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ZIKA VIRUS / ZIKA FEVER : A COMPREHENSIVE UPDATE

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ABSTRACT

Zika virus (ZIKV) has attracted global attention after its first large-scale outbreak in Pacific, Micronesian island of Yap (Year 2007). The virus spreads rapidly and owes increased virulence than the ZIKV which appeared nearly six decades ago, where it was associated with sporadic cases and mild illness. The World Health Organization declared ZIKA as a ‘Public Health Emergency of International Concern’ due to severe illness and associated several complications such as neurological disorders, autoimmune disorder, fetal anomalies, impaired central nervous system (CNS) of the fetus, microcephaly

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Diagnosis

Vaccines

Drugs

Treatment

Prevention, control

in newborns and Guillain Barre'Syndrome (GBS). Recently, this virus has posed a pandemic threat to global human population. The virus is transmitted primarily by a mosquito (*Aedes aegypti*), whereas, other routes of viral transmission includes monkey bite, coitus and body fluids such as blood, semen, and saliva which needs further confirmaton. Furthermore, implementation of appropriate mechanical, chemical and biological control methodologies can help to avoid mosquito bites and ultimately limit the viral spread. Another potential approach could be the development of ZIKV resistant mosquito strains such as *Wolbachia*-harboring mosquitoes which can reduce the incidences of ZIKV by lowering the availability of vectors for virus transmission. In-use ZIKV diagnosis relies on serological, molecular and few other advanced detection methods. Nowadays, worldwide researchers and biomedical and pharmaceutical authorities are paying attention on designing and developing effective vaccines, drugs, medicines, and therapeutics to counter this virus. The reasons behind the shift of virus virulence need to be explored by understanding the genetic and molecular characteristics, host-pathogen interactions and immunobiology of the virus, which would help to design effective antiviral drugs, prophylactics, and vaccines. The present review highlights various aspects of ZIKV and its clinical manifestations, progress, and advances in developing effective diagnostics, vaccines and drugs/therapeutics along with adopting suitable prevention and control strategies to tackle this deadly emerging disease.

1 Introduction

Zika virus (ZIKV) is a mosquito-borne virus of the Spondweni serocomplex, genus *Flavivirus*, family *Flaviviridae*. Owing to the climate changes like global warming, increasing population dynamics, fast globalization and travel, the human population is facing a rising emergence and outbreaks of mosquito-borne viruses such as Dengue virus, Japanese encephalitis virus, Chikungunya virus, West Nile virus and Zika virus (Chen & Wilson, 2010; Dhiman et al., 2010; Dhama et al., 2013a; Hubalek et al., 2014; Medlock & Leach, 2015; Parham et al., 2015; Carneiro & Travassos, 2016; Gautret & Simon, 2016; Musso et al., 2017). Soon after the deadly outbreaks of Ebola virus in Western Africa, the most recent emerging virus threatening the global human population is the Zika virus (ZIKV), declared as an emergency situation (Public Health Emergency of International Concern) on February 1, 2016 by the World Health Organization (WHO) for its quick spread, affecting large human population in different countries with pandemic threats (Dhama et al., 2015; Chang et al., 2016; Chen & Hamer, 2016; ECDC, 2016; Gulland, 2016; Higgs, 2016; Singh et al., 2016; Krauer et al., 2017; Singh et al., 2017). Being remained harmless for six decades (first reported in 1947), the sudden emergence of ZIKV with higher virulence, speedy spread and inducing severe clinical manifestations (especially associated with the cases of microcephaly, unexpected fetal anomalies during gestation period as placental insufficiency, hampered fetal growth, impaired Central Nervous System (CNS) of fetus, fetal death and other neurologic disorders as well as a cluster of Guillain-Barré

syndrome) along with little knowledge on suitable prevention and therapeutic measures created massive threats for the human health (Zanluca & dos Santos, 2016; Cao-Lormeau et al., 2016; Duhaime-Ross, 2016; Gatherer & Kohl, 2016; Petersen et al., 2016a; Samarasekera & Triunfol, 2016; Singh et al., 2016; Molko et al., 2017).

Earlier reports on ZIKV were limited to Africa and Asia, while now it has worldwide presence (Hayes, 2009; Heang et al., 2012; Grard et al., 2014; Brown, 2015; Chang et al., 2016; Fauci & Morens, 2016; Lucey & Gostin, 2016; Vest, 2017; Zhang et al., 2017). It is noteworthy that since the first report of the disease from the African continent, only 14 cases in humans had been reported before its first large epidemic in the year 2007 on the Island of Yap (Duffy et al., 2009; Marano et al., 2016; Reveiz et al., 2017), followed by the largest outbreak in French Polynesia (October 2013 to April 2014) (Cao-Lormeau et al., 2014; Reveiz et al., 2017). After that in 2015, ZIKV expanded its horizons and also emerged in Vanuatu, Fiji, Solomon and Samoa (ECDC, 2016; Musso et al., 2017). The sequences of ZIKV from Brazil and Suriname upon phylogenetic analysis have revealed their Asian origin. Pacific Islands have been found to be the region from where the virus has entered into the Latin America during some sports events during the year 2014 (Waggoner & Pinsky, 2016). Since 2015, 76 countries and territories around the world have reported ZIKV transmission, predominantly the South Americas, where Brazil was the most affected country with more than 1.4 million affected cases of Zika alone (Jamil et al., 2016; WHO, 2016; Krauer et al., 2017). With the noticed severity of the recent

ZIKV outbreak, several countries geared up for epidemiological investigations to know out further disease spread and the serious health concerns (Van Kerkhove et al., 2016; Reveiz et al., 2017).

Notably, in Asia the incidence of ZIKV infection is relatively low when viral detection was done by employing reverse transcription-polymerase chain reaction (RT-PCR). Viremia induced by ZIKV infection is relatively low; thereby decreasing the probability of detecting the virus in blood samples in acute cases. This has led the researchers to make the interpretation of the results by taking extra caution (Shan et al., 2016; Duong et al., 2017). In Asia and America, the strain difference (as far as the infectivity is concerned) could have been responsible for the fundamental difference in the epidemiology as well as the burden of ZIKV infection. The Asian lineage of ZIKV is responsible for most of the recent outbreaks in Asia as well as America (Haddow et al., 2012). There is a requirement of using viruses generated *de novo* from diverse geographical as well as clinical sources to describe the pattern of ZIKV infection in Asia and America (Setoh et al., 2017).

ZIKV infection impacts any nation's economy adversely besides being a toll on human health (Jamil et al., 2016). International agencies including WHO, Pan American Health Organization (PAHO), the Consortium for the Standardization of Influenza Seroepidemiology (CONSISE), Institute Pasteur, the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), Fiocruz, and others have taken up collective steps and are coordinating to synchronize the ongoing research on this virus and complications associated with it (Reveiz et al., 2017).

The emergence of this virus with increased virulence and potential of rapid spread posed pandemic threats to global human population (Chitti et al., 2016; Petersen et al., 2016a). Of note, till 2015 nearly 100 research articles were available in Pubmed and Pubmed Central, while now in January 2018, there are more than 3500 research articles on different aspects of the virus and the disease it causes, which altogether reflects the high concerns and wide attention this pathogen has gained in just past 20 months.

Researchers in many countries are trying hard to counter ZIKV and the Zika fever by carrying out detailed virological, pathological and molecular studies, developing rapid diagnostics, finding out potential drugs, prophylactics, vaccines as well as adopting appropriate prevention and control measures (Keasey et al., 2017; Munjal et al., 2017a; Rather et al., 2017; Shankar et al., 2017; Sharma & Lal, 2017; Singh et al., 2018a). Rapid diagnostics are now existing for detecting ZIKV infection, many drug and vaccine candidates have also been identified, but still any effective / approved treatment or vaccine is practically lacking against this virus (Dyer, 2016a; Fernandez & Diamond, 2017;

Munjal et al., 2017a; Munjal et al., 2017b; Passi et al., 2017; Singh et al., 2018b). Appropriate prevention and control strategies include limiting the spread/bite of the vector mosquitoes by checking their population expansion, safe precautions during sexual intercourse and blood transfusions, avoiding travel to Zika endemic countries and surveillance and monitoring are the only feasible options to keep ZIKV infection under limits (Rather et al., 2017; von Seidlein et al., 2017). Here, we present a compilation on the Zika virus/ Zika fever, covering different aspects of the virus and the disease it causes, and describes the ongoing progress and advances being made in the field of designing and developing diagnostics, vaccines, drugs along with prevention and control measures to be adapted to combat this viral pathogen of high public health concerns.

2 Etiology, Epidemiology and Transmission / Spread

Zika virus belongs to the genus *Flavivirus*, family *Flaviviridae* (Gold & Josephson, 2016; Paz-Bailey et al., 2017; Uncini et al., 2017). It is a ss-RNA virus of 11 kb genome size with single open reading frame (ORF) encoding a polyprotein with 03 structural proteins (capsid, pre-membrane, envelope) and 07 non-structural (NS) proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) (Musso & Gubler, 2016; Kumar et al., 2017). Among these NS5 has multiple roles and protein E plays a pivotal role in binding and fusion of virus as an important basic step for the establishment of ZIKV infection (Dasti, 2016). Various antigenic epitopes are present in the third domain of the E protein and thus essentially targeted as far as the serological tests are concerned. It is also an important target for vaccine development. It is assumed that the global spread of the ZIKV is due to loss of the E protein glycosylation site: N154. This helps the virus to adapt to a broader range of vector mosquitoes (Faye et al., 2014; Chan et al., 2016). From Zika forests of Uganda, the first ZIKV isolation was done in 1947 from rhesus monkey. ZIKV strain 766 particle size ranged between 30 and 45 nm (Dick, 1952). Recently, the viral structure has been elucidated using cryo-electron microscopy which could assist in designing of antiviral drugs and vaccines (Sirohi et al., 2016).

