Literature Review on Zika Virus

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Abstract: Zika virus is a vector born virus which belongs to the genus Flavivirus of family Flaviviridae. It was discovered in 1947 in the forest of Zika which is found on the peninsula of Entebbe, Uganda. Zika virus was primarily isolated from the serum of a sentinel rhesus macaque monkey. First human cases were identified in 1952. Little attention was given to zika virus till an extensive incidence of epidemics in the Pacific Island and Latin America between 2013 and 2016. Typically Zika infection is not show symptoms though it may cause mild illness in a few cases. On the other hand the clinical signs are broad and it has similarity with other infectious diseases, mainly those due to vector born viruses such as dengue and chikungunya. Human being can be infected by the virus through the bite of infected female mosquito. Aedes aegypti and Aedes albopictus are the main mosquito species which are involved in the transmission of ZIKV. Another way of transmission of virus can be through non-vector-borne form of ZIKV trans-mission, including animal bite, sexual transmission, laboratory exposure, breastfeeding or blood transfusion. Until recent time specific treatment for zika infection is not identified, due to this reason control measures are chosen. Zika infection can be controlled by measures taken on reduction of density of Mosquitos and personal protection measures.

Keywords: ZIKV, Aedes aegypti, vector

Abbreviations: ZIKV: zika virus; RNA: NAT Ribonuclic Acid Nucleic acid test; Zika MAC ELISA: Zika IgM Antibody Capture Enzyme-Linked Immunosorbt Assay

1. INTRODUCTION

Zika virus disease (ZVD) has recently generated an important concern of peoples around the world. Outbreaks of Zika virus at recent time is becoming a major challenge due to a change from its earlier known spectrum of clinical features to the neurologic complications that are now seen. [1] Global attention in the Zika virus (ZIKV) has been generated by the recent extensive epidemics in Latin America especially in Brazil, which led the Pan American Health Organization to issue an alert for northeast Brazil on 7 May 2015. Epidemics and indications of transmission of zika infection are observed throughout the world especially in Americas and Africa. The worldwide interest is largely due to a possible link to an increased incidence of microcephaly and neurological disorders, including Guillain-Barre syndrome (GBS), in the affected areas. [2, 3]

Zika virus infection is a re-emerging arthropod-borne disease caused by ZIKV, which uses positive sense, single-stranded RNA as its genetic material. Which is belongs to genus flavivirus of family Flaviviridae. The family Flaviviridae includes other arthropod born viruses such as Tick-borne encephalitis virus (TBEV), Dengue virus and West Nile virus which has clinical significance.

Family Flaviviridae has a virus which is closely relate to ZIKV which is known as Spondweni virus. The genome of zika virus contains 10,794 NT which encode 3, 419aa. [4]

ZIKV was first identified in the forest of zika located in peninsula of Entebbe, Uganda. It was primarily isolated from the serum of a sentinel monkey in 1947. Several consecutive epidemiological studies show that ZIKV had been widely distributed to other part of Africa and Southeast Asia. The first Zika virus infection in human was recorded in Nigeria. However it was later nebulous with another Flaviviridae family disease such as Spondweni. The first confirmed human infection was reported in Uganda in 1962–63. [5] The bite of infected mosquito is the main way for the transmission of the zika virus. Clinical signs of Zika infection are broad and it is difficult to distinguish with other infectious diseases especially it may be incorrectly diagnosed and it may be difficult to distinguish with other arthropod born viruses such as chikungunya and dengue. [6] In general the Clinical signs of ZIKV include intermittent fever, pruritic
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erythematous maculopapular rash, and arthralgia, non-purulent conjunctival hyperemia without itching, headache, and myalgia. Those symptoms disappear spontaneously within 3 to 7 days. [7] The present paper discusses on zika virus and the disease it causes, method of transmission, pathogenesis, clinical feature, diagnostic techniques, control and prevention methods.

