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REVIEW OF ZIKA VIRUS

Pavan Dhondu Tagad[1], Yash Ganesh Kulkarni[2], Mr. Sandesh S. Dahiwal[3]

[1,2]Student, Ojas College Of Pharmacy, Jalna -431203, Maharashtra, India

[3]Assistant Professor & Guide, Ojas College Of Pharmacy, Jalna -431203, Maharashtra, India

ABSTRACT

The Zika virus (ZIKV) is an arbovirus belonging to the family Flaviviridae and the genus Flavivirus. ZIKV infections in humans were intermittent for fifty years before appearing in the Pacific and the Americas. ZIKV was originally isolated from a nonhuman primate in 1947 and from mosquitoes in 1948 in Africa. The usual method of ZIKV transmission is through mosquito bites. Zika fever has a non-specific clinical appearance that makes it easy to confuse with other infectious disorders, particularly those caused by arboviruses like dengue and chikungunya. Prior to the huge French Polynesian outbreak in 2013 and 2014, when severe neurological problems were documented, and the appearance in Brazil of a dramatically increased rate of severe congenital diseases, ZIKV infection was solely linked to mild illness. microcephaly, a deformity thought to be linked to ZIKV. Zika virus isolation or the identification of ZIKV-specific RNA are required for the laboratory diagnosis of Zika fever. Cross-reactivity among Flavivirus species makes serological diagnosis more challenging. Urban areas in the tropics that are plagued with capable mosquito vectors like Aedes aegypti and Aedes albopictus have a significant potential for ZIKV emergence.

Keywords: Zika virus, arbovirus, flavivirus, viruses, emerging infectious diseases, zoonoses, microcephaly, craniofacial abnormalities, mosquitoes, Aedes, review literature as topic

1. INTRODUCTION

Zika virus (ZIKV) is a mosquito-borne Flavivirus s belonging to the Flaviviridae family.[1] It was first isolated from a rhesus monkey in the Zika forest of Uganda in 1947.It is closely related to several other flaviviruses that cause global disease, including dengue virus (DENV), yellow fever virus (YFV), Japanese encephalitis virus (JEV), West Nile virus (WNV), and tick-borne encephalitis virus (TBEV) [2]. The virus spreads primarily through the bite of infected Aedes aegypti mosquitoes, and can also be transmitted through sexual intercourse, and during pregnancy, from a mother to her fetus.[3] It was not until 1952 that The first case of infection in humans was described in a 10-year-old female from Nigeria in 1954 [4] In 2007, the first major outbreak of Zika fever took place on the Western Pacific Island of Yap in the Federated States of Micronesia [5]Since then, multiple outbreaks of ZIKV have been reported worldwide. Two larger epidemics affecting over 30,000 people took place in 2013 and 2014 in French Polynesia [6,7]. In 2016, the World Health Organization declared the ZIKV epidemic as an international health emergency . ZIKV infection is mostly asymptomatic and often causes a self-limiting febrile illness in 20% of adults [8]; however, it has been causally associated with congenital malformations and neurological disorders, the virus has recently raised a “Public Health Emergency of International Concern” due to the dramatic increase in the cases of prenatal microcephaly and Guillain-Barré Syndrome (GBS) in ZIKV endemic regions [9]. Microcephaly is characterized by at least two standard deviation reduction in brain volume intellectual and motor disabilities, and behavioral issues [10]. Multiple development factors, such as genetic, environmental, and infectious exposure, during pregnancy are known to contribute to the onset of prenatal microcephaly.GBS, on the other hand, is a rare autoimmune disorder of the peripheral nervous system which could result in muscle weakness, paralysis, or even death [11].

