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Zika Virus and Its Association with Neurological Disorders

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Abstract

Zika virus (ZIKV) is a flavivirus that can be identified as a small envelope with a positive-stranded RNA and an important medical pathogen, which causes deadly human diseases. The virus is carried by *Aedes aegypti* mosquitoes through a blood meal and it is also spread through body fluids. ZIKV infection may present with symptoms like fever, myalgia, maculopapular rash as well as neurological sequelae, which include, microcephaly, epilepsy, and Guillain Barré syndrome (GBS). This put the virus on a scale of the public health burden of almost 87 countries. The potential threat of ZIKV infection is not completely eradicated in many countries in Africa, America, and the Western Pacific regions. There are no vaccines and treatments available to date. Since ZIKV causes microcephaly in utero by targeting neural progenitor cells, inducing apoptosis, and impairing neurodevelopment, this article hopes to evaluate the neurological disorders associated with the Zika virus infection while elucidating the current trends in the development of vaccines and drugs.

Keywords

Zika Virus (ZIKV), Microcephaly, Guillain Barré Syndrome, Epilepsy, Neurological Disorders

1. Introduction

There are over 50 arthropod-borne viruses that can cause neurological complications and are classified as arboviruses. They belong to the genus flavivirus and family Flaviviridae, which includes dengue virus (DENV), Japanese encephalitis virus (JEV), West Nile virus (WNV), and tick-borne encephalitis virus (TBEV) [1] [2]. Among these viruses, the most widespread is ZIKV. It has spread almost across the world and is associated with serious neurological consequences such as microcephaly, GBS, and nervous system (CNS) disorders [3]. ZIKV was first isolated in 1947 from a rhesus monkey in the Zika forest, which is in Uganda. Later in the same year, it was isolated and identified in the Republic of Tanzania [4] [5]. Human infection was first discovered in Nigeria in 1954 [6], transmitted mainly by infected mosquitoes called *Aedes aegypti* [7] [8]. It is a single-stranded RNA virus with an approximately 10.7-kb positive-sense RNA genome encoding a polyprotein [9] and it is recognized as a group of small enveloped positive-stranded RNA viruses causing serious human diseases [9]. The polyprotein consists of three structural proteins: capsid [C], pre membrane [prM], and envelope [E]; and seven nonstructural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 [10] [11] [12] (**Figure 1**). Moreover, you can find the ZIKV virus in human body fluids such as urine [13] [14], saliva [15] [16], and even semen [17] [18]. This virus can be spread through the placenta from the pregnant mother to the fetus during pregnancy [19], during sexual intercourse [20] [21] [22], and via blood transfusion [23] [24] (**Figure 2**). ZIKV infection is either asymptomatic or symptomatic; when symptomatic, it results in mild illness with fever, muscle pain, and maculopapular rash [25] [26]. Between 1947 and 2007, a few sporadic human cases of ZIKV were reported from several African and Asian countries [27] [28] (**Figure 3**). In 2007, a massive epidemic of ZIKV infection in humans occurred in Yap, Federated States of Micronesia, and in the Pacific region. A seroprevalence survey estimated 73% of the population to have been infected [29]. Another sporadic case of ZIKV occurred in the Philippines and then in Thailand from 2012 to 2014 [29] [30]. Subsequently, a few cases were reported in Colorado, USA, and Indonesia from travelers returning from Africa [31] and Southeast Asia [32] in 2013. Then, widespread outbreaks were reported in 2013 and 2014 in the Pacific Islands, including Cook Island, French Polynesia, Easter Island, and New Caledonia [33] [34]. However, these infections were not investigated further, and the pathogens were not identified clearly [35]. The rapid transmission of this virus continued and affected 29 countries in America from 2015 until the beginning of 2016 [36]. In Brazil, a serious outbreak of 6000 cases of "exanthematic disease" was documented, but only a few were identified as having ZIKV. Furthermore, in mid-2015, the government of Brazil reported 40,000 cases of infection again with 24,000 suspected cases of Zika fever. However, in the absence of routine laboratory testing, the exact number of infections remained unknown [37]. On 29 April 2015, the Bahia State Laboratory in Brazil officially reported to the World Health Organization (WHO)

