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ZIKV: Epidemiology, infection mechanism and current therapeutics

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The Zika virus (ZIKV) is a vector-borne flavivirus that has been detected in 87 countries worldwide. Outbreaks of ZIKV infection have been reported from various places around the world and the disease has been declared a public health emergency of international concern. ZIKV has two modes of transmission: vector and non-vector. The ability of ZIKV to vertically transmit in its competent vectors, such as *Aedes aegypti* and *Aedes albopictus*, helps it to cope with adverse conditions, and this could be the reason for the major outbreaks that occur from time to time. ZIKV outbreaks are a global threat and, therefore, there is a need for safe and effective drugs and vaccines to fight the virus. In more than 80% of cases, ZIKV infection is asymptomatic and leads to complications, such as microcephaly in newborns and Guillain−Barré syndrome (GBS) in adults. Drugs such as sofosbuvir, chloroquine, and suramin have been found to be effective against ZIKV infections, but further evaluation of their safety in pregnant women is needed. Although temoporfin can be given to pregnant women, it needs to be tested further for side effects. Many vaccine types based on protein, vector, DNA, and mRNA have been formulated. Some vaccines, such as mRNA-1325 and VRC-ZKADNA090-00-VP, have reached Phase II clinical trials. Some new techniques should be used for formulating and testing the efficacy of vaccines. Although there have been no recent outbreaks of ZIKV infection, several studies have shown continuous circulation of ZIKV in mosquito vectors, and there is a risk of re-emergence of ZIKV in the near future. Therefore, vaccines and drugs for ZIKV should be tested further, and safe and effective therapeutic techniques should be licensed for use during outbreaks.

KEYWORDS

transmission, vaccines, therapeutics, Zika (ZIKV), epidemiology

Introduction

The Zika virus (ZIKA) has affected about 87 countries worldwide since 2019, especially countries in tropical and subtropical regions (1). ZIKA is a *Flavivirus*, having a positive-sense, single-stranded RNA encoding for three structural proteins [i.e., precursor membrane protein (prM), capsid protein (C), and envelope protein (E)] and seven non-structural proteins (i.e., NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) (2). In 1950, the first case of human infection with ZIKA was reported in Africa. In 2016, the WHO declared ZIKA infection a public health emergency of international concern (3). ZIKV is found in several WHO regions (i.e., the African Region, Region of the Americas, South-East Asia Region, and the Western Pacific Region) (4). Recently, in India in 2021, a total of 150 cases of ZIKV infection were reported. Most patients were asymptomatic or had a mild fever (5). Figure 1 shows the regions at risk of ZIKV infection.

Transmission of ZIKV

The Zika virus mainly spreads through an *Aedes* mosquito bite, but can also spread by non-vector transmission, for example by congenital transmission, blood transfusion, organ transplantation, sexual transmission, and vertical transmission (4). The vertical transmission capacity of ZIKV has been studied in *Aedes* mosquitoes, and vertical transmission has been found to help ZIKV to cope with harsh conditions (7). ZIKV is an arbovirus that is transmitted by two cycles: a sylvatic cycle involving transmission between non-human primates and arboreal insects in forests, and an urban cycle between humans and urban mosquitoes (8). The ZIKV transmission cycle is shown in Figure 2.

Vector competency for ZIKV

In Asian and African mosquitos, *Ae. aegypti, Ae. albopictus, Ae. vexans*, *Ae.* (*Rampamyia*) *notoscriptus, Ae.* (*Ochlerotatus*) *camptorhynchus, Ae. vittatus, Ae. luteocephalus*, and *Culex quinquefasciatus* act as potential vectors (9, 10). *Anopheles gambiae, A. stephensi*, and *Cx pipiens* have also been shown to be probable vectors (11). *Ae.* (*Stegomyia*) *hensilli* and *Ae.* (*Stegomyia*) *polynesiensis* were found to be probable vectors during the ZIKV outbreak in Yap Island and French Polynesia (12). Vectorial capacity (i.e., vector-borne transmission ability) is affected by the ecological traits and abundance of vectors, and poor vectors with limited vector competence can lead to outbreaks worldwide (10, 13). Del Carpio et al. (2018) revealed that in Mexico a variety of species of Culicidae were present. In Mexico, *Ae. Aegypti* and *Ae. albopictus, A.* species such as *A. albimanus* and *A.*

pseudopunctipennis, and *Culex* family members, such as *Cx perfuscus, Cx pipens*, and *Cx quinquefasciatus*, act as potential vectors during outbreaks. However, some mosquito species endemic to Mexico, for example, *Ae. sumidero, Ae. tehuantepec, Ae. guerrero, Ae. ramirezi, Ae. laguna, Ae. cozumelensis, Cx jalisco, Cx sandrae, Cx schicki, Cx arizonensis*, and *A. aztecus*, could act as a vector in the absence of potential vectors. In America, the Culicidae family is highly diversified and competes with *Aedes* species for being a potential vector to transmit ZIKV (14). A comprehensive assessment of vector competency in Brazil concluded that *Aedes* species can cause a pandemic in the absence of arboviral-specific vectors, such as *Ae. Aegypti*, while other species like *Ae. albopictus* or *Ae. japonicus* can act as potential vectors for arboviruses (15). The distribution of probable vectors is shown in Figure 3.

Symptoms of ZIKV infection

The incubation period of ZIKV is approximately 3–14 days. The majority of people, ≈80%, do not show any symptoms of infection. Symptoms that are observed in 20%–25% of ZIKV patients with an acute infection include joint pain, conjunctivitis, malaise, muscle pain, headache, fever, and rash, as shown in Figure 4. These symptoms generally last for 2–7 days (1).

Complications of ZIKV disease

ZIKV infection during pregnancy can result in fetal loss, stillbirth, and preterm birth. In newborns, ZIKV can cause congenital abnormalities such as microcephaly (16). ZIKV infection also triggers myelitis, Guillain–Barré syndrome (GBS), and neuropathy in adults and older children (1). The complications, such as microcephaly, are shown in Figures 5, 6.

Acute ZIKV infection is self-limiting, and patients recover, but the matter of serious concern is neonatal complications, which are associated with chronic ZIKV infection. In 2015, during a ZIKV outbreak in Brazil, the number of cases of newborns with microcephaly increased (17). Complications such as optic neuropathy, glaucoma, lissencephaly, microcephaly, and ventriculomegaly are also associated with ZIKV infection, as ZIKV mRNA was observed in the amniotic fluid of pregnant women (18). ZIKV infection in pregnant women has been shown to be harmful to fetuses. In the first and second trimesters of pregnancy, ZIKV infection can have severe effects, such as spontaneous abortion, congenital abnormalities, and fetal death, or necessitate therapeutic abortion due to congenital malformation. Congenital abnormalities such as microcephaly, hydrocephalus, hypoplasia, hypertonicity, cerebellar calcification, and seizures related to the neurological system, osteoskeletal system abnormalities, such as arthrogryposis and clubfoot, and