2. ZIKA VIRUS MORPHOLOGY

Virion of ZIKV shows icosahedral symmetry in its nucleocapsid, which has a diameter of 50 nm that is surrounded by a lipid bilayer containing the structural proteins (prM/M and E) approximately (50–60) nm in size. ZIKV genome consists of an 11 kb positive-stranded RNA molecule that encodes three structural and seven non-structural proteins. Which are 10794 bases long with two non-coding regions flanking regions known as the 5′ NCR and the 3′ NCR. Recently, cryoelectron microscopic structure of the mature ZIKV was elucidated, that reflects structural similarities with other members of the Flaviviridae, including dengue virus (DENV) and West-Nile virus. Virus carries a positive sensed RNA of approximately, 11 kb in size with an estimated mutation rate up to 12 to 25 bases per year [8-10]

Although Zika virus particle and other flavivirus species has the similar general structure whereas there is basic difference between Zika virus and other flaviviruses. One structural difference between Zika virus and other flaviviruses is a loop of amino acids exposed on the surface of the particle. This sequence of the E glycoprotein, and a sugar molecule attached to it, might be involved in regulating Zika virus tropism and pathogenesis. [11, 12] The cell type of human body that is targeted by Zika virus is unknown however, studies with cultured cells (cells grown in a dish) show that Zika can infect a variety of immune cells found in human skin. [13]

3. HISTORY

Zika virus was discovered in 1947 in the forest of Zika which is found in the peninsula of Entebbe, Uganda. It was primarily isolated from the serum of a sentinel rhesus macaque monkey, during the course of surveillance for YFV.

Primarily isolated ZIKV is one of strain of ZIKV it belongs to African prototype, which is known as MR-766. Shortly thereafter, the virus was also detected from mosquito species known as A. africanus near to the zika forest. Even though the presence of antibody against ZIKV with in serum was approximately 10 -20%, indications of Zika infection were not identified [14, 15]. In 1952 the first human zika infection was recorded. Primarily it was identified from the serum of Ugandan individuals. Then the virus was distributed to other part of Africa and it was successfully identified in 1954 from a young Nigerian girl. From 1969 to 1983 the geographical expansion of Zika virus expanded to equatorial Asia – including Pakistan, Malaysia, India and Indonesia. For example, in 1983 13% of human volunteers based in Lombok, Indonesia, had neutralizing antibodies to Zika virus [16]

In Recent time, a great growth was observed in the distribution of ZIKV worldwide; primarily zika virus was restricted to Africa and Asia however later it was distributed to other part of the world. Americas, Europe and Oceania are continents where the virus was widespread begun from Africa. From places with established autochthonous transmission, such as Brazil, viraemic travellers have the capacity to introduce ZIKV into new countries, where Aedes mosquitoes would become infected and perpetuate local transmission cycles. In South America, Brazil had large concentration of cases of Zika, especially in the Northeast region, and serious complications occurred simultaneously with the outbreak of these arboviruses. [17] Federated States of Micronesia was got the virus in 2007, causing 185 cases of suspected Zika disease. An estimated 73% of the population over three years of age were found to be infected. Indication of viral mutation was not found, and it was supposed that the advanced reported occurrence of the disease in Yap may have been caused by lack of population immunity in Micronesia and the under-reporting of cases before 2007. It appears that Zika in Latin America belongs to the Asian lineage. In 2013 and 2014, the virus spread to other Pacific Islands and it has now been found in 72 countries [18]
Recent analysis of Phylogeny is discovered that the current strain belongs to the Asian subtype and shares more than 99.7% of nucleotides and 99.9% of amino acid identity with the strain of French Polynesian outbreak in 2013. These phylogenetic results suggested that the epidemic of French Polynesia in 2013 was spread across the Pacific Ocean and reach south America. [19]

4. TRANSMISSION

4.1. Vector-Borne

The transmission circulation of Zika virus can be categorized in to two distinct transmission cycles the first one is a sylvatic cycle, which is involved in the maintenance of ZIKV between non-human primates and arboreal mosquitoes in forests. Another one is an urban cycle; this one is involved in the transmission of ZIKV between humans and urban mosquitoes in towns. [20]

The main vector for the transmission of ZIKV is mosquito particularly genus Aedes. Infected A. aegypti live closely to human and it feed on the blood of human. Because of this, they are the main way for the transmission of ZIKV. Tropical section of the world is recognized as the home for many Aedes species and they are assumed as the main vector for Zika virus. This mosquito species ordinarily feed blood during early morning and late afternoon. They are the same mosquito species that transmits dengue, chikungunya and yellow fever. [3] A. aegypti is assumed to have a high level of efficiency in the transmission of ZIKV and they favours humans for their blood meal, they are lives near to home and can infect a lot of persons through single blood meal. [21]