2. VIROLOGY OF ZIKV

ZIKV is an 11 kb positive single-stranded RNA virus with a diameter of approximately 40–60 nm that belongs to Flavivirus genus. ZIKV is related to other flaviviruses, more closely with dengue virus (DENV), Japanese encephalitis virus (JEV), yellow fever virus (YFV), and distantly to West Nile virus (WNV). Two important lineages, African and Asian, were identified based on the phylogenetic analyses (12).ZIKV genome consists of two non-coding regions and one coding region. The coding region encodes a polyprotein that makes three structural proteins (capsid, envelope, membrane precursor) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). The three N-terminal structural proteins, capsid protein (C), precursor of membrane(prM), and envelope protein (E) are the skeletal elements for the formation of virus particles. Among them, C combines with viral genomic RNA to form a nucleocapsid core, whereas prM and E are viral surface glycoproteins that are adsorbed to the host cytoplasmic membrane [13]. The M protein is expressed as a glycosylated prM and attached to thehost-derived lipid envelope, whereas the E protein may or may not be glycosylated and this is a determinant of neuroinvasion, acting to increase both transepithelial and axonaltransportation [14].The seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) at the C-terminus of the genome that participate in multiple stages and functions of the viral life cycle, such as RNA replication, virus particle assembly, and immune escape.Structure of ZIKV is similar to other flaviviruses, except at Asn180

glycosylation site in glycoproteins that make up the icosahedral shell. The glycosylated moiety at Asn180 was required for viral attachment of host cells and varies among ZIKV strains and flaviviruses (15). Like other flaviviruses, ZIKV may likely infect host cells by endocytosis after the interaction of virus particles with host cell surface receptors. Receptors such as C-type lectin, phosphatidylserine, T cell immunoglobin and mucin (TIM) and AXL, Tyro3, and Mertk (TAM) are identified as entry factors for various flaviviruses. In case of DENV, AXL receptor was considered as a major receptor for viral entry. AXL activates a cascade of events such as activation of AXL kinase, recruitment of interferon receptor (INFAR), inhibition of innate immune response, and replication of the virus inside the host cells. Role of AXL as a receptor required for the entry of ZIKV is contradictory since in vitro results support and most in vivo mice results question its role as a receptor mediating the viral entry (17,18,19,20,21).

3. ZIKA VIRUS TRANSMISSION

ZIKV transmission can be classified into vector-borne and non-vector borne. In vector-borne transmission, several species of Aedes mosquitos were reported. In non-vector borne human transmission, routes such as transplacental transmission, blood transfusion, and sexual transmission were reported (22,23).

1. Vector Borne Transmission Or Mosquito-Borne Transmission

ZIKV transmission to humans occur primarily through bites of an infected, day-dwelling female Aedes aegypti or Aedes albopictus mosquito, similar to the transmission of chikungunya virus (CHIKV) and DENV.Transmission dynamics of ZIKV via mosquitoes is complex, mainly due to the involvement of several mosquito species in ZIKV maintenance. To date, ZIKV has been isolated from 17 Aedes mosquito species as well as Anopheles gambiae, Anopheles coustani, Culex perfuscus, and Mansonia uniformis mosquitoes (24,25,26). Among these several mosquito types, ZIKV transmission to humans has been Hu only for female Aedes aegypti, Aedes albopictus, A. hensilli (responsible for Yap Island outbreak), and A. polynesiensis (responsible for French Polynesia outbreak) (11).albopictus mosquitoes are suspected of broader transmission of virus due to their extensive geographic distribution in tropical, sub-tropical, and temperate regions. In Americas, A. aegypti and A. albopictus are identified as the major vectors for human transmission (10). It is presumed that uninfected mosquitoes acquire ZIKV through infected humans, although further studies are needed to confirm whether the viral titer of infected humans are sufficient to infect mosquitoes. It was suggested that the incubation period for ZIKV in mosquitoes for viral transmission is ~ 10 days (27). An important strategy to prevent mosquito-borne transmission is avoidance of exposure to mosquitos. When possible, pregnant women should delay the travel to the areas of active ZIKV transmission. If travel is unavoidable, women are encouraged to use insect repellents such as DEET and permethrin.

4. NON-VECTOR-BORNE

A. Sexual Transmission

ZIKV is also capable of trasmitting through sexual intercourse. Multiple cases of male to female transmission of ZIKV have been reported .Sexual transmission is possible from both asymptomatic and symptomatic infections through genital, oral, and anal intercourse, and male to male, male to female, and female to male contact.(28) Sexual transmission is reported to have occurred up to 44 days after symptom onset; infectious viral particles have been isolated up to 69 days after symptom onset in semen and up to 2 days after symptom onset in the female genital tract.(29,30)Zika virus RNA has been detected for up to 6 months after symptom onset in semen and up to 13 days after symptom onset in the female genital tract,(30) which does not necessarily associate with the presence of infectious virus.(31) Therefore, the exact duration of infectivity of genital fluids is unknown.(30) sexual transmission might play a part in non-endemic areas, the main mode of Zika virus transmission is through mosquito bites.The effect of sexual transmission in endemic areas is impossible to assess because the entire population is exposed to mosquitoes.