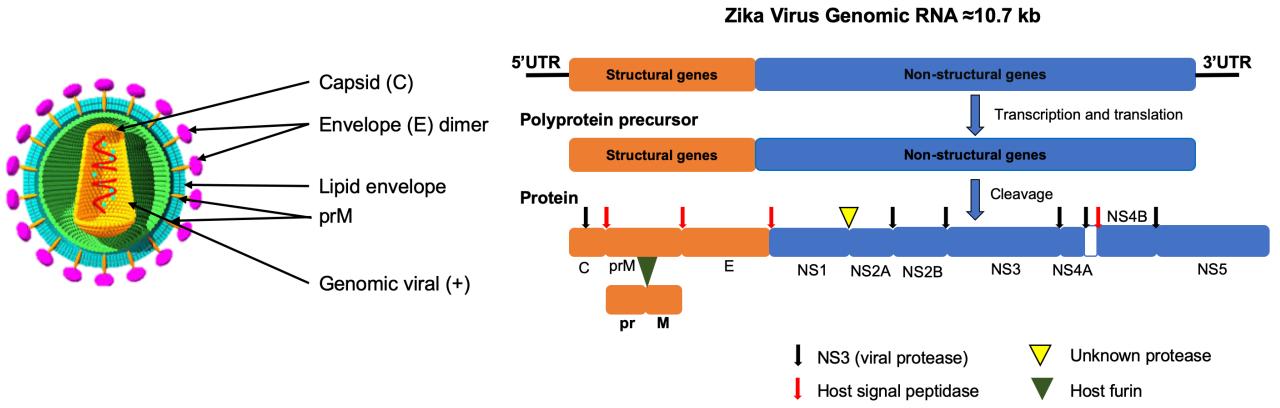

Figure 1. Virion structure and genomic of ZIKV. Zika virus is an enveloped virus, with an approximately 10.7-kb positive-sense RNA genome, that contains a single unique ORF, encodes a polyprotein consisting of three structural proteins such as (capsid [C], pre membrane [prM], and envelope [E]) and seven nonstructural proteins such as NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. UTR, untranslated transcribed region [38].

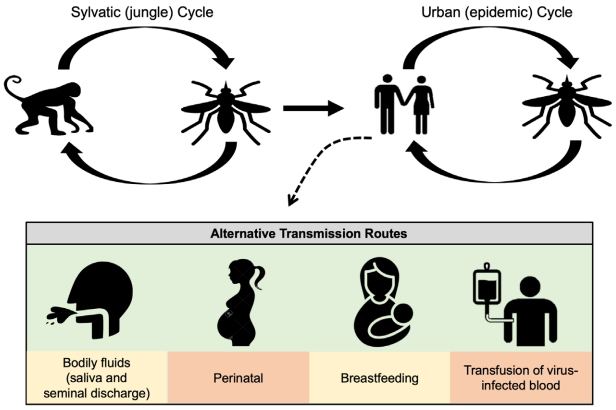

Figure 2. Vector-borne transmission of ZIKV. There are two cycles of transmission caused by mosquitoes: 1) a sylvatic cycle in the jungle, in which the virus cycles occur between non-human primates and *Aedes aegypti* mosquitoes; and 2) an urban cycle, in which the virus circulates between humans and urban mosquitoes. Under certain circumstances, ZIKV can likely be transmitted from non-human primates to humans by *Aedes aegypti* mosquitoes [39] [40].

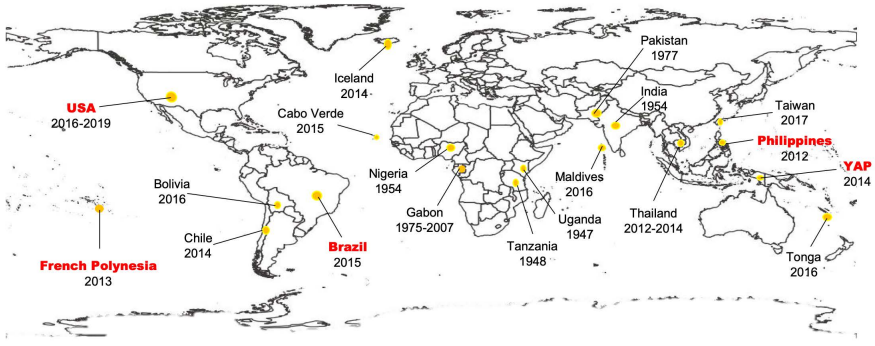

Figure 3. Global distribution of ZIKV infection. The ZIKA virus has been detected almost over the world, but since 2007 there have been several epidemics in some countries, including the USA, Federated States of Micronesia (YAP), Brazil, and French Polynesia (highlighted in red text) [41].