Consequent to early 2015 Zika disease outbreak in Brazil, the Zika fever spread rapidly across South and Central America, North America, Latin America, Mexico, Colombia, French Polynesia, Cook Islands, Haiti, Panama, Trinidad and Tobago, Samoa, and American Samoa (Campos et al., 2015; Zanluca & dos Santos, 2016; Rodriguez-Morales, 2015; Nereida, 2015; Summers et al., 2015; Chang et al., 2016; Chen & Hamer, 2016; ECDC, 2016; Hennessey et al., 2016; Higgs, 2016; Pastula et al., 2016; Petersen et al., 2016b). As per the updates of the Pan American Health Organization (PAHO) vector-borne ZIKV infections have been confirmed in 48 countries and sexual

transmission in 5 countries regionally. Imported cases have been recorded in people visiting areas where the epidemic infection is prevalent and subsequently returning to Europe, Asia-Pacific and the Americas (Pan American Health Organization/ World Health Organization, 2016; Goorhuis et al., 2016). ZIKV autochthonous (locally transmitted) cases have been reported from many countries or territories (Zanluca & dos Santos, 2016; Calvet et al. 2016a). The year 2016 also marked the report of first ZIKV infection in Taiwan and PCR followed by further analysis showed that it was Asian lineage virus having close proximity with Cambodian virus (Huang et al., 2016).

The ZIKV transmission mainly takes place via mosquito (*Aedes* sp.-*Aedes aegypti* and *A. albopictus*) in an anthroponotic manner (human-to-vector-to-human), perinatal transmission, sexual intercourse, and blood transfusion (Besnard et al., 2014; Musso et al., 2014, Musso et al., 2015; Franchini & Velati, 2015; Carneiro & Travassos, 2016; Marcondes & Ximenes, 2016; Shoaib et al., 2016). *Aedes aegypti* was originated from *A. aegyptiformosus*, a zoophilic tree hole mosquito from African countries while *Aedes albopictus* is a zoophilic forest mosquito, belongs mainly to Asian countries. *A. aegypti* mosquito is a most important vector in spreading of ZIKV (Kaddumukasa et al., 2014; Carneiro & Travassos, 2016). Apart from *Aedes* mosquito vector other vectors like *Culex* spp. have also been reported. Studies suggested that around ten species of genus *Aedes*, *Culex perfuscus*, *Anopheles coustani* and *Mansonia uniformis* have also been reported as a vector for ZIKV (Ayres, 2016). *Culex quinquefasciatus* was also suspected to play a role in ZIKV transmission as ZIKV RNA was detected from these mosquitoes from North Eastern Brazil and later from China. Thus there may an array of vectors involved in ZIKV transmission which has to be elucidated swiftly to prevent further transmission (van den Hurk et al., 2017). ZIKV transmission from infected pregnant woman occurs through transplacental route and thus affects the brain of the fetus (Roa, 2016; Torjesen, 2016). The mosquito *A. aegypti* and *A. albopictus* mainly transmit ZIKV in urban areas while in niche ecotypes *A. hensili* and *A. polynesiensis* are found to be the vectors. Even though the dominance of the vector *A. albopictus* is mainly in Asia but the vector has got potential to spread ZIKV infection globally because of its invasive nature and broader distribution geographically (Grard et al., 2014; Ledermann et al., 2014; Weaver et al., 2016). In the tropical and subtropical climate, the rainy season is conducive for the *Aedes* mosquitoes allowing them to breed and most of the people suffer from mosquito bite during the day (from dawn to dusk) (Ibrahim, 2016). Brain lesions in the non-human primate fetus have developed due to subcutaneous inoculation of ZIKV. Susceptibility in neonatal pigs is also on the higher side (Waldorf et al., 2016; Darbellay et al., 2017). ZIKV transmission from mother to fetus is high in rhesus macaques when the Asian lineage of the virus is inoculated subcutaneously.

Such study is also indicative of the possibilities of mother-fetus transmission in case of human. Studies suggested the transfer of ZIKV from a pregnant mother to fetus and from lactating mother to newborn as well (Jamil et al., 2016). Following inoculation through rectum or vagina in macaques (adult) the rate of infection was found high (Haddow et al., 2017; Nguyen et al., 2017). Some of the cases of asymptomatic ZIKV infections have been found to spread through transfusion of blood during acute viremia. The role of saliva to spread the viral infection is still under study (Oster et al., 2016; Petersen et al., 2016a). Reports are suggestive of ZIKV transmission through infected monkey bite also (Leung et al., 2015).

The isolation of ZIKV from semen is an indication of transmission through coitus (Musso et al., 2015). The first confirmatory case of sexually transmitted ZIKV infection is from France in 2016 in a woman where her husband acquired the infection during his recent visit to Brazil (Elgot et al., 2016). Recently, a study was conducted to know the site of ZIKV replication in the genital organs which aid in the sexual transmission of the virus. Stromal mesenchymal stem cells and epithelial cells of the human prostate were studied with 3 different ZIKV isolates, and the result showed that ZIKV infection is higher in stromal cells than epithelial cells of the prostate. Thus, findings confirmed that replication of ZIKV can occur in prostate and can spread further through semen (Spencer et al., 2017). RT-*in situ* PCR of the sperm showed that ZIKV was confined to the midpiece of the spermatozoa and hence it was speculated that receptors for ZIKV might be present in the midpiece of the sperm (Bagasra et al., 2017). Present knowledge on ZIKV shows that transmission can occur from male to a female partner, and male can shed ZIKV through semen, but there is no evidence regarding the shedding of virus from the female genital tract. Further research may pave way to find the exact mechanism of transmission and the receptors responsible for ZIKV infection (Epelboin et al., 2017).

3 Zika Fever - Clinical picture, Pathology and Pathogenesis

Infection with ZIKV were earlier reported to be asymptomatic in 50 to 80% cases, and the symptoms of illness being mild and self-limiting, a febrile disease of 3-7 days with no mortality and lesser hospitalizations (Duffy et al., 2009; CDC, 2016; Reveiz et al., 2017). The symptoms are more or less similar to dengue infection expressing fever, anxiety, joint pain, body ache, indicating no special reason to consider Zika virus as the primary cause of illness unless until any neurological or auto-immune disorder develop (Jamil et al., 2016). However, the most recent outbreaks of ZIKV revealed microcephaly in newborn babies (abnormal small heads and brains), and congenital neurological malformations and disabilities in babies, while in adults it mainly

presented Guillain-Barré syndrome (GBS); apart from these visual impairment cases have also been recorded (de Araújo et al., 2016; Brasil et al., 2016; Cauchemez et al., 2016; Cao-Lormeau et al., 2016; Dos Santos et al., 2016; Cuevas et al., 2016; Martines et al., 2016a; Mlakar et al., 2016; Schuler-Faccini et al., 2016; Shuaib et al., 2016; Rodriguez- Morales, 2016; Reveiz et al., 2017; Ventura et al., 2017). It is reported that ZIKV may not cause congenital brain abnormalities or GBS by itself and some unknown cofactors might be associated along with this virus to cause such serious complications (Reveiz et al., 2017). GBS, an immune-mediated ascending flaccid paralysis, is implicated within a month of ZIKV infection (Willison et al., 2016; Krauer et al., 2017). In patients suffering from GBS, respiratory muscles become gradually weak which led to difficulty in breathing and lead to death or lifetime impaired functions of affected muscles (Jamil et al., 2016). Recently, transient myocarditis has also been found associated with ZIKV infection, and researchers advise electrocardiogram and troponin tests if cardiac signs are suspected of ZIKV infection (Aletti et al., 2017). It is also speculated that hearing loss may also be associated with ZIKV. A study among 104 infants supposed to be infected with ZIKV in Brazil showed 9% cases affected by hearing loss. Further detailed studies are warranted to unearth the relationship between ZIKV and hearing loss (Mittal et al., 2017). The possibility of vertical transmission of ZIKV is documented in the literature. Calvet et al. (2016b) reported the presence of the ZIKV genome in the amniotic fluid along with the presence of anti-ZIKV IgM antibodies. This implies the ability of the virus to reach the fetal environment thereby suggestive of the possibility of vertical transmission. The presence of ZIKV in the brain tissues of the fetus is also suggestive of vertical transmission (Mlakar et al., 2016). But as IgM cannot cross the placenta, its presence in the fetus is an indication of vertical transmission of ZIKV to cause fetal infection.

The GBS is reported to have an incidence of 0.24 per 1000 cases of ZIKV infections (Cao-Lormeau et al., 2016; Uncini et al., 2017). A recent analysis of Zika-associated GBS from seven countries (Brazil, the Dominican Republic, Colombia, Honduras, El Salvador, Venezuela and Suriname) documented the rapid surge of GBS (2.0–9.8 times higher) as compared to the pre-Zika era (Parra et al., 2016; Dos Santos et al., 2016; Uncini et al., 2017). This remarkable upsurge in GBS cases could inundate hospital and intensive care resources with well-equipped healthcare services (Uncini et al., 2017). It is noteworthy that there is involvement of the Asian/ Pacific lineage of the virus in case of microcephaly cases in Latin America. The rate of restoring the walking capacity in patients with GBS at the post-infection stage is found to be 56% (Cao-Lormeau et al., 2016; Teruya & Versalovic, 2017). The other sequel of the disease is the visual impairment in congenital cases which is mainly due to

chorioretinal atrophy, mottling of retinal pigment, retinal vasculature and optic nerve abnormalities (Benzekri et al., 2017; Ventura et al., 2017). The congenital Zika syndrome is also associated with arthrogryposis, brain parenchymal atrophy, intracranial calcification, ventriculomegaly, hypoplasia of corpus callosum, brain stem and cerebellum (Mehrijardi et al., 2017; Sousa et al., 2017). The recent ZIKV epidemic in Latin America has also been implicated with observations of severe fetal abnormalities such as spontaneous abortion, stillbirth, microcephaly, hydranencephaly, and placental insufficiency, which might lead to limiting the intrauterine growth of fetuses (Ferguson et al., 2016; Musso & Gubler, 2016; Kumar et al., 2017). The brain development of the fetus is inhibited by ZIKV which is evident from the neural stem cell death in case of this viral infection. Studies have been conducted in mice time-to-time wherein intraperitoneal injection of the infected materials has resulted in the development of neuropathological lesions involving the brain. There is very less fatality as far as the acute infection is concerned, but certainly, it has been reported in Colombian children suffering from sickle cell disease. There has been no any report of haemorrhagic symptoms in patients infected with ZIKV (Koenig et al., 2016; Tian et al., 2016).

