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Review Article

Comprehensive Review on Zika Virus: Epidemiology, Mode of Transmission, Treatment, and Future Perspectives

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Abstract

Zika Virus (ZIKV), a mosquito-borne flavivirus, has gained significant global attention due to its rapid spread and its association with severe public health complications, particularly microcephaly in newborns and Guillain-Barre Syndrome (GBS) in adults. First identified in Africa, ZIKV is primarily transmitted by Aedes mosquitoes, especially *Aedes aegypti* and *Aedes albopictus*, though human-to-human transmission via sexual contact, blood transfusion, and vertical transmission during pregnancy has also been documented. A single-stranded, enveloped RNA genome characterizes the virus and is genetically related to other flaviviruses such as dengue (DENV) and Chikungunya (CHIKV). The clinical presentation of ZIKV infection is typically mild, with symptoms such as fever, rash, headache, conjunctivitis, and arthralgia. Despite these mild symptoms in most cases, ZIKV infection has been linked to severe neurological and congenital complications, particularly in infants born to infected mothers. The 2015 outbreak in Brazil highlighted the virus's association with birth defects, mainly microcephaly, which led to significant global concern. This review aims to provide a comprehensive overview of the pathology, clinical manifestations, transmission dynamics, and complications associated with ZIKV. Additionally, the review discusses current diagnostic methods, treatment strategies, and ongoing research efforts focused on vaccine development, vector control, and potential therapeutic options. Furthermore, the review emphasizes the global public health impact of ZIKV and the urgent need for continued research and coordinated public health initiatives to control its spread. Addressing the challenges posed by ZIKV will require a combination of modern diagnostic techniques, vector control strategies, and the development of effective vaccines and therapies. This review offers a consolidated understanding of ZIKV to aid in future research, clinical practices, and global health strategies.

Keywords

Aedes Mosquito, CHIVKV, DENV, Epidemiology, GBS, Microcephaly, ZIKV Infection

1. Background

The mosquito-borne Zika virus (strain MR 766) belongs to the *Flavivirus* and shares close phylogenies with dengue and yellow fever infectious diseases [1]. In May 2015, the Pan American Health Organization issued an epidemiological

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alert and guidelines for managing infections caused by the Zika virus [2, 3], first identified in April 1947 in a rhesus macaque monkey being used for study by researchers at the Yellow Fever Study Institute, which lies next to Lake Victoria in Zika Forest, Uganda [4]. In 1948, these scientists gave this transmissible pathogen with a filter the name "Zika Virus" [5]. The ZIKV was also isolated from Aedes aegypti in January 1948, and the initial countries that recorded cases involving humans were Tanzania and Uganda; the results were initially made public in 1952 [6]. In 2007, Yap Island, Micronesia, saw the first known human epidemic, with over 19,000 cases, roughly 73% of the total population reported [7]. There were only 14 reported human infections before the Yap Island pandemic [5], and indicated to be endemic in several Asian nations [8]. In French Polynesia, an outbreak that was expected to cause 32,000 infections occurred in 2013 and 2014, respectively. Other conditions have now spread to multiple Pacific Island states. The latest epidemic originated in Brazil in 2015, and it thereafter spread to the Americas, Pacific Asia, and Africa, and now 16 cases of laboratory-confirmed Zika infections in 16 US states [9]. Zika has been found in more than forty countries and territories [10]. In February 2015, a dengue-like outbreak occurred in the Northeastern regions of Brazil with symptoms of a rash, pruritus, low-grade fever, pain in joints and muscles, and eye pain in an estimated 400,000 (or 1.3 million) suspected human cases [2].

The Brazilian Ministry of Health reported an increase in the proportion of kids born with an abnormally small skull and an immature brain. This sparked concerns about a potential link between ZIKV in pregnant women and microcephaly in infants. The ZIKV outbreak and the rise in microcephaly cases prompted extensive epidemiologic and virologic studies to better understand its transmission and public health impact [11]. The World Health Organization (WHO) formally designated ZIKV as a Public Health Crisis of Global Concern on February 1, 2016 [12]. There are currently 9 confirmed ZIKV cases among pregnant women who have visited South America, reported by the Centers for Disease Control (CDC), and a total of 5,716 reported cases in the United States [13]. By April 2016, ZIKV transmission had been documented in 27 countries across the Americas [14]. In July 2016, a landmark case of locally transmitted ZIKV on the US continent was reported [15]. The Florida Department of Health has recognized a total of 321 ZIKV disease cases in both residents and visitors to Florida [16].

More than 86 nations, territories, or subnational locations in the world where ZIKV was identified and its propagation is recorded [17]. The primary foreign case of ZIKV occurred in January 2016 during Spain's reign. From February 1-29, 2016, a total of 9 cases of ZIKV were found in China [18]. Following an acute ZIKV infection and Guillain-Barre Syndrome (GBS), a 47-year-old man is believed to have returned to New Zealand. Sexual contact was associated with 6 of the 1,080 incidents that occurred in the US (2017) [19]. The CDC reported 74 out of 108 ZIKV outbreaks occurring in the US between January to August 1, 2018, showing regional origins [20]. When considering ZIKV as a whole, its dismal aspect becomes obvious. As of January 2018, 223,477 cases worldwide have been confirmed to have the ZIKV epidemic. Since 80% of infections are silent and the public lacks suitable diagnostic tools in the initial phases of epidemics, prevalence rates are higher. Globally, the recurrence of ZIKV may be caused by novel disease modifiers, newly discovered routes of transmission, and the emergence of highly aggressive strains [17, 21]. The purpose of the following in-depth review is to provide an overview of current knowledge about the epidemiology, transmission, clinical symptoms, challenges, pathology, therapy, and prospects of ZIKV infection.

