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Clinical Review

Zika Virus- What we all Need to Know

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Abstract

Among the mosquito borne infections in the tropical and sub-tropical areas of the world, Zika virus disease has emerged as one of the most serious cause of health concern. Zika virus infected people usually have no signs and symptoms, some may present with a general feeling of discomfort, mild fever, rash and headache. Infections during pregnancy can miscarriage and cause microcephaly other neurological disorders include Guillain-Barre syndrome. Since no Zika virus vaccine is available best is to prevent mosquito bites and eliminate mosquito habitats.

Keywords: Zika Virus; Mosquito Borne Infections; Guillain-Barre Syndrome

Introduction

Originally isolated in a caged Rhesus monkey at a yellow fever surveillance camp in the Zika forest in Uganda in 1947, Zika virus was subsequently identified as a member of the Spondweni virus complex belonging to the family Flaviviridae. After a relatively dormant timeline Zika virus became the first major infectious disease linked to birth defects in the last half century. The alarm raised subsequently was of such magnitude that the World Health Organisation (WHO) declared it as a Public Health Emergency of International Concern in February 2016. Currently Zika virus disease is an epidemic in 31 countries across the world [1-3].

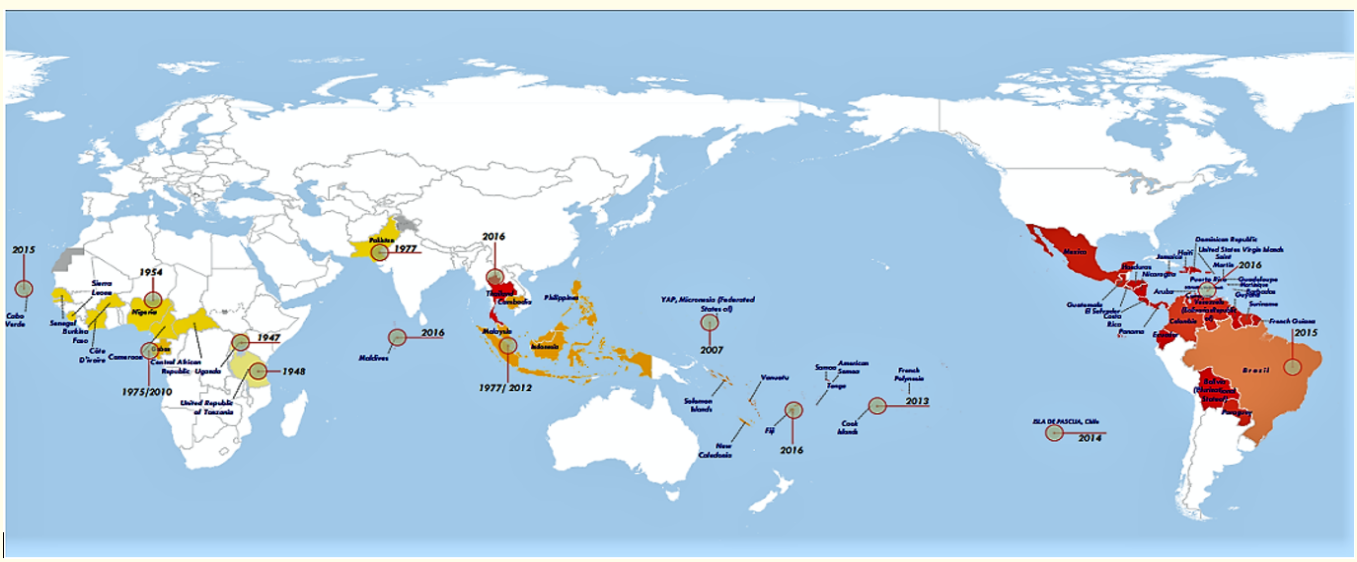

Figure 1: Timeline of Zika virus (Image source: WHO) [4].