There are still ongoing researches for understanding the mechanism of development of microcephaly along with other neurological disorders in case of ZIKV infection (Araujo et al., 2016; Faizan et al., 2016). There may be involvement of the neural progenitor cells, and most importantly direct suppressive effects of the NS4A and NS4B proteins of the virus on the process of neurogenesis is evident. Cellular death is the outcome of stem cell infection of brain thereby reducing the genesis of neurons further ultimately resulting in retarded brain growth (Li et al., 2016; Nayak et al., 2016). It has been found that the subcutaneous inoculation of ZIKV in guinea pig can result in viral invasion and replication in the brain. It has also been shown previously that in mice viz., A129 and AG129 (that have a defect in interferon responses) the concentration of the virus in the brain, as well as spinal cord, is high. In primates (non-human) the viral RNA has been demonstrated after subcutaneous injection of the infected material. However, there is the scope of further researches to determine and to increase our understanding regarding the exact mechanisms involved in microcephaly mediated by ZIKV (Lazear et al., 2016; Kumar et al., 2017). Ancestral analysis of the ZIKV showed that a single point mutation at 139 position of viral polyprotein from serine to asparagine (S139N) led to the increased infection of both mouse and human neural progenitor cells. This alteration also led to higher cases of microcephaly and mortality in infant mice. This study also revealed that this mutational change occurred before French Polynesia ZIKV outbreak in 2013 and it remained constant throughout the outbreak (Yuan et al., 2017).

Anomalies of the eye may develop due to tropism/ affinity of the virus towards the developing ocular cells (Li et al., 2016). It is important to note that due to interference with the mitotic function ZIKV can cause microcephaly (Bullerdiek et al., 2016). Immune-mediated damage of the fetal brain cells may occur if the virus crosses the placental barrier (Wang et al., 2017a).

The neural progenitor cells can be infected by ZIKV thereby producing viremia in the infected mother. This further leads to transfer of the virus maternally (from blood to the fetus) resulting in teratogenic effect (viz., neurological lesions). There is a decrease in posterior white matter along with white matter gliosis (bilateral) in the fetal brain infected with ZIKV in non-human primates. Apoptotic and mitotic figures may appear (Tang et al., 2016; Waldorf et al., 2016). Atrophy of the brain of the fetus along with coarse calcification in the white matter of frontal lobes and reduction of circumference of the brain s revealed by ultrasonography analysis (Melo et al., 2016). Recently, it was found that ZIKV also leads to testicular atrophy upon infection in mouse thereby suggesting serious complications of non-vector transmission of this virus along with reproductive deficiency in males (Uraki et al., 2017). Prolonged viremia is a feature in pregnant women due to replication of the virus in fetus and placenta (Suy et al., 2016). Thrombocytopenia and hemorrhagic signs have been most recently reported (Boyer Chammard et al., 2017).

The ZIKV enters the host cell by binding to virus-specific (AXL, DC-SIGN, Tyro3, and members of the TIM and TAM families of phosphatidylserine receptors) or general (Sulfated polysaccharides) receptors, and after endocytosis via clathrin-coated pits ZIKV replicates in the cell cytoplasm (Hamel et al., 2015; Nowakowski et al., 2016). After entry, Flavivirus (Dengue virus) has been reported to activate RIG-I, MDA-5, and TLR3 genes which recognize various pathogen-associated molecular patterns (PAMPs), that plays a role in innate antiviral immunity (Streblow et al., 2015; Surasombatpattana et al., 2011). The virus derived PAMPs have been reported to stimulate the expression of transcription factor IRF7, which on binding to interferon-stimulated response element and lead to the expression of IFN- α and IFN- β and several other antiviral genes like OAS2, ISG15, and MX1 (Honda et al., 2005). ZIKV induces autophagy of the infected cell which serves a dual purpose of both activating viral replication as well as an anti-viral effect (Olagnier et al., 2016). Various pro-inflammatory cytokines (IFN- γ , IL-18, IL-6, TNF- α) and chemokines (CCL2, CCL5, CCL7, CXCL1, CXCL10) induced after viral infection are responsible for systemic inflammation caused by ZIKV. High levels of cytokines such as IP-10, IL-6, IL-8, VEGF, MCP-1 and G-CSF demonstrated in the amniotic fluid of ZIKV infected pregnant women can be responsible for brain malformation of the fetus (Ornelas et al.,

2017). Activation of the cytokines and chemokines can lead to damage of the tissues. ZIKV can also activate apoptosis and glial cells (Wang et al., 2017b). A non-apoptotic form of cell death can also be induced by ZIKV which is caspase-independent and associated with the appearance of large cytoplasmic vacuoles derived from the endoplasmic reticulum (Monel et al., 2017). Dengue virus antibodies in humans are highly cross-reactive to ZIKV (Priyamvada et al., 2016). Due to the cross-reactivity of anti-flaviviral antibodies, ZIKV infection is facilitated by antibody-dependent enhancement (ADE) phenomenon (Dejnirattisai et al., 2016). Memory T cells elicited against Dengue virus can identify later ZIKV infection and prior Dengue infection influence the speed, quality, and magnitude of T cell response against ZIKV (Grifoni et al., 2017). An overview on Zika virus entry, interferon induction, and autophagy during viral infection is depicted in Figure 1.

NS1 protein of ZIKV plays an important role in escaping from immune response through complement antagonism. The secreted hexamer molecule (sNS1) present in extracellular environment interacts with the complement system and leads to progeny virus survival (Conde et al., 2016). ZIKV NS4A and NS4B protein inhibits the activation of Akt-mTOR signaling pathway (Asif et al., 2017), which is an important step in regulation of development, proliferation, and inhibition of autophagy in neuronal progenitor cells (Franke, 2008). Also, NS5 protein of ZIKV further inhibit interferon pathway through degrading STAT2 (Laurent-Rolle et al., 2014) in a UBR4 independent method (Morrison et al., 2013).

4 Advances in Diagnosis, Monitoring and Surveillance

Since there is no pathognomonic clinical sign observed in ZIKV infection, the diagnosis of ZIKV can be made by isolation and identification of the virus, serological diagnosis by ELISA, genomic detection by RT-PCR and employing other advanced diagnostics (Singh et al., 2016; Singh et al., 2018a). Clinical samples for diagnosis include urine, serum, saliva, amniotic fluid, placenta and cerebrospinal fluid (Paz-Bailey et al., 2017). Histopathology and immunohistochemistry of placenta and umbilical cord can also be carried out to detect the presence of ZIKV (Landry & George, 2017). Isolation of ZIKV can be attempted from mosquitoes in newborn Swiss albino mice following various routes of inoculation namely intracerebral, subcutaneous and intraperitoneal (Marchette et al., 1969; Way et al., 1976). Cell culture can also be employed for isolation of virus using various cell line like rhesus monkey kidney cells (LLC- 192 MK2), Vero cells, and mosquito origin cells like C6/36 (*A. albopictus* origin), MOS61 or AP-61 cells (*A. pseudoscutellaris* origin) (Barzon et al., 2016; Waggoner & Pinsky, 2016). Tests like serum neutralization tests, complement fixation test, and

Figure 1 Zika virus (ZIKV) entry, induction of interferons and autophagy: The paradigm during ZIKV infection

- (1) a. AXL, b. DC-SIGN, c. Tyro3, d. Phosphatidylserine receptors (TIM / TAM families) or e. Sulfated polysaccharide receptors mediate ZIKV entry,
- (2) through clathrin-mediated endocytosis,
- (3) ZIKV is released and replicated inside the cytoplasm,
- (4) Viral RNA is recognized by TLR3,
- (5) Receptor complex activates phosphorylation of IRF3 and IRF7,
- (6) Phosphorylated IRF3 and IRF7 moves into the nucleus and binds to antiviral gene elements to express OAS2, ISG15 and MX1,
- (7) TLR3-ZIKV complex is degraded by
- (8) Formation of autophagosome and
- (9) Fusion of autophagosome to lysosome, and
- (10) Autophagy enhances ZIKV replication.