that some of the samples were diagnosed positive for ZIKV [37], which was confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR) [42]. For diagnostic molecular testing of ZIKV, it is better to use the RT-PCR on serum, urine, or other body fluids of the patients [43]. Following RT-PCR, serological diagnosis is performed with enzyme-linked immunosorbent assay (ELISA) and confirmed by plaque reduction neutralization test (PRNT) according to the international standard protocol [44]. In the French Polynesia outbreak, indirect ELISA with recombinant antigens was used for serology during the outbreak [45].

Some of the cases were identified with a correlation to neurological complications and congenital malformations [46]. For the first time, during the Pacific Island and French Polynesia outbreak in 2014, ZIKV was identified to be associated with microcephaly [46] and GBS [47]. And also, a strong association between epilepsy and Zika-linked microcephaly in infants was reported [48]. A subsequent serological test was done in some countries, including the Pacific region, and almost 7000 cases were found with acute fever and skin rash similar to ZIKV from February to April 2015 [35] [49]. It has an average incubation period of 4 - 10 days [50]. Based on a recent study, this virus has been implicated in the etiology of serious pathologies of the human nervous system like microcephaly and epilepsy in newborns and Guillain-Barré syndrome in adults [51] [52]. Also, a growing body of evidence on ZIKV-related neurological complications suggests the disease to be of great public health importance [51]. Here, we review the literature on ZIKV-associated congenital malformations and neurological abnormalities during and after birth. We further went on to explore the clinical manifestations, management of infection, and vaccine development. Additionally, we also searched PubMed, Science Direct, Web of Science, and Google scholar and reviewed the relevant literature on ZIKV infection, its tropism, and pathogenicity, particularly in the CNS. The reference lists and relevant articles from review articles were also examined to write this review.

2. Epidemiology of ZIKV-Induced Neurological Sequelae

During the ZIKV epidemic in French Polynesia, studies identified an increase in the incidence of central nervous system anomalies (e.g., microcephaly) due to viral infection [53]. Moreover, the outbreaks in Brazil have proven difficult in identifying the association between ZIKV and microcephaly in the fetus or neonate. This is because not all regions have cases of Zika associated with microcephaly. Notwithstanding, the common outcome was reported as an increased rate of microcephaly, stillbirth, as well as brain malformations among infected patients [1] [54]. The reported annual number of cases of microcephaly in Brazil was persistingly increasing from 2010 to 2014 [55]. A relationship between ZIKV and microcephaly during gestation was first suspected in Brazil at the end of October 2015 [56]. About 90% of 1501 live births were diagnosed with microcephaly from November 2015 to February 2016 [57]. In response, the Brazilian

Ministry of Health declared a national public health emergency on 11 November. Three other alerts were issued by the Pan American Health Organization (PAHO) on 17 November November [58], by the European Centre for Disease Control, Prevention (ECDC) on 24 November [59], and by the ECDC on 10 December [60]. To better understand these situations, a working group was formed to investigate microcephaly caused by vertically transmitted ZIKV [1]. In 13 cities in Brazil, a serological diagnosis was made with 1761 reported cases [61]. Also, at the beginning of 2016, Brazil announced 3893 cases of newborns with microcephaly induced by ZIKV [62]. Other neurological, ophthalmologic, and auditory complications have also been reported in neonates with ZIKV [62] [63] [64]. Due to the neurological complications of ZIKV during pregnancy, a spectrum of fetal malformations has been declared and given the name Congenital Zika Syndrome (CZS) [65].