2. ZIKV Epidemiology

Globally, Zika virus is transmitted by mosquitoes and is classified within the *Flavivirus* genus of the *Flaviviridae* family [17], an RNA virus characterized by a non-segmented positive-sense RNA genome [6]. The ZIKV is transmitted by a variety of mosquito species, including *Aedes africanus*, *Aedes aegypti*, *Aedes albopictus*, *Aedes hensilli* [22-24]. The 4 viruses that had the greatest impact on human health are dengue, chikungunya, Zika virus, and yellow fever infection. All of these viruses are primarily transmitted by *Aedes aegypti* [25]. Moreover, ZIKV has been isolated from various mosquito species prevalent in Africa and Asia, including *Aedes africanus*, typically found in trees, and *Aedes aegypti* and *Aedes albopictus*, both widespread in extensive tropical and subtropical regions [24, 26]. ZIKV is present in nearly half of North Africa, including Vietnam, the Philippines, Malaysia, India, Indonesia, Thailand, Pakistan, and other countries, based on epidemiological research shown in Figure 1 [27].

Over 55 nations and geographic areas where ZIKV infection has been reported. Only 41 of them had native transmission confirmed in 2015–2016; in others, 3 countries had a local infection, 5 had ceased outbreaks, and 6 showed signs of indirect viral propagation [28]. Recently, it emerged that the ZIKV strain that arose in the Americas and moved to Angola was linked to a cluster of microcephaly [29]. Moreover, Hill et al. showed identical findings from their research using entire viral genomes [30]. A review of the ZIKV strain's mosquito-borne propagation from the Americas to the African continent is offered by all of the previous studies. Because of the widespread panic that ZIKV caused as the worst viral infection and birth deformity to be found in decades, the WHO designated it as a health crisis with global significance [31].

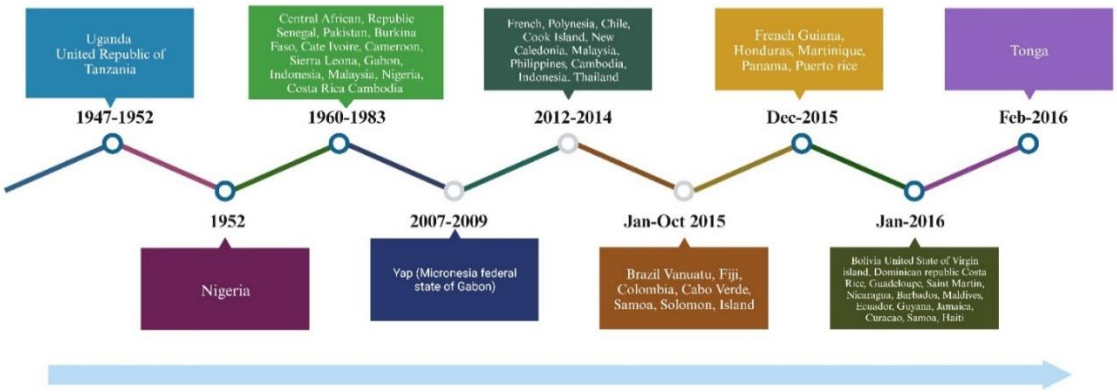

Figure 1. *A history of the Zika virus and its outbreak from 1947 to 2016.*

In the US (2016), 5,168 cases of non-congenital ZIKV infections were diagnosed. As of March 2017, 2,767 cases of microcephaly or other brain anomalies caused by ZIKV infection in pregnancy had been reported in 24 American nations. Three cases from Gujarat State and one case from Tamil Nadu were the first indications of ZIKV infection in India in 2017. In 2018, a Zika Virus (ZIKV) outbreak was reported in Rajasthan, India. By December 2018, the India National CDC, under the Ministry of Health and Family Welfare, had received reports of 159 confirmed ZIKV infections from Rajasthan, including 63 cases among pregnant women. Additionally, 130 cases were reported from Madhya Pradesh, and one case was reported from Gujarat, as outlined in Table 1 [32, 33].

Table 1. *The global transmission of the mosquito-borne ZIKV Infection [32, 33].*

Year	ZIKV feature	Affected population
1947	ZikV was first identified from a febrile sentinel rhesus monkey in Uganda's Zika Forests (Rhesus 766).	
1947-1948	Uganda: The first identification of Zika neutralization antibodies in sentinel rhesus monkeys	
1952	ZIKV first human infection in Nigeria	
1954	In Nigeria, ZIKV was first isolated from human serum	
1964	Uganda, the first well-documented human ZIKV infection study	
2007-2008	First epidemic in Yap Island, Micronesia	49 confirmed cases
2008	First Sexually transmitted case of Zika virus	
2009-2012	Africa. Asia, Europe, North America, and Australia reported a few cases (including those related to travel).	
2013	Second epidemic in French Polynesia	>400 cases
	First reported case of Zika virus with Guillain-Barre syndrome	
2015	Brazil reported the first autochthonous cases	500,000-1,500,000 Approx
	The third epidemic in South America and October 2015	>15 Million Cases
-	The first incidence of microcephaly with ZIKV infection	3000 Approx
2016	US Non >congenital Zika infection reported	$168 Cases
	In February WHO declared ZIKV a public health emergency	
2017	The Americas had cases of microcephaly or central nervous system malformations related to ZIKV infection during pregnancy	2767 confirmed cases
	First reported in India in Gujarat state, and a case in Tamil Nadu	3 cases

Year	ZIKV feature	Affected population
2018	India National Center for Disease Control, Ministry of Health and Family Welfare reported ZIKV infection	159 confirmed cases of

3. ZIKV Genomic Organization

The genus *Flaviviridae*, comprising four genera, is related to clinically relevant arboviruses: *Flavivirus* (53 species), *Pegivirus* (2 species), *Hepacivirus* (1 species, hepatitis C virus), and *Pestivirus* (4 species). The majority of viruses with therapeutic value belong to the *Flavivirus* genus [34]. In most cases, encephalitis, rash, fever, visceral involvement, and bleeding fever are the clinical signs caused by *Flaviviruses* [35]. Virion RNA is transmissible and serves as the messenger RNA (mRNA) and viral genome. The genome is translated into a 3419 amino acid polyprotein, which is subsequently degraded co- and post-translationally by host and viral proteases [36]. It initiates the reproductive cycle by binding to the host cell membrane via its envelope protein, facilitating endocytosis. Following entry, the viral membrane fuses with the endosomal membrane, releasing the single-stranded RNA (ssRNA) genome into the host cytoplasm. Translation begins, producing a polyprotein that is subsequently cleaved to release structural and nonstructural proteins. Viral replication occurs in the endoplasmic reticulum (ER), where cytoplasmic viral factories produce double-stranded RNA (dsRNA) intermediates. Transcription of the dsRNA generates new ssRNA genomes, which are packaged within the ER to form new virions. These virions are transported to the Golgi apparatus and released to infect additional cells. The ZIKV genome is a 10,794 kb positive-sense ssRNA molecule with two noncoding regions (5′ and 3′ NCR) and a single open reading frame encoding a polyprotein. This polyprotein is divided into seven nonstructural proteins, a capsid, an envelope, and a precursor membrane protein, as illustrated in Figure 2 [37].