World Map of Areas with Risk of Zika
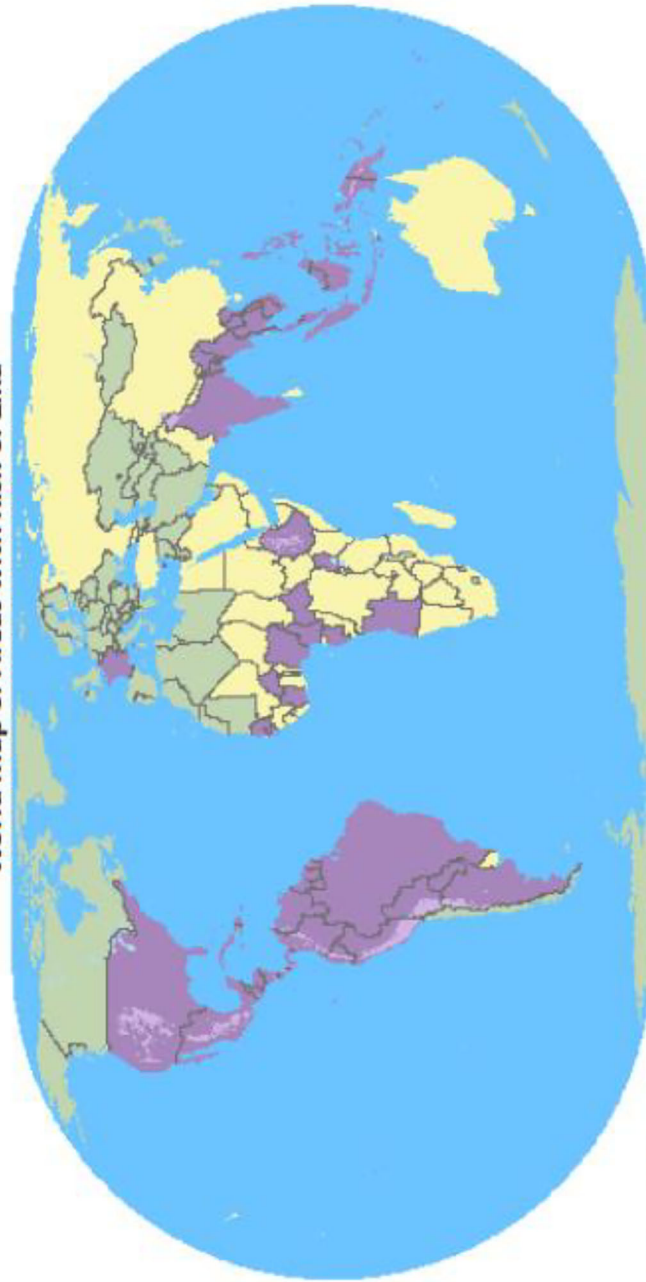
Map Legend

- Country or territory with current Zika outbreak[1]
- Country or territory that has ever reported Zika cases[2] (past or current)
- Areas with low likelihood of Zika infection because of high elevation (above 6,500 feet/2,000 meters)
- Country or territory with mosquito[3] but no reported Zika cases[2]
- Country or territory with no mosquitoes that spread Zika

[1] No areas are currently reporting Zika outbreaks
[2] Locally acquired, mosquito-borne Zika cases
[3] *Aedes aegypti*

FIGURE 1
World map of areas at risk of ZIKV (6).

FIGURE 2
Transmission modes of ZIKV (created with BioRender.com).
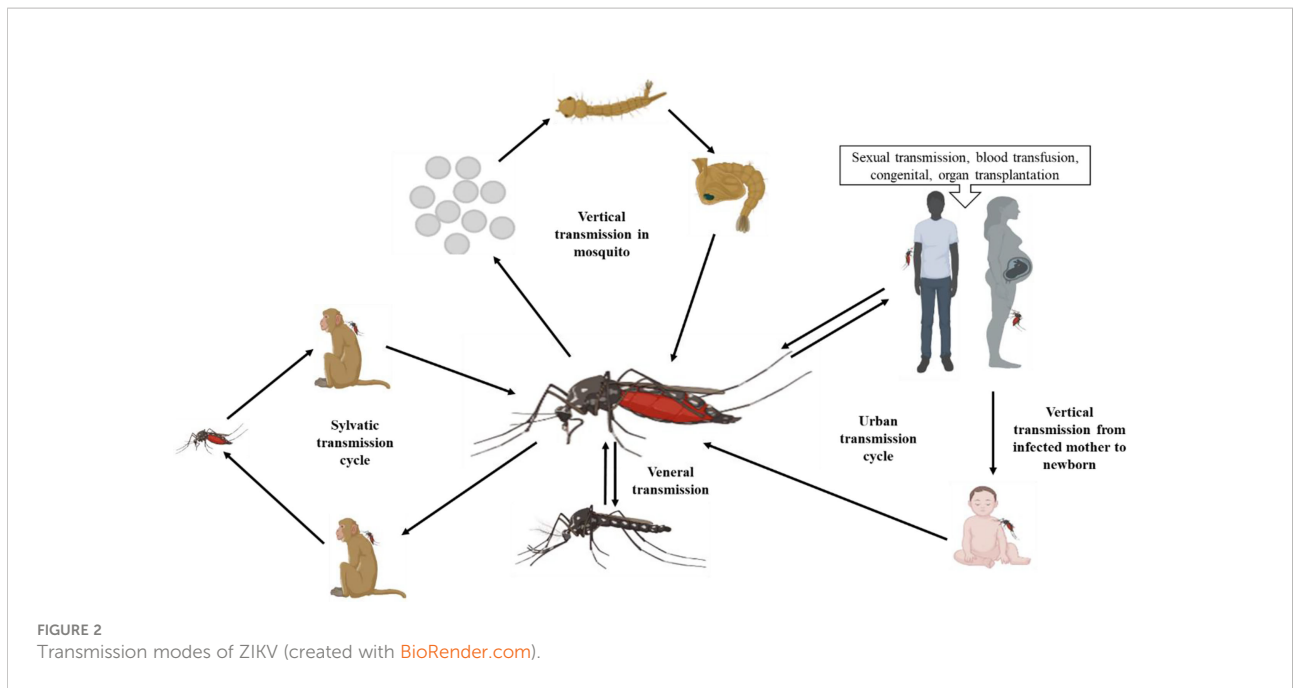
optic system abnormalities, such as ophthalmic changes in the posterior and anterior segments, and abnormal visual functions, were observed in neonates with the help of image tests (19). An acute infection of ZIKV may lead to GBS. GBS is an autoimmune condition in which gradual muscle weakness, reduced nerve function, and paralysis are observed as myelinated neural cells are attacked by cell-mediated immunity (20, 21). In French Polynesia, during a ZIKV outbreak in 2013–14, cases of GBS

increased 20-fold, and a close relationship was seen between the manifestation of ZIKV and GBS (20). In other studies, it has been reported that the prevalence of GBS with ZIKV is 42% and 24% in Brazil and America, respectively. The variations in prevalence, which have been reported, may be due to the reduced incidence as a result of the low virulence and pathogenicity of the virus. Other GBS-causing agents include a species of *Campylobacter* and various arboviruses related to ZIKV (22, 23).

FIGURE 3
Distribution of vector species infected with ZIKV (10).