Morphology

Zika virus is an icosahedral virus with a lipid envelope covered with dense surface projections of glycoproteins. It is sensitive to heat, UV radiations, disinfectants and acidic pH and is unstable in the environment. It has a positive sense single stranded non-segmented 11 kb RNA with a 10 kb open-reading frame that codes for three structural and seven non-structural proteins. Phylogenetic analysis has revealed the existence of two major lineages - African and Asian [5].

Transmission [6-13]

Transmission of Zika virus takes place by the following:

- Bite of an infected mosquito
- Sexual intercourse (including vaginal, anal, and oral sex)
- Materno-foetal transmission
- Blood product transfusion
- Organ transplantation
- Laboratory exposure to infected clinical samples.

The primary mode of transmission of Zika virus is by the bite of *Aedes aegypti* mosquito which can also transmit dengue and chikungunya viruses.

Pathogenesis

As with other flaviviruses, Zika virus is adapted to survive in cells of multiple types of hosts (mosquitoes, monkeys, man). The virus enters the host cell by endocytosis mediated by unidentified receptors. Further acidic changes induced by the virus lead to fusion and uncoating of the nucleocapsid; releasing the genome. The nascent virions mature through the Golgi apparatus and are then released from the cell [2,5].

Epidemiology

Outbreaks of Zika virus infection have occurred in Africa, Southeast Asia, and the Pacific Islands; currently, there is an ongoing Zika virus outbreak in the Americas, the Caribbean, and the Pacific.

Though Zika virus was first isolated at a Yellow fever surveillance camp in the Zika forest (Uganda) in 1947 it was not until 1952 when the first human cases were detected in Uganda and Tanzania. After this sporadic case were reported as the virus started spreading across equatorial Africa and Asia. In 2007 Zika virus emerged with a major outbreak in the Yap Islands of Micronesia with more than 70 percent of the population ≥ 3 years of age being infected. Subsequently an outbreak occurred in French Polynesia in 2013 to 2014 affecting about two-thirds of the population.

In the Western hemisphere Zika virus infections was first detected in February 2014 on Chile's Easter Island followed by Brazil in May 2015 where infection and complication rate prompted WHO to declare it as an International Health Emergency.

The World Health Organisation has classified 148 countries across the world into 4 categories on the basis of distribution of ongoing infection with India being in Category 2 i.e. area either with evidence of virus circulation before 2015 or area with ongoing transmission that is no longer in the new or re-introduction phase, but where there is no evidence of interruption.

On 15 May 2017, three laboratory-confirmed cases of Zika virus disease in Bapunagar area, Ahmedabad District were reported by the Ministry of Health and Family Welfare-Government of India (MoHFW). Taking into consideration the high risk of spread of Zika virus disease due to prevalence of vector in the country as well as the fatal outcomes of the disease National Guidelines and Action

Figure 2: Locations of three Zika cases revealed by surveillance in the Gujarat state of India [17].

Plan on Zika virus disease were formulated for the prevention and containment of spread in case of any outbreak. Other than these no other case has been reported owing to the strict surveillance and implementation of these guidelines [14-17].

Clinical Features

The clinical presentation and course of infection with Zika virus is most consistent with a dengue fever–like illness without haemorrhagic manifestations. The symptoms observed most commonly are:

- Fever
- Arthralgia
- Non-purulent conjunctivitis
- Headache

Incubation period of Zika virus infection is 3 days, with the first symptoms a frontal headache followed by fever. Clinical illness lasts for 5 days and then resolved. Laboratory findings include a mild leukopenia and minimal changes in liver function test results and platelet counts.

Gastrointestinal symptoms and mucous ulceration have been observed less commonly. Generally, illness has been usually mild and self-limited, and lasts for several days to 1 week. It is estimated that approximately 80% of Zika virus infections are asymptomatic [9,18,19].

Complications [9,18-27]

- Perinatal complications most notably microcephaly.
- Guillain-Barré syndrome.
- Encephalitis.
- Transverse myelitis.
- Encephalomyelitis.
- Meningoencephalitis.
- Chronic inflammatory demyelinating polyneuropathy.
- Brain ischemia.
- Neuropsychiatric and cognitive symptoms.