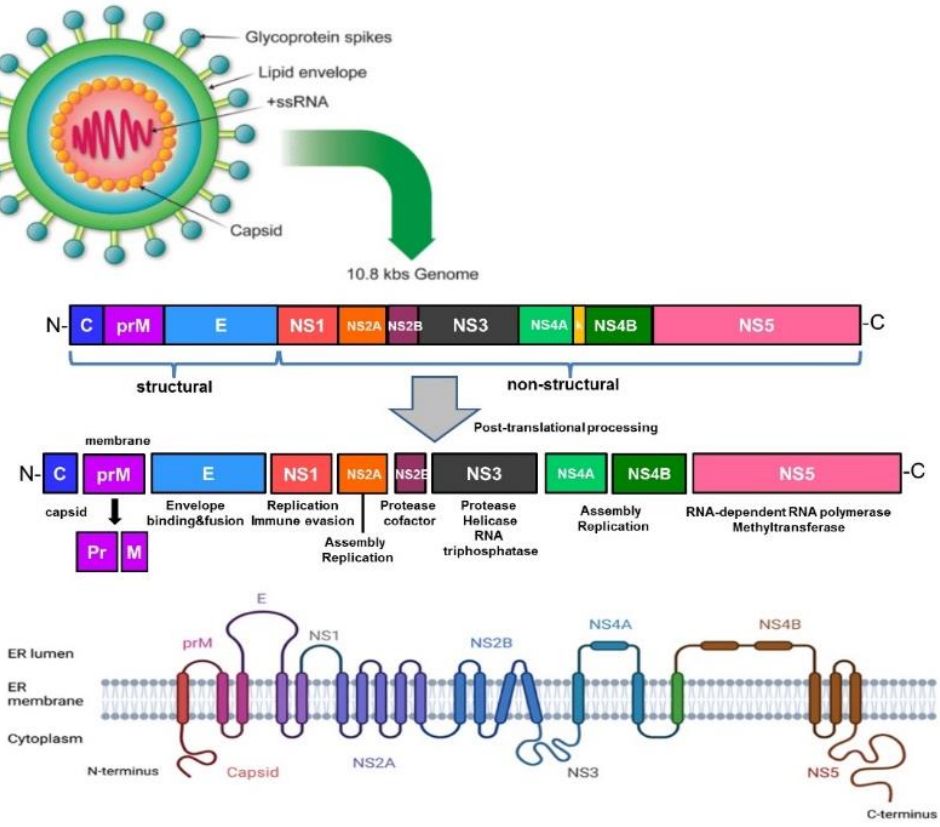

Figure 2. *ZIKV life cycle and schematic representation of the organization and processing of ZIKV-polyprotein (A) ZIKV life cycle. (B) The polyprotein structural and non-structural proteins are organized in an ordered manner. (C) Based on biochemical and biological studies, the membrane's polyprotein organization is anticipated.*

The primary surface protein of the virion, the E protein, facilitates binding and membrane fusion, among other vital aspects of the viral cycle. However, the C-terminal region of the largest viral protein, NS5, exhibits RNA-dependent RNA polymerase (RdRP) activity. Its N-terminus contributes to RNA processing by methyl transferase activity, resulting in RNA capping [38]. The 39 NCRs of the ZIKV genome consist of 428 nucleotides and 27 folding motifs [37]. These nucleotides and folding patterns certainly affect an array of processes, including translation, cyclization, RNA packaging, recognition by viral protein, and genomic stabilization [38]. The outermost layer of the ZIKV consists of two unique proteins, each present in 180 copies. A distinctive feature of ZIKV is a glycosylation site on its surface, absent in *flaviviruses*, which serves as a carbohydrate-binding site. This enables the attachment of various sugars to the viral protein surface, potentially enhancing ZIKV's ability to adhere to human cells. Specific residues and glycosylation sites in ZIKV influence its interaction with host cell receptors, contributing to its ability to target a wide range of human cell types due to the variability in their amino acid profiles. Targeting this glycosylation site with antiviral medications could be an effective therapeutic strategy, drawing parallels to approaches used for dengue virus (DENV), which involves interfering with host cell receptor binding. This highlights the potential for developing glycosylation-focused antiviral treatments to mitigate ZIKV infections [39].

4. Virus Transmission and Pathology

The transmission of diseases carried by mosquitoes is facilitated partially by poverty [40, 41]. Mosquito-borne viruses are prone to infect populations with inadequate healthcare and sanitation [6]. The ZIKV can be transmitted by two methods: human and human-to-human vectors [32].

4.1. Transmission of Vectors Borne ZIKV Is by *Aedes Spp*

The spread of disease and other species beyond Africa is attributed to *Aedes aegypti* [32]. Zika Virus (ZIKV) is primarily transmitted by *Aedes aegypti*, *Aedes polynesiensis*, and *Aedes albopictus* mosquitoes. *Aedes aegypti*, also the main vector for dengue and Chikungunya, has been shown to replicate ZIKV, particularly in experimental studies. After the ZIKV outbreak in French Polynesia, mosquitoes from these species were collected and tested using RT-PCR, with ZIKV RNA found in one *Aedes aegypti* mosquito, confirming its role in transmission [42]. The female *Aedes aegypti* is frequently aggressive throughout the day and must consume blood to produce eggs. Furthermore, the infection was limited to a variety of *Aedes arboreal* species, including *A. africanus, A. apicoargenteus, A. furcifer, A. hensilli, A. luteocephalus*, and *A. vittatus*, with an insignificant incubation period of about 10 days in mosquitoes [43]. Thus far, 61 countries and 6 territories in WHO regions have confirmed the presence of conventionally proficient *Aedes aegypti* vectors; ZIKV infection has not been reported [44].