B. Blood Transfusion-Related Transmission

During the French Polynesia outbreak, ZIKV RNA was detected in approximately 3% of asymptomatic blood donors (acute phase of infection) thus, making blood transfusion a novel potential mode of ZIKV transmission (32,9).ZIKV transmission via blood transfusion is plausible as ZIKV infections are primarily asymptomatic and blood transfusion-related transmission of other Flaviviruses have been reported (33).The first confirmed case of blood transfusion-related ZIKV transmission has been recently reported in Brazil . To address this issue, on 19 February 2016, the WHO issued strict guidelines for blood transfusion/donation in regions where ZIKV was endemic In multiple countries, donated blood is screened via nucleic acid testing to detect WNV RNA (34).As most infections are asymptomatic, the most effective mitigation strategies to prevent transfusion-transmitted infection are nucleic acid testing of blood donations or pathogen inactivation.(46)

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C. MATERNAL TRANSMISSION

i. PRENATAL TRANSMISSION

Perinatal transmission of Zika virus was first reported during the French Polynesian outbreak in 2013.(22) Intrauterine transmission was subsequently confirmed during the Brazilian outbreak. ZIKV has reportedly been detected in microcephalic neonates born to mothers with a history of ZIKV infection during pregnancy (22). It is postulated that ZIKV has the ability to cross the placenta and subsequently, infect fetal nervous tissues. The suggested mechanism is supported by the evident detection of ZIKV RNA and antigens in the amniotic fluid, placenta, and fetal brain tissue as well as visualization of ZIKV particles in fetal brain via electron microscopy (87,11,10). It is a known fact that the placenta acts as an effective immunological barrier between the mother and the fetus, protecting the fetus from microorganisms in the mother's circulation. The mechanism used by ZIKV to circumvent the placental barrier is yet to be discovered .

ii. NURSING MOTHERS

ZIKV RNA and infectious viral particles have been detected in high loads in the breast milk of infected mothers (36). This introduces a novel transmission mechanism in which ZIKV transmission occurs from the mother to the nursing child. According to a mother-infant pair study, ZIKV RNA was detected in the breast milk and serum of two mothers and in the serum of their respective infants (22). Particularly, serum sample from one of the infants tested positive via RT-PCR after breastfeeding. However, ZIKV replication was not detected upon inoculation of the breast milk on Vero cells hence, making transmission via breast milk uncertain yet plausible. Other potential confounding mother-tochild ZIKV transmission routes should be further investigated. Flavivirus transmission, such as DENV and WNV, via breast milk have been previously reported (38).