Lab Diagnosis [29-31]

Zika virus RNA has been detected in blood, urine, semen, saliva, female genital tract secretions, cerebrospinal fluid, amniotic fluid, and breast milk.

Differential Diagnosis [28]		
Other viral causes of arthritis	Dengue	It usually presents with high fever, severe muscle pain, and headache and may also be associated with haemorrhage. It is typically not associated with conjunctivitis.
	Chikungunya	It usually presents with high fever and intense joint pain affecting the hands, feet, knees, and back and is not associated with conjunctivitis.
	Parvovirus	It can present with acute and symmetric arthritis or arthralgia, most frequently involving the small joints of the hands, wrists, knees, and feet. Rash may or may not be present. The diagnosis is established via serology
	Rubella	Clinical manifestations include low-grade fever and coryza. Macular rash (beginning on the face and spreading to the trunk), arthritis and lymphadenopathy may be present. The diagnosis is established via serology.
Measles	Clinical manifestations include fever, cough, sore throat, coryza, conjunctivitis, and lymphadenitis. Koplik spots may precede the generalized rash. The diagnosis is established via serology	
Leptospirosis	It is characterized by fever, rigors, myalgia, conjunctival suffusion, and headache. Less commonly observed are cough, nausea, vomiting, diarrhea, abdominal pain, and arthralgia. It may be distinguished by the presence of jaundice. The diagnosis is established via serology.	
Malaria	It is characterized by fever, malaise, nausea, vomiting, abdominal pain, diarrhea, myalgia, and anemia. The diagnosis is established by visualization of parasites on peripheral smear.	
Rickettsia infection	Rickettsial infections with similar manifestations include African tick bite fever and relapsing fever. African tick bite fever is observed among travellers to Africa and the Caribbean and is characterized by headache, fever, myalgia, solitary or multiple eschars with regional lymphadenopathy, and generalized rash; the diagnosis is established via serology. Relapsing fever is characterized by fever, headache, neck stiffness, arthralgia, myalgia, and nausea; diagnostic tools include direct smear and polymerase chain reaction.	
Group A *Streptococcus*	Clinical manifestations of include fever, myalgia, cutaneous manifestations (cellulitis, fasciitis), pharyngitis, and shock. The diagnosis established by positive cultures from the blood or other tissues.	

Table 1

Demonstration of Zika Virus RNA in Different Body Fluids		
Type of Specimen	**Usual Detectable Time***	**Detection Range**
Blood	2 weeks	
Urine	6 weeks	Up to 91 days
Semen	About 3 months	7 days to 188 days
Female genital tract secretions	More than 14 days	
Saliva		Up to 91 days
Tears		Up to 30 days
*since onset of symptoms		

Table 2

Inclusion/exclusion criteria

Zika virus testing should be done in case of:

- Pregnant women who are symptomatic and with possible exposure to Zika virus.
- Pregnant women who are asymptomatic and exposure to Zika virus is suspected.
- Antenatal mothers with ultrasonographic findings sugges tive of congenital Zika virus infection and expo sure to Zika virus is suspected.
- Individuals who are symptomatic with suspected exposure to Zika virus

Zika virus testing to be decided on case basis:

- Pregnant women with suspected but no ongoing expo sure to Zika virus (i.e. travellers).

Testing Zika virus NOT suggestive in case of:

- Asymptomatic and non-pregnant persons.
- As a part of antenatal screening procedures.

