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Zika virus (ZIKV) disease: past, present and future

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ABSTRACT

The mosquito-borne arbovirus Zika virus (positive-stranded RNA virus, ZIKV, Flavivirus, Flaviviridae), has caused an outbreak imposing by its extent and quick spread. This became the focus of a current pandemic and public health crisis all around the world because of the incessant geographic growth of both the virus and its mosquito vectors; it is often misdiagnosed with other disease like yellow fever, west nile, dengue and chikungunya because of same clinical manifestation. After unprecedented huge scale outbreak of ZIKV in Pacific, Micronesian island of Yap in 2007, though ZIKV infections are in general sporadic cases or causing mild self-limiting illness, harsh symptoms have been explained including neurological disorders, autoimmune disorder, fetal anomalies, impaired central nervous system of the fetus, microcephaly in newborns, meningoencephalitis, myelitis and Guillain Barre´Syndrome supposed to be linked with ZIKV. The virus is transmitted mainly by a mosquito Aedes aegypti, whereas, other routes of viral broadcast includes monkey bite, coitus and body fluids such as semen, blood and saliva which needs further corroboration. The relationship between these conditions with ZIKV infection is still not established and is under assessment. Till now there is no vaccine or specific antiviral against ZIKV, therefore the public health authority focuses on preventing infection, mainly in pregnant women and virus transmitted area. WHO and other health officials are working on the expansion of new projects and mosquito control techniques to manage up with infection as there is very fewer literature present on the pathogenesis of the ZIKV to help understand the clinical disease spectrum and target treatments to decrease or stop infection. The future status of ZIKV dispersal to other parts of the world is still unknown. The present review emphasizes various features of ZIKV and its history, epidemiology, transmission, clinical manifestations, progress and advances in developing effective diagnostics, vaccines and drugs/therapeutics along with accepting suitable avoidance and control strategies to undertake this deadly emerging disease.

Keywords: Zika virus, Flavivirus, Aedes aegypti, Pregnancy, Transmission, Microcephaly, Africa

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INTRODUCTION

Among numerous public healths attentive, the global extend of arboviruses is of concern and alarm. Zika virus disease (ZVD) has lately generated important concern worldwide. The current outbreaks have become a major confront due to a change from its earlier known spectrum of clinical characteristics to the neurologic complications that are now seen[1]. ZIKV is a mosquito-borne virus of the Spondweni serocomplex, genus Flavivirus, family Flaviviridae. Due to the climate transforms like global warming, increasing population dynamics, fast globalization and travel, the human population is facing a growing emergence and outbreaks of mosquito-borne viruses such as chikungunya, dengue, Japanese encephalitis, West Nile and Zika virus[2-6]. Rapidly after the lethal outbreaks of Ebola virus in Western Africa, the most current emerging virus intimidating the worldwide human population is the ZIKV, affirmed as an emergency situation on Feb. 1, 2016 by the WHO for its rapid spread, affecting large human population in different countries with pandemic threats[7-9]. Being stayed harmless for six decades (first reported in 1947), the unexpected emergence of ZIKV with higher virulence, quick spread and inducing harsh clinical manifestations along with modest knowledge on appropriate prevention and therapeutic measures created massive threats for the human health[10]. Particularly, in Asia the occurrence of ZIKV infection is comparatively low when viral finding was done by employing RT-PCR. Viremia induced by ZIKV infection is comparatively low; thereby lessening the chance of detecting the virus in blood samples in acute cases. This has led the researchers to make the understanding of the results by taking extra care[11, 12]. In Asia and America, the strain dissimilarity could have been accountable for the fundamental dissimilarity in the epidemiology as well as the burden of ZIKV infection. The Asian ancestry of ZIKV is responsible for most of the current outbreaks in Asia as well as America[13]. There is a

obligation of using viruses generated de novo from diverse geographical as well as clinical sources to explain the pattern of ZIKV infection in Asia and America[14]. Researchers in numerous countries are trying hard to counter ZIKV and the Zika fever by carrying out detailed pathological, virological and molecular studies, rising rapid diagnostics, finding out potential prophylactics, drugs, vaccines as well as adopting suitable prevention and control measures[15-19]. Rapid diagnostics now survive for detecting ZIKV infection, many drug and vaccine candidates have also been recognized, but still any effective or approved treatment or vaccine is practically missing against this virus[10]. Suitable 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 observation and monitoring are the only possible options to keep ZIKV infection below limits[20,21]. Previous reports on ZIKV were limited to Africa and Asia, as now it has global presence. ZIKV infection impacts any nation's economy unfavorably besides being a toll on human health[22]. Here, we present a compilation on the Zika virus, covering different features of the virus and the disease it causes and explains the ongoing progress and advances being made in the field of scheming and developing diagnostics, drugs, vaccines along with avoidance and control measures to be modified to battle this viral pathogen of elevated public health alarms.

