Zika Virus: Epidemiology, Clinical Manifestations, and Public Health Implications

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Abstract: The Zika virus (ZIKV), a member of the Flavivirus genus, has garnered significant attention since its discovery in 1947, primarily due to its association with neurological complications and congenital anomalies. This abstract synthesises key insights into the epidemiology, aetiology, pathogenesis, diagnosis, management, and prognosis of Zika virus infection. ZIKV primarily spreads through Aedes mosquitoes but can also transmit through sexual contact, blood transfusions, and perinatal transmission. Its genetic diversity encompasses African and Asian lineages, with the Asian lineage implicated in severe outbreaks and congenital abnormalities. The virus's pathogenesis involves interactions with host cell receptors, viral replication, and evasion of immune responses. Clinical manifestations range from mild febrile illness to severe neurological disorders such as Guillain-Barré syndrome and congenital microcephaly. Differential diagnosis is crucial due to overlapping symptoms with other arboviruses and infectious diseases. Management focuses on supportive care and symptom management, with no specific antiviral therapy available. Prognosis varies, with most cases being self-limiting, but severe neurologic consequences and congenital abnormalities pose significant risks, especially during pregnancy. Public health measures emphasize vector control, travel advisories, and patient education. Further research is essential to understand the full spectrum of ZIKV pathogenesis, improve diagnostic capabilities, and develop effective preventive and therapeutic interventions.

Keywords: *Transmissions, Hemorrhagic Syndrome, Arboviral Illness, Reye's Syndrome, Nucleocapsid Uncoating, Microcephaly, Japanese Encephalitis Virus (JEV).*

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I. INTRODUCTION

One prominent arbovirus that belongs to the Flavivirus genus in the Flaviviridae family is the Zika virus (ZIKV). First discovered in 1947 in a rhesus monkey in Kampala, Uganda's Zika woodland (Dick et al., 1952), the virus first infected humans in Tanzania and Uganda in 1952. Later, in 1953, a 10-year-old Nigerian girl became the first known human host to contract ZIKV (MacNamara 1954). Since its discovery, ZIKV has spread to several nations in Africa, Asia, Oceania, and the Americas. As a result, human populations from these locations have occasionally seen isolated cases of the virus.

ZIKV is a member of the Flavivirus genus, which consists of 53 different virus species that are mainly spread by mosquitoes (https://talk.ictvonline.org/taxonomy/). ZIKV is closely linked to other flaviviruses that are spread by mosquitoes, including dengue viral, Japanese encephalitis virus, yellow fever virus, and West Nile virus. These viruses—among them, ZIKV—are classified as emerging or reemerging diseases because of their ability to spread to new regions (Weaver et al. 2016). Two different lineages, African and Asian, both originating from East Africa, have been found by genomic and phylogenetic analysis of ZIKV isolates (Gatherer and Kohl 2016). Aedes spp. mosquitoes, which include A. aegypti, A. albopictus, A. hensilli, A. africanus, and A. polynesiensis, are the main vectors that cause ZIKV infection in humans (Boyer et al. 2018). Furthermore, the illness might spread through unusual channels like maternal-fetal transmission, sexual interaction, and the transfusion of contaminated blood products (Petersen et al. 2016).

Similar to chikungunya and dengue infections, the majority of ZIKV infections are asymptomatic or present as a self-limiting fever illness. Due to the self-limiting nature of ZIKV infections, many cases remain unreported in areas

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where the virus is widespread, making it difficult to determine the precise disease burden. Research carried out within Zika virus epidemics in Brazil and French Polynesia has demonstrated a link between virus infection and neurological disorders such as Guillain-Barré Syndrome (GBS) and congenital microcephaly (Oehler et al. 2014; Schuler-Faccini et al. 2016; de Araújo et al. 2016). The disease spreads quickly because of ZIKV's complex transmission cycle and asymptomatic infections that are difficult to differentiate from those caused by other flaviviruses. Important details on ZIKV, including virology, transmission, clinical symptoms, diagnosis, treatment, and therapy, are emphasized in this synopsis.[1]

II. ETIOLOGY (ORIGIN)

The primary mode of transmission for the Zika virus is through the bites of female Aedes aegypti and Aedesalbopictus mosquitoes, which are known to transmit arboviralillnesses. Apart from mosquito bites, there are several other ways in which infection can spread, including sexual contact, blood transfusions, organ transplants, and perinatal transmission (when the virus is transferred from mother to fetus). The Japanese encephalitis virus, tick-borne encephalitis virus, West Nile virus, dengue virus, and yellow fever virus are among the several other arboviruses that cause illnesses in humans that are closely related to the Zika virus. [4][2]