Viral ribonucleic acid (RNA) is the first analyte that can be detected in an infected person. The development of an immune response is usually accompanied by rising titres of Immunoglobulin M (IgM) and gradual decline in the levels of viral RNA usually by 6 weeks after symptom onset when Nucleic acid test (NAT) is most informative. IgM antibodies on the other hand are detectable up to 12 weeks after symptom onset. However, both viral RNA and IgM antibodies can be detected beyond these time frames. This persistence of IgM antibodies beyond 12 weeks has limited the ability to determine the timing of occurrence of the disease in the pre and post conception period. Another hurdle in the diagnosis of Zika virus infection is the similarity of clinical presentations, transmission cycles, geographic distributions and cross-reactivity on serologic assays for Zika virus and other arboviruses especially dengue and chikungunya. Thus, to establish a diagnosis assays for testing these closely related viruses are necessary.

Testing Methods

1. **Nucleic acid test, or NAT*:*** Nucleic acid test is a very specific technique, but false positive results have been reported rarely. This largely depends on the type of assay performed as well as patient population.

2. **Antibody Detection Methods:** Owing to the temporal nature of Zika virus RNA in serum and urine, a negative NAT is not sufficient to rule out recent Zika infection. In areas of low endemicity this problem can be sorted out by using serological diagnostic techniques because as viral RNA starts waning antibodies (IgM) against Zika virus are typically first detected.

3. **Confirmatory testing*:*** IgM assays for Zika virus need to be confirmed by additional results from the plaque reduction neutralization test (PRNT). PRNT testing which is a confirmatory test is usually done for serum specimens with non-negative IgM result. However, these cannot be used for the analysis of the timing of Zika virus infection. PRNT is not specific for the type of flavivirus causing infection especially in case of prior infection with flavivirus. Hence PRNT confirmation is not recommended in areas with high prevalence of flaviviruses.

Management

Zika virus causes mild disease that does not requires specific treatment. Most cases can be managed by rest, proper hydration and drugs like paracetamol with antipyretic and analgesic actions. Medical intervention is required in case of worsening of symptoms.

Prevention [32-35]

<table>
<tr><th colspan="2">Travel Advisory</th></tr>
<tr><td colspan="2">1. Travel to the affected countries should be deferred/ cancelled with special respect to pre and post conception period.

2. Protective measures should be practised by all individuals travelling to affected areas, especially during day time, to prevent mosquito bites.

3. To avoid complications in case of co-morbid conditions (diabetes, hypertension, chronic respiratory illness, Immune disorders etc) individuals should adhere to all medical advice before, during and after travel to affected countries.

4. In case of fever within two weeks of return from an affected country medical advice should be sought.

5. Travel details to affected areas are essential for appropriate ante-natal assessment and management.</td></tr>
<tr><th>DO's</th><th>DON'T's</th></tr>
<tr><td>For preventing/ controlling mosquito breeding

1. All water tanks and containers should be covered.

2. Unused containers and potential sites for collection of water and breeding of mosquitoes should be destroyed.

3. Coolers should be emptied and cleaned on weekly basis.

4. Larvivores fish can be used for mosquito control e.g. in ornamental tanks

5. All water holding containers like flower vase should be emptied and cleaned every week,</td><td rowspan="3">• Water should not be allowed to stagnate.

• Disposal of damaged and broken materials that can serve as water collection points should not be done in the environment as Aedes mosquitoes breed in these objects.

• Aspirin should not be used for management of fever.

• Self-medication should be avoided, and expert opinion sought in case symptoms worsen.</td></tr>
<tr><td>For Personal Protection

1. Mosquito nets should be used at night to prevent mosquito bite.

2. During day time wearing full sleeved clothing and applying mosquito repellent can help in preventing mosquito bites.</td></tr>
<tr><td>For managing fever

• Drugs like paracetamol should be prescribed.</td></tr>
</table>

Table 3

In India [14,35,36]

The Integrated Vector Borne Disease Control Programme (IVBDCP) under the Directorate General of Health Services, Ministry of Health and Family Welfare (Govt. of India) has laid down Guidelines for integrated vector management for control of *Aedes* mosquito that encompass vector management and surveillance, legislative measures, community mobilisation and education as well as inter-sectoral convergence.