A. aegypti usually laid its eggs near to stagnant water in things such as like buckets, toys, old tires, flower pots, and vases. Typically such mosquitoes favour to bite people, and live within and outside of house close to the people. Mosquitoes that spread chikungunya, dengue, and Zika bite during the day and night. When a mosquito feed on infected person they became infected. Then those infected mosquitoes disseminate the virus to other people through their bite. [22] Even if the main vector linked with transmission of Zika is Aedes aegypti, transmission can also occur with A albopictus, A africanus, A luteocephalus, A vittatus, A furcifer, A hensili, and A apicoargenteus. [23]

The main reason for the consideration of A. aegypti to be the primary vector in relation to outbreaks of ZIKV is associated with ZIKV outbreaks, is (1) identification of the virus in a pool of A. aegypti mosquitoes; (2) showing the susceptibility of A. aegypti mosquitoes to infection with the virus and (3) demonstrating the transmission of the virus from artificially fed A. aegypti mosquitoes to rhesus monkeys and mice. [20]

Generally in Africa, ZIKV circulates in a sylvatic transmission cycle involving nonhuman primates (NHPs) and forest-dwelling Aedes species mosquitoes. However in Asia, no evidence exists for a sylvatic transmission cycle, but surveillance for sylvatic arbo-viruses is lacking in that region. [24]

4.2. Non Vector Born Transmission

Formerly it has been assumed that transmission of Zika virus was only by the bites of mosquitoes from the genus Aedes (subgenus Stegomyia). This perception was questioned as other modes of transmission were identified. Saliva and urine are now accepted as vehicles for Zika virus transmission, since viable Zika virus particles were isolated from the saliva and urine of two acute-phase patients in Brazil. Other identified vehicles for of ZIKV include amniotic and seminal fluids. These vehicles increased the potential of alternative sources of non-vector-borne transmission of the disease. [11, 25]

Evidence shows that there is an increased non-vector-borne form of ZIKV trans-mission, including animal bite, sexual transmission, laboratory exposure, breastfeeding or blood transfusion. Among non-vector transmission of ZIKV, transmission of the virus from an infected mother to her foetus during pregnancy is the most common way of spread of the virus, as evidenced not only by the detection of viral RNA in the amniotic fluid, urine, or serum of mothers whose foetuses had brain abnormalities. [26, 20]

ZIKV can be sexually transmitted from an infected person to his or her partners. The virus was isolated from semen in returning travellers typically developed up to 6 days after brief travel to Indonesia where Zika was endemic, symptoms in the patient with presumed sexually transmitted infection were noted 10 days after sexual intercourse with the index case. In Sexual transmission of zika virus, male to female transmission is more common than female to male transmission. [27-29] another way for the transmission of ZIKV is through blood transfusion. It is common in Zika endemic area such as Brazil and other Latin America countries. To avoid such way of transmission there should be careful diagnosis of the donator before donation of blood. [30, 31, 23]
Currently, autochthonous Zika transmission has occurred in 27 counties in the Americas including Colombia; Guatemala, Mexico, Panama, Paraguay, Venezuela, El Salvador, Honduras, and Martinique. Bolivia, Guyana, Ecuador, Guadeloupe, Guatemala, Puerto Rico, Barbados, Saint Martin, and Haiti have reported sporadic transmission following recent introduction. [32]

5. CLINICAL FEATURES OF ZIKA VIRUS INFECTIONS

The period between the infection of an animal by the virus and showing the clinical signs is estimated to be 3–14 days. Usually zika virus infection does not develop symptoms in peoples who are infected by the infection. Clinical signs are generally mild including fever, rash, conjunctivitis, muscle and joint pain, malaise, and headache and usually last for 2–7 days. [3]

Most of time, the disease is mild with symptoms enduring for a few days to a week. Usually the disease is not severe plus the proportion of death among positive person is low. Nevertheless, in the patients who are doubted with zika virus infection, cases such as Guillain-Barre syndrome are reported. As [33] study shows that a pregnant women who is infected with zika may give a birth with abnormal small size in head and fetal brain defect. Due to concerns of microcephaly caused by infection of zika in mother, foetuses and infants of women infected with Zika virus during pregnancy should be evaluated for possible congenital infection and neurologic abnormalities. [33] The neurological consequences of Zika viral infection in adults include a decrease in bilateral acuity of hearing, transient dull or metallic hearing, and a delay between acoustic emission and sound perception. While these all signs disappear after 10 days. [34]