FIGURE 4
Common symptoms of an acute ZIKV infection (created with BioRender.com).
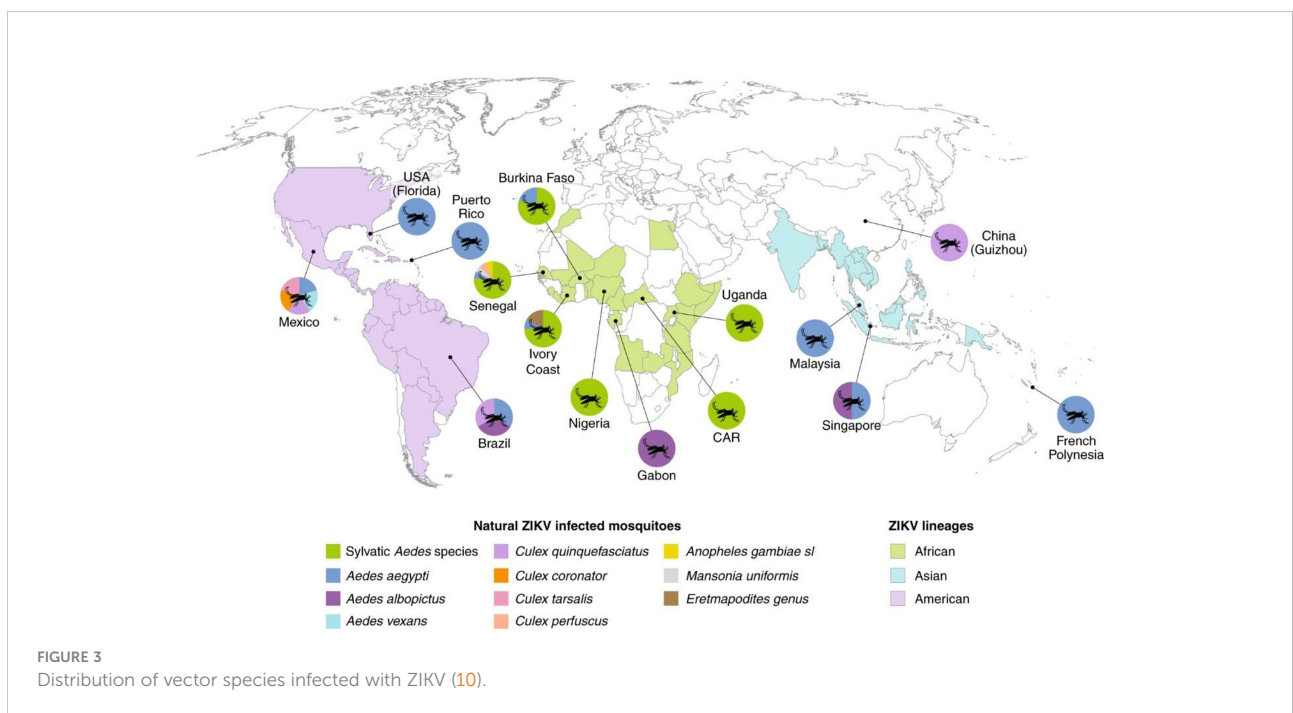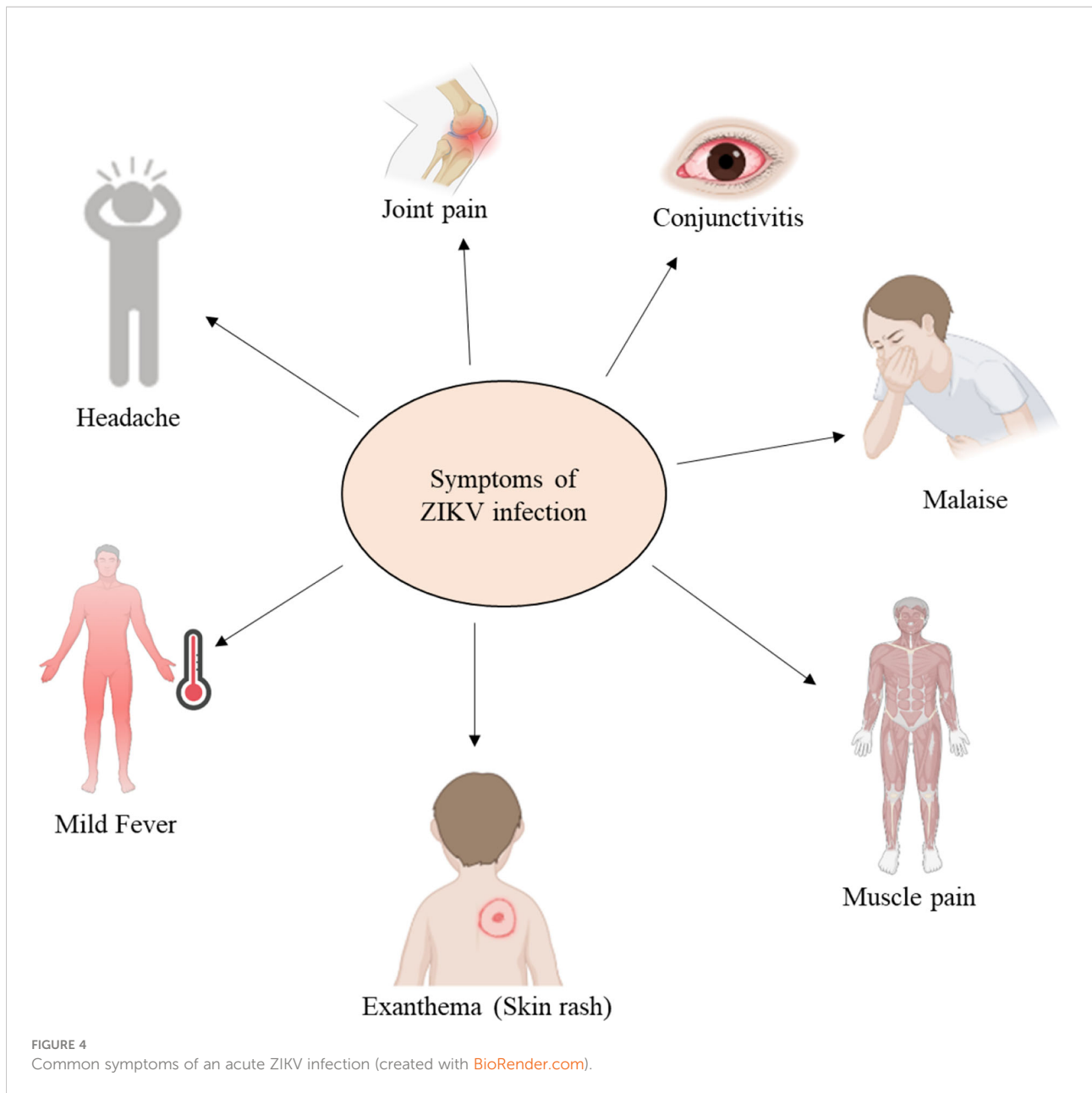
Mechanism of ZIKV neuropathogenesis

ZIKV infection leads to neuropathogenesis through various mechanisms, neuronal apoptosis of the immune response, an inflammatory response, and cell-cycle dysregulation (24). In many studies, it has been found that, during vertical transfer from an infected mother to a developing fetus, ZIKV can successfully infect human neural progenitor cells (hNPCs) (25). During the first trimester of pregnancy, hNPCs generate brain organoids and neurospheres for fetal brain development, but either hNPCs infected with ZIKV show a cytopathic effect

and die, or the cytopathic effect is reduced by virus replication, leading to brain abnormalities such as microcephaly and restriction of fetal brain development (24, 26). It has been observed previously that cells with highly expressed Axl receptor tyrosine kinase (AXL) receptors are more susceptible to ZIKV infection (27). The AXL receptor mediates the ZIKV infection to keratinocytes and fibroblasts. The various cellular receptors known to be involved in ZIKV neuropathogenesis are dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), phosphatidylserine receptor proteins, such as T-cell immunoglobulin mucin-1 (TIM-1), TIM-4, AXL, and tyrosine–protein kinase receptor 3 (TYRO3), and heat shock proteins (HSPs), glucose-regulating