There is still a possibility of ZIKV spreading to other countries, potentially due to underreporting and detection challenges. It has been reintroduced or reemerged in regions where previous infections were confirmed. Among the mosquitoes tested, P6-740 was identified from the Asian lineage (Malaysia/1966), while eight others were from the African lineage. Notably, an outbreak of ZIKV occurred in 2007 among patients infected with *Aedes albopictus* mosquitoes from West Africa [45]. However, the more inclined vector responsible for the pandemic in Micronesia is believed to be *Aedes (stregomyia) hensilli* [46]. After being mainly extended to French Polynesia in 2013, the ZIKV eventually expanded to Oceanian islands, such as Easter Island, the Cook Islands, and New Caledonia. The main symptoms reported by 11% of the population were GBS, conjunctivitis, slight fever, painful joints, and irritation [47]. Furthermore, throughout Central and South America, *Aedes aegypti* is thought to be the main DENV vector. *Aedes aegypti* and *albopictus* strains from the New World were found to be inefficient ZIKV transmitters, which is a factor that the Asian lineage continues to evolve, as Chouin-Carneiro (2006) identified [48]. These strains have switched to a different method of propagation that involves direct, vector-free person-to-person contact. Even while Aedes is often referred to as the ZIKV vector, the findings suggest a deeper understanding of transmission dynamics [49, 50].

ZIKV replicates in the midgut and salivary cells of the mosquito vector, with the infectious virus appearing in the saliva for about 5 days. During a blood meal, the mosquito transmits the virus to the human host's skin. The virus has the potential to infect fibroblasts, Langerhans cells, and epidermal keratinocytes before spreading to the veins and lymph nodes. While ZIKV antigens are detected in infected nuclei, their replication occurs in the cytoplasm. Infected cells produce type I interferons as part of an immune response to the virus. Autophagosome production is observed in infected fibroblasts, promoting viral replication and activation of antiviral antigen clusters (RIG-1, MDA-5, TLR3) that recognize pathogen-associated patterns. The presence of autophagosome-like vesicles confirms ZIKV-induced autophagy. During the critical phase of ZIKV fever, lymphocyte activation occurs. The virus attaches to host cell receptors through its E glycoprotein, followed by the release of viral RNA and nucleocapsid into the cytoplasm, which provides further insight into the virus's complex mechanisms. The antigen expressed in the host cell nucleus serves as a distinguishing feature among flaviviruses [32]. Studies found that ZIKV can proliferate and infect the salivary glands and midgut. The virus was also found in the saliva of Culex species [51]. Ultimately, the present study suggests that the range of the ZIKV infection

vector may be longer than formerly anticipated [5].

4.2. Non-vector-borne Transmission

As shown in Figure 3, non-vector-borne modes of propagation for the Zika virus comprise sexual contact, transplanted organs, blood donations, and delivery [5]. The transplacental route, trophoblastic plug leakage, or the delivery of an infected mother's child with an infection spreading inside the amniotic sac are the three ways that ZIKV can transfer from person to person. Further, a study on blood transfusions was conducted in Brazil, and there are allegations of sexual contact, but it is especially dangerous when one partner is pregnant due to the neurological effects on the growing fetus In addition, placental exposure to ZIKV causes placental deficiency, which impairs growth and causes microcephaly [10, 52]. An infection during labor has been associated with assisting in the newborn's neural development. In utero, serious viral infections are linked to the formation of microcephalus; however, low infection can lead to neurocognitive dysfunction in adults [53, 54]. In April 2016, after 2 Zika-related blood transmission cases from Brazil were fully reported, the US Food and Drug Administration (FDA) recommended monitoring other vulnerable donors and all blood donors for 4 weeks [32].