In the first year of life, epilepsy is a crucial component of CZS in some children with ZIKV infection [1] [66]. In Brazil (2015), a comparison of the patients with CZS showed that the prevalence of epilepsy was four times more common at birth than congenital microcephaly [67] [68]. According to Van der Linden *et al.*, 74% of infants with ZIKV had seizures within the first six months of life, and the average age of diagnosis of epilepsy was 4.9 months. Different types of epilepsy have been reported like infantile spams, and tonic seizures, however, a single seizure was more common, accounting for 77% of cases [69].

ZIKV is a neurotropic virus and a major cause of GBS in adults [43]. The French Ministry of Health reported the first case of GBS associated with a ZIKV infection in Martinique in 2012 [70]. Data from the French Polynesia epidemic showed that an estimated incidence of GBS in neonates was more than the annual 1 to 3 cases per 100,000 inhabitants [71] [72]. Between 2009 to 2012, the annual number of reported cases was 5, 10, 3, and 3 [73] [74]. Moreover, there was a strong temporal relationship between the occurrence of ZIKV in French Polynesia and the unusually higher number of GBS cases [75]. Following this situation, GBS has been reported to be a neurological complication for adults similar to DENV [76] and WNV [77]. Subsequently, an increasing incidence of ZIKV induced GBS was reported in three American countries [70]. From January to July 2015, Brazil announced 121 cases in the northeastern states, with 62% of patients confirmed to have symptoms compatible with Zika fever and GBS [39] [78]. The second examination was done on 22 cases in December 2015; 54% of them also had symptoms similar to ZIKV infection and were confirmed to have GBS [65]. Furthermore, Venezuela and Colombia recognized an increase in Zika-related GBS of about 2 to 3 times the normal incidence [71]. Collectively, these epidemiological data reinforce the hypothesis that GBS is related to ZIKV infection.

The recent emergence of ZIKV worldwide has raised considerable concern because of its potential to cause severe neurological complications during fetal development, as earlier outlined [42] [56] [67]. On 1 February 2016, WHO declared that microcephaly, GBS, and other neurological disorders linked to the

Zika virus be treated as a Public Health Emergency of International Concern (PHEIC) [79] [80]. According to the WHO, the incidence of ZIKV infection peaked in 2016 and was reported in many countries, including Africa and America, but gradually decreased between 2017 and 2018, especially in American countries [52]. However, in July 2019, ZIKV and its vectors were still visible in some countries and regions, particularly in North and South America, Africa, South-East Asia, and the Western Pacific [81]. Therefore, the fear of the potential threat of ZIKV infection is not yet completely gone since the virus-carrying vectors are still circulating in the population, especially where this virus is spreading. The possibility of an outbreak of ZIKV infection may occur again in the future.

3. Brain Injury Caused by Zika Virus

Flaviviruses are vector-borne RNA viruses that can cause a variety of potentially severe diseases in humans, including acute flaccid paralysis, congenital anomalies, and fetal mortality. Generally, ZIKV infection is a mild disease, and hospitalization is only needed in severe cases of infection. For instance in Brazil, the estimated case fatality rate is low, around 8.3%, based on recent studies [82]. However, if the disease is left untreated, serious complications can result in death [83].

3.1. Microcephaly

The critical period of neurological development is the first trimester of pregnancy, and congenital malformations are more common in this period [42]. Microcephaly is described as an abnormally small head in which the head size at birth, measured by occipitofrontal head circumference (OFC) is below −3 standard deviations (SD) of the normal value for the patient's age and sex [84] [85] [86] [87]. Severe cases of microcephaly are often accompanied by various neurological abnormalities such as seizures, cerebral palsy, abnormal ocular development, and mental retardation [85] [88]. According to the previous reports from autopsy and ultrasound examination of ZIKV infected cases, calcification of the placental villi, without inflammation, leads to ventriculomegaly in the fetal brain with a dramatic loss of the brain parenchyma and subsequent microcephaly or microencephaly [89].

In vivo and *in vitro* models have been constructed to better understand the mechanism of ZIKV replication and its capacity to affect nerve cells [89]. These models successfully used stem cells to identify neural progenitor cells (NPCs), glial cells, and neurons specifically infected by the virus [90] [91]. For instance, an animal model infected by ZIKV showed that the mouse sustained damage to the corticospinal neurons and had depletion of proliferating cells in the ventricular area of the neural stem cell compartment [92]. Moreover, a study conducted on pregnant women with ZIKV demonstrated an active infection in the placenta, as well as the brain, eyes, and reproductive tracts of the fetus [50].