FIGURE 5
Different complications observed during pregnancy due to ZIKV infection (created with BioRender.com).
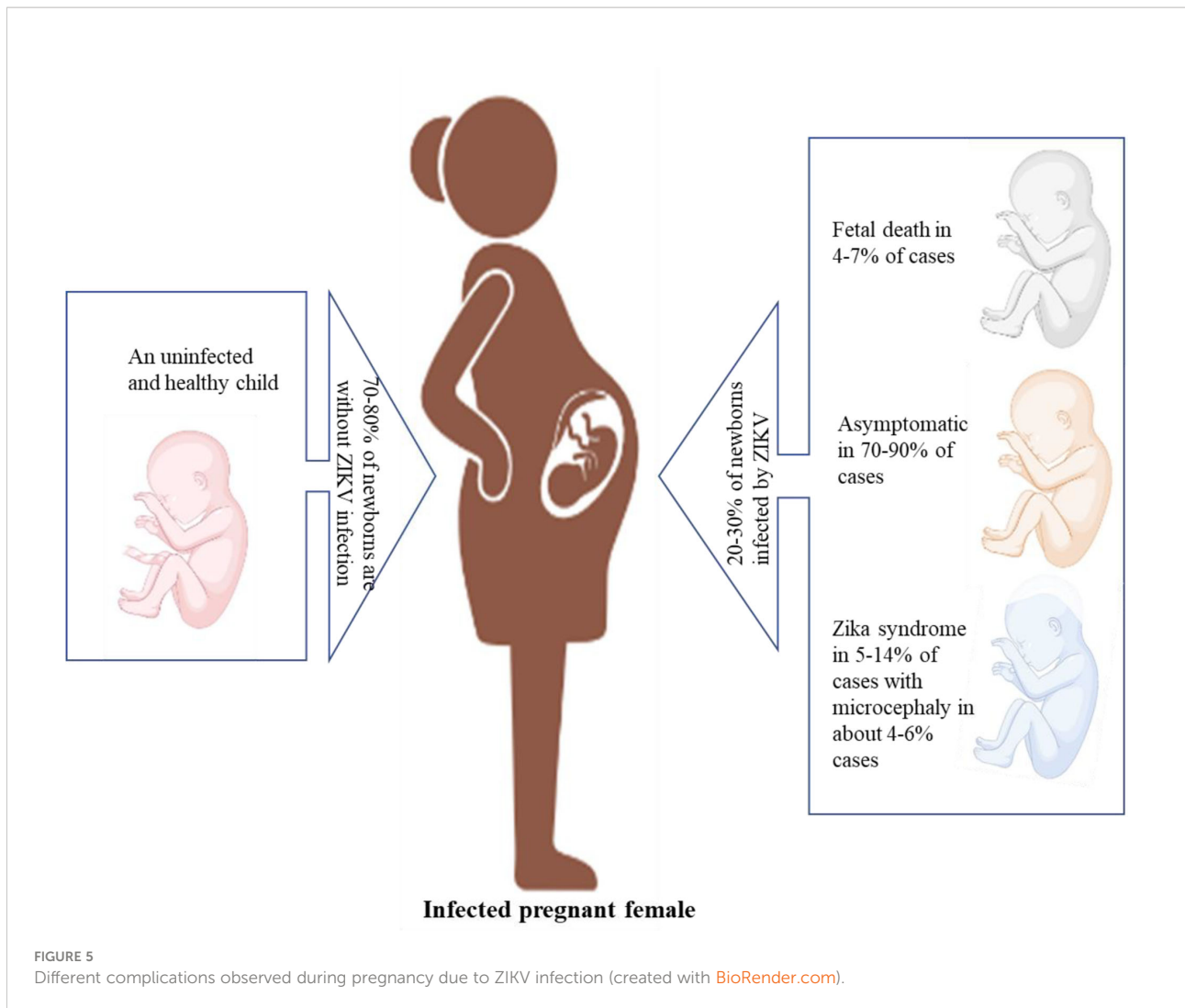
protein 78 (GRP78/BiP), and a cluster of differentiation (CD) 14-associated molecules (28–30). In addition, ZIKV interacts with toll-like receptor 3 (TLR3) and induces an interferon response. ZIKV has to overcome the innate immune barrier by degrading the signal transducer and activator of transcription 2 (STAT2) (2). It has been found that silencing of the *AXL* gene up-regulates type I interferon signaling, indicating that AXL helps in increasing ZIKV infection by down-regulating type I interferon signaling (31). Recent studies have revealed that ZIKV infection is not solely dependent on AXL, limiting the possibility of developing any therapeutics (32). The vertical transmission and neuropathogenesis mechanism of ZIKV infection in humans is shown in Figure 7.

Aedes mosquitoes are the probable vector for ZIKV transmission. Figure 7A shows how ZIKV can infect dermal fibroblasts and epidermal keratinocytes, which might then spread the virus to dermal dendritic cells (also known as Langerhans cells) and aid the spread of ZIKV. Figure 7B shows how infection of cytotrophoblasts or transmigration of infected primary human placental macrophages (Hofbauer cells) may result in the transplacental transfer of ZIKV to the fetus, indicating a unique pathway for intrauterine transmission. Hofbauer placental macrophages release type I IFN and increase interferon-stimulated genes (ISGs) in response to ZIKV infection, but the cells still allow ZIKV replication. Figure 7C shows how the placental syncytiotrophoblasts' production of IFN-λ1 and ISGs during the later stages of pregnancy may have protective effects that prevent ZIKV infection. Figure 7D shows how ZIKV specifically targets neural progenitor cells during the embryonic brain's development in first trimester. The entry of ZIKV into brain cells may be significantly influenced by the TAM receptor AXL. Deregulation of genes involved in neuronal development and apoptosis brought on by ZIKV-dependent activation of TLR3-mediated immune responses leads to significant damage to the embryonic brain, including microcephaly (33).

FIGURE 6
Microcephaly observed in newborns (www.cdc.gov.in).
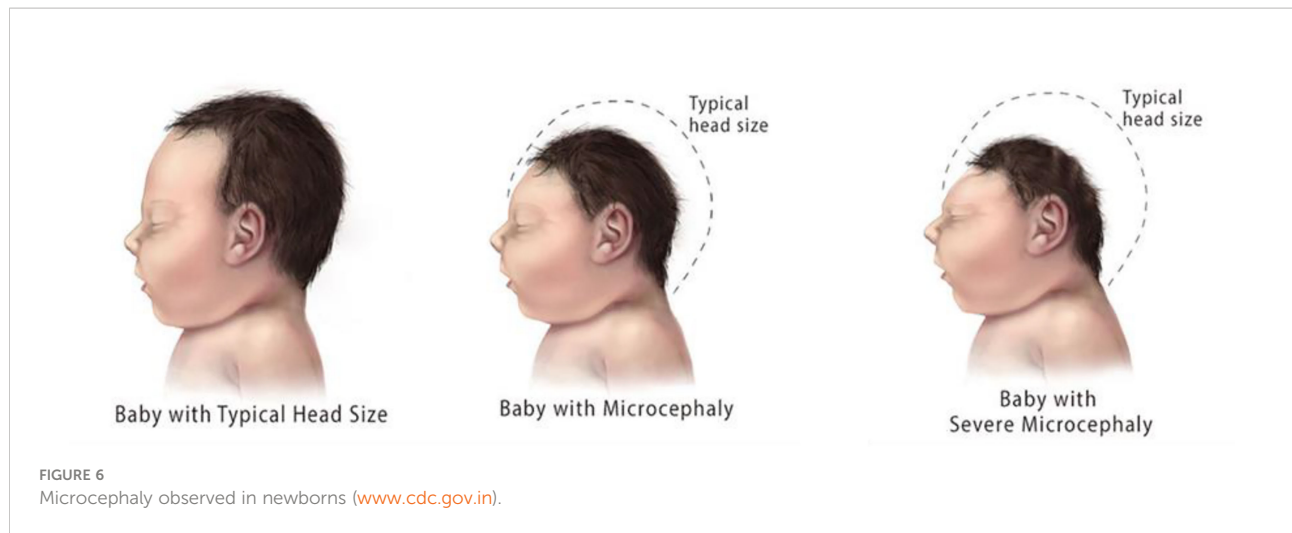
Cellular mechanism of ZIKV

ZIKV presumably enters the cell by receptor-mediated endocytosis (28). The endocytosis is either clathrin or receptor mediated. A fusion between the virus and the host cell occurs because of the acidic environment and genomic RNA released inside the host cell. After its release, viral RNA is translated to the polyprotein in the vicinity of the endoplasmic reticulum (ER) with the help of viral-encoded proteins and the host. Later, viral replication and packaging occur on the surface of ER of the host cell. Furin-mediated cleavage occurs at the Golgi complex, resulting in the formation of a mature virus. Virus particles are released with the help of exocytosis, and ZIKV activates a TLR3-mediated immune response and autophagy pathway (34, 35). This may mediate viral survival and replication inside the cell, and then exosomes containing the ZIKV proteins are released by the infected cells (36). ZIKV may activate the unfolded protein response pathway, which may lead to cell death, DNA repair, or homeostasis (37, 38). The cellular mechanism of ZIKV is shown in Figure 8.

Diagnosis of ZIKV

It is difficult to diagnose ZIKV infections because in more than 80% of cases ZIKV is asymptomatic. The symptoms of ZIKV infection overlap with those of infection with other flaviviruses. To date, five serological assays and 14 molecular diagnostics tests (Table 1), based on serum, saliva, and urine samples collected from patients, have been approved by the United States Food and Drug Administration (FDA) (39). In the case of individuals whose symptoms started within the previous 7 days, ZIKV infection can be diagnosed by subjecting whole blood or serum to an RT-PCR (reverse transcription-polymerase chain reaction) test known as nucleic acid testing (NAT).