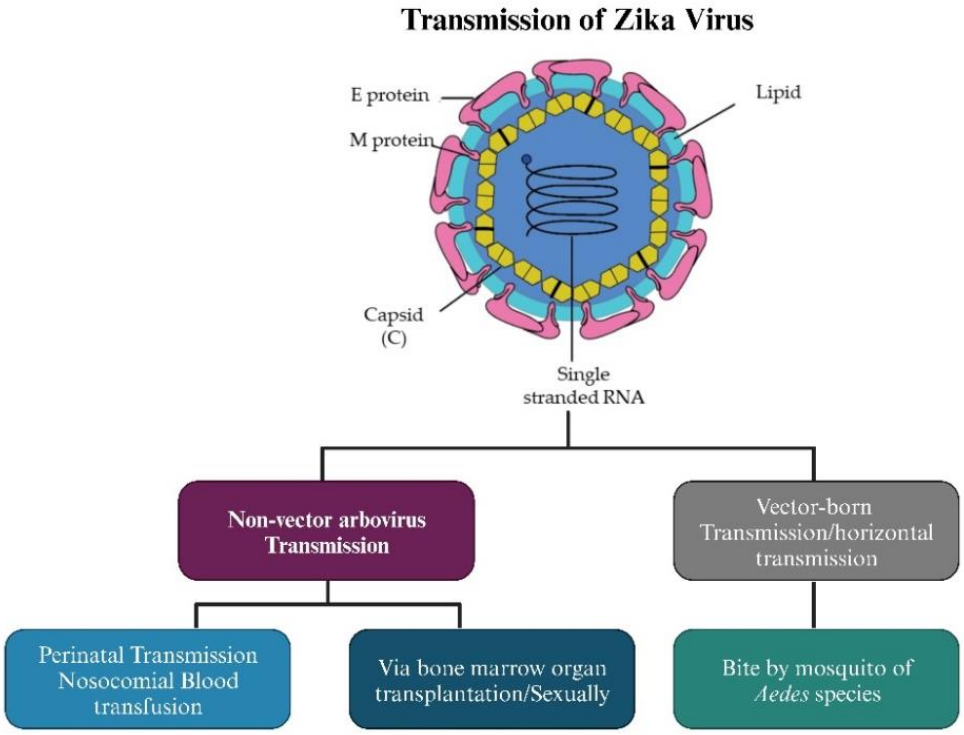

Figure 3. *Diagrammatic representation of the Zika virus transmission.*

As shown in Figure 4, Mosquitoes need 5 to 8 days to grow from eggs to larvae and pupal phases, and it takes an extra 3 days for them to mature into adults [55]. The adult mosquito of its replication cycle picks up the virus from the blood of the sick monkey when it feeds on the monkey. After entering the mosquito's epithelial cells, ZIKV multiplies, moves through its bloodstream, and ultimately exits the insect through its saliva. As vectors, mosquitoes can disseminate the virus to humans and other non-human primates (NHPs) through successive bites [25]. Antibodies against ZIKV were found by serosurvey studies on goats, sheep, bats, and rodents (Tatera indica and Meriones hurrianae). These results imply that the association between ZIKV and some specific species may not be entirely obvious [56]. It is spread to humans through the bite of a carrier mosquito, which is often found in tropical and subtropical regions near dwellings in household water reservoirs [57]. If there is more ZIKV RNA in the mother's milk, nursing may contribute to its propagation. In Brazil (2015), a study found that ZIKV is transmissible by donor blood, as the first case of ZIKV infection was documented [5, 7]. The Zika virus can proliferate during enzootic times and in residential places, both transmitted by vectors and non-vector-borne replication facilitated by humans and *Aedes* mosquitoes [5].

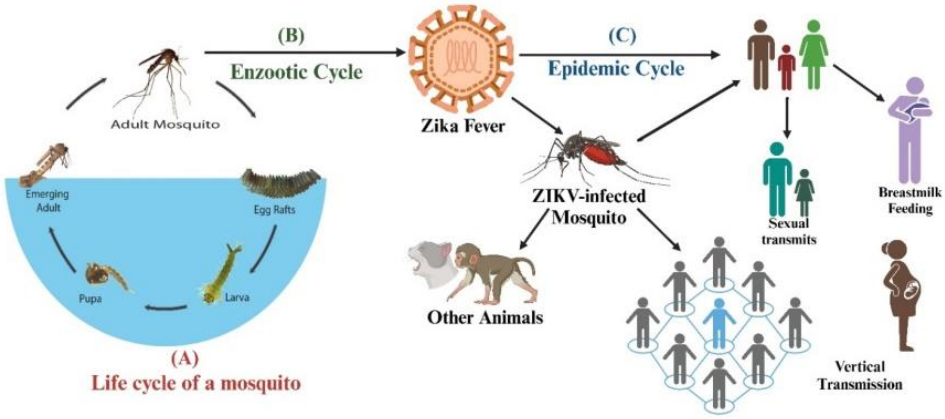

Figure 4. *(A) The mosquito's life span. (B) The spread of ZIKV and human or NHP propagation. (C) Various Zika virus infection modes throughout infectious diseases.*

5. Clinical Symptoms and Signs

The incubation period of ZIKV-caused infection might range from 2 to 7 days [58], Flu, fever, tiredness, headache, dizziness, indigestion, a lack of appetite, and allergy reactions with maculopapular characteristics [59]. Moreover, it could cause a lymph node infection, nausea, swelling, and retro-orbital eye irritation [32]. In certain regions, when ZIKV is common, it may be mistaken for other arboviruses or microbial infections. During a global pandemic, major neurological symptoms due to GBS caused a 20-fold outbreak in French Polynesia [1, 5]. Additional symptoms of Zika virus infection include encephalitis, microcephaly, meningoencephalitis, myelitis, paraesthesia, vertigo, facial and ophthalmological paralysis, and hearing loss, while 80% of cases show no clinical signs. When symptomatic, the infection typically presents as a mild, self-limiting illness lasting 3-12 days, with fever, maculopapular rash, arthralgia (especially in small joints), conjunctivitis, and headaches. The rash usually fades within two days, and the fever subsides within three days, though the rash may persist. Rare clinical signs include skin ulcers, uveitis, palatal petechiae, diarrhea, nausea, and bloating. Major complications of in-utero Zika virus infection can lead to microcephaly and GBS is characterized by progressive weakness, polyneuropathy, multi-organ failure, clotting disorders, and purpura. Congenital Zika infections can also cause retinal flecks, lens subluxation, blurred vision, hearing loss, and other eye disorders [60, 61].

Guillain-Barre Syndrome (GBS) is an unusual and rapid-onset paralysis often triggered by an infection, with symptoms typically appearing a few days to weeks after the initial infection. The first case of Zika virus exacerbating GBS was reported in March 2014. GBS has an annual incidence of 0.34-1.34 cases per million individuals under age 18 and is the leading cause of acute flaccid paralysis in healthy newborns and children worldwide. Men are affected 1.5 times more often than women across all age groups. The most common form of GBS, acute inflammatory demyelinating polyradiculopathy (AIDP), usually manifests with neural symptoms up to four weeks after a mild gastrointestinal or respiratory infection. Pain and difficulty walking are typical symptoms of GBS in children. The primary treatments for GBS include intravenous immunoglobulins and plasmapheresis [62, 63]. Fetal Zika Syndrome involves neurological issues, intellectual disabilities, ischemic stroke, microcephaly (small head size), sensory hearing loss, eye problems, and heart defects. Microcephaly is diagnosed when the occipitofrontal diameter falls below the third percentile for the mother's age and sex, helping to identify abnormal head size in infants born to mothers infected with ZIKV during pregnancy [64, 65]. In late November, three deaths related to ZIKV were recorded in Brazil. These included a baby, two individuals with brain disorders, and an adult male with rheumatism, chronic lupus erythematosus, steroid use, and alcoholism. Additionally, a 15-year-old girl with sickle cell anemia died after presenting with fever, chest pain, jaundice, and an enlarged liver. A newborn also passed away within five minutes of birth due to microcephaly, fetal anasarca, and polyhydramnios [32].