HISTORY AND EPIDEMIOLOGY

ZIKV (strain MR 766) was first remote[23] from the serum sample of a Rhesus monkey during a research on yellow fever virus in the Zika forest, Uganda 1947. In 1948, the virus was remote from a pool of Aedes Africanus (Stegomya) mosquitoes in the same forest[24-26]. Although there was no sign that ZIKV caused disease in the occupants of Uganda, the occurrence of antibodies against the virus in their serum was around 10-20%. Despite the need for care because of antibody cross reactivity with other flaviviruses, a huge number of serological studies in the half century since the detection of ZIKV have exposed a broad but restricted geographic allocation of human infection with the virus, across a comparatively narrow equatorial belt running from Africa to Asia[27] In 1966, the first non-African ZIKV strain, designated P6-740, was isolated from a pool of A. aegypti mosquitoes collected in Malaysia[28]. Human sickness caused by ZIKV infection was first reported in 1954 during an outbreak of jaundice in Nigeria, when infection was established in 3 patients by isolation of the virus or an increase in serum antibody titer, with a correlation observed between the development of ZIKV neutralizing antibodies and jaundice[29]. From that time until the early 2000s, only about a dozen cases of kind human ZIKV-associated illness were recognized in countries in Africa and Asia such as Nigeria, Uganda and Indonesia[27]. In 2007, however, ZIKV caused the first big outbreak outside of Africa and Asia on Yap Island, a part of the Federated States of Micronesia in the northwestern Pacific Ocean, with a comparatively mild disease characterized by fever, rash, arthralgia and conjunctivitis[30, 31]. During this outbreak, ~73% of the 6892 Yap residents aged ≥3 years were estimated to be infected with ZIKV and ~18% of the infected people had a clinical sickness that was most likely attributable to ZIKV infection[30]. Sequence analysis suggested that ZIKV was introduced to Yap Island from Southeast Asia. In the early to mid-2010s, a handful of intermittent cases of ZIKV infection were also reported in Southeast Asian countries, such as Cambodia, Thailand, Indonesia, Malaysia and the Philippines[27]. In 2013-2014, a major plague of ZIKV occurred in French Polynesia, a French overseas territory situated in the middle of the southern Pacific Ocean, with its ~270,000 people living on 67 islands distributed among five archipelagoes[32]. During this outbreak, ~11% of the total population was predictable to have required medical treatment for suspected ZIKV infection[33]. The magnitude of the outbreak was most probably the result of a combination of the low level of preexisting immunity to ZIKV and the high density of capable mosquito vectors in that area[34]. Although a huge majority of the clinical cases seen in this outbreak were alike to those pragmatic in the 2007 Yap outbreak, a little fraction of harsh cases were linked with neurological complications, such as Guillain-Barré syndrome, in the context of co-circulating dengue and chikungunya[33,35]. Retrospectively, the incidence of Guillain-Barré syndrome was predictable to be increased by ~20-fold in French Polynesia[35]. Although the origin of the ZIKV in French Polynesia remains unknown, it is genetically related to the strains isolated from Yap Island in 2007 and from Cambodia in 2010[32]. During or shortly after the French Polynesia outbreak, ZIKV extend further to other adjacent islands in the South Pacific Ocean, including the Cook Islands, New Caledonia and Easter Island. Also, it was imported to other distant countries such as Italy, Australia, Japan and Norway[27]. At the start of 2015, the first autochthonous broadcast of ZIKV was detected in the northeastern part of Brazil, in relationship with an outbreak of an acute exanthematous sickness[36]. Toward the end of 2015, ZIKV activity prolonged into at least 14 Brazilian states[37], with an estimated 440,000-1,300,000 suspected cases. To our shock, it was noted in Brazil that the number of newborn infants with microcephaly had increased in the ZIKV-affected areas by Sep. 2015[38] and N4000 cases of supposed microcephaly were reported by Feb. 2016, although these cases may have been misdiagnosed in some cases or over-reported[39]. In agreement with this finding, retrospective studies in French Polynesia indicated an increased number of examples of microcephaly and other fetal abnormalities after the 2013-2014 ZIKV outbreaks. In Oct. 2015, Colombia reported the local transmission of ZIKV infection outside Brazil and by March 2016, a total of 51,473 suspected ZIKV infections were recorded in that country, with 2090 laboratory-confirmed cases. Since its appearance in Brazil, ZIKV has spread at an alarming rate throughout much of Central and South America and the Caribbean and the possibility that microcephaly is linked to ZIKV has increased, prompting the WHO to speak out a public health emergency of international concern from Feb. to Nov. 2016 [40,41]. ZIKV is still causing an unprecedented ongoing plague in Latin America and threatening North America and potentially the rest of the world. As of Nov. 17, 2016, 48 countries and territories in the Americas had reported the autochthonous mosquito-borne transmission of ZIKV, with an accumulated number of 171,553 confirmed cases. Sexually transmitted cases have also been reported in Chile, Argentina, Canada, Peru and the US. In Nov. 2016, a decreasing tendency in ZIKV cases had been noted in all the ZIKV-affected countries and territories in the Americas, except for Mexico, Panama and the islands of Turks and Caicos[42]. To date, a total of 20 countries and territories in the Americas have documented 2311 confirmed cases of ZIKV-associated congenital syndrome[42, 43]. In the US states and federal districts, there were 4444 confirmed ZIKV cases reported to ArboNET as of Nov. 23, 2016; of these, 36 were sexually transmitted cases throughout the country and 182 were locally acquired