Clustering of acute febrile illness in the community is being monitored by the Integrated Disease Surveillance Programme (IDSP). Indian Council of Medical Research (ICMR) has strengthened 25 laboratories for laboratory diagnosis in addition to National Institute of Virology (NIV), Pune, and National Center Disease Control (NCDC) in Delhi. Zika virus testing on mosquito samples is being conducted by three entomological laboratories. On 15 May 2017, the Ministry of Health and Family Welfare-Government of India (MoHFW) reported three laboratory-confirmed cases of Zika virus disease in Bapunagar area, Ahmedabad District, Gujarat, State, India.

ICMR has tested 34 233 human samples and 12 647 mosquito samples for the presence of Zika virus. Close to 500 mosquitos' samples collected from Bapunagar area, Ahmedabad District, in Gujarat, were found negative for Zika Virus.

Microcephaly is being monitored from 55 sentinel sites by the Rashtriya Bal Swasthya Karyakram (RBSK) and no increase in number of cases or clustering of microcephaly has been reported from these centers.

Vaccines [37]

A WHO report from March 2016, showed that there were 18 known Zika virus vaccines in development, although none had progressed beyond early preclinical development at that point. These vaccine candidates include inactivated Zika virus, attenuated Zika virus strains, live or inactivated viral recombinants expressing Zika virus proteins (e.g. dengue virus, modified vaccinia virus Ankara, adenovirus, lentivirus, measles virus), viral-like particles expressing Zika virus membrane proteins, recombinant protein vaccines, DNA plasmid vaccines, mRNA-based vaccines, protein-nanoparticle conjugates, and peptide-based vaccines.

Conclusion

The symptoms of Zika virus disease are nonspecific, laboratory diagnosis is not uniformly available, and flavivirus antibody cross-reactivity complicates serologic assessment in areas where dengue and chikungunya are endemic. Hence there is a need to rapidly and systematically address research gaps including a complete understanding of the clinical spectrum of outcomes resulting from in utero infections and of the environmental factors that influence emergence, as well as the development of diagnostic tools, animal models for studying fetal developmental effects, vector control and preventive strategies, effective therapeutics and vaccines.

Bibliography

1. Loos S., *et al*. "Current Zika virus epidemiology and recent epidemics". *Medicine et Maladies Infectieuses* 44.7 (2014): 302-307.

2. Petersen LR., *et al*. "Zika virus". *The New England Journal of Medicine* 374 (2016): 294-295.

3. Gulland A. "Zika virus is a global public health emergency, declares WHO". *British Medical Journal* 352 (2016): i657.

4. World Health Organisation, Geneva. The history of Zika virus.

5. Thomas SJ., *et al*. "Flaviviruses (Dengue, Yellow Fever, Japanese Encephalitis, West Nile Encephalitis, St. Louis Encephalitis, Tick-Borne Encephalitis, Kyasanur Forest Disease, Alkhurma Hemorrhagic Fever, Zika). In: Bennet JE, Dolin R, Blaser MJ. editors. Mandell, Douglas and Bennett's Principles and Practices of Infectious Diseases. 8th edition Canada: Saunders (2015): 1881-1903.

6. Likos A., *et al*. "Local Mosquito-Borne Transmission of Zika Virus - Miami-Dade and Broward Counties, Florida". *Morbidity and Mortality Weekly Report* 65.38 (2016): 1032-1038.

7. Baca-Carrasco D and Velasco-Hernández JX. "Sex, Mosquitoes and Epidemics: An Evaluation of Zika Disease Dynamics". *Bulletin of Mathematical Biology* 78.11 (2016): 2228-2242.

8. Grischott F., *et al*. "Non-vector-borne transmission of Zika virus: A systematic review". *Travel Medicine and Infectious Disease* 14.4 (2016): 313-330.

9. Duffy MR., *et al*. "Zika virus outbreak on Yap Island, Federated States of Micronesia". *The New England Journal of Medicine* (2009): 2536-2543.