5. ZIKA VIRUS LIFE CYCLE

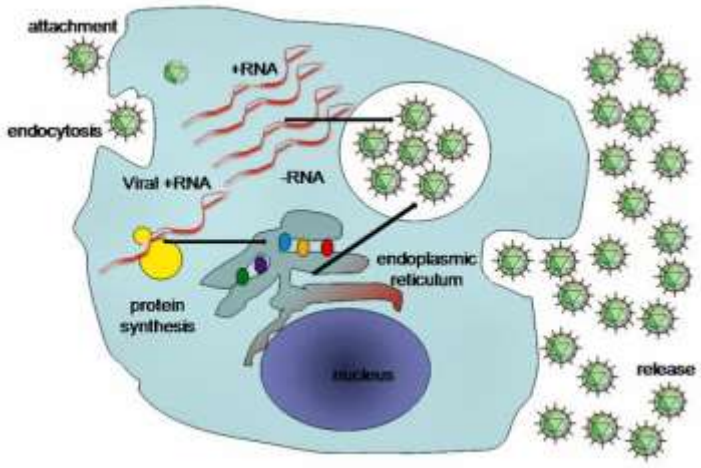

Fig no1 zika virus life cycle

Similar to other known flaviviruses, the viral life cycle of ZIKV could be roughly divided into stages of binding, entry, translation, replication, assembly, and release [43].Briefly, the E protein is involved in the attachment of virus to receptors on the host cell membrane, and the virus is internalized through endocytosis that is mediated by clathrin proteins in the acid pH environment [20,44]. Several cell surface receptors facilitate ZIKV viral entry, such as Tyro3, DC-SIGN, AXL, and TIM-1 [45]. Subsequently, fusion of viral membrane with endosome membrane occurs, the positive-strand viral genomic RNA releases from nucleocapsid into cytoplasm, and the synthesis of negative-strand genomic RNA using viral positive-strand genome as template by RdRp [9]. On surface of endoplasmic reticulum, the negative-strand RNA is used to synthesize new viral positive-strand genomes and viral mRNAs, which are further translated into viral polyproteins via host machinery. The resulting polyprotein is cleaved into the three nonstructural and seven structural proteins by the viral protease as mentioned above [42]. The newly-synthetized positive RNAs could be recruited for further activities of translation/replication or incorporated into the virions, which initiates their assembly [46]. Immature virions are assembled in the endoplasmic reticulum and transfer to the Golgi apparatus through budding formaturation, until their final release into the extracellular space [15,46]. Virions attach to the cell surface receptors and subsequently enter cells by receptor-mediated endocytosis and are internalized into clathrin-coated vesicles. Endosome acidification triggers conformational changes, fusion of viral membrane with endosome membrane, and particle disassembly and the viral genomic RNA is released from nucleocapsid into the cytoplasm. The ssRNA then is translated into a single polyprotein that is further processed co-translationally and post-translationally by viral and

cellular proteases. This cleavage makes three structural proteins and seven nonstructural proteins. Viral genome replication initiates with negative-strand RNA synthesis, and further serves as a template for thesynthesis of the positive-strand genomic RNA. Virus assembly take places in the endoplasmic reticulum (ER) surface by budding, and immature virus particles travel along the host secretory pathway through the trans-Golgi network, where virion maturation occurs followed by release from the cell via exocytosis. Additionally, the below table shows where the inhibitor/antivirals of ZIKV act during the ZIKV life cycle. Life cycle of ZIKV. Virions attach to the cell surface receptors and subsequently enter cells by receptor-mediated endocytosis and are internalized into clathrin-coated vesicles. Endosome acidification triggers conformational changes, fusion of viral membrane with endosome membrane,and particle disassembly and the viral genomic RNA is released from nucleocapsid into the cytoplasm.The ssRNA then is translated into a single polyprotein that is further processed co-translationally and post-translationally by viral and cellular proteases. This cleavage makes three structural proteins and seven nonstructural proteins. Viral genome replication initiates with negative-strand RNA synthesis, and further serves as a template for the synthesis of the positive-strand genomic RNA. Virus assembly take places in the endoplasmic reticulum (ER) surface by budding, and immature virus particles travel along the host secretory pathway through the trans-Golgi network, where virion maturation occurs followed by release from the cell via exocytosis. Additionally, the below table shows where the inhibitor/antivirals of ZIKV act during the zikv life cycle.

6. ZIKV-ASSOCIATED NEUROLOGICAL DISORDERS

1. **Microcephaly**
2. **Guillain-Barré Syndrome**

7. MICROCEPHALY

Microcephaly is a neurological condition in which the brain of a baby does not develop properly, causing the head to be smaller than normal (39,40).

It is divided into two types:

(1) primary or congenital microcephaly, which is present in utero or at birth; and

(2) secondary or postnatal microcephaly, which develops after birth (41).

While primary microcephaly is likely caused by a decrease in the number of neurons produced during neurogenesis, secondary microcephaly is presumably caused by a reduction in the number of dendritic processes and synaptic connections. Microcephaly can be caused by a variety of genetic mutations, peri- and post-natal brain injuries, teratogenic agents, and congenital infectionsThe ZIKV outbreak in Brazil in 2016 had received much attention because of the surge of ZIKV-associated microcephaly cases, suspecting a possible association. At first a link between ZIKV and microcephaly was not widely accepted and alternate proposals for a causative agent included pesticides and a bovine-like viral diarrhea virus [42], but a number of lines of evidence subsequently supported the association. Firstly epidemiological studies supported the association showing that microcephaly was associated with ZIKV infection during pregnancy, particularly when the infection took place in the first trimester [43].