Enzyme immunoassays (EIAs), immunofluorescence assays (IFAs), and neutralization assays, such as plaque-reduction neutralization tests (PRNTs), are crucial serological diagnostic tools, nonetheless, and should be used in individuals with symptoms that have persisted for more than 7 days (40). Serological assays should be interpreted carefully, as cross-reactivity between dengue and ZIKV antibodies may lead to misidentification of the causative agent, and prior exposure may also give false-positive results. Thus, serological assays alone cannot confirm ZIKV infection (41). Quantitative reverse transcription is used in *in vitro* diagnostics (IVDs). The most accurate molecular diagnostic method for ZIKV is PCR (i.e., qRT-PCR); however, due to its high cost and mobility issues, its use as a point-of-care (POC) test during monitoring programs is constrained (42). Instead, because of their low cost and simple logistical handling, reverse transcription loop-mediated amplification (RT-LAMP) and microfluidic cassettes are more popular (40, 43). Pregnant women with ZIKV infection living in endemic areas and with a history of clinical illness should undergo routine ultrasound scans in early pregnancy to check for abnormalities or fetal malformation (44). In pregnant women, ZIKV infection should be diagnosed based on laboratory evidence. Detection of RNA in blood and urine confirms ZIKV infection, whereas detection by IgM testing may give a false-positive result because of prior infection (41).

Treatment of ZIKV

As yet, no specific vaccine against ZIKV infection is available, and treatment includes symptomatic care, for example, plenty of water intake, rest, antipyretics, and analgesics (45). ZIKV vaccine development is the subject of extensive study and includes several vaccine types, e.g., DNA-based vaccines, subunit vaccines, inactivated vaccines, and live-
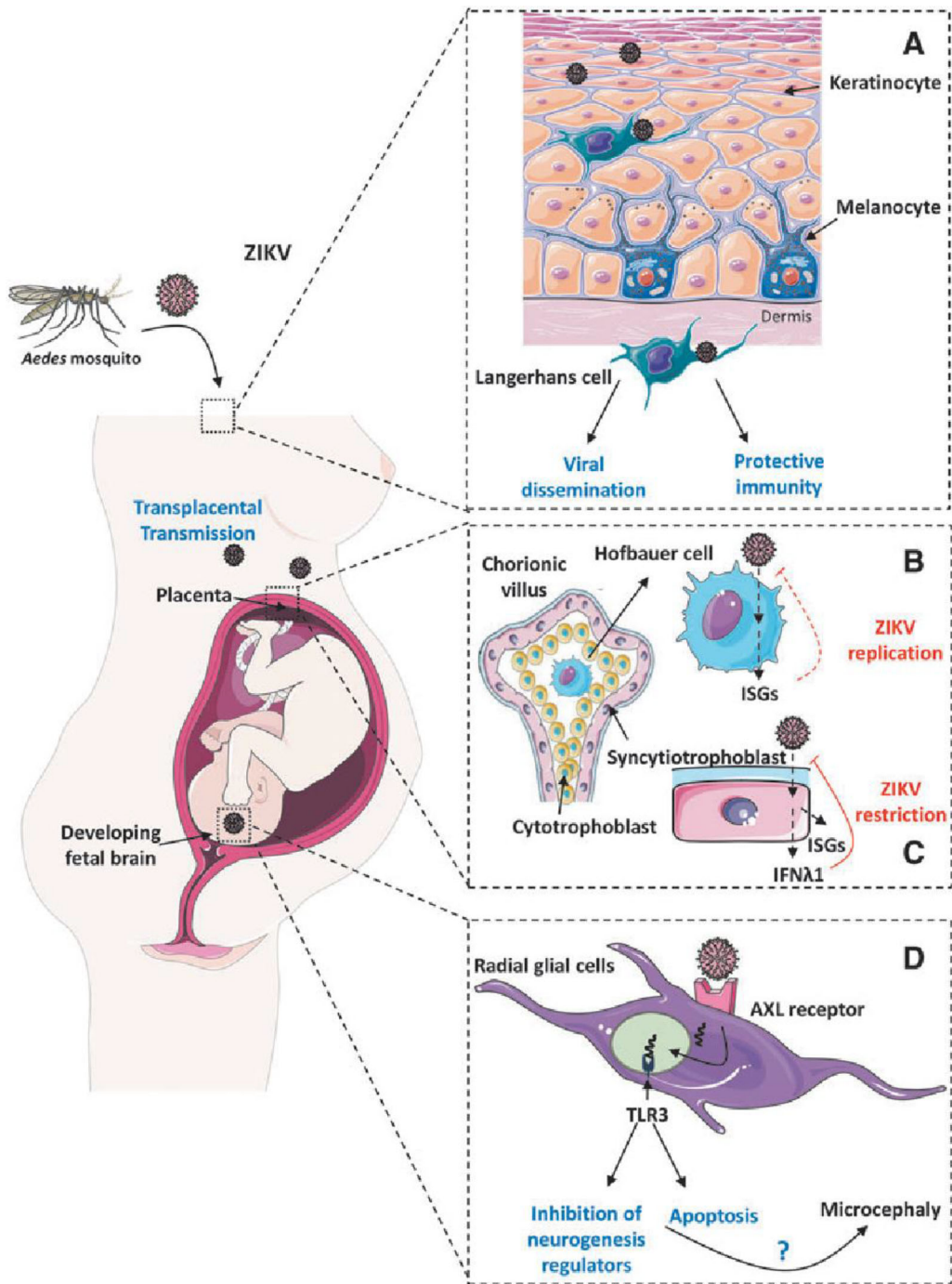
FIGURE 7
ZIKV infection mechanisms and neuropathogenesis (ISGs, interferon-stimulated genes; ZIKV, Zika virus) (33). **(A)** Infection of ZIKV in dermatocytes, **(B)** Infection of ZIKV in hofbauer cells, **(C)** Protective immune response of syncytiotrophoblast, **(D)** ZIKV targeting neural progenitor cells.

FIGURE 8

Cellular mechanism of ZIKV (created with BioRender.com).
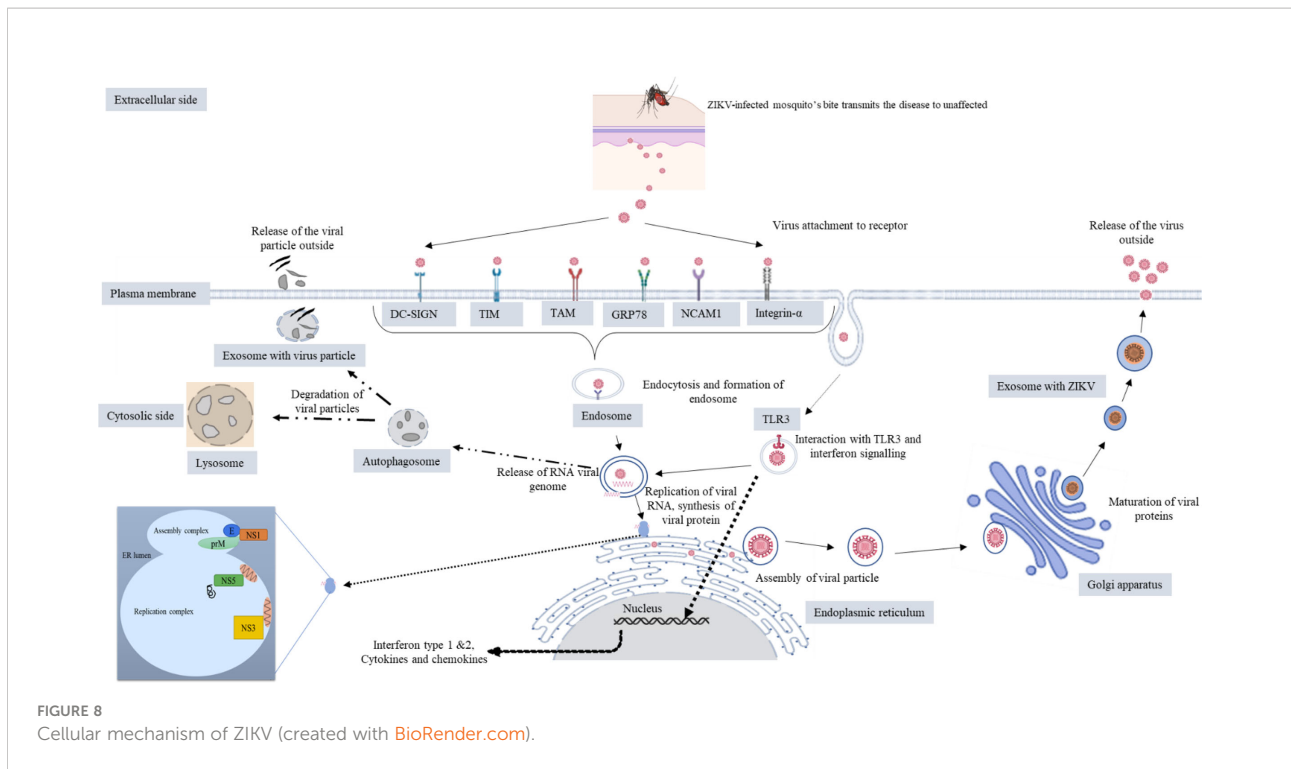
attenuated vaccines (46). Some antiviral drugs are also prescribed against ZIKV. GBS can be treated by intravenous injection of immunoglobins (0.4 g/kg body weight daily for 5 days) and by plasma exchange (200–250 ml plasma/kg body weight in five sessions) (47).

