highly deadly virus remained in semen and eye fluid for months. The virus can continue to persist and or multiply. Zika may persist in the fetal brain because it is an immunologically privileged site. It is of prime concern about Zika that it can be harbored in immune protected sites and hence could be transmitted sexually through semen.

Diagnosis

Sample collection: Bureau of Public Health Laboratories (BPHL)-Tampa or BPHL Jacksonville recommends Serum sample collection within the first 7 days of illness (2 ml serum/red or tiger top tube) AND/OR urine sample collected ≤21 days of illness (10 ml collected in a sterile container). Other samples that may be tested using PCR if available: CSF, amniotic fluid, birth cord blood, and tissues. [22]

Hayes E B suggested that diagnostic testing for flavivirus infections should include an acute-phase serum sample collected as early as possible after onset of illness and a second sample collected 2 to 3 weeks after the first. [8] The virus was isolated from urine and semen of experimentally infected animals, and viremia developed in female boars that were artificially inseminated with the infected semen. [6]

Reverse-transcriptase PCR (RT-PCR) can be used to detect the Zika virus during the first 1 week (in blood and serum) to 2 weeks (in urine) of the illness. Virus-specific IgM and neutralizing antibodies typically develop toward the end of the first week of illness; cross-reaction with related flaviviruses (e.g., dengue and yellow fever viruses) is common and may be difficult to discern. Plaque-reduction neutralization testing can be performed to measure virus-specific neutralizing antibodies and discriminate between cross-reacting antibodies in primary flavivirus infection. [22] An ELISA has been developed at the Arboviral Diagnostic and Reference Laboratory of the Centers for Disease Control and Prevention (Atlanta, GA, USA) to detect immunoglobulin (Ig) M to ZIKV.

For pregnant ladies: Zika virus RT-PCR and serology assays can be performed on maternal serum or plasma. Zika virus RT-PCR can also be performed on amniotic fluid. Other testing that can be performed includes the following: 1) histopathology examination and immune histochemical staining of the placenta and umbilical cord, 2) Zika virus testing of frozen placental tissue and cord tissue, and 3) IgM and neutralizing antibody testing of cord blood.

Timing of amniocentesis should be individualized based on the patient’s clinical circumstances. Amniocentesis is not recommended until after 15 weeks of gestation. Amniocentesis performed ≥15 weeks of gestation is associated with lower rates of complications than those performed at earlier gestational ages (≤14 weeks of gestation). However, the exact timing of amniocentesis should be individualized based on the patient’s clinical circumstances. Referral to a maternal-fetal medicine or infectious disease specialist with expertise in pregnancy management may be warranted. Risk and benefits of performing the amniocentesis should be discussed with the patient. [23]

A positive Zika virus RT-PCR result from amniotic fluid would be suggestive of intrauterine infection. This information would be useful for pregnant women and their healthcare providers to assist in determining clinical management (e.g., antepartum testing, delivery planning). A negative Zika virus RT-PCR result from amniotic fluid may prompt a work up for other causes of microcephaly (e.g., other infections, genetic disorders). [24,25]

Treatment

There is no licensed vaccine to prevent or specific medicine to treat Zika infections. Zika vaccines would, however, face the same problem as vaccines for chikungunya, West Nile, St. Louis encephalitis, and other arboviruses: since epidemics appear sporadically and unpredictably, preemptively vaccinating large populations in anticipation of outbreaks may be prohibitively expensive and not cost-effective, yet vaccine stockpiling followed by rapid deployment may be too slow to counter sudden explosive epidemics.

Mainstay of management is bed rest and supportive care by drinking plenty of fluids to prevent dehydration. Medications like acetaminophen are indicated to relieve fever and pain. Aspirin and NSAIDs are generally avoided.

Prevention and control strategies:

Actions taken by PAHO/WHO regarding Zika fever include:

a) Early warning and dissemination of information: PAHO disseminates information on public health events of international concern by publishing alerts, interactive maps, and reports. The Epidemiological Alerts provide information on international public health events that have been confirmed with the Member States, along with the recommendations the Pan American Health Organization.
b) Continuous communication and coordination with the WHO Collaborating Center, CDC Fort Collins, regarding the disease.

c) Preparation of algorithms and technical recommendations for laboratory detection

d) Materials for clinical case management in development

e) Communication

Travel advisory

Recommends that women who are pregnant or plan to become pregnant in the near term must consider delaying travel to areas with Zika virus present. Serologic testing in asymptomatic pregnant women can be done in 2 and 12 weeks after pregnant women return from travel to areas with ongoing Zika virus transmission. A negative IgM test result 2-12 weeks after known exposure suggests that a recent Zika virus infection did not occur, which may obviate the need for serial ultrasounds.

If travelling in Zika infected areas, women who are pregnant or plan to become pregnant should consult with their healthcare provider. All travelers should take all precautions to avoid mosquito bites, including [26]:

- Wear long-sleeved shirts and long pants.
- Use insect repellents containing DEET, picaridin, oil of lemon eucalyptus (OLE), or IR3535. Always use as directed.
- Insect repellents containing DEET, picaridin, and IR3535 are safe for pregnant and nursing women and children older than 2 months when used according to the product label. Oil of lemon eucalyptus products should not be used on Children under 3 years of age.
- If you use both sunscreen and insect repellent, apply the sunscreen first and then the repellent.
- Use permethrin-treated clothing and gear (such as boots, pants, socks, and tents).
- Use bed nets as necessary.
- Stay and sleep in screened-in or air-conditioned rooms.
- Be particularly vigilant for the 2 hours after sunrise and the 2 hours before sunset.

Until more is known, both men and women are advised to use appropriate contraception for four weeks after returning from areas which have current active transmissions of Zika virus, even if they're not experiencing symptoms.

CONCLUSION

Human Zika virus infection appears to have changed in character while expanding its geographical range of inhabitation. The change is from an endemic, mosquito-borne infection causing mild illness across equatorial Africa and Asia, to an infection causing robust outbreaks linked with neurological disorders including Guillain-Barré syndrome and microcephaly. The future transmission of Zika infection is likely to coincide mainly with the distribution of Aedes mosquito vectors, although there may be rare instances of person-to-person transmission (other than mother to child & through semen).

In areas where potential vectors are present, vigilance should be enhanced to detect imported cases of ZIKV, and laboratory capacity to confirm suspected ZIKV infections should be strengthened. Public awareness about this silent monster virus should also be propagated, which would otherwise lead to the substitution of a deformed human population.

Additional research at international level is necessary to determine the link between Zika virus and fetal damage. Hence the main importance of focus is in improving the strategies for early detection and diagnosis of Zika virus especially in pregnant ladies to decrease the incidence of microcephaly and also G-B syndrome which is of growing concern.

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