Haemagglutination inhibition tests are also used for ZIKV diagnosis (Fagbami, 1979; Monath et al., 1980). It is helpful to collect paired serum samples during the infection to know the status of infection which can be achieved by the use of IgG and IgM level through ELISA (Pyke et al., 2014). Detection of ZIKV IgG in the mother during pregnancy can help to find the relationship between ZIKV and congenital abnormalities associated with it (Sumita et al., 2016). Since, IgM does not cross placenta its detection in neonates serum is an important marker for neonatal infection while CSF act as a good indicator of neurologic infection (Cordeiro et al., 2016). Cross-reaction with other flavivirus family members is the major limitation with ELISA,

hence plaque reduction neutralization test (PRNT) could be employed for detecting ZIKV to overcome this disadvantage (Granger et al., 2017). Other developments using recombinant non-structural protein 1 (NS1) of ZIKV based ELISA showed a lesser cross-reaction with dengue virus (Steinhagen et al., 2016). Lateral flow assay based on IgG/IgM antibodies of ZIKV has been marketed by Chembio Diagnostic Systems (Acharya et al., 2016). Multiplex microsphere immunoassay (MIA) is highly useful in diagnosis ZIKV infection by using a small volume of specimen (Wong et al., 2017). For detecting and quantifying neutralizing antibodies (virus-specific) plaque reduction neutralization test (PRNT) which is having higher specificity than

ELISA is performed. The false positivity in these serological test can be eliminated by performing this assay along with ELISA (Charrel et al., 2016; Rabe et al., 2016). Several laboratory parameters viz., blood cell count; lactate dehydrogenase in the serum; rise in the concentration of markers (protein) are indicative of ZIKV infection. Assays based on PCR have been approved by the United States Food and Administration (USDA) (Plourde & Bloch, 2016).

RT-PCR has been used to detect ZIKV genome from saliva, blood, amniotic fluid and amniotic fluid (Faye et al., 2008; Hills et al., 2016; Rather et al., 2017). A recent report states that urine is a better choice for detection of ZIKV by RT-PCR (Bingham et al., 2016). Urine sample offers the ease of sample collection hence identification of ZIKV can be carried out easily with RT-PCR (St George et al., 2017). Altona Diagnostics markets RealStar Zika RT-PCR kit has been reported sensitive and specific in ZIKV detection (L'Huillier et al., 2017). SYBR based real-time RT-PCR has been developed that can detect up to 1 PFU/mL (Xu et al., 2016a). Real-time RT-PCR assay targeting 5'-untranslated conserved region (5'-UTR) was developed that can detect 5-10 ZIKV RNA copies/reaction, and this assay was very specific for ZIKV detection (Chan et al., 2017a). DNA sequencing NS5, NS3, and envelope gene can help to identify the strains of ZIKV (Fonseca et al., 2014; Grard et al., 2014; Tognarelli et al., 2015). Aptima assay (automated Panther system) for ZIKV detection is based on transcription-mediated amplification (TMA) of highly conserved sequences in NS2 and NS4/5 regions of ZIKV RNA in urine and serum samples. This test is rapid, and yields result in 3.5 hours performed in a single tube (Ren et al., 2017). Recently, multiplex microsphere immunoassay has been developed for ZIKV diagnosis. This test combinedly detects structural envelope proteins of flaviviruses and differentially non-structural proteins (NS1, NS5) thus making it more specific as well (Wong et al., 2017). The diagnosis of ZIKV is also essential to establish its treatment. Recently, a novel real-time multiplex PCR was developed to detect ZIKV and Chikungunya virus. The sensitivity of the developed assay was 0.5 and 1 PFU for Chikungunya virus and ZIKV, respectively (Liu et al., 2017).

One-week post infection detection of IgM antibodies (virus-specific) along with neutralizing antibodies is possible. The virus can be detected by employing another rapid test like RNA-biosensors and RT-loop-mediated isothermal amplification (RT-LAMP) too (Tappe et al., 2014; Gourinat et al., 2015). The RT-LAMP assay has been reported to be highly specific and sensitive as compared to RT-PCR and real-time PCR (Wang et al., 2016a). Recently, another RT-LAMP was developed to detect ZIKV RNA from urine, and serum samples and the sensitivity was 10 times higher than Real-time RT-PCR, and it could detect 1.2 RNA copies/ μ l of the sample (Calvert et al., 2017). At later stages of

viral infection, the real-time RT-PCR (rRT-PCR) technique has been found useful diagnostic tool for detecting viral load in urine as well as serum (Gourinat et al., 2015). RT-LAMP clubbed with lateral flow assay showed detection limit of even single copy number of ZIKV (Lee et al., 2016). Other recent diagnostic techniques like RT-isothermal recombinase polymerase amplification assay (RT-RPA) based on NS2A region of ZIKV was found to be specific and sensitive (Abd El Wahed et al., 2017). Advances in the diagnostics have led to the development of a RT-LAMP assay employing smartphone which is provided with chromaticity algorithm to scan the fluorescent light (Priye et al., 2017). Other techniques like nucleic acid sequence based amplification (NASBA) and RT-strand invasion based amplification (RT-SIBA) were developed for the early diagnosis of ZIKV (Pardee et al., 2016; Eboigbodin et al., 2016). Since, the adverse effects of ZIKV infection are devastating thus it is essential to develop a specific antibody-based nano-enabled electrochemical immunosensing system for rapid diagnosis and immediate care of patients (Kaushik et al., 2017).

Both molecular, as well as serological tests, must be performed in the case of congenital infection. To detect viral antigen immunohistochemistry is recommended. Analysis of the cerebrospinal fluid; placenta or umbilical cord is mandatory to detect a congenital form of ZIKV infection (Martines et al., 2016b; Staples et al., 2016).

The recent advent of the nerve electrophysiology has been attributed to play a critical role in ZIKV associated GBS diagnosis by verifying the occurrence of neuropathy. As pathogenesis of GBS linked with ZIKV has not been explored thoroughly, therefore the interpretation of the results of electrophysiology could establish with regards to what are the components of the peripheral nerve, myelin/axon which are affected primarily (Uncini et al., 2017).

The detection of viral RNA by employing molecular methods is complicated by factors viz., lower load of virus; complexity of the decision making procedure on correct selection of specimen; and specimen collection timing. Moreover, during primary infection, patients mostly remain asymptomatic thereby making the calculation of timing of collection of specimen difficult. But it must be noted that laboratory testing should still be given priority especially in pregnant ladies (George & Pinsky, 2018).

Animal models always remain critical to understand and to develop counter measures for the epidemic of various animal and human diseases. The guinea pig model act like an animal of choice for diagnosis of ZIKV since it shows similar kind of clinical features and viral kinetics as observed in ZIKV-infected patients, and therefore it may serve to study ZIKV pathogenesis,

evaluation of vaccines and therapeutics (Kumar et al., 2017). Researchers have documented the mouse model also to study the pathogenesis of ZIKA virus infection (Lazear, 2017).

Surveillance of ZIKV is essential to prevent its transmission further. Geographical information system (GIS) and other surveillance measures can be employed to know the exact status of the disease and its vector density (Dhama et al., 2013b). ZIKA Tracker (zikatracker.net), a mobile application has been developed to report the status of ZIKV aiding in early treatment and control (Kelvin et al., 2016). GeoSentinel Surveillance Network data platform was used during the last outbreak of ZIKV in America and travelers from Canada were screened for acute ZIKV infection (Boggild et al., 2017). During the recent Rio Olympics and Paralympic games athletes, travelers were screened for ZIKV by urine and blood samples using real-time RT-PCR (Shadgan et al., 2016). Advanced diagnostic techniques like biosensors, nanodiagnostics, microarray, LAMP and lateral flow assay should be employed on a regular basis to know the exact status of the disease to aid in prevention and control of ZIKV (Dhama et al., 2014a; Lambe et al., 2016).

5 Vaccines

A live attenuated vaccine possessing deletion at the 3' untranslated region (ZIKV-3'UTR-LAV) was evaluated for its efficacy in male and female mice. Results showed that challenge with ZIKV after a single dose of the vaccine to male mice protected testes damage while in female mice there was a lower level of ZIKV RNA in the fetus and also in the placenta. Hence, further investigation is required using this vaccine candidate to reach the market (Shan et al., 2017). Plasmid DNA immunization with pre-membrane (prM) and envelope (E) protein has been observed to be protective in mice after ZIKV challenge, mainly owing to the induction of antibodies against E protein (Larocca et al., 2016; Dowd et al., 2016a). It has been proven by a study in mice that when a DNA vaccine that encodes the prM and the E proteins (full length) is injected intramuscularly, a stronger humoral response is generated compared to a vaccine not encoding the protein prM. Invoice Pharmaceuticals has manufactured another DNA vaccine that provides immunity in rabbit (Dyer, 2016b; Larocca et al., 2016). Inactivated and DNA vaccine for ZIKV has also been verified in rhesus macaques model and the success obtained has upraised the hope for developing suitable ZIKV vaccine for humans (Abbink et al., 2016). DNA vaccines including of GLS5700, VRC5283, and VRC5288, have been studied to provide protection against ZIKV in monkeys (Dyer, 2016a; Hampton, 2016). Phase I study of GLS5700 DNA vaccine among 40 participants divided into 2 groups showed that there were no severe adverse side effects to the vaccine administered by electroporation. The study also reported the rise in anti ZIKV antibodies thus further clinical

studies are needed so that this vaccine can reach the market soon to fight against the important disease (Tebas et al., 2017). Designing of an adenovirus serotype 5-vectored vaccine (Ad5.ZIKV-Efl) has also been reported (Kennedy, 2016; Kim et al., 2016). Computer-aided synthetic peptide vaccine has been designed by targeting ZIKV E, NS3 and NS5 proteins (Mirza et al., 2016). Lipid nanoparticle-encapsulated nucleoside modified mRNA (mRNA-LNP) encoding ZIKV prM and E glycoproteins was found to induce protection from ZIKV challenge in mice (Richner et al., 2017), and a stronger immune response in non-human primates, which raised hope for use as a putative vaccine candidate (Pardi et al., 2017). The ZIKV has got structural similarity with Dengue virus (DENV). Partial protection can be provided to mice pups against a lethal challenge of the virus by use of vaccine produced by fusion of recombinant E (envelop) gene of ZIKV with T4 fibrin foldon trimerization domain (Efl). Delivery of such vaccine can be done by microneedle array (MNA) which uses carboxymethyl cellulose (Kim et al., 2016; Kostyuchenko et al., 2016).