Secondly, ZIKV was recovered from the brain of a foetus medically aborted for reasons of microcephaly [44], and thirdly experimental evidence showed that ZIKV was able to infect human neural progenitor cells [45].Animal model systems also provided data supporting the association between ZIKV infection and microcephaly [46]. Further supporting evidence of an association between Zika virus infection of pregnant women was provided after a retrospective review of data from French Polynesia [47], as well as an increase in the occurrence of microcephaly and other birth defects in babies born in other countries or territories which had experienced the introduction on ZIKV such as Columbia [49], Puerto Rico , and Mexico.

8. GUILLAIN–BARRÉ SYNDROME (GBS)

is one of the new complications and manifestations of ZIKV infection [49]. GBS is a serious and life threatening neurological disorder eventually resulting in respiratory failure characterized by progressive muscular weakness [50].GBS is an autoimmune demyelinating disorder that causes reduced signal transmissions, progressive muscle weakness, and paralysis.

(GBS) is a rapid-onset muscle weakness caused by the immune system damaging the peripheral nervous system.[51] Typically, both sides of the body are involved, and the initial symptoms are changes in sensation or pain often in the back along with muscle weakness, beginning in the feet and hands, often spreading to the arms and upper body.[51] The symptoms may develop over hours to a few weeks.[51] During the acute phase, the disorder can be life-threatening, with about 15% of people developing weakness of the breathing muscles and, therefore,

requiring mechanical ventilation. Some are affected by changes in the function of the autonomic nervous system, which can lead to dangerous abnormalities in heart rate and blood pressure.

In those with severe weakness, prompt treatment with intravenous immunoglobulins or plasmapheresis, together with supportive care, will lead to good recovery in the majority of cases.[51] Recovery may take weeks to years, with about a third having some permanent weakness. Globally, death occurs in approximately 7.5% of those affected. Guillain–Barré syndrome is rare, at 1 or 2 cases per 100,000 people every year. Both sexes and all parts of the world have similar rates of disease.The syndrome is named after the French neurologists Georges Guillain and Jean Alexandre Barré, who, together with French physician André Strohl, described the condition in 1916.[53,54]

9. OTHER COMPLICATIONS ASSOCIATED WITH ZIKV INFECTIONS

1. Eye Diseases

ZIKV causes mild eye infections in adults with symptoms such as conjunctivitis and uveitis in adults (59,60). However, ZIKV-related eye infections in infants are much severe and include blindness, optic neuritis, chorioretinal atrophy, bilateral iris coloboma, and intraretinal hemorrhages. ZIKV-related microcephaly case studies revealed ocular abnormalities in 10 out of 29 infants (63). ZIKV is found to cause panuveitis in mice and sheds from tears (61). The presence of ZIKV in eyes suggests that eyes may act as one of the reservoir hosts for ZIKV following the acute phase of infection.

2. Meningoencephalitis

ZIKV-related meningoencephalitis can occur rarely. To date, it was observed only in a single case of 81-year-old male returned from ZIKV endemic area (62). Brain infection resembling meningoencephalitis was seen in immunodeficient mice subjected to intravenous ZIKV injections (64). These shreds of evidence suggest a possible association of ZIKV infections to meningoencephalitis and thus merit further studies in this direction.

10. SYMPTOMS

Not everyone who is infected will experience symptoms. These are the symptoms that can appear within 2 weeks of being bitten:

- Fever
- Rash
- Joint pain
- Muscle pain
- Headache
- Conjunctivitis (red eyes)

The symptoms are usually mild and only affect 1 out of 5 infected people.