III. THE STUDY OF EPIDEMIOLOGY

The Zika virus (ZIKV) was first discovered in Aedes Africanus mosquitoes in the same location in 1948, after it was first isolated from a rhesus monkey in Uganda in 1947 (Dick et al. 1952). Serosurveillance research following the virus's 1952 discovery in humans showed that ZIKV was present throughout many African and Asian nations (MacNamara1954; Weaver et al. 2016). Seroprevalence investigations in the majority of African countries—Central Africa, Egypt, Gabon, Nigeria, Sierra Leone, Tanzania, and Uganda—showed that human populations had antibodies against ZIKV (Smithburn 1952; Dick 1953; Smithburn et al. 1954a; Moore et al. 1975; Weaver et al. 2016).

When reports of ZIKV outside of Africa began to come from Malaysia, it was clear that the virus was spreading beyond the continent. Human infections were reported in Indonesia after it was isolated from Aedes aegypti mosquitoes (Marchette et al. 1969; Olson et al. 1981). Serological evidence of ZIKV infection first appeared in a number of Asian nations between the 1950s and 1980s, including Vietnam, Thailand, India, Indonesia, Malaysia, Pakistan, the Philippines, and the Philippines (Table 1) (Smithburn et al. 1954b; Smithburn1954; Hammon et al. 1958; Pond 1963; Darwish et al. 1983).[1]

IV. PHYSIOPATHOLOGY

Encompassing three structural proteins (core [C], pre-membrane [prM], and envelope [E]) and seven non-structural (NS) proteins, the 10.7 kb Zika virus genome is split into structural and non-structural portions [1]. The prM and E proteins are essential for the attachment of the virus to the transmembrane receptor tyrosine kinase protein (AXL) on the host cell membrane. This attachment triggers the absorption of the virus into the cytoplasm, nucleocapsid uncoating, and endocytic uptake. In a replication complex made up of the NS proteins, positive-sense RNA is created from negative-sense RNA. The resultant viral polyprotein is altered in the endoplasmic reticulum, which produces immature virions that are gathered in secretory vesicles and the endoplasmic reticulum before being released. Cell cycle arrest, apoptosis, and cell death are all brought on by the C protein and other NS proteins [1, 2].

Based on cryo electron microscopy, the mature ZIKV structure is similar to other known flavivirus structures. Interestingly, each of the 180 envelope glycoproteins has a deviation of around 10 amino acids around the Asn154 glycosylation site, which may be the place where the virus attaches itself to host cells [7].

Phylogenetic research of the Zika virus reveals three genotypes (West African, East African, and Asian) and two lineages (Asian and African). It is hypothesised that the Asian lineage, which extended from Asia to the Americas and the Pacific Islands, is linked to severe outbreaks and congenital abnormalities. On the other hand, the African ancestry is thought to be more inherently pathogenic, associated with severe infections and worse pregnancy outcomes [8]. With the ability to adapt to different hosts, the Zika virus can infect a variety of organs, including skin, blood, placenta cells, testes, retinal cells, neural stem cells, and neural progenitor cells. Additionally, the virus infects monocytes, which helps it pass across placental and blood-brain barriers. Fetal loss results from the apoptosis, necrosis, and death of infected host cells, which mostly affects neural progenitor cells and causes abnormalities in the fetal brain and placental insufficiency [9].

The initial line of defence against the Zika virus is the innate immune system, which inhibits viral replication through the activation of type I interferon (IFN) and IFN-stimulated genes (ISG). But the Zika virus has evolved defenses against the immune system, and one of them is that NS proteins block the signaling cascade that triggers the activation of IFN and ISG. To completely understand the processes that underlie the Zikavirus's immune evasion, more research is necessary. These strategies include the control of nonsense-mediated mRNA decay machinery and the prevention of stress granule formation, both of which boost viral replication [10, 11].