10. Levi ME. "Zika virus: a cause of concern in transplantation?" *Current Opinion in Infectious Diseases* 30.4 (2017): 340-345.

11. Motta IJ., *et al*. "Evidence for Transmission of Zika Virus by Platelet Transfusion". *The New England Journal of Medicine* 375.11 (2016): 1101-1103.

12. Visseaux B., *et al*. "Zika virus in the female genital tract". *Lancet Infectious Diseases* 16.11 (2016): 1220.

13. Centre for disease Control and Prevention, Atlanta. Transmission Methods (2018).

14. World Health Organisation, Geneva. "The History of Zika virus infection".

15. World Health Organisation, Geneva. "Zika virus classification table".

16. World Health Organisation, Geneva. "Zika virus infection – India". *Disease Outbreak News* (2017).

17. Sapkal GN., *et al*. **"**First laboratory confirmation on the existence of Zika virus disease in India". *Journal of Infection* 76.3 (2018): 314-317.

18. Paz-Bailey G., *et al*. "Persistence of Zika Virus in Body Fluids-Preliminary Report". *The New England Journal of Medicine* (2017).

19. Centre for disease Control and Prevention, Atlanta. Symptoms.

20. Leal MC., *et al*. "Hearing Loss in Infants with Microcephaly and Evidence of Congenital Zika Virus Infection – Brazil, November 2015-May 2016". *Morbidity and Mortality Weekly Report* 65.34 (2016): 917-919.

21. de Araújo TVB., *et al*. "Association between Zika virus infection and microcephaly in Brazil, January to May 2016: preliminary report of a case-control study". *The Lancet Infectious Diseases* 16.12 (2016): 1356-1363.

22. Oehler E., *et al*. "Zika virus infection complicated by Guillain-Barre syndrome--case report, French Polynesia, December 2013". *Euro Surveillance* 19.9 (2014).

23. Cao-Lormeau VM., *et al*. "Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study". *Lancet* 387.10027 (2016):1531-1539.

24. Soares CN., *et al*. "Fatal encephalitis associated with Zika virus infection in an adult". *Journal of Clinical Virology* 83 (2016): 63-65.

25. Acosta-Ampudia Y., *et al*. "Autoimmune Neurological Conditions Associated with Zika Virus Infection". *Frontiers in Molecular Neuroscience* 11 (2018): 116.

26. da Silva IRF., et al. "Neurologic Complications Associated with the Zika Virus in Brazilian Adults". *JAMA Neurology* 74.10 (2017): 1190-1198.

27. Zucker J., *et al*. "Zika Virus-Associated Cognitive Impairment in Adolescent, 2016". *Emerging Infectious Diseases* 23.6 (2017): 1047-1048.

28. LaBeaud AD. "Zika virus infection; An Overview-Differential Diagnosis".

29. Oduyebo T., *et al*. "Update: Interim Guidance for Health Care Providers Caring for Pregnant Women with Possible Zika Virus Exposure — United States (Including U.S. Territories), July 2017". *Morbidity and Mortality Weekly Report* 66 (2017): 781-783.

30. Centre for disease Control and Prevention, Atlanta. "Guidance for US Laboratories Testing for Zika Virus Infection July 24, (2017)".

31. Algorithm for Zika virus diagnosis, National Institute of Virology, Pune.

32. Centre for disease Control and Prevention, Atlanta. Prevention and Transmission.

33. National Vector Borne Disease Control Programme, Directorate General of Health Services, Ministry of Health and Family Welfare, Govt. of India. Guidelines for integrated vector management for control of *Aedes* mosquito.

34. Government of India Ministry of Health and FW (Directorate General of Health Services). Travel and related Health Advisory on Zika Virus Disease.

35. Government of India Ministry of Health & FW (Directorate General of Health Services). Zika Virus Disease Do's And Don't's.

36. WHO | Zika virus infection – India.

37. Poland GA., *et al*. "Development of vaccines against Zika virus". *Lancet Infectious Diseases* 18.7 (2018): e211-e219.

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