6. PATHOGENESIS OF ZIKA VIRUS INFECTION

Primarily, mosquitoes become infected when they feed on a person already infected with the virus. Following the initial infection of mosquito, replication of the virus is takes place in the epithelial lining of midgut and salivary cells of the mosquito vector. 5 days later the virus presents in the saliva of the mosquito and it became infectious. While feeding blood, mosquito inoculates the virus into another human host. After primary inoculation of the virus in to skin, epidermal keratinocytes, the fibroblast and the Langerhans cells may be infected by the virus. The development of the infection in human remains mostly unknown, however before distribution to ward local lymph nodes and enters to circulation they are thought to be replicate in primary inoculation site within skin dendrites. The virus spends 4 to 5 days within human in order to complete its development. Then after initial infection of mosquito, the virus require 8 to 12 day to complete its replication with in mosquito later it disseminates to mosquitos saliva to infect other human host. [35-37] multiple entry and adhesion factors (e.g., AXL receptor tyrosine kinase) contribute for the infection, and the cellular autophagy required for flavivirus replication enhances Zika virus replication in dermal fibroblasts. Once entry into the cell, flaviviruses typically replicate in vesicles derived from the endoplasmic reticulum. However, location for the replication of zika viruses is takes place within nucleus this shows that ZIKV replication is differ from other flaviviruses and it deserve further investigation. [4, 38]

Consequently, Viraemia occurs and the main target of ZIKV is monocytes for both Asian and African strains. Monocytes have the potential to infiltrate immune sanctuary sites such as the brain, testes and placenta. [37] The neurotropic nature of the virus continues to be characterized. ZIKV has a predilection for fetal neural progenitor and neural retinal cells, with infection resulting in marked inflammation, reduced cellular proliferation, and apoptosis. Approximately 1 of 3 Infants which are infected by zika during their utero life has a chance to have abnormal small size in head, fetal brain defect, blindness and ventriculomegaly [39, 40]

7. DIAGNOSIS

7.1. Ribonucel Acid Nucleic Acid Test (RNA NAT Testing)

Genetic particles in a blood, urine, and other body fluids can be rapidly amplified by a technology known as RNA NAT, that amplify from few thousands to over billion. By doing so, the lab can see up-close if there is any genetic evidence of a Zika infection. A person who is suspected of having the Zika virus, Specimens for nucleic acid testing (NAT) testing: Whole blood, serum collected in a dry tube and/or urine collected from patients presenting with onset of symptoms ≤ 7 days. Nucleic acid test has an advantage that the test can be performed soon after the onset of symptoms. With that being said, the level of viral RNA will decline rapidly as the immune system starts to gain control over the infection.
If NAT testing is performed with in 14 day of the first symptoms, it is considered to be useful way of testing. (The only exception is in symptomatic pregnant women in whom viral RNA can persist for up to 12 weeks.) For the reason that of such limitations of NAT, a negative NAT result does not exclude a Zika virus infection. [41]

7.2. Zika MAC-ELISA

The Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA) is used for the qualitative detection of Zika virus IgM antibodies in serum or cerebrospinal fluid; however, due to cross-reaction with other flaviviruses and possible nonspecific reactivity, results may be difficult to interpret. Consequently, presumed positive, equivocal, or inconclusive tests must be forwarded for confirmation by plaque-reduction neutralization testing (PRNT). [42]

In the Zika MAC-ELISA, anti-IgM (the capture antibody) is glazed onto microwell plate. After glazing of antibody on microwell plate, the patient’s serum is successively added to the well which is followed by addition of viral antigen. The viral antigen should be identified by using enzyme-conjugated anti-viral antibody and it should be non-infectious. The reaction between the enzyme and chromogenic substrate gives clear colorimetric result which is detected by using ELISA reader. Before the result can be calculated using the Zika MAC-ELISA, the test must be validated. The validation process involves the determination of a positive control to normal serum optical density (OD) ratio. [43]

7.3. Virus Culture

Principally ZIKV is isolated from monkey serum and Ae. africanus mosquito then it is inoculated to mouse brain. Cell cultures, chorioallantoic membrane, chicken embryo yolk sacs, and allantoic sacs are other forms of isolation methods for ZIKV. [44].