11. ZIKV DIAGNOSIS

An accurate and timely diagnosis of ZIKV infection is essential to choose correct treatment strategies. Clinical diagnosis of ZIKV is difficult because of its symptoms overlap with other arboviruses and cross-reactivity to other faviviral antibodies present in the serum at the time of infection. Laboratory approval is necessary for diagnosis of Zika infection considering that there is no pathognomonic presentation that differentiates Zika fever from other infections as well as congenital ZIKV infection from other etiologies of congenital abnormalities

Current diagnosis of ZIKV infection includes :-

1. Reverse Transcription Polymerase Chain Reaction (RT-PCR)
2. Immunoglobulin (Ig) G/M Enzyme-Linked Immunosorbent Assay (ELISA)
3. Plaque Reduction Neutralization Test (PRNT)

1. RT-PCR

Real-time and conventional RT-PCR are the most common approaches utilized in diagnostic.Molecular methods to detect ZIKV-specific nucleic acids by RT-PCR are preferred during the acute phase of ZIKV infection because of its high specificity and sensitivity. ZIKV DNA by RT-PCR can be detected up to 2 weeks of symptom onset in urine and saliva samples, and up to 2 months in blood samples. RT-PCR methods that detect either conserved regions of the viral genome or multiplex assays that allows simultaneous detection of ZIKV, DENV, and CHIKV have been developed (63,64,65,67,68,69,70).the ZIKV envelope genes (prM/E protein coding regions) are targeted for amplification due to their unique characteristics which allow differentiation from other Flaviviruses (33). Two specific sets of primers for the Asian ZIKV strain have been tested and established (66). To further increase specificity, the use of TaqMan probe

is recommended . Commercial kits (for research purposes) for ZIKV RNA detection via RT-PCR have recently entered the market (71). Peripheral blood samples are predominantly used for PCR-based assays (70). However, RT-PCR on blood and serum samples is associated with reduced sensitivity due to low viremia in humans (72). More recently, detection of higher viral RNA load over a longer duration was reported in urine and semen samples . Related studies coherently reported detection of higher DENV and WNV RNA load over a longer duration in urine samples, as compared blood serum. ZIKV RNA has also been reported to be detected in the saliva of infected individuals,often more readily compared to blood samples. The choice and combination of samples chosen for is highly dependent on the stage of infection . It is recommended to perform RT-PCR on both blood and saliva/urine samples in order to increase test sensitivity, during the late stage of infection (73). In addition, alternative sampling of urine or saliva reduces invasiveness and hence, is advantageous for diagnosis in neonates and infants (71). For prenatal testing, amniotic fluid is predominantly collected molecular analysis. A positive RT-PCR for ZIKV RNA is suggestive of intrauterine infection and plausible reduction in fetus fitness (10). Ultimately, products of ZIKV RNA specific RT-PCR amplification, regardless of sample source, cam also be sequenced and aligned against established ZIKV genome sequences for confirmation (32).

2. ELISA - Enzyme-Linked Immunosorbent Assay

IgM/IgG ELISA involves the detection of ZIKV-specific antibodies in the serum (74). IgM antibodies are known to develop within a few days post onset of symptoms and can last up to 3 months. IgG antibodies on the other hand, develop after IgM and can last from a few months to years.

3. Plaque Reduction Neutralization Test (PRNT)

PRNT is used for virus-specific neutralizing antibody titer quantification (75). The test is reported to have improved specificity compared to ELISA hence, it is often used in addition to ELISA to rule-out false positive antibody response (75,70). The PRNT was used in addition to ELISA for diagnosis and confirmation of ZIKV in 185 patients during the French Polynesia outbreak. To perform the PRNT, firstly, serum sample from the patient was diluted and mixed with a suspension of ZIKV. Subsequently, the mixture was poured over a monolayer of cells, often Vero or LLC-MK2 cell lines . The cells were subsequently covered with a thin layer of agar to avoid viral movement. PRNT against other Flaviviruses are concurrently performed as a control (75). At least a 4-fold increase in ZIKV-specific neutralizing antibody titer is recommended for confirmation of ZIKV infection . However, interpretation of results could be complicated if high Flavivirus background is observed in the patient, often due to history of vaccination against Flaviviruses (66,75).