The ZIKV vaccine can be effectively designed for all the circulating viral strains due to lesser variations reported among the strains (Awasthi, 2016). For Asian-lineage ZIKV, the immune response induced in Indian-origin rhesus macaques against the infecting strain was found to protect from re-infection with homologous viral strain revealing broader immunity (Dudley et al., 2016). Since, only a single ZIKV serotype exists, thus vaccination employing single lineage could stimulate immunity against all the virus lineages (Dowd et al., 2016b). ZIKV primary infection has been reported to be protective against challenge with the heterologous virus by activating T cells, NK cells, B cells and neutralizing antibodies (Osuna et al., 2016). Glycosylation site is essential for effective ZIKV replication in primates; continuous passages of ZIKV in mice brain or cell culture could induct loss of glycosylation site, an important aspect to be considered for developing an effective vaccine against this virus (Aliota et al., 2016a; Dai et al., 2016). The African Strain of ZIKV viz., MR 766 has been used for developing an inactivated vaccine; 100 percent efficacy was observed in AG 129 mice (lacking type I, II interferons) with double vaccine doses after a viral challenge of MR 766 (homotypic) and FSS 13025 (heterotypic) strains (Sumathy et al., 2017).

Analysis of pdmH1N1 influenza virus hemagglutinin subunit 1 (HA1) and ZIKV=E protein indicated that H1 protein antibodies could neutralize ZIKV. Therefore seasonal influenza vaccine constituted with pdmH1N1 has been suggested to prevent the spread of ZIKV (Veljkovic & Paessler, 2016). The field of vaccinomics by including individual host genetic differences could pave the novel way to develop a suitable vaccine against ZIKV, as has been exploited by other viruses (Poland et al., 2011;

Poland et al., 2013). By employing immunoinformatics, linear and conformational B-cell epitopes, and cytotoxic T-lymphocyte (CTL) epitopes could be predicted. Analyzing the immunogenic CTL epitopes with regards to MHC antigen presentation and confirming stability can be done by employing the tool of molecular dynamics. Using 15 conformational CTL epitopes for docking three MHC I proteins and generating virtual state for their interactions, could help in predicting the preliminary set of peptide / antigenic epitopes for generation of peptide-based ZIKV vaccine (Mirza et al., 2016). QTLTPVGRL (MHC class I) and IRCIGVSNRDFV (MHC class II) peptides were reported to be highly conserved antigenic T cell epitopes of Zika virus (Ashfaq & Ahmed, 2016).

Subunit vaccines are less time consuming to prepare and at the same time safe, but multiple dosing is required (Shan et al., 2016). A subunit vaccine viz., ZIKV E (zE) has been generated, and its production has been made possible by expressing transiently in plant *Nicotiana benthamiana*. The potency of this new vaccine (plant-based) is either similar or even more than the vaccine platform currently available. The safety level of the plant produced ZIKV E (PzE) is high as the risk of genome getting incorporated, or oncogenesis of nucleic acid-based vaccine (more precisely DNA vaccines) is eliminated. The production cost is also less for such plant-based ZIKV vaccine which encourages its use especially in developing nations where outbreaks of ZIKV infection are most frequent (Tuse et al., 2014; Nandi et al., 2016; Yang et al., 2017).

ZIKV is closely related to other flaviviruses, and the phenomenon of antibody-dependent enhancement (ADE) has been attributed to increasing pathogenicity of ZIKV in the presence of highly cross-reactive anti-flavivirus antibodies, which pose multifaceted risk including hindering vaccine development/efficacy (Martins et al., 2016; Barouch et al., 2017). Dengue virus antibodies have been found to promote ZIKV infection *in vitro*, indicating the role of ADE in viral pathogenesis (Dejnirattisai et al., 2016; Paul et al., 2016).

The genome comparison of ZIKV Asian lineage with other lineages revealed that NS1 of the strain is adapted its codon usage similar to human housekeeping genes (Freire et al., 2015). Poor codon optimization leads to the attenuation of the virus and has vaccinal potential. Knowledge of genetic elements and codon usage may be useful in getting a vaccine strain with optimized immunogenicity and improved safety.

The transmission blocking vaccines (TBVs) could abruptly stop infection (new) in insects that are transmission competent. This is actually a tool that targets the capacity of transmission in the vector and the pathogen can not complete its life cycle within the

vector. Potential TBVs can be designed against ZIKV by using proteins of the mosquitoes that are required for infection of the vector (mosquito) by the virus. For reduction of population of vector mosquitoes, implementation of TBVs should be done along with other methods of transmission control viz., insecticides as well as bed nets (Dickson et al., 2014; Londono-Renteria et al., 2016; Anglero-Rodriguez et al., 2017). Of the note, the antigen used in TBVs are intended for vector and does not originate from human source; thereby the antibody titre in vaccinated person is maintained (Coutinho-Abreu & Ramalho-Ortigao, 2010; Neelakanta & Sultana, 2015).

The recent scientific advancements made in designing efficient vaccines such as DNA vaccines, plant-based oral vaccines, vectored vaccines, and exploring the novel fields of immunomics, vaccinomics reverse immunology, mathematic modeling, bioinformatics and computer-aided designing of vaccines are suggested to be exploited for developing effective vaccines against Zika fever (Kennedy & Poland, 2011; Koff et al., 2013; Singh et al., 2015; Kim et al., 2016; Morrison, 2016; Barouch et al., 2017; Bonin et al., 2017; Ding & Greenberg 2017; Munjal et al., 2017a; Singh et al., 2018b). The utility of toll-like receptor (TLR) agonists, novel adjuvants, and nanotechnology-based delivery would be highly helpful in boosting immune responses and providing sufficient protection to combat ZIKV. Exploring the generation of more knowledge towards knowing the immune mechanisms, viral pathogenesis, molecular and genetic studies, and discovering appropriate and novel vaccine candidates by gaining further information on ZIKV would be of immense help in formulating effective disease prevention and control strategies (Pierson & Graham, 2016; Kim et al., 2016; Morrison, 2016; Ding & Greenberg 2017). Nevertheless, the ZIKV immunity must be thoroughly understood, and various vaccine candidates must be identified properly for complete eradication of this viral disease (Barzon et al., 2016; Kennedy, 2016; Munjal et al., 2017b). An illustration on ZIKV pathology, diagnosis and vaccines are presented in Figure 2.

6 Treatment: Drugs and Therapeutics

Till date, no specific anti-viral drug is available to combat ZIKV infection and to protect from its dreadful pandemic threats. Designing of effective/ specific antiviral drugs and therapeutics for safeguarding the health of humans against ZIKV is under high progress (Munjal et al., 2017b; Khandia et al., 2017; Kumar et al., 2017). Some relief to the patient can be provided by timely symptomatic treatment in accordance with the clinical signs. Supportive therapy includes sufficient rest, administration of fluids for preventing dehydration, analgesics for pain relief, antipyretics (acetaminophen or dipyrone) for reducing fever, and checking pruritic rashes by the use of anti-histamines

Figure 2 An overview of Zika Virus (ZIKV) pathology, diagnosis and vaccines

(Singh et al., 2016). However, the use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) is contra-indicated to avoid any complications such as hemorrhages as noticed in the case of other flaviviruses (DENV and Chikungunya) and also need not be used during pregnancy (Mukherjee & Era, 2016).

For the fast discovery of anti-ZIKV drugs, several advanced, multidisciplinary and interactive platforms have been initiated globally. For instance, International Business Machines (IBM) has started computer-based world community grid project, Open Zika, where researchers discuss a variety of drug molecules acting against various structures of ZIKV globally (Ekins et al., 2016). Another integrative multi-omics platform, ZikaVR (<http://bioinfo.imtech.res.in/manojk/zikavr/>), has also been framed for exploring valuable therapeutic regimens like siRNAs, miRNAs, sgRNAs (CRISPR/Cas9 targets). Out of 725 tested compounds, FDA has approved 29 compounds with anti-ZIKV activity and many broad acting anti-viral agents are also offering therapeutic solution against the ZIKV (Adcock et al., 2016; Pascoalino et al., 2016). Among the library of FDA approved drugs, Sorafenib, bortezomib, mycophenolic acid and daptomycin were capable of checking the replication of this virus in human

cervical, placental, neural stem and primary human amniotic cells (Barrows et al., 2016; Cheng et al., 2016). ZIKV associated neurodegeneration mimics the hyperactivation of the N-methyl-D-aspartate receptor (NMDAR), which leads to accumulation of Ca^{2+} and subsequent neuronal cell death. Since neurodegeneration is enhanced by N-methyl-D-aspartate (NMDAR) receptor-mediated neurotoxicity, ZIKV associated neurological complications can be tackled by using NMDAR blockers viz. memantine, dizocilpine, agmatine sulfate or ifenprodil (Costa et al., 2017). Nanchangmycin, a natural product derived from bacteria was found to inhibit the early entry step of this virus in the host cell (Rausch et al., 2017). Memantine, MK-801, agmatine, and ifenprodil are the FDA approved drugs, used in treating Alzheimer's disease and have shown to ameliorate ZIKV mediated neurodegeneration; however it doesn't affect the process of virus replication (Costa et al., 2017). Bromocriptine also has shown some promise in inhibiting ZIKV replication *in-vitro* possibly through occupying the active site pocket of ZIKV-NS2B-NS3 protease (Chan et al., 2017a; Chan et al., 2017b). Antitrypanosomal drug suramin has been reported to inhibit early steps of viral entry and binding, thereby decreasing the number of infective particles (Albulescu et al., 2017; Tan et al., 2017). Post

attachment step is inhibited by nitazoxanide, an anti-protozoan, and broad spectrum anti-viral pediatric drug (FDA approved). It depletes intracellular Ca^{2+} levels and inhibits ZIKV replication through an unknown mechanism (Cao et al., 2017). Thus, such compounds in future may be found to provide early intervention in the case of an outbreak (Rausch et al., 2017). Various chemicals / drug formulations are being found to be potent in preclinical studies wherein their clinical translation needs further validations and optimization. Chloroquine is a popular drug which was revealed to lessen the ZIKV infected neural cell counts in mouse neurospheres model by preventing the fusion of virus envelope and endosomal membrane and thus protect mice from fatality (Delvecchio et al., 2016). Another molecule Emricasan, protect neural cells monolayer and organoid cultures by reducing the ZIKV-induced caspase-3 activity, while niclosamide could hamper virus replication and therefore, protect the ZIKV infected cells (Xu et al., 2016b). Azithromycin inhibits ZIKV proliferation in brain cells, consequently can be used for preventing the symptomatic complication of GBS and microcephaly in ZIKV infection (Retallack et al., 2016). Quinacrine, Mefloquine, and GSK369796 like anti-malarial drugs exhibited anti-ZIKV actions by inducing inhibition of autophagy (Balasubramanian et al., 2016).