6. Identification and Pathology

The transmission of ZIKV was first mislabeled as a dengue virus infection, and there are two ways to recognize the Zika virus [5]. The primary methods for diagnosing Zika infection involve detecting viral proteins and confirming an active infection. Immune assays are used to identify the viral proteins responsible for transmission, while viral isolation confirms the presence of viable ZIKV. Additionally, therapeutic approaches focus on analyzing antibodies produced during infection, using immunohistochemical testing and reverse transcription PCR [66]. Various molecular and serological tests are employed to detect Zika virus infection. Serum tests help monitor the immune response by identifying antibodies, while molecular analyses detect genetic changes associated

with the virus [67]. Diagnostic evaluation is not sufficient to fully comprehend ZIKV recognition because of its major interactions with different arboviruses [25]. The acute and subacute sample range limits and *Flavivirus* interference are two of the challenges preventing the widespread adoption of serological approaches. However, isolating infectious agents is a painstaking activity that may require weeks or even days. ZIKV can be isolated by cultivating cells, and it requires specialized lab equipment [68, 69].

The emergence of ZIKV is confirmed by RT-PCR, whereas ZIKV-specific antibody levels (IgM) are often identified by an ELISA technique [70]. There are several competitive serology assays available; two notable companies that have developed the tests are InBios (United States of America) and Euroimmun AG (Germany). The Euroimmun assay was the initial serological test made accessible to the general public; it was thoroughly studied in the literature [71, 72]. Using the Euroimmun antibodies ELISAs, MAC-ELISA, and then PRNT, L'Huillier et al. [67] performed a comparison study to ascertain whether the results were definitive. The Euroimmun paired IgG/IgM screening offers a higher specificity (95% of responses) than MAC-ELISA, which presents an intriguing result. Notably, the test's (39.5%) specificity was far lower than the MAC-ELISA's. Another trademark for the InBios test is the Zika DetectTM 2.0 IgM Capture ELISA Kit, which is designed exclusively for intravenous clinical purposes. Through its use, ZIKV IgM antibody levels in a person's blood can be qualitatively identified. In May 2019, this test made history by being the first market serology kit in the US to acquire FDA Market Permission.

With several significant modifications from the prior version, the ZIKV DetectTM 2.0 IgM Capture ELISA Kit has recently superseded the ZIKV DetectTM IgM Capture ELISA Kit. The Zika virus DetectTM 2.0 IgM Retrieval Assay Kit has markedly raised mean response from 90.4-92.5% and precision from 79.5-97.4%, showing an impressive rise of 17.9%, as stated by Basile et al., [73]. Further, the lab consistency improved from 79.5% to 97.4%, a 17.5% gain, and the dependability of the modified test increased to 89%, a staggering 25.1% difference from the initial test's accuracy of 63.9%. Consequently, the data suggests that the Zika DetectTM 2.0 IgM Acquisition ELISA Tool is a potential comprehensive screening technique that could reduce the demand for Plaque-Reduction Neutralization Test (PRNT) confirmatory research. These methods have great promise for frequent use in medical labs; however, more research is needed to determine whether they adequately cover all phases of a systemic clinical analysis [25].

Moreover, it was found that saliva provides better molecular screening for the Zika virus in the early stages, especially in infants and toddlers, when taking blood presents difficulties [74]. According to the PAHO, genotyping occurs following a substantial RT-PCR finding of Zika fever. Immunofluorescence and ELISA analysis occur in IgM serology for Zika diagnosis; a PRNT is used for confirmation either results are satisfactory or uncertain [75]. Since viral RNA can still be found in the bloodstream, the RT-PCR analysis is a reliable clinical method, but it is unable to be utilized for recognizing serious infections [67]. The efficacy of the RT-PCR test has to be maintained to avoid erroneous results. However, there are restrictions since ZIKV fluctuates. Between the approved sequence of the Asian-lineage ZIKV viral strain and the oligonucleotide patterns from published studies, up to 10 nucleotide mistakes were found. Furthermore, the genetic variation of the Asian-lineage Zika strain may result in a limit of 5 variants for certain primers or tags, which could lower the sensitivity of the RT-PCR experiment [76, 77].

The primers and probe patterns are updated, and continual study is needed to find unique Zika variations to reduce discrepancies and improve diagnostic accuracy. While MAC-ELISA is capable of screening for IgG in serum or cerebrospinal fluid qualitatively, the lack of specific antibody response may make it difficult to interpret the results. The "preeminent" method for flavivirus serological identification, known as PRNT, stops plaque formation in a cell monolayer by blocking the virus using specific immune cells. Although PRNT is very effective, it is costly and requires specialized facilities with authorized staff to handle virus specimens and appropriate instruments for cultured cells. Because the test is complex and results take 5 -10 days to process, proper education is essential for safe and efficient use [77, 78].

7. ZIKV Prevention and Management

None of the 4 infections attributed to flaviviruses have an FDA-approved remedy or antibody at present. Conversely, Zika vaccinations can be administered with both active and inactive attenuated viral therapy. Moreover, treatments against the Japanese encephalitis virus (JEV), the Dengue virus (DENV), the Tick-Borne encephalitis virus (TBEV) (inactivated), and the yellow fever virus (YFV) (live attenuated) are available as shown in Table 2. The cleaning agents that are prone to the spread of ZIKV are a solution of 70% ethanol, 2% glutaraldehyde, 3%–6% hydrogen peroxide, 1% sodium hypochlorite, and 3%–8% formaldehyde. The primary goal of ZIKV precautions is to fight off or minimize bug bites. Dressing in long sleeves and shoes, using bug repellent, and spending as much time indoors as possible are all part of it. Insecticides containing diethyltoluamide (DEET), picaridin, eucalyptus oil, IR3535, oil of lemon, and para-menthane-diol are advised for use by breastfeeding or pregnant women [79]. Blood donations should be halted promptly if there is an outbreak, and Men with expectant partners who relocated from affected areas should continue using condoms [80, 81]. The primary causes of ZIKV infection are insects and the areas where they breed are imperative to manage and stop their spread. By using mosquito nets, insect repellents, and sealing, human-mosquito contact can be reduced to a minimum. In addition, to target larvae of mosquitoes and limit their growth are recommended by the WHO Pesticide Evalu-

ation Scheme should be used as larvicides [5, 82].