Antiviral drugs

A variety of methods have been used to find medications that can fight ZIKV infection. Despite the serious consequences for public health, there is presently no cure or medicine to prevent ZIKV infections. On the basis of mode of action, ZIKV antivirals can be classified into host-directing antivirals and direct-acting antivirals. Efforts to develop effective antiviral drugs have focused on drug repositioning, as this minimizes the number of clinical trial steps. The search for drugs suitable for repositioning has helped pregnant women and newborns to withstand the outbreaks of ZIKV (48, 49). Of the repositioning drugs listed in Table 2, only temoporfin can be given to pregnant women (49). The anti-ZIKV medications sofosbuvir, chloroquine, and suramin produced better outcomes because more experimental data were available for evaluation (48). To facilitate the search for and increase the chances of finding a suitable anti-ZIKV medicine, other medications' effectiveness against ZIKV should also be assessed.

ZIKV vaccines

ZIKV infection induces both innate and adaptive immune responses. The innate immune response is the first line of defense against ZIKV. ZIKV infection triggers type I interferons and signaling, which may inhibit ZIKV, but ZIKV exhibits different mechanisms to interfere with IFN induction. Non-structural proteins play an important role in IFN inhibition. The humoral immune response is protective against ZIKV, and specific neutralizing antibodies are produced against the E protein. Vertical transmission is inhibited by recognizing a quaternary epitope on the E protein dimer–dimer, by recognizing the lateral ridge epitope of domain III of the E protein, and by recognizing a quaternary epitope spanning all three domains of the E protein. However, this may lead to the enhancement of dengue virus replication and a phenomenon known as ADE (i.e., antibody-dependent enhancement) (72). Therefore, the vaccine must be designed by taking into consideration the phenomenon of ADE. In addition, understanding the correlation between immunity and infection is difficult, as different levels of adaptive immune response also differ from individual to individual, depending on age, sex, and health conditions, and correlation also differs in animal models, making it difficult to understand the effect on human beings, especially neonates, as ethical issues will be faced. Despite these shortcomings and limitations, many vaccine candidates have been developed to fight against ZIKV. Developing a safe and effective

TABLE 1   Various serological ZIKV assays (39, 40).

Method for detection	ZIKV antigen	Sample type	Method	Name
Serological assays	Complete virus	Serum	MAC-ELISA	ZIKV MAC-ELISA
	Envelope	Serum	MAC-ELISA	ZIKV Detect IgM capture ELISA
	NS1	Serum	Microparticle IgM capture immunoassay	Liaison XL Zika capture IgM assay
		Serum, plasma	Microparticle IgM capture immunoassay	ADVIA Centaur Zika test
		Fingerstick or venous whole blood, serum, plasma	Immunochromatographic	DPP Zika IgM system
Molecular diagnostic test	Envelope	Whole blood, serum, cerebrospinal fluid, urine, amniotic fluid	RT-PCR (TaqMan)	Trioplex Real-time RT-PCR Assay
		Serum, urine	RT-PCR (TaqMan)	Zika virus RNA qualitative real-time RT PCR
	NS1	Serum, urine	RT-PCR (TaqMan)	RealStar Zika virus RT-PCR kit
		Serum, plasma, urine	Transcription-mediated amplification	Aptima Zika virus assay
	NS4/NS5	Serum, plasma, urine	Transcription-mediated amplification	Aptima Zika virus assay
		Serum, plasma, urine	RT-PCR	Sentosa SA ZIKV RT-PCR test
	3′ untranslated region	Serum, urine	RT-PCR	CII-ArboViroPlexrRT-PCR
	NS3 and Premembrane	Whole blood, serum, plasma, urine	RT-PCR	RealTime Zika, Zika ELITe MGB kit U.S.
	Not specified	Serum, plasma, urine	RT-PCR (TaqMan)	Zika virus real-time RT-PCR test, Versant Zika RNA 1.0 assay, xMAPMultiFLEX Zika RNA assay, Zika virus detection by RT-PCR, Gene-RADAR Zika virus test, TaqPath Zika virus kit

vaccine against ZIKV will help in preventing the spread of ZIKV, and save people from its adverse effects. Various kinds of vaccines against ZIKV infection, for example, DNA vaccines, mRNA vaccines, live-attenuated vaccines, virus-like protein vaccines, subunit vaccines, virus-vectored vaccines, and purified inactivated vaccines, have been tested in preclinical studies in non-human primates and in clinical trials in humans (Tables 3, 4).

Preventive measures for ZIKV

As there is no treatment, prevention is the best method of protecting against ZIKV, either by protection from mosquito bites or by controlling the vector population (105). In ZIKV-prone areas, populations should be controlled by using mosquito repellents, such as DEET (*N*,*N*-diethyl-*m*-toluamide), bed nets, window screens, and applying permethrin cream on skin and clothes (106). At the moment, the best method for preventing

and controlling arboviral infections such as Zika is comprehensive vector management. Vector management includes environment management practices such as destroying breeding sites (e.g., stagnant water, dumping grounds, landfill sites) by spraying larvicides and insecticides (105). Prevention of the sexual transmission of ZIKV requires the use of reliable contraceptives or abstinence at the time of ZIKV infection (107). All of these are temporary methods, as mosquitoes are becoming insecticide resistant. A safe and effective vaccination or antiviral medication is, thus, required to treat ZIKV infection permanently.

Conclusion

The re-emergence of ZIKV has frightened the world. Although there are now fewer cases, there remains the risk of outbreaks in the future. There is uncertainty about the

TABLE 2 Repositioned anti-ZIKV drugs.