Immunogenicity and consequences of the disease are affected by interactions between the immune responses to the dengue and zika viruses. Research indicates that people who have previously contracted dengue virus may be immune to the Zika virus as CD4+ and CD8+ T cell responses inhibit the virus's ability to replicate. On the other hand, those infected with dengue virus are more likely to suffer from severe illness if they had already contracted Zika virus as shown in figure 1 [8]

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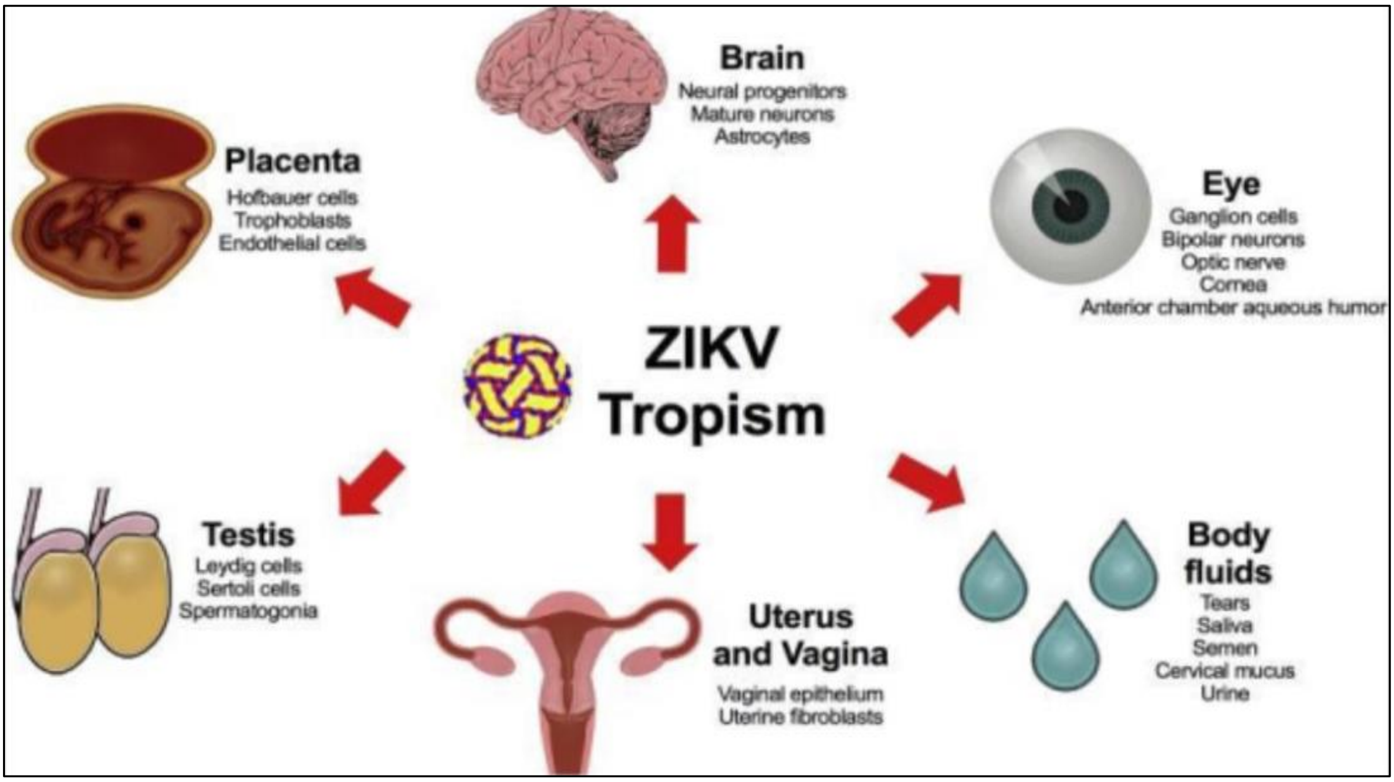

Fig 1 Zika Virus Infection in Various Parts of the Body. Adopted From Miner and Diamond, (2017)

V. ZIKV'S PAST

As a member of the Flaviviridae family, the Zika virus (ZIKV) is spread by the Aedes genus and is related to other arboviruses as the Japanese encephalitis and dengue viruses [11]. Antibodies against Zika virus have been found in a number of animal species, including non-human primates [12]. Many mosquito species in Africa and Asia have been found to carry the virus, including arboreal species like Aedesafricanus and mosquitoes with wide tropical and subtropical distributions like Aedes aegypti and Aedes albopictus, respectively [13, 14]. Three primary ZIKV lineages have been identified through genetic research; two of these lineages originated in Africa and one in Asia [15, 16]. East and West African clusters emerged from the further divergence of the African lineage [17, 18]. In contrast, the Asian lineage emerged in South America [20, 21] and the Pacific Ocean [19],

Demonstrating a wider geographic dispersion. A strain of the Asian lineage known as the "American strain" was identified as the cause of the 2015–16 pandemic in the Americas [22, 23]. The American epidemic strain is thought to represent a separate lineage by certain researchers. According to epidemiological research, ZIKV is distributed throughout Pakistan, Vietnam, Malaysia, Indonesia, the Philippines, India, Thailand, and half of North Africa [11, 24].