Culture and Isolation of viruses is an actual significance to determine the phenotypic characters of the virus. In ZIKV diagnosis, culture based method is used in research laboratories and public health however it is not available for clinical purpose. The reference method for the isolation of ZIKV and other arboviruses is intracerebral mouse inoculation. ZIKV is also culturable in several cell lines, including African green monkey (Vero) and rhesus monkey kidney (LLC-MK2), as well as Aedes pseudocutellaris (MOS61 or AP-61) and Aedes albopictus (C6/36). If the infectious ZIKV is unavailable, it is impossible to do further serological test and it is difficult to measure intrinsic ability of a mosquito to become infected [44, 45]

7.4. Prevention and Control

Until recent time specific treatment for zika infection is not identified by reason of this control measures are chosen. Meanwhile scientists had for long assumed the virus to be benign. So to contain the epidemic prophylactic measures are bifurcated into following approaches: control vector density and personal protection. [46]

7.5. Control Vector Density

Reduction of mosquito’s density is one of the major measures for controlling the spread of Zika infection. As WHO recommendation shows that Integrated Vector Management (IVM) is one of important way in controlling of zika infections. Using the IVM model, overall sustainability, efficacy and cost-effectiveness of the strategy can be improved.

(IMS – Dengue) is a program which was applied to control the epidemics and outbreaks of dengue by strengthen and collaborating different national programs. This management was helped in controlling of mortality, morbidity, and social and economic problem produced by the outbreak. This model can be applied for controlling of ZIKV infection. Therefore, different organizations should participate and collaborate in order to explore IVM model. A. aegypti can be found in both human made objects such as bowl, toys, old tyre as well as they can be found in natural habitats that can serve water. There is a critical need of consistent implementation of the three-pronged IVM Model. [47]

Other important measure for controlling the vector should include the followings methods. Measures that target all lifecycle levels of mosquito may include educating community in clean-up of environment to eliminate small objects that hold water as water receptacles such as toys, old tyres, and bowls. For containers which are sized from medium to large, that serves water for domestic purpose: before refilling the container it has to empty the container, clean and brush to eliminate eggs and other immature stages. For other large containers such as ornamental pools, wells and cisterns, introduce native larvivorous fish or other larvivorous aquatic insects. Measures
targeting adult mosquito may consists of Targeted residual spraying is the primary vector control intervention for immediate response. It is performed using appropriate insecticides applied on Ae. Aegypti resting sites such as exposed lower sections of walls (<1.5m), under furniture, inside closets, in dark and moist surface where mosquitoes may rest in and to a lesser extent, around houses. [48] Insecticides that is applied on insects includes: pyrethroids, organochloride, and organophosphorus, which primarily act on the nervous system of the vector Imidacloprid, thiacloprid, and thiamethoxam have larvicidal and adulticidal efficacies in different mosquito species. [49]

7.6. Personal Prevention Measure

Another key measure for controlling of the infection is Personal protection. A person can protect himself from the disease by Wearing insect repellent on exposed skin and clothing, by Staying in places with air conditioning and window and door screens to keep mosquitoes outside. When staying outdoors sleep under a mosquito net if an individual are not able to protect himself from mosquito bites. [50]

The risk of Sexual transmission of zika infection for a person who is returned from zika endemic area can be reduced by using condoms during sexual intercourses. If symptoms were experienced, condoms should be used for six months following the cessation of symptoms. Travellers returning from Zika-affected areas are not allowed to donate blood until the risk of infection has passed, which is 28 days after returning from a Zika-affected area. [51]

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<tr>
<th>Strategy</th>
<th>Action</th>
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<tbody>
<tr>
<td>Control vector design</td>
<td>Diligent management and control of environmental factors.</td>
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<td>Eliminate or reduce vector breeding sites in common areas.</td>
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<td>Conduct mass sanitation campaigns to educate the public.</td>
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<td>Ensure Mosquitoes are removed within the determined radius of critical places like schools, hospitals, transport terminals, using risk stratification paradigms.</td>
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<td>In areas with viral activity, use mosquito adulticidal sprays to interrupt ZIKV transmission.</td>
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<td>Ensure proper monitoring and follow-up during integrated actions for vector control.</td>
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<tr>
<td>Preventative measure</td>
<td>Individual protection</td>
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<td>Encourage individuals to use Bed-nets.</td>
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<td>Appropriate clothing to cover exposed skin.</td>
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<td>Use repellents.</td>
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<td>Household/residential protection</td>
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<td>Encourage installation and use of wire-mesh screens on doors and windows.</td>
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<td>Once per week emptying, cleaning, turning over, and discarding of containers that can hold water inside or outside the houses to reduce any mosquito breeding sites.</td>
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</tbody>
</table>

Prevention recommendation (copied from Sikka et al., 2016) [52]

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