Sr. No.	Drug	Mechanism	Primary specification	Reference
1.	Sofosbuvir	Inhibit ZIKV RNA polymerase	Hepatitis C infection	50
2.	Chloroquine and its derivatives	Inhibit ZIKV replication by inhibiting RNA polymerase and protein synthesis	Antimalarial compound	51
3.	Suramin	Blocking viral adsorption	Anthelmintic drug	52
4.	Niclosamide	Inhibit interaction between NS3 and NS2B, protease inactivation	Anthelmintic drug	53
5.	Mefloquine	Prevent ZIKV replication and autophagy	Antimalaria drug	54
6.	Non-steroidal anti-inflammatory drugs (NSAIDs)	Reduced expression of AXL receptors	Against fever and analgesia	55
7.	Statins	Inhibit ZIKV replication	Cancer and neurological disorders	56
8.	Ribavirin	NS5 polymerase inhibitor	Hepatitis C infection	57
9.	Emetine	NS5 polymerase inhibitor Disruption of lysosomal function	Dengue virus infection	58
10.	Temoporfin	Inhibit interaction between NS3 and NS2B	Adenocarcinoma and other cancers	53
11.	Artemisinin	Prevent ZIKV replication	Malaria treatment	59
12.	Berberine	Inhibit ZIKV replication by binding with NS3 protease	Anti-diabetic and anti-cancer	60
13.	Cephalotaxine	Blocks RNA translation, interferes with cell cycle progression	Anti-cancer	61
14.	Quercetin	Inhibits viral protease and ZIKV replication	Anti-carcinogenic and anti-histamine	62
15.	Nanchangmycin	Envelope glycoprotein inhibitor	Insecticidal and anti-bacterial	63
16.	MYD1	Binds to Gas6, blocks ZIKV binding to the AXL receptor	Antagonist of the AXL/Gas6 pathway	31
17.	R428	Inhibits phosphorylation of AXL	Antagonist of the AXL/Gas6 pathway	31
18.	Emricasan	Proliferation decreases, and ZIKV replication should be somewhat protected for hNPC	Pan-caspase inhibitor	64
19.	Seliciclib	Caspase inhibitor, inhibits ZIKV replication	Anti-cancer	64
20.	Bithionol	Blocks ZIKV-induced caspases	Anti-helminthic	65
21.	NGI-1	Inhibits viral RNA production and replication	Oligosaccharyltransferase inhibitor	66
22.	6-Methylmercaptopurine riboside/6MMPr	Blocks *de novo* production of purines	Antiviral against hepatitis C virus, dengue virus, and yellow fever virus	67
23.	Heparin	Exhibits anti-apoptotic activity in hNPCs	Anti-coagulant	68
24.	Memantine	Inhibits glutamate receptors and reduces neurodegeneration	Alzheimer's disease treatment	69
25.	Azithromycin	Lowers the rate of cellular apoptosis in cellular glial cells	Antibiotic	70
26.	IL-1 receptor antagonist/anakinra (Kineret)	Prenatal microglial activity is inhibited to reduce fetal neuroinflammation.	Rheumatoid arthritis treatment	71
27.	Favipiravir (6-fluoro-3- hydroxy-2-pyrazinecarboxamide or T-705)	Up-regulates AKT phosphorylation, promotes neuronal cell growth	RdRp inhibitor and antiviral	57

TABLE 3 Different pre-clinical studies of ZIKV vaccine.

Sr. No.	Vaccine type	Component of vaccine	Name of vaccine	Animal model	Vaccine dose	Administration mode	Virus challenged	Results	Reference
1	DNA vaccine	prM and E	ZIKV-prME	Type I interferon knockout mice	Two doses are given 2 weeks apart	Intramuscular injection	Puerto Rico Strain PRVABC59	Completely protected mice against sperm and testes damage brought on by ZIKV and stopped the virus' persistence in the testes	73
			pVAX1-ZME	BALB/c mice	Three doses of vaccine given in 3 weeks	Intramuscular injection	(SMGC-1 strain, GenBank accession number KX266255	Passive defense against ZIKV infection in newborn mice by eliciting potent, long-lasting adaptive immune responses with high and sustained ZIKV-specific neutralizing activity	74
			GLS-5700	C57BL/6J mice and IFNAR$^{-/-}$ mice	Two doses were given, 2 weeks apart	Intramuscular injection	Puerto Rico Strain PRVABC59	Prevented male IFNAR/mice from losing their fertility	75
			ABC/prM-E	C57BL/6c mice	Days 0, 24, 42, and 199: four doses	Intramuscular injection	Puerto Rico Strain PRVABC59	Elicited defenses against many different ZIKV isolates	76
		NS1	pVAX-NS1, pVAX-tpaNS1, pVAX-tpaNS1-IMX313P (NS1)	BALB/c and, type I IFN receptor–deficient$^{-/-}$ mice	Three doses were given, one every 2 weeks	Intradermal injection	ZIKVzkv2015	When compared to pVAX-NS1 and pVAX-tpaNS1-IMX313P, pVAX-tpaNS1 immunization dramatically increased NS1-specific antibody titers and CD4+ and CD8+ T-cell responses	77
2	Subunit vaccine	E	Recombinant ZIKV E	Swiss Webster, BALB/c, and C57BL/6 mice	In 3 weeks, three doses of vaccine were given	Intramuscular injection	Puerto Rico Strain PRVABC59	The animals produced significant amounts of neutralizing antibodies and antigen-binding IgG titers, which offered protection from viremia after ZIKV infection	78
			Recombinant ZIKV E	Cynomolgus macaques and BALB/c mice	Three doses of vaccine spaced 3 weeks apart	Intramuscular injection	Puerto Rico Strain PRVABC59	High neutralizing antibody titers were induced	79
		E-Domain III	EDIII	C57BL/6 mice	Four doses were given at intervals of 3 weeks	Subcutaneous injection	Puerto Rico Strain PRVABC59	No signs of ADE development were exhibited in mouse serum and produced strong titers of IgG and ZIKV-neutralizing antibodies	80
			EDIII (having fragments 296 to 406; 298 to 409; 301 to 404)	BALB/c mice and A129 mice	Five doses of vaccine were given at time intervals of 0,	Intramuscular injection	R103451 and FLR strains	ZIKV infection was prevented in infants and immunocompromised adults by passive transfer of the vaccine-specific antibodies and induced persistent broad-spectrum neutralizing antibodies	81

(Continued)

TABLE 3 Continued

Sr. No.	Vaccine type	Component of vaccine	Name of vaccine	Animal model	Vaccine dose	Administration mode	Virus challenged	Results	Reference
					21, 42, 210, and 300				
		450 amino acids of E-protein	E90	CR (CD-1 immunocompetent) mice; BALB/c mice	In 2 weeks, two dosages of vaccine were given	Intraperitoneal injection	GZ01 and FSS13025 strains	E90 immunization of pregnant mice protected against ZIKV infection and microcephaly by protecting brain development in offspring both during gestation and in the neonatal period. E90 induced strong humoral responses that were unique to the ZIKV in adult BALB/c mice	82
3	Live attenuated vaccine	ZIKV RNA genome	ZIKV-30 UTR-10-LAV	A129 mice	One dosage	Subcutaneous injection	Cambodian strain FSS13025 and Puerto Rico strain PRVABC59	Demonstrated total protection against viremia and elicited a saturation neutralizing antibody response	83
			ZIKV-30 UTR-20-LAV	A129 mice and rhesus macaques	One dosage	Subcutaneous injection	Cambodian strain FSS13025 and Puerto Rico strain PRVABC59	Generated potent immune responses and protected mice against ZIKV-induced testicular injury; promoted sterilizing immunity in non-human primates	83
		NS1	ZIKV-NS1-LAV (NS1)	A129 mice and rhesus macaques	One dosage	Subcutaneous injection	Puerto Rico strain PRVABC59	Significantly reduced viral RNA levels were found in the tissues of the mother, the placenta, and the fetus, and this provided protection against placental injury and fetal mortality	84
		9 amino-acids deleted region of C-protein	LAV	A129 mice	One dosage	Subcutaneous injection	Puerto Rico strain PRVABC59	In addition to inducing protective immunity that entirely shielded against viremia, morbidity, and death, it also entirely protected against infection in pregnant mice and transfer from mother to fetus	85
4	Virus vector-based vaccine	prM and E gene, E1 region of Adenovirus 4 & 5	Ad4-prM-E and Ad5-prM-E	C57BL/6 mice	In 3 weeks, two doses of vaccine were given	Intramuscular injection	Puerto Rico strain PRVABC59	Vaccination with Ad5-prM-E elicited both humoral and cellular responses, whereas Ad4-prM-E elicited cellular response	86
		prM and E gene, replication deficient human Ad5	hAd5-prM-E	C57BL/6 mice and Ifnar1$^{-/-}$ mice	One dosage	Intranasal injection	Puerto Rico strain PRVABC59	Immunological responses were triggered on the humoral and cell-mediated levels, providing defense against ZIKV infection	87
		Ad5, prM, E, signal peptide and Ad5, E	Ad5-Sig-prM-Env	BALB/c mice and A129 mice	One dosage	Intramuscular injection	Puerto Rico strain PRVABC59	Both vaccines produced strong adaptive immunity in immunodeficient BALB/c mice and A129 mice, although Ad5-Sig-prM-Env-vaccinated animals exhibited significantly	88

(Continued)