12. TREATMENT OF ZIKV

In ZIKV infection, individuals should have adequate water intake, ample rest and treat pain and fever with liquid solutions. If the symptoms aggravate, they should look for counselling and therapeutic consideration. Tere are no specifc medications or vaccine available to treat or prevent ZIKV infections until now; only medications for symptomatic relief can be considered such as paracetamol to relieve pain and fever associated with this infection [77]. Nonsteroidal anti-infammatory drugs (NSAIDs) should be avoided and individuals should seek medical advice before taking additional medication if they are already taking medicines for another medical condition [78]. Homeopathy is a worthy treatment option in ZIKV infection as it proved to be efective in Japanese encephalitis virus which is included in the same genus like Zika virus [79]. Treatment with belladonna efcaciously reduced the severity of Japanese encephalitis virus infection [81]. Atropa belladonna plant belongs to family Solanaceae [80]. It has been efective in numerous medical conditions having great commercial signifcance as a major source of alkaloids, mainly scopolamine and hyoscyamine that are pharmaceutical bioactive compounds [80]1. Belladonna is native to North Africa, Western Asia and Europe. In Atropa belladonna majority of alkaloidal contents are present in ripe fruit and green leaves. It has been used from ancient times in order to treat various human ailments including menstrual disorders, headache, peptic ulcer, infammation and histaminic reaction [82]. Ultra diluted belladonna concentrations like 1:10 or 1:100 are used in homeopathy and they are recommended for management of all the infectious diseases and illnesses [83].Eupatorium is a naturally occurring pharmaceutical homeopathic compound efective against the symptoms of ZIKV disease, so it can be utilized as prophylactic treatment against ZIKV infection [84]. Eupatorium perfoliatum, Rhustox and Atropa belladonna are the homeopathic prescriptions that may be utilized for ZIKV infection treatment. Tese medicinal agents are efective against the symptoms of ZIKV infection [85]. During epidemics homeopathic pharmaceuticals are more efective in reduction of mortality and morbidity as compare to conventional system of medicines [86]. One of the utmost momentous features of ayurvedic structure is that they are natural substances and free from side efects and there is no scientifc evidence of danger for human use [87]. It is a primordial medical science that contains herbal medicines of natural origin with minimal side efects. Tinospora cordifolia is a herb and utilized for years as potential immunomodulator and efective natural remedy for viral disease of any nature. It boosts up the immune system and make body resistant enough to fght

against infections. Teses herbs potentiate phagocytic abilities of macrophages [87]. Intestinal sickness, urinary tract infections, dengue and swine infuenza are efectively treated by the astringent characteristics of these ayurvedic plants so they might also be efective for ZIKV [78].Beside homeopathic and ayurveda medicines, engineering approaches were also applied to develop peptidetherapeutics and support the potential of a brain-penetrating peptide to treat neurotropic viral infections. Terapeutic treatment protected against mortality and evidently lessened symptoms, neuroinfammation and viral loads, furthermore mitigated microgliosis, neurodegeneration and brain damage [87]. Current medical recommendations are directed towards resolving symptoms and not the actual infection; however, ZIKV treatments and vaccines are in development. In 2016, WHO enlist all publicly afrmed commercial, government and academic-led projects focused at ZIKV interventions, together with vaccines [90]. Te list encompasses numerous approaches, comprising vaccines via purifed inactivated virus, Virus-like particles (VLP), protein subunits, DNA and live recombinant attenuated viruses. Since April 2019, no vaccines have been permitted for clinical usage, though utmost were in the clinical stages of development [91,92].

13. CONCLUSION

Alarming concerns have been generated by the recent ZIKV epidemics in the Americas over the potential link between ZIKV infection and unexpected clinical symptoms, such as premature. GBS and microcephaly. Due to a lack of standardised ZIKV detection methods and a limited understanding of ZIKV transmission dynamics, it has been challenging to assess the risks and severity of ZIKV infection. To this purpose, evidence from published papers suggesting a possible connection between prenatal microcephaly and ZIKV infection and GBS has been compiled in this review. This review also included recent developments in ZIKV transmission and detection and emphasised the significance of comprehending transmission dynamics for the later creation of a quick, inexpensive, and expedient ZIKV detection assay and control strategy. The development of strict surveillance systems (for people and mosquitoes) is advocated as a final preventive measure, especially in tropical areas where the likelihood of a ZIKV outbreak is higher.Case-control studies could be used in future research to examine the relationship between ZIKV infection and microcephaly/GBS and to rule out any potential etiological confounding variables. Future research might potentially look into more potential ZIKV reservoirs and go deeper into the host cellular response and ZIKV pathogenesis pathways in order to produce a reliable detection assay, a ZIKV vaccine, and antiviral treatments.

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