In 1952, a study in Uganda revealed the existence of neutralizing antibodies to ZIKV in serum, leading to the identification of the first known human case of the virus [25]. There were very few documented occurrences of human infection before 2007. Yap, Federated States of Micronesia, in the Pacific area, saw the first significant outbreak of ZIKV infection in people in 2007 [26]. The greatest outbreak of ZIKV in French Polynesia occurred in 2013–2014, and it spread to other Pacific Islands, Easter Island, Cook Islands, Vanuatu, New Caledonia, and the Solomon Islands [5]. There are records of ZIKV transmission in 55 nations and territories.Only 41 of them had indigenous transmission documented, and those reports were from 2015 to 2016 [27]. Six of those nations had indirect evidence of virus circulation, five had ended outbreaks, and three had local illnesses.[4]

VI. DISTINCTIVE DIAGNOSIS

Healthcare practitioners should assess the likelihood of other infectious diseases while evaluating potential differential diagnosis for a patient presenting with symptoms that could be linked to the Zika virus. The disorders listed below have certain clinical characteristics in common with Zika virus infection:

- Chikungunya Virus
- Coronavirus Disease 2019 (COVID-19)
- Dengue
- Enteroviruses
- Group A Streptococcal (GAS) Infections
- Leptospirosis
- Malaria
- Measles
- Parvovirus B19 Infection
- Rickettsial Infection
- Yellow Fever
- West Nile
- Japanese encephalitis

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When diagnosing a patient and choosing a course of therapy, medical professionals must carefully assess the patient's symptoms, travel history, and possible exposure to particular vectors. The fact that many illnesses share many symptoms highlights how crucial thorough clinical evaluations and laboratory work are to a precise diagnosis and prompt treatment.[3]

VII. HANDLING AND MEDICATIONS

There isn't currently a specific preventative therapy for Zikavirus infection. The goals of management are supportive care and symptom management. When deciding how to treat patients who have a suspected or confirmed Zika virus infection, medical professionals should bear the following in mind:

- *Differential Diagnosis:*

In order to rule out co-infections and administer the proper care, healthcare professionals should conduct a comprehensive differential diagnosis because the symptoms of dengue fever, chikungunya, and malaria are similar.

- *Symptomatic Treatment:*

Treating symptoms is the main strategy for controlling Zika virus infection. This entails drinking plenty of water, managing pain, and applying antihistamines to rashes that are itchy.

- *Med Care Caution:*

If dengue is not ruled out as the cause of the illness, then acetylsalicylic acid (aspirin) and non-steroidal anti-inflammatory medications (NSAIDs) should be used with extreme caution. This warning is because there may be a higher risk of hemorrhagic syndrome in dengue cases when using these drugs. Furthermore, because acetylsalicylic acid increases the risk of Reye's syndrome following viral infections, it is not recommended for use in children or teenagers.

The treatment of Zika virus infection emphasizes the value of tailored therapy, taking into account the patient's medical background, general health, and possible co-infections. To guarantee the safest and most efficient management techniques, healthcare providers should remain up to date on the most recent directives and suggestions from health authorities.[5]

VIII. PROGNOSIS

The majority of Zika virus infections are moderate and self-limiting, meaning that the prognosis is usually good. It is estimated that over 80% of Zika virus infections may go undetected due to the disease's mild nature Serious neurologic consequences, such as Guillain-Barrésyndrome, have been documented in a small number of cases. Affected individuals may experience substantial effects.

The biggest worries are the possible negative effects on pregnancy and the emergence of congenital Zika syndrome as a result of the virus spreading vertically from mother to fetus. The long-term prognosis for these cases may be poor, posing serious health risks to the affected infants.