TABLE 3 Continued

Sr. No.	Vaccine type	Component of vaccine	Name of vaccine	Animal model	Vaccine dose	Administration mode	Virus challenged	Results	Reference
		(prM-E) and Ad5-Env (E)						higher ZIKV-specific neutralizing antibody titers and lower viral loads than Ad5-Env-vaccinated mice	
		Chimpanze Ad, prM, E	ChAdOx1	BALB/c mice	One dose	Intramuscular injection	Brazilian ZIKV	A strong immune response generated against ZIKV in challenged mice	89
		prM, E, Rhesus Ad52	RhAd52-prMEnv	Rhesus monkeys and BALB/c mice	One dose	Intramuscular injection	Brazilian ZIKV and Puerto Rico strain PRVABC59	Rhesus monkeys were induced to produce ZIKV-specific neutralizing antibodies; mice developed antibodies protective enough against ZIKV challenge	90
		prM, E, NS1	rVSV-prM-E-NS1	A129 mice and BALB/c mice	One dose	Intranasal injection	Cambodian strain FSS13025	T-cell immune responses and ZIKV-specific antibodies were induced, providing significant protection against infection	91
		Vesicular stomatitis virus (VSV)- capsid and VSV, E (260–425)	VSV-Capsid and VSV-ZikaE	BALB/c mice	One dose	Intranasal injection	Puerto Rico strain PRVABC59	In inoculated BALB/c mice, both vaccines produced potent ZIKV-specific humoral responses; however, the VSV-capsid vaccine elicited noticeably larger numbers of IFN+ CD8+ and CD4+ T-cells than the VSV-ZikaE260–425 vaccine	92
5	Purified in activated vaccine	Purified inactivated ZIKV vaccine with alum-adjuvant	PIZV	CD-1 and AG129 mice	In 4 weeks, three doses of the vaccine were given	Intramuscular injection	Puerto Rico strain PRVABC59	A fatal ZIKV challenge could not kill AG129 mice after and was found to be immunogenic in a model animal. Complete protection against a deadly ZIKV challenge was also demonstrated by the passive transfer of ZIKV-immune serum to naive mice	93
				BALB/c mice and cynomolgus macaques	Two doses at 3/ 4-week intervals	Intramuscular injection	Puerto Rico strain PRVABC59	Provided full protection against ZIKV similar strain and produced strong neutralizing antibody responses	94
		Purified inactivated ZIKV vaccine	PIZV	Indian rhesus macaques	Two doses of vaccine at a 4 weeks spaced	Intramuscular injection	Puerto Rico strain PRVABC59	Induced long-lasting, dose-dependent neutralizing antibody reactions	95
				Rhesus macaques	In 4 weeks, two doses of the vaccine were given	Subcutaneous injection, Intramuscular injection	Brazil ZKV2015	A strong defense against the ZIKV challenge was provided by the two doses of vaccine	96
6	Virus-like particle-based vaccine	prM and E with HEK293 vector	ZIKV VPLs	AG129 mice	Two doses were given on days 0 and 32	Intramuscular injection	Prototype Zika Nica 2–16 strain	Induced a protective antibody response	97
				BALB/c mice					98

(Continued)

TABLE 3 Continued

Sr. No.	Vaccine type	Component of vaccine	Name of vaccine	Animal model	Vaccine dose	Administration mode	Virus challenged	Results	Reference
		prM and E with baculovirus vector			Three dosages of vaccine in 2 weeks	Intramuscular injection	ZIKV strain SZ-WIV01	T-cell responses, ZIKV-specific IgG, and neutralizing antibodies were stimulated	
		EDIII with *Nicotiana benthamiana*		C57BL/6 mice	Three dosages were given in 3 weeks	Subcutaneous injection	Puerto Rico strain PRVABC59	Immune responses that were elicited were strong on the humoral and cellular levels, and they were protective against various strains	99
7	mRNA-based vaccine	prM and E	sr-prM-E-mRNA ZIKV vaccine	BALB/c and IFNAR$^{-/-}$ C57BL/6 mice	In 4 weeks, two doses of the vaccine were given	Intradermal injection	ZIKV strain MR-766	As little as 1 µg of this vaccine electroporated into the skin of BALB/c and IFNAR/C57BL/6 mice evoked powerful humoral and cellular immunological responses, completely protecting the mice from ZIKV infection	100
			IgE-prM-E LNP vaccine	AG129, BALB/c and C57BL/6 mice	A single dose and two doses were given in 3 weeks	Intramuscular injection	African ZIKV strain (Dakar 41519)	When immune-competent mice were protected from ZIKV infection and provided sterilizing immunity, ADE was reduced both *in vitro* and *in vivo*	101
			Nucleoside-modified ZIKV prM-E mRNA-LNP vaccine	BALB/c and C57BL/6 mice; rhesus macaques (*Macaca mulatta*)	One dosage	Intradermal injection	Puerto Rico strain PRVABC59	Robust and long-lasting protective responses in mice and non-human primates	102

•This table has been adopted from (104) with some modifications.

TABLE 4 ZIKV vaccines that are currently undergoing clinical trials (103).

Type of vaccine	Vaccine name	Immunogen	Vaccine trials accession no.	Phase
DNA vaccine	GLS-5700	prM and E	NCT02809443	1
	GLS-5700	prM and E	NCT02887482	1
	VRC-ZKADNA085-00-VP	prM and E	NCT02840487	1
	VRC-ZKADNA090-00-VP	prM and E	NCT02996461	1
	VRC-ZKADNA090-00-VP	prM and E	NCT03110770	2
Inactivated complete ZIKV	Zika virus, purified inactivated VACCINE (ZIKV PIV)	Inactivated virus and aluminum salts	NCT02963909	1
	ZIKV PIV	Inactivated virus and aluminum salts	NCT02952833	1
	ZIKV PIV	Inactivated virus and aluminum salts	NCT02937233	1
	ZIKV PIV	Inactivated virus and aluminum salts	NCT03008122	1
	PIZV or TAK-426	Inactivated virus and aluminum salts	NCT03343626	1
	VLA1601	Inactivated virus and aluminum salts	NCT03425149	1
	BBV121	Inactivated virus and aluminum salts	CTRI/2017/05/008539	1
Virus-vectored vaccine	ZIKV/D4Δ30-713	Backbone of DENV, prM, and E	NCT03611946	1
	MV-Zika	prM and E	NCT02996890	1
Peptide	AGS-v	Mosquito salivary proteins	NCT03055000	1
mRNA vaccine	mRNA-1325	prM and E	NCT03014089	2

occurrence of ZIKV. Scientists, governments, public health officials, and pharmaceutical companies should come together and prepare to fight strongly the next ZIKV outbreak. There is a need for a safe and effective vaccine to fight against ZIKV, as there are some unknown mechanisms that help the virus to escape. It is possible that the ability of the virus to vertically transmit in mosquitoes, and its increasing vector competency, helps it to cope with harsh conditions and re-emerge as an outbreak. More studies should be carried out in this context. Understanding the interaction between the host and ZIKV will also help in developing different therapeutics against ZIKV infection. There is a need for more effort to prevent and treat ZIKV. Vaccine development and the use of vaccines against any pandemic depends on factors such as animal models for preclinical studies, validation of vaccines by assuring their safety (including safety for pregnant women and neonates), production at massive levels, and clinical trials. More studies should be conducted to determine the effects of vaccines on pregnant women, fetal development, infants, and elderly individuals. As some vaccines are under clinical trial, they should be tested further for any side effects. Work/tests must also be carried out to bring a ZIKV vaccine to licensure and public use. As cases of ZIKV have significantly reduced, a controlled human infection model should be developed to test the efficacy and correlation in humans; however, due to a lack of support, it has become difficult to develop such models. This will adversely affect ZIKV vaccine development projects and can threaten the public in the event of a sudden outbreak, as was seen in the case of COVID-19. Therefore, there is a need for a scientific society that can predict outbreaks and prepare to fight against such outbreaks.

Author contributions

ND: manuscript drafting, writing, and reviewing. MY: information collection, reviewing the manuscript, and editing. HS and RJ helped in reviewing and editing. NS: manuscript conceptualization, reviewing, and editing. All authors contributed to the article and approved the submitted version.

Acknowledgments

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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