Avoid using insecticides comprising paramenthane-diol, lemon oil, or eucalyptus oil on little ones (under 3 years old). To eliminate insects inside the residence, employ indoor mosquito-killing lotions with chemicals like imidacloprid and β-Cyfuthrin. Moreover, vectors can be easily repelled with airborne bug foggers containing active agents notably tetramethrin and cypermethrin [5]. The evaluation of ZIKV viruses can be done before allowing blood donations to prevent infection associated with transplants. Since Zika exposure is linked to hydrocephalus, childbirth must be avoided in locations where the virus is likely to spread before complete eradication is mandatory [81]. Many vector control methods can be applied to repellents and interior sprays to halt the spread of the Zika virus. A way to reduce the prevalence of mosquitoes is to use a bacterium that can infect them. Another approach is to introduce inside bacteria, such as *Wolbachia*, which controls insect populations by acting as a biopesticide. The larvae of the *Toxorhynchites splendens* mosquito species eat on the larval stage of other insect species instead of blood, but adults of that species eat honeydew, fruits, and pollen. They offer multiple options for managing mosquitoes while decreasing the possibility that the Zika virus might replicate [82]. Further, fertile female *Aedes* mosquitoes can be mated with sterile males to produce sterility and reduce mosquito populations [83].

Table 2. *The distinction of a ZIKV infection encompasses a variety of viral diseases that show similar signs and symptoms to the Zika virus [84].*

Viral diseases	Zika virus similarity	ZIKV divergences	Diagnostic test
Dengue fever	High fever, intense migraines, and muscular aches may also be related to hemorrhage	Area related to the conjunctiva	Serology
Chikungunya	Higher body temperature and severe arthritis in joints	A spot linked to the conjunctiva	Serology
Parvovirus	Uniform, intense inflammation or osteoarthritis	The rash could be there or absent.	Serology
Rubella	rheumatism, lymphadenopathy, macular rash, and a mild fever	Coryza disappears in ZIKV infection and is not related to conjunctiva	Serology
Measles	Conjunctiva cough, fever, lymphadenitis, and extensive redness	Coryza and throat pain aren't the signs of a the Zika virus	Serology
Leptospirosis	Fever, migraine, joint pain, myalgia, corneal suffusion, and shocks	Jaundice is the hallmark of a widespread the Zika virus	Serology
Malaria	high fever, fatigue, indigestion, vomiting, stools, and myalgia	The conjunctivitis-related dot	Visualization of parasites on Peripheral smear
Rickettsial InfectionAffrican tick bite	Relapsing high fever and African tick bite fever. head pain, fatigue, fever, local lymphadenopathy, and widespread redness	The dot linked to conjunctiva	Direct smear and PCR reaction

It is advised that patients take oral medications for their discomfort and fever, and maintain adequate hydration. As seen in Figure 5, therapy and medical attention are advised if symptoms manifest. There are currently no specific drugs or treatments licensed to cure or prevent the Zika virus outbreak. The purpose is to decrease symptoms; drugs such as paracetamol help ease fever and discomfort brought on by the viral infection [85]. The alternative method to produce antivirals for fighting infection is to produce antagonists to prevent ZIKV from spreading. One approach is to treat ZIKV infections with currently available drugs that have been invented for various uses. Antiviral enzyme studies and viral infection tests are useful for screening catalogs of inhibitor drugs. Making medicinal antibodies is a potential Zika infection treatment option. Myalgia, headaches, and flu-like symptoms are treated with acetaminophen for those with Zika infection. Anti-inflammatory drugs, such as aspirin, raise the risk of bleeding in children with Reye's disease and clotting disorders; hence, they cannot be used [86]. It is not advised to take non-steroidal anti-inflammatory drugs because of a higher risk of hemorrhagic disease. Rehydrating sufficiently is necessary to minimize fluid loss. Intravenous immunoglobulins serve as the first-line remedy for brain diseases. It is urged that pregnant women who exhibit Zika fever-like symptoms over or within 14 days of ZIKV contact undergo a fetal ultrasound and virological screening to identify this outbreak and evalu-

ate the potential of cerebral calcification or baby microcephalus [87]. The blood will be collected from the umbilical vein or the growing baby within 2 days of delivery to test for ZIKV-neutralizing antibody neutralization [32].

Moreover, Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided before starting a new prescription, especially if they already use one for other medical problems; people ought to talk with their physician [79]. Natural remedies such as homeopathy are an excellent choice for managing Zika replication since they serve well for treating Japanese brain damage, a disorder that is linked to the Zika virus carried by mosquitoes [88]. The effectiveness of belladonna therapy reduced the level of infection attributed to the encephalitis in a Japanese population [5]. Thus, Belladonna showed efficacy in treating a range of clinical issues, leading to its enormous economic worth as a key supplier of minerals, primarily scopolamine and hyoscyamine. It is indigenous to Europe, Western Asia, and North Africa. Fresh fruit and leafy vegetation contain the majority of the alkaloidal contents in Atropa belladonna. It was used historically to treat an array of medical issues such as migraines, stomach ulcers, irritation, bleeding issues, and histaminic responses [15]. In homeopathy, ultra-diluted belladonna dosages of 1:10 or 1:100 are used and recommended for the management of all viral medical conditions [89]. *Euphorbia vulgaris*, a prevalent medicinal product, can be taken as a preventive measure in combating Zika virus complications [90]. Rhustox, Atropa belladonna, and Eupatorium perfoliatum are the herbal remedies that are commonly administered for Zika virus outbreaks [91].

As compared to the typical pharmaceutical structure, herbal drugs are superior in reducing morbidity and death throughout the pandemic [5]. For decades, *Tinospora cordifolia* was utilized as an intriguing immunomodulator and a potent organic medicine treating infectious diseases across all categories. Certain inhibitory attributes of ayurvedic flora are effective in controlling bowel disease, bladder infections, dengue fever, and pig flu; therefore, they might be effective in treating the Zika virus [79]. In addition, neuroscience methods were utilized to advance the possibility of a brain-penetrating peptide for treating neurotropic viral diseases and to pursue peptide medications [33]. Most modern medicinal methods focus on alleviating symptoms rather than the disease itself. Currently, efforts are being made to create ZIKV treatments and vaccinations. In 2016, the WHO compiled a comprehensive list of known activities that were done by corporations, governments, and research centers and centered on ZIKV therapies, particularly vaccine development. It includes distinct methods beyond live transgenic attenuated viruses, protein elements, DNA, and a pure inactivated viral vaccine. No immunizations were yet licensed for clinical trials as of April 2019, even though many were in advanced phases of research. Virtual drug screening based on docking can also be used to evaluate chemicals using phenotypic and genotypic analysis or more sophisticated homology models. The compounds found via docking could be given priority for in vitro parallel investigation. The next phases are standard for a drug discovery pipeline: animal modeling, clinical studies, and, if results are encouraging, scaling up production of the drugs against the Zika virus, followed by marketing and distribution [81].