The USDA approved drug sofosbuvir (SOF) inhibiting the RNA dependent RNA polymerase (RdRp) of the Hepatitis C virus can give both *in vitro* as well as *in vivo* protection against ZIKV as evidenced from its protective effect on neural progenitor cells (NPCs) along with the 3D neurospheres from ZIKV induced cellular death. Moreover, SOF treatment re-established antiviral immune responses in the NPCs, and reduced residual virus burden in immune deficient mouse model (Mesci et al., 2018).

Significant overlapping of residues between antigenic sites on the ZIKV polyprotein and other flavivirus proteins has been documented in the epitope-based analysis. Functional antibody epitope sites were found to be shared by E and NS1 proteins, while T cell reactivity was conserved within NS3 and NS5 for ZIKV. This could help in selecting suitable viral regions to act most likely as potential targets of ZIKV-specific antibodies, which could pave the way for developing antibody and T cell-based therapeutics and prophylaxis (Xu et al., 2016c). Progress in elucidating the structural details of viral proteins will also help in identifying various drug targets to suppress it. NS5 (important protein for ZIKV replication) structure reveals conserved features along with its N-terminal methyltransferase and C-terminal RNA dependent RNA polymerase domains (Stephen et al., 2016; Duan et al., 2017). Sinefungin (pan methyltransferase inhibitor), an adenosine derivative, was found to have selective affinity for this protein hence can serve as a potential inhibitor of ZIKV replication (Coutard et al., 2017; Hercik et al., 2017). *In silico*

approach will certainly help in designing potent drug molecule inhibiting such conserved structures inevitable for viral survival and its pathogenicity (Byler et al., 2016; Ramharack & Soliman, 2017).

Molecular studies have reported the anti-ZIKV potentials of Berberine (quaternary ammonium salt) and tetrapeptide-Boronic acid compounds as they are capable of inhibiting ZIKV replication and propagation (Sahoo et al., 2016). Obatoclast is a Bcl-2 inhibitor compound and has been recommended for anti-ZIKV therapy as the mesylate salt of Obatoclast prevented the entry of the virus into the cell by hindering the viral fusion (Varghese et al., 2017). ZINC33683341 and ZINC49605556 are ZIKV envelope protein inhibitory molecules because they bind with viral receptors and adversely affect the virulence (Fernando et al., 2016).

Nucleoside inhibitors of ZIKV such as 2'-C-methylated nucleosides which directly destroy the viral RNA chain (Eyer et al., 2016) and 7-deaza-2'-C-methyladenosine (7DMA) inhibiting the ZIKV replication in Vero cells and mice model, delayed the establishment of disease (Zmurko et al., 2016). 7DMA, being a viral polymerase inhibitor, can restrain ZIKV replication, decrease viremia and impede morbidity and mortality in experimentally infected AG129 (IFN- α/β and IFN- γ receptor knock-out) mice model (Zmurko et al., 2016). The 2' -C-ethynyl and 2' -C-methyl analog of 5' -triphosphates inhibited RNA-dependent RNA Polymerase of ZIKV and hence inhibit the viral RNA synthesis by direct termination of the RNA chain translation (Lu et al., 2017). Various patents have already been in progress and granted for antiviral agents among which carba-nucleoside analogs used for flavivirus treatment can also be studied for treatment against ZIKV (Butler et al., 2001). *In vitro* and *in vivo* studies conducted in mice documented that Adenosine analog NITD008 also have remedial potentials against ZIKV (Deng et al., 2016a). Another nucleotide analog inhibitor Sofosbuvir (Sovaldi) showed the ZIKV inhibitory activities in human tumor cell lines, human fetal-derived neuronal stem cells, men and non-pregnant women with efficient anti-ZIKA properties but cannot be used in pregnant women (Reznik & Ashby, 2016; Bullard-Feibelman et al., 2017). This particular drug inhibits the RNA polymerase of ZIKV directly apart from inducing an accelerated A-to-G mutation in the genome of the virus (Sacramento et al., 2017).

Studies have been made in identifying immune related compounds for combating ZIKV infection. Among interferons, IFN- α , IFN- β , and IFN- γ showed inhibitory effect on ZIKV replication, and when added in *in-vitro* cell culture system used for ZIKV cultivation, IFNs inhibited the ZIKV replication and growth (Contreras & Arumugaswami, 2016). Anti-TLR molecules can be

helpful in preventing ZIKV disease outcome by preventing the activation of TLR-3 (Hennessy et al., 2010; Dang et al., 2016). Similarly, Bithionol, caspases inhibitory drug and QL-XII-47's, covalent inhibitors can hamper the Zika viral protein expression to impede the infection (de Wispelaere et al., 2016).

The membrane-associated interferon-inducible transmembrane proteins (IFITMs) are able to inhibit the replication of a wide range of pathogenic viruses including ZIKV. IFITM3 alters the plasma membrane properties and stops fusion pore formation, which is an early stage of virus infection and in result intracellular amount of ZIKV RNA is greatly reduced (Perreira et al., 2013; Savidis et al., 2016). Polyamines are small, positively charged molecules, which are required for life cycle of several RNA viruses. Interferon mediated induction of spermidine/spermine N1-acetyltransferase (SAT1) enzyme, results in conversion of spermidine and spermine into putrescine which leads to restricted ZIKV replication (Pegg, 2008). Cholesterol-25-hydroxylase (CH25H), has been found to be induced upon ZIKV infection and its enzymatic product 25-hydroxycholesterol (25HC), has been revealed to mediate the protection. For instance, synthetically produced and introduced 25HC blocks ZIKV entry in mice and rhesus macaques, provided protection, prevented microcephaly and reduced viremia (Li et al., 2017). Host innate immunity against ZIKV may be improved using M8, a 99-nucleotide long uridine-rich hairpin, which elicits strong interferon response. It is an agonist of the retinoic acid-inducible gene I and inhibits influenza virus and DENV replication *in vitro* (Chiang et al., 2015) and likely to act against ZIKV too. Another gene RyDEN, is upregulated when interferon treatment is given and in the result, virus yield is reduced (Suzuki et al., 2016). RyDEN forms complex with cellular mRNA-binding proteins and hampers the translation of DENV proteins. Improvement of innate immunity may be used as a universal antiviral system and adapted in case of ZIKV infection also.

Neutralizing antibodies are also effective in controlling ZIKV infection such as, C10, 2A10G6, targeting ZIKV envelope (E) proteins is protective against ZIKV infection *in vivo* (Dai et al., 2016; Zhang et al., 2016), ZIKV-117 mAb effectively diminishes the ZIKV infection and maternal to fetal viral transfer by neutralizing the several ZIKV lineages at large scale (Sapparapu et al., 2016). Z23 and Z3L1, two MAbs obtained from ZIKV infected patient, were protective in mice which were earlier exposed to ZIKV (Wang et al., 2016b). Convalescent serum possesses ZIKV neutralizing activity due to the presence of high amount of neutralizing serum/antibodies. Studies documented that neutralizing antibodies are capable of crossing the placental and blood-brain barrier of the fetus and cause a reduction in ZIKV infected brain cells and prevent microcephaly in fetal mice when administered intraperitoneally to pregnant mice and hence safety

and efficacy need to be ascertained in pregnant women (Wang et al., 2016c). To counteract ADE in ZIKV infection, a monoclonal antibody with LALA (leucine (L) to alanine (A) substitution at the position 234 and 235 in Fc region of IgG antibody) mutation can be used as these cannot bind with FcγRs. Hence, such monoclonal antibodies can eliminate ADE of DENV *in vitro* and *in vivo* (Williams et al., 2013).

To cure the ZIKV associated ailments, already available drugs may be repurposed after high throughput screening. Khandia et al. (2017) summarized a list of FDA approved drugs, which includes antibiotic, antiemetic, antifungal, antidepressant, anticancer and anti-worm agents and possess activity against ZIKV. The ability of these drugs to pass the blood brain barrier, their chemical properties like hydrophobicity and absorption by gastrointestinal tract are some critical features, which were analysed by Devnarain et al. (2017) using SWISS ADME website. It allows the computation of physicochemical descriptors, pharmacokinetics, druggability and medicinal chemistry friendliness, analysis of compounds. The compounds proposed by Barrows et al. (2016) with potential anti-ZIKV activity were analysed with SWISS ADME; and Fingolimod, Methoxsalen, Palonosetron HCl, Pyrimethamine and Sertraline were found to have ability to permeate the blood brain barrier (Devnarain et al., 2017).