ZIKV infection of the brain at different stages of development leads to several forms of abnormalities, including microcephaly, by targeting NPCs [93]. Also, infection of the developing brain inhibits cell proliferation and migration of neurons by causing apoptosis, altered myelin formation, and impaired synaptogenesis [93]. According to a recent report, the central nervous system is vulnerable to ZIKV, mostly around 13 weeks of gestation, and infection at this stage leads to a higher risk of microcephaly [51]. Moreover, microcephaly can be classified into primary (or true microcephaly) and secondary. The primary microcephaly occurs around 32 weeks of gestation and is inherited as an autosomal recessive disorder, while the second happens after birth [94]. These two types of microcephaly differ in CNS abnormality progression: primary microcephaly is usually a static developmental anomaly, whereas secondary microcephaly indicates a progressive neurodegenerative condition [95] [96]. Interestingly, ZIKV is known to cause both forms of microcephaly [97]. The molecular pathway involved in ZIKV neurological complications is unclear. Identification of the protein receptors and genes involved in ZIKV-induced microcephaly is essential in clarifying and improving our understanding of ZIKV infection.

3.2. Guillain-Barré Syndrome (GBS)

GBS is an autoimmune syndrome that attacks the peripheral nerves, causing progressive paralysis over 1 to 3 weeks [98]. Its infection triggers autoantibodies targeting gangliosides in the membrane of nerve cells or spinal roots, which can cause symptoms such as muscle weakness, inability to walk, facial palsy, and respiratory distress [98] [99]. Patients infected by ZIKV had neurological symptoms during or immediately after the ZIKV infection, suggesting a para infectious rather than a post-infectious pattern that is typically seen in GBS [100]. This syndrome has a low mortality rate of about 5%, but 20% of all GBS cases are left with significant disability [101]. Furthermore, the most common cause of death in GBS is pneumonia, cardiac arrest, respiratory failure, and autonomic dysfunction [102]. Approximately 20% - 30% of severe manifestations of GBS cases are provoked by respiratory failure [103]. Additionally, ZIKV related GBS might be associated with other infections, including cytomegalovirus (CMV), Epstein-Barr virus, influenza A virus, mycoplasma pneumonia, and Hemophilus influenza [104] [105] to cause neurological complications.

Different mechanisms regarding GBS in ZIKV patients have been suggested: myelitis, which is the inflammation of the spinal cord that disrupts the usual response in the CNS, and a post-infectious immune-mediated response that leads to demyelinating polyradiculopathy [73]. Based on a recent survey in Colombia, 75% of patients with ZIKV and other flavivirus are prone to have acute inflammatory demyelinating polyradiculoneuropathy (AIDP) based on the electrodiagnosis done in 2016 [106]. However, the differentiation of these two mechanisms can be difficult clinically, due to immune dysregulation, abnormal nerve conduction velocity (NCV), and other similar symptoms, including muscle

weakness, and ascending paralysis. But in most cases, NCV has been the key to differentiating between these two mechanisms. A study conducted on ZIKV-infected mice demonstrated that in the brain and spinal cord, direct infection by live viruses leads to myelitis [107]. Furthermore, recent studies revealed that myelitis in ZIKV infected humans was the main cause of ZIKV-induced GBS [108]. RT-PCR positive patients with weakness and clear clinical viral symptoms have acute transient polyneuritis a few weeks after the symptom onset, which is possibly caused by the effect of ZIKV on the peripherical nerves. We speculate that the primary mechanism of ZIKV-induced GBS is through a combined autoimmune response and direct infection of nerves by the virus.