It's crucial to remember that a Zika virus infection can have short-term negative effects on fertility. This emphasises the need for close observation and thorough assessment of any potential difficulties in infected persons, particularly for those who are presently or plan to become pregnant. Following recommended protocols and seeing a doctor on a regular basis are crucial for controlling and reducing the risks of Zika virus infection.[3]

IX. INSTRUCTION FOR PATIENTS

Patients should be well-informed about the risks of Zika virus during travel and preventive measures against mosquito bites. To stay updated on Zika virus transmission internationally and within U.S. states and territories, patients are advised to regularly check the CDC website.

For pregnant women or those planning pregnancy, the CDC provides crucial information on the implications of Zika virus infection. This includes guidance on travel, testing procedures, and effective management strategies [23]. Breastfeeding is recommended for mothers with Zika virus, even if their infants have microcephaly. While Zika virus has been found in breast milk, there is currently no evidence of transmission through breastfeeding, and the benefits of breastfeeding outweigh potential risks [24].[3]

X. PRESENTATION OF CLINICAL DATA

The Zika virus (ZIKV) exhibits a wide range of clinical symptoms, with emerging research suggesting associations with severe conditions such as microcephaly and Guillain-Barré syndrome.

- *Typical Symptoms and Signs*

Approximately 20–25% of ZIKV-infected individuals experience mild, self-limiting symptoms with an incubation period of 4–10 days. Common nonspecific symptoms include low-grade fever, itchy rash, arthritis, and nonpurulent conjunctivitis. Less frequently, symptoms like retro-orbital pain, headache, myalgia, edema, and vomiting may occur. Subcutaneous bleeding, hematospermia, hearing loss, and thrombocytopenia are also observed. Symptoms, except for arthralgia, usually correlate with viremia and resolve within a week [Foy et al., 2011].

- *Syndrome of Guillain-Barré*

ZIKV infection is linked to Guillain-Barré syndrome, an autoimmune condition affecting the peripheral nervous system. The temporal and geographic correlation was observed in outbreaks in French Polynesia and the Americas. A case-control study revealed a substantial correlation between anti-ZIKV antibodies and Guillain-Barré syndrome, with higher incidences during outbreaks [Cao-Lormeau et al., 2016]. Guillain-Barré syndrome caused by ZIKV is generally temporary, with most patients fully recovering. The mechanism behind this association is under active investigation.

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➢ *Brain Damage*

ZIKV infection during pregnancy is associated with microcephaly, a neurological disorder where the baby's brain is malformed. The causal link was established during the ZIKV outbreak in Brazil, with subsequent studies in French Polynesia and Brazil supporting this association. The CDC defines congenital microcephaly based on head circumference, and evidence suggests a connection between congenital abnormalities and ZIKV infection during pregnancy. Additionally, congenital ZIKV infection is linked to hearing loss and visual abnormalities.

➢ *Additional Neurological Complications*

Case reports suggest that ZIKV infection may be associated with other neurological complications, including meningoencephalitis and acute myelitis. Further case-control or cohort studies are needed to understand additional neurological and non-neurological consequences induced by ZIKV infection in both adults and infants [Musso and Baud, 2016; Rasmussen et al., 2016].[6

XI. CONCLUSION

The Zika virus represents a significant public health challenge due to its rapid spread, diverse modes of transmission, and severe complications, particularly congenital abnormalities. Understanding the epidemiology of Zika is crucial in anticipating and mitigating future outbreaks, especially in regions vulnerable to mosquito-borne diseases. The virus's clinical manifestations, ranging from mild symptoms to severe neurological disorders, underscore the need for ongoing research into effective diagnostic, therapeutic, and preventive measures.

Public health strategies must prioritise surveillance, vector control, and education to prevent Zika's spread, while also addressing the social and economic impacts on affected communities. Global collaboration, robust funding, and a commitment to research are essential to controlling the Zika virus and reducing its impact on public health. Continued vigilance is required to adapt to the evolving landscape of Zika virus epidemiology and to protect populations worldwide from future outbreaks.

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CONFLICT OF INTEREST

Authors do not have any Conflict of interest with any individual.

COMPLICATIONS

➢ *Pregnancy:*

Microcephaly, other birth defects, miscarriage, stillbirth.

➢ *Adults/Children:*

Guillain-Barré syndrome, neuropathy, myelitis.

➢ *Diagnosis:*

Blood tests confirm infection.

➢ *Treatment:*

No specific treatment available.

➢ *Prevention:*

Mosquito bite avoidance (repellent, clothing, nets), safe sex practices, travel precautions for pregnant women.

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