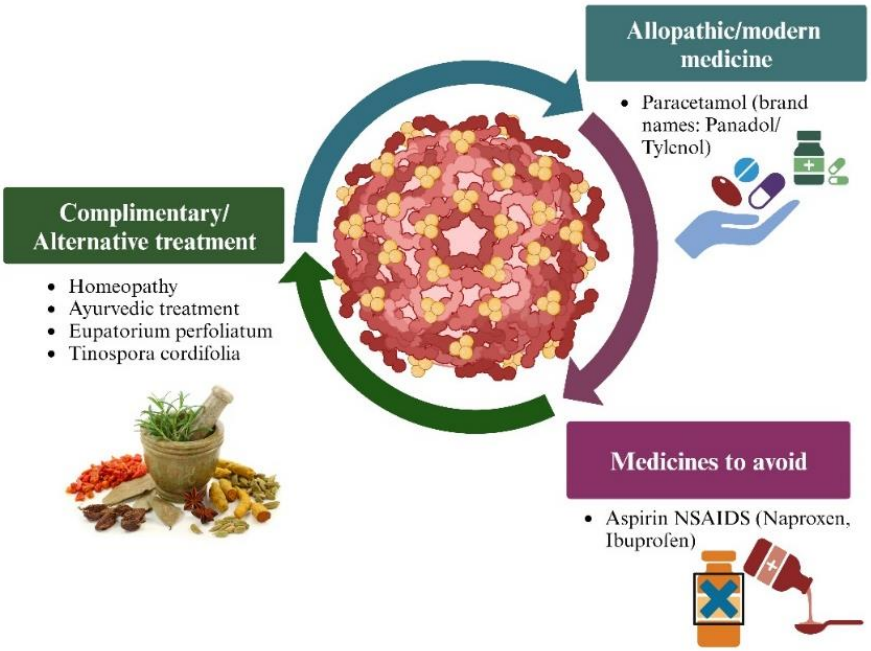

Figure 5. *An illustration depicting a potential ZIKV infection.*

8. Future Outlook and Limitations

The future of ZIKV research presents promising opportunities, particularly in the development of vaccines, diagnostic advancements, and enhanced mosquito control strategies. As our understanding of ZIKV's molecular biology deepens, targeted vaccines aimed at specific viral proteins will likely become a key focus. Moreover, the introduction of rapid DNA testing could significantly improve early detection, enabling more effective prevention of complications like microcephaly and GBS. In parallel, novel mosquito control approaches, including new insecticides, genetic modifications, and better environmental management, are critical for combating the spread of Aedes mosquitoes in endemic regions. Future research will need to explore the precise mechanisms by which ZIKV causes congenital defects, such as microcephaly, and its broader effects on organ systems. Animal models and human tissue studies are crucial for understanding how the virus disrupts fetal development. Continued epidemiological studies will help monitor the virus's genetic evolution and long-term effects on those born to mothers infected during pregnancy. Additionally, strengthening global health infrastructure to improve surveillance, response times, and healthcare systems will be vital for managing potential future outbreaks, especially in tropical and subtropical regions.

Despite the optimistic outlook, several challenges remain. The absence of an approved ZIKV vaccine is a significant hurdle, with the development process being complex and requiring rigorous testing for both safety and efficacy, particularly in pregnant women. Mosquito control, the primary method of prevention, is being undermined by insecticide resistance, and alternative control measures are still in the experimental phase. Additionally, the exact pathogenesis of ZIKV, particularly how it causes severe birth defects, is still not fully understood, making the development of effective treatments more difficult. Environmental factors, including climate change and urbanization, contribute to the spread of ZIKV, complicating efforts to manage outbreaks. Socioeconomic conditions also affect the ability of populations to respond effectively, with limited access to healthcare and education hindering proper responses. ZIKV's genetic variability, particularly between African and Asian strains, adds complexity to efforts aimed at developing a universal vaccine or treatment. There is also limited long-term data on the potential chronic effects of ZIKV infection, especially in individuals who experienced mild or asymptomatic infections. In conclusion, while progress is being made in understanding and controlling ZIKV, challenges remain. Ongoing research into vaccine development, mosquito control strategies, and the virus's pathogenesis is essential for mitigating its public health impact and preventing future outbreaks.

9. Conclusion

In conclusion, the Zika virus remains a significant global health concern, with the potential for severe outcomes such as congenital defects, including microcephaly, and neurological complications such as GBS. Despite ongoing research into its pathology, transmission, and prevention, substantial gaps remain in understanding the precise mechanisms through which ZIKV causes these severe outcomes. Current efforts to develop a vaccine, improve diagnostic tools, and enhance mosquito control strategies are critical in mitigating the spread of the virus. However, challenges such as mosquito resistance to insecticides, the genetic diversity of the virus, and the lack of long-term data on ZIKV infection underscore the need for continued research. Preventive measures, including vector control, protection from insect bites, and public health awareness, remain the cornerstone of controlling ZIKV transmission. Ultimately, a coordinated, global approach involving research, public health strategies, and effective vaccine development will be key to reducing the impact of ZIKV and preventing future outbreaks.

Abbreviations

CDC	Centers for Disease Control
DENV	Dengue Virus
ER	Endoplasmic Reticulum
GBS	Guillain-Barre Syndrome
JEV	Japanese encephalitis virus
NHPs	Non-Human Primates
TBEV	Tick-Borne Encephalitis Virus
WHO	World Health Organization
YFV	Yellow Fever Virus
ZIKV	Zika Virus

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Conflicts of Interest

The authors declare no conflicts of interest.

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