The inhibition of flaviviral genome itself may serve as a therapeutic approach. The flaviviral genome is flanked by 5' and 3' untranslated regions (UTR). The UTRs are responsible for recruitment of RNA polymerase to initiate viral RNA synthesis. Both the 5' and 3' UTR regions are folded to form a stem-loop structure, which is essential for viral replication, and elimination of these stem-loop structure results in abolished replication (Wang et al., 2017a). The 3' stem-loop is structurally conserved in flaviviruses and plays a vital role in the host and viral proteins interaction and is responsible for the regulation of viral multiplication and pathogenicity (Ng et al., 2017). Hence, it is an ideal target to interfere the ZIKV replication through advanced computational approaches so as to design effective siRNAs against 3'UTR (Hashem et al., 2017).

Researches based on herbal compounds are also being undertaken as a potent alternative for the remedial approaches. Among herbal treatments, a study with semi-synthetic compound Xiyangping from *Andrographis paniculata* was performed for treating Zika fever (Deng et al., 2016b). Andrographolide from *Andrographis* inhibited NS5 polymerase activity while bisabolol or levomenol obtained from *Matricaria recutita* and *Myoporum crassifolium* were found to block NS3 protease (Feranchuk et al., 2016). *In vitro* studies demonstrated the anti-ZIKV properties of polyphenol and (-)-epigallocatechin gallate (EGCG) present in green tea (Carneiro et al., 2016). Quercetin and Myricetin flavonoids

allosterically inhibited NS2B-NS3 protease of ZIKV (Roy et al., 2016; Lim et al., 2016; Lim et al., 2017). The computer-based study revealed the promising potential of balsacone B, kanzanol V, cinnamoylchinoxantholcimiphenol and rosmarinic acid against ZIKV (Byler et al., 2016; Byler & Setzer, 2016). Cucurmin (a component of turmeric) under *in vitro* condition was found to inhibit ZIKV binding to its cell surface receptors thereby diminishing its infectivity (Mounce et al., 2017). Plant polyphenolic compound like myricetin has been found efficient in inhibiting NS2B-NS3 protease in a fluorescence resonance energy transfer-based assay (Lim et al., 2017). CN-716, a boronic acid compound forms a complex with NS2B-NS3 protease and inhibits polyprotein processing (Lei et al., 2016). The compound is non-toxic to cultured cells and may be evaluated for its therapeutic efficacy against ZIKV.

A combined use of Chinese (traditional) along with western medicine has been reported in recent past wherein injection of xianping has been given intravenously along with administration of ibuprofen (for reduction of fever) and drops of chloramphenicol (for countering conjunctival congestion). Subsequently, the virus has been found to be absent in blood as well as urine (Abushouk et al., 2016). Sophoraflavone G, isolated from *Sophora flavescens*, which are used in Chinese medicine were studied for their antiviral activity against flaviviruses. Results revealed that there was inhibition of viral RNA polymerase thus can be used for the treatment of ZIKV infection (Sze et al., 2017).

Few of the upcoming anti-viral therapeutic options may be explored for their possibilities to treat Zika fever and lessen the serious ill effects of ZIKV. These comprise of cytokines, RNA polymerase inhibitors, microRNA, si-RNA, avian egg yolk antibodies (IgY), TLRs, probiotics, herbal remedies, immunomodulators, and nanotechnology based therapeutics / medicines (Blecher et al., 2011; Kawadkar et al., 2011; Dhama et al., 2013c; Dhama et al., 2014b; Dhama et al., 2016; Dhama et al., 2018; Malik et al., 2013; Junquera et al., 2014; Singh et al., 2016; Iqbal et al., 2017; Prasad et al., 2018; Tiwari et al., 2018).

7 Dissecting Antibody dependent enhancement (ADE) of ZIKV infection

The ADE is a phenomenon of enhancement of infection due to cross-reactive, but not cross-protective, poorly neutralizing antibodies. The ADE is present in several flaviviruses including DENV, yellow fever virus, Japanese encephalitis virus (Gould & Buckley, 1989) and West Nile virus (Diamond et al., 2008). The ADE of ZIKV in the presence of DENV antibodies is a matter of debate and particularly becomes important due to the presence of both the viruses in same geographical area. It is not well

established that presence of pre-existing DENV antibodies may enhance the risk of ZIKV disease severity or not. *In-vitro* results of DENV antibodies mediated enhancement of ZIKV infection (Dejnirattisai et al., 2016) and vice-versa have been documented (Kawiecki et al., 2016; Mahalingam et al., 2017); however, the same phenomenon is controversial in *in vivo* experiments. A study conducted on rhesus macaques indicated that in case of secondary DENV1 and DENV4 infection viremia decreased, where during secondary infection with DENV2, viremia increased by 13 folds (Halstead et al., 1973). Using subneutralization concentrations of DENV mAb 1A5, the DENV4 ADE was reported to enhance by 100 folds (Goncalvez et al., 2007). Contradictory, another experiment with two cohorts of rhesus macaques, previously exposed to DENV infection and had DENV antibodies did not exhibit severe ZIKV symptoms in comparison to naïve macaques (Pantoja et al., 2017). In fact, pre-existing antibodies to DENV1 resulted in higher ZIKV neutralization titer in a cohort study comprising 405 individuals in Brazil and Mexico (Robbiani et al., 2017). Wen et al. (2017) observed that immunity to DENV significantly reduces the ZIKV virus load in different tissues; however the protection was owing to the participation of DENV-specific CD8+ T cells. The contradictory results regarding ADE in *in vivo* results can be explained on the basis of fact that there are several mice and primate ZIKV infection models present, however the infection pattern does not recapitulate the symptoms occurring in human. The titer is at least 1000 times less in these models than human (Clark et al., 2013) and this might affect the results of ADE also. ZIKV antibody mediated ADE of DENV also has been reported in Rhesus Macaques, where ZIKV antibodies enhanced DENV2 viremia (George et al., 2017). Several other factors like the DENV serotype responsible for antibodies production prior to ZIKV infection, the time interval between DENV and ZIKV infection and parity of DENV serotypes and species under the study are some critical factors which influence the ADE phenomenon and must be taken into account.

8 Prevention and control strategies

8.1 Strategies for mosquito control

Due to the lack of any effective vaccine and drugs to fight against ZIKV, presently prevention appears the only way left to keep this virus at bay. Singh et al. (2018b) have recently reviewed the prevention and control strategies to counteract ZIKV. Prevention is mainly aimed at the control of mosquitoes that spread the virus by destroying the breeding space for mosquitoes at any place, avoiding their bites to limit spread of the virus and by developing ZIKV resistant mosquito strains as *Wolbachia* harboring mosquitoes to reduce the incidences of ZIKV by lowering the availability of vectors for virus transmission (Jamil et al., 2016).

Methods like chemical, mechanical, biological and sterile male techniques can be employed for control of *Aedes* sp. (Araujo et al., 2015; Hajra et al., 2016; Singh et al., 2016). Pyrethroids, organophosphorus and organochloride compounds can be used for chemical control of mosquitoes (van den Berg et al., 2012). Use of *Wolbachia* spp., the intracellular bacterium, reduces mosquito lifespan and releasing mosquitoes infected with *Wolbachia* has been found effective to control of mosquitoes population, thus reduces transmission of ZIKV by *Aedes aegypti* by lowering vector competence for the virus (Aliota et al., 2016b; Callaway, 2016). *Wolbachia pipientis* is a bacteria living in an endosymbiotic manner in mosquito and showed that infectious ZIKV particles are not present in the saliva of *Wolbachia*-harboring mosquitoes. Employing the mechanism of reproductive parasitism, *Wolbachia* affects the host mosquito population rapidly and render the cytoplasm incompatible for the growth of other pathogens such as *Plasmodium*, chikungunya and dengue virus, hence can be used as part of Zika control strategy (Bian et al., 2013; Bourtzis et al., 2014). Such mosquitoes diminish the transmission of Zika. Researchers have confirmed the reduction in levels of ZIKV in saliva and tissues of the abdomen, head, and thoraces of *Wolbachia* containing mosquito by using TaqMan-based qRT-PCR assay (Caragata et al., 2016; Dutra et al., 2016).

The use of predatory tadpoles of frogs to check the larval population of various species of mosquitoes has gained special attention. To study the predatory action on eggs of *Aedes aegypti* mosquitoes, the tadpoles of various species of frogs namely *Bufo*; *Hoplobatrachus*; *Ramanella*; *Polypedates*; and *Euphyctis* have been taken into consideration. It is interesting to note that in the tadpole guts, the eggs of this particular mosquito species *Ae. aegypti* have been found indicating the predatory nature for eggs of mosquitoes (Bowatte et al., 2013). The used of silver nanoparticles (synthesized) and leaves of *Artemisia vulgaris* enhanced the larvivorous characters of tadpole of *Hoplobatrachus tigerinus* (Murugan et al., 2015a). Scientists are of the opinion that mostly the tadpoles are herbivorous in nature and this finding is inconsistent with respect to earlier findings (Weterings, 2015).

Zingiber cernuum essential oil has been reported to be larvicidal and oviposition deterrent against a wide range of mosquito species (Rajeswary et al., 2017). Bacteria of the genus *Asaia* is a normal inhabitant of the gut of female mosquitoes and reproductive tract of male mosquitoes. Hence, genetic manipulation of *Asaia* can help to reduce the lifespan of mosquitoes as the bacterium is transmitted vertically and horizontally (Rossi et al., 2015). *Bacillus thuringiensis israelensis* was also found effective against larva and adult mosquitoes (Kollars, 2016). Plant extract of *Limonia acidissima* (Linn.) was found to possess ovicidal activity against *Culex quinquefasciatus* and *A. aegypti* (Reegan et al.,

2015). *Clusia fluminensis* extract (clusianone) showed inhibitory activity against *A. aegypti* (Anholeti et al., 2015).