mosquito borne cases in Florida, where autochthonous transmission was first reported in July 2016 and is currently ongoing in the area of Miami Beach and in the county of Miami Dade. By Nov. 17, 2016, a total of 33 newborn infants and pregnancy losses with birth defects had been reported to the US Zika Pregnancy Registry[44].

VIROLOGY

The ZIKV belongs to the family Flaviviridae and the kind Flavivirus. Flaviviruses belong to a group of viruses labeled as arborviruses, which is an expressive term that refers to hundreds of RNA viruses which rely on arthropods such as mosquitoes or ticks for broadcast. Arboviruses cause some of the most overwhelming diseases in humans and animals universal. There are a total of 7 groups of mosquito-borne flaviviruses, according to the International Committee on Taxonomy of Viruses. The groups are categorized based on antigenic and genetic deliberations. The genus Flavivirus consists of 39 diverse mosquito-borne viruses[45]. The ZIKV (Fig.1) is composed of a positive sense, single strand RNA genome. It is an enveloped, icosahedral virus that is an associate of the Spondweni clade. The ZIKV is a positive polarity RNA virus with a genomic size of about 12 kb that is uncoated immediately after virus entry into the host cells[46]. The single open reading frame sequence of its RNA genome encodes a polyprotein which comprises the structural architecture of the virus[47]. This polyprotein contains 3 components, including a capsid (105 aa), membrane and premembrane piece (187 aa) termed C, M and P, respectively. There is also an envelope protein (E, 505 aa) and an adding 7 components that are non-structural (NS). These 7 proteins are selected NS1 (352 aa), NS2a (217 aa), ND2b (139 aa), NS3 (619 aa), NS4a (127 aa), NS4b (255 aa) and NS5 904 aa) [48]. The NS protein NS2B/NS3 includes a serine protease that along with host proteases cotranslationally and post translation cleaves the polyprotein into its components. The envelope protein is the primary flavivirus antigenic site and says attachment of the virion and penetration into the host cell. Folding of the E protein is controlled by the premembrane protein, which is cleaved by furin to form the membrane protein prior to mature virion release from the cell[49]. The purpose of the remaining NS proteins remains unknown, but may have precise essential roles in various replication stages. For example, NS5, the most highly preserved of the flavivirus NS proteins functions as a RNA-dependent RNA polymerase[50]. Phylogenetic study of the ZIKV genome indicates the survival of three lineages: West Africa, Asian/American[51,52] and Brazilian ZIKV[53]. Further analyses of Asiatic and African ZIKV strains isolated from infected mosquitoes, monkeys and humans showed important amino acid variations throughout the sequence of the viral polyprotein[54]. The same study associated the human strains isolated during the recent outbreaks with the viral strain P6-740 (from Asian mosquito, 1966