3.3. Epilepsy

ZIKV can lead to not only microcephaly but has also been associated with postnatal epilepsy [88]. Patients who acquire ZIKV in utero have a higher risk of developing refractory epilepsy [109]. Epilepsy is "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition" [110]. However, Fisher *et al.* argued that it was a disease rather than a disorder by the rules adopted by International League Against Epilepsy (ILAE) in 2014 [110]. Epilepsy causes a neonatal neurological disorder characterized by immediate recurrent and unprovoked seizures with sensory disturbance and loss of consciousness within a few minutes [111]. Recent studies based on using neuroimaging showed that infants with ZIKV who have microcephaly develop severe diffuse atrophy of the cerebral volume, ventriculomegaly, cerebral-subcortical punctate calcifications can subsequently lead to lissencephaly [112]. A strong relationship between lissencephaly and CZS has been confirmed by neuroimaging [112] [113]. Moreover, lissencephaly is clinically considered a major cause of pediatric epilepsy [112] [114], which is more difficult to control, especially in the early onset of seizures [113]. However, the exact mechanism of ZIKV induced epilepsy is not clear, but it is apparent that with zika-linked microcephaly, there is an increased risk of early epilepsy among the children population [44] [115].

4. Diagnosis and Treatment

Infections caused by ZIKV are rapidly transmitted, resulting in severe public health crises. Therefore, a rapid, sensitive, specific, and cost-effective diagnostic test is crucial for better controlling the disease [116]. Molecular testing is key to the detection of the virus but is limited in its utility in diagnosing acute infections because 80% of infected people do not present any symptoms to alert themselves or their clinicians, so, detecting the virus at the exact time of infection is difficult [117]. Molecular testing is most helpful for the initial screening of patients that have clinical symptoms such as rash, fever, and conjunctivitis. The WHO has advised using RT-PCR and serological tests to confirm suspected Zika virus cases [116].

4.1. Detection

Suspected cases of ZIKV infection are confirmed with RNA RT-PCR and serology (ELISA) (Table 1). It should be noted that seven days after infection, there is a production of ZIKV-specific IgM, which takes about two weeks to reach a detectable level. And approximately three months after symptom onset, IgM levels generally continue to be detectable within the diagnostic range [118]. However, the detection of the ZIKV varies depending on the different samples used. With saliva and urine samples, the ZIKV genome can be detected from 20 - 30 days after the symptoms' onset, while less time is required for detection with blood samples [15] [33] [119]. During the French Polynesia outbreak, 748 cases were confirmed within 3 - 10 days from the symptom onset using serum samples [120]. With semen samples, a comparably more extended period is needed for detection, as it takes up to 62 days for the virus to appear in the semen [17].

Currently, ZIKV serology is available in most laboratories in the world. It is generally carried out by a monoclonal antibody-based ELISA with confirmation using PRNT following standard international protocols [121] [122]. When serology is performed, the result should be followed and confirmed by PRNT. PRNT (an anti-Flavivirus antibody differentiation test) is the "gold standard" for the detection of ZIKV because of its precision and specificity for the diagnosis of primary *Flavivirus* infections, which is clinically and epidemiologically crucial in determining the level of IgM [123]. However, it is costly and can only be carried out in highly specialized laboratories because of the difficulty of manipulating live viruses [124]. During the French Polynesia outbreak of ZIKV, indirect ELISA

Table 1. Detection of ZIKV infection. ZIKV RT-PCR is performed on body fluid like serum, urine, semen. If Flavivirus RT-PCR shows a positive result, sequencing is performed. ZIKV IgM serology consists of detection by using ELISA; confirmation by PRNT is required if the results are positive or equivocal [70] [118].

	TEST		
	RT-PCR	**Serology**	**PRNT**
Samples[a]	Serum, Urine, CSF	CSF, Serum	Serum, urine
Detection of infection	Recent	Recent	Confirms the presence of zika-specific IgM. Also measures IgG
Remarks	Prone to False-negative results in recent infections	Sensitive but not specific to the ZIKV as other flaviviruses antibodies can cross-react. Need confirmation with PRNT	Prone to False-positive in patients with previous flaviviral infection or vaccination. Might not distinguish maternal from fetal IgG within the first 18 months of life.

[a]Testing for other tissues and body fluids may also be available [70] [118]; PRNT = Plaque Reduction Neutralization Test.

was used as the serological test to detect IgM with recombinant antigens for the suspected cases [41].