The predatory effect of crustacean *Mesocyclops aspericornis* increased when a lower concentration of gold nanoparticles synthesized from *Cymbopogon citratus* was used (Murugan et al., 2015b). Similarly, the predatory activity of Goldfish has been reported to be increased by the use of silver nanoparticles synthesized from *Azadirachta indica* seed kernel (Chandramohan et al., 2016). *Ichnocarpus frutescens* silver nanoparticle possess larvicidal activity against different *Aedes* sp. mosquitoes (Govindarajan et al., 2016). Essential oil from *Syzygium lanceolatum* possesses larvicidal activity hence can be used as mosquito repellent (Benelli et al., 2016). *Beauveria bassiana* and *Metarhizium anisopliae* fungus can also be used for control of mosquitoes (Tiago et al., 2014). Predatory fishes like *Gambusia affinis*, *Poecilia reticulata*, etc., can be used as a larvicidal agent in water bodies (Sarwar, 2015).

The ZIKV transmission cycle can be hindered by genetic manipulation using certain bacteria viz., *Wolbachia* which will create a cascading effect upon entry into a vector population (cycling pool). The cascade effect is due to the subsequent increase in the population of mosquitoes carrying *Wolbachia* (Weaver, 2013; Nguyen et al., 2015). Genetic tailoring of mosquitoes can be done for transmitting lethal gene (in offspring) and this is governed genetically by the tetracycline gene. Thus there is requirement of tetracycline in the aquatic environment (usually absent in environmental water) by the offsprings of the mosquitoes that are tailored genetically. Ultimately the larva dies (Specter, 2012; von Seidlein et al., 2017). Sterile male technique by modulating the genes reduces the life cycle of the mosquitoes (Benelli, 2016). The use of mosquito strains that are genetically modified viz., OX513A can reduce the population of *A. aegypti* locally. This is because there will be the elimination of the female mosquitoes (wild-type) due to mating with male mosquitoes that are genetically modified (Alphey & Alphey, 2014). The disadvantage of the sterile male technique is the involvement of high cost for engineering the mosquitoes on large scale basis (Vythilingam et al., 2016). On the other hand, the advantage is that there will be enhancement of communication between the policy makers and practitioners (both from public and health sector) to use mosquitoes (modified genetically) to counteract ZIKV infection (Adalja et al., 2016). RNAi technique is employed to suppress the genes expressed in testes of the male mosquitoes (Whyard et al., 2015). Over a period of time the population of mosquitoes can be reduced by use of sterile males for induction of sterility in females (wild as well as fertile). Identification of 37 genes has been done by use of a suppression subtractive hybridization technique. Expression of such genes mainly takes

place in the testes of the mosquito (*Aedes aegypti*). For the purpose of knockdown (mediated by RNAi) for the induction of sterility in males 10 genes (subsets) are chosen. There is introduction of sterility in males by 9/10 knockdowns (in above 50 per cent males) and the fecundity is reduced in rest of the insects (Whyard et al., 2015; Singh et al., 2016). Mating with sterile males alters blood feeding capability and oviposition in female mosquitoes (Alfonso-Parra et al., 2016). Pyriproxyfen as a synthetic hormone analog also prevents *A. aegypti* mosquitoes (von Seidlein et al., 2017).

8.2 Strategies for Human Interventions

Vector transmission is not the only way by which ZIKV spreads. There are many non-vector borne routes that have to be kept in mind while designing control strategies against this virus spread. Most importantly the general public needs to be aware of the health complications of ZIKV to follow basic steps of cleanliness to ensure no breeding space for larvae of vector mosquito (Grischott et al., 2016). It is now known that ZIKV is detected in saliva and also from semen hence safe sexual contact (using contraceptives) is advised (Musso et al., 2015; Mansuy et al., 2016; D'Ortenzio et al., 2016; Atkinson et al., 2016). ZIKV has also been detected in breast milk yet there is no report of Zika transmission through breast milk (Dupont-Rouzeyrole et al., 2016). Hence, CDC advises Zika infected mothers to feed their child. Transfusion-transmitted arboviruses remained a challenge for blood transfusion. In this context, the possibility of ZIKV through blood transfusion cannot be ruled out, hence pasteurization of plasma-based products can nullify the virus (Blümel et al., 2016; Kühnel et al., 2016; Farcet & Kreil, 2017). Along with it, possible preventive measures also include nucleic acid test (NAT) and pathogen inactivation (PI) using amotosalen-ultraviolet A (UVA) illumination (Musso et al., 2014; Musso et al., 2017). These preventive measures (NAT & PI) were adopted during the French Polynesian ZIKV outbreak in 2013-2014 (Musso et al., 2014; Musso et al., 2017). In the areas where co-circulation of several arboviruses has been reported, implementation of multiple licensed blood screening tests or designing a cost-effective multiplex assay (including ZIKV, DENV, and CHIKV) for testing of multiplexes of pathogens in the single reaction should be emphasized in the near future (Musso et al., 2017). Inactivation of ZIKV by amotosalen-UVA illumination has recently been demonstrated (Aubry et al., 2016; Santa Maria et al., 2017). By the use of amotosalen combined with UVA light ZIKV was inactivated in fresh-frozen plasma by $6.57 \log_{10}$ TICD₅₀/mL for infectious particles and $10.25 \log_{10}$ copies/mL for viral RNA (Aubry et al., 2016; Musso et al., 2017).

It is advisable to avoid sexual intercourse during traveling the infected area, or in case one of the partners is virus infected. Individuals must wait for at least 28 days allowing an incubation period of 2 weeks and an additional 2 weeks for the period of viremia to get over if they are planning to conceive after returning from endemic areas. Recently, it was reported that higher percentage of ZIKV infected travelers (99%) showed symptoms within 2 weeks, of which 50% showed symptoms within a week of infection. It was also reported that mode of transmission may be sexual or through the local mosquitoes bite and may not be associated with traveling if the symptoms develop after 2 weeks (Krow-Lucal et al., 2017). A surveillance period of at least one month is recommended for such visitors (Maharajan et al., 2016; Rather et al., 2017). The microcephaly associated with ZIKV infection can be minimized in endemic nations by the provision of parental care along with contraceptives (Sharma & Lal, 2017).

The European Centre for Disease Prevention and Control (ECDC, 2016) and the Food and Drug Administration (FDA, 2016) have issued recommendations to prevent the transmission and spread of ZIKV during a blood transfusion. In areas without having an active circulation of ZIKV, the main recommendation is a postponement of blood donors at risk of ZIKV infection. In areas with active ZIKV circulation, the main recommendations are to supply blood banks with blood products collected in areas without active circulation of ZIKV, or, in the case of blood products are collected locally (especially for at-risk recipients: pregnant women and fetuses given intrauterine transfusion), postponement of blood donors at risk of ZIKV infection, exertion of PI for platelets and plasma, use of NAT and post-donation follow-up should be recommended (Musso et al., 2017). Pregnant women should avoid travel to countries endemic for Zika. Surveillance and monitoring measures at places where people crowd most need to be followed. Enhanced biosecurity principles and necessary guidelines need to be executed globally to prevent as well as check the spread and transmission of ZIKV to different parts of the world (Maharajan et al., 2016; Marano et al., 2016).

Development of preventive vaccines; an improved understanding and knowledge of the immunity to ZIKV for determining the efficacy as well as immunogenicity of the vaccine against the virus and thereby providing protection should be among the top priorities in the research arena. Side by side the molecular basis of neurological outcomes and congenital disorder in relation to infection due to ZIKV should also be studied and communicated rigorously among research groups (Makhluף & Shresta, 2018; Poland et al., 2018). An illustration summarizing mosquito prevention and control approaches for ZIKV is presented in Figure 3.

Figure 3: Mosquito prevention and control approaches for Zika virus

Conclusion and Future Directions

ZIKV has acquired a prominent place among several dreaded infectious diseases which are of great concern among the people around the globe. Its major concern is in pregnant women wherein it causes microcephaly, visual impairment and autoimmune disorders namely Guillain Barre Syndrome. The virus mainly spreads through the bite of mosquito (*Aedes* spp.), hence prevention and control of mosquitoes become of prime importance to keep transmission of Zika under check. Randomized control trials (RCT) must be carried out for preventing an epidemic. In addition to checking vector transmission, it is also necessary to prevent non-vector transmission of ZIKV as it also has some role to play in maintaining its cycle. For this purpose, public awareness about the disease epidemiology and transmission is essential. Diagnosis of ZIKV can be achieved by the isolation and identification which requires biosafety procedures, serological assays like ELISA which can show cross-reaction with other flaviviruses, nucleic acid detection methods like RT-PCR, real-time RT-PCR, RT-LAMP, etc. Samples like urine, amniotic fluid, and other body

fluids can be used for diagnosis of ZIKV. Advanced diagnostic techniques like LAMP, lateral flow assay, microarray, nanotechnology can be used for accurate and effective diagnosis of Zika. Accurate phenotyping and serial electrophysiology can provide insight into GBS pathogenesis, especially on the occasions during lack of pathological samples. Presently, several companies are on the verge of designing an effective vaccine against ZIKV. Point-of-care diagnostic kit is the need of the hour to give an early diagnosis for implementing patient care with immediate effect. Efforts must be made for discovering effective drugs to counter ZIKV infection. Several herbal drugs have also been studied to find out an effective control strategy. Further insights into the viral pathogenesis and molecular studies can aid in sketching a better vaccine and treatment options to control ZIKV disease. The research gaps such as the frequency and spectrum of outcomes in the case of ZIKV infection of the fetus must be understood fully; vis-à-vis, there is also need to understand the environmental factors that influence outbreaks. All these will ultimately help to design new products for control of vectors; therapeutics with high efficacy; and effective vaccines for protection of humans.

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Conflicts of interest

All authors declare that there exists no potential conflict of interest.

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