4.2. Vaccine and Treatment

In recent years, increased ZIKV infections in pregnant women in countries where the virus is endemic (like Brazil and India) [116] have been reported [82] [125]. The development of vaccines for ZIKV continues to be an important research area, and different types of vaccines, such as DNA-based, live-attenuated, inactivated, and subunit vaccines, are currently in phase 3 clinical trials [126] [127]. 18 vaccine candidates have been identified and are in various phases of preclinical and clinical research [128]. However, no effective vaccine to prevent Zika infection is licensed or accessible as of March 2022; yet, it is gravely needed [128]. Until treatment is developed, prevention is the best way to avoid contracting ZIKV. We need to protect ourselves from mosquito bites and control vector populations [129].

From the first day of symptom onset, patients with this virus must be isolated as soon as possible to avoid the transmission of infections to healthy persons by mosquito bites and other possible routes of transmission [130]. Currently, there are no specific treatments available for ZIKV infection [130] [131]. But for patients with acute symptomatic infections, the general care across the hospitals in the world is that patients are encouraged to drink a lot of water and enough rest [131]. Also, it is recommended that patients with neurological symptoms should be managed in the intensive care unit, and pregnant women with positive or inconclusive ZIKV laboratory screening undergo repetitive ultrasonography [132]. After the delivery, the measurement of the occipitofrontal circumference, a complete physical examination, a postnatal ultrasound, and an audiology screening of infants whose infection with ZIKV was suspected or confirmed during pregnancy are all recommended for better diagnosis and care of the infant [133]. Moreover, psychotherapy for the families of children affected by ZIKV has been recommended by the CDC and the American Academy of Pediatrics [134].

There is an urgent need for the development of drugs and vaccines against ZIKV infection to avoid neurological complications and other congenital syndromes. Consequently, some researchers focusing on 774 FDA (Food and Drug Administration) approved drugs demonstrated that bortezomib, ivermectin, cyclosporin A, mycophenolic acid, daptomycin, sertraline-HCl, and pyrimethamine were potentially effective in reducing flaviviruses infections [135]. Also, type I interferons (IFN-α and IFN-β, IFN-λ1 and IFN-α, β, γ) have been used to inhibit the replication of ZIKV [136]. In 2016, other researchers focused on herbal therapies like *philoxeroides, Andrographispaniculata, Azidarachtaindica, Euphorbia hirta, Eupatorium perfoliatum, Tinosporacordifolia, and Psidiumguajava*, which are known to have an antiviral activity that can combat ZIKV infection [136]. The use of Obatoclax mesylate (a Bcl-2 antagonist) and neutralizing

antibodies are the common strategies used by scientists in trials to inhibit the replication of ZIKV via the production of an acidic environment in endolysosomal vesicles [137]. On the other hand, the use of some drugs such as acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs in patients with ZIKV or other flaviviruses infection is strictly forbidden due to the increased risk of hemorrhagic complications [131]. The development of a successful treatment strategy will require cooperation from various fields in medicine, especially between virologists and clinicians [138] [139]. Additionally, the CDC and WHO have recommended the use of insect repellants registered by the Environmental Protection Agency, long-sleeved shirts and pants, bed nets, permethrin-treated clothing, and gear (https://wwwnc.cdc.gov/travel/page/zika-information) to avoid mosquito bites as well as the use of condoms to prevent sexual transmission.

5. Conclusion

During the last ZIKV pandemic, it was recognized that a threat existed almost everywhere in the world regarding its spread and the unusual connection with neurological complications during or after the gestation period. The recognized neurological sequelae include microcephaly, epilepsy, and GBS. Even though many drugs inhibit viral replication and prevent neuronal abnormalities, there is still no vaccine or treatment available to eliminate the ZIKV infection. The trend of vaccine development against emerging and re-emerging infectious diseases is taking its heavy weight on ZIKV as well. While some are promising, the therapeutic strategies will be effective for the treatment of neurological. Some researchers and scientists around the world are exploring various solutions; however, they are not successful yet. Finally, more resources and clinical trials focusing on the treatment and elimination of the ZIKV infection are urgently needed.

Conflicts of Interest

The authors declare that there was no interest in competing in the publication of this review.

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Authors' Contribution

D. F. H. M. had the main idea and wrote the review.

PP, AS, YH, SW, RZ, ZH, CD, and PL searched for information about this topic.
IBM, LG, HY, DC, and AL read and edited the manuscript.
Both ZX and JH read and approved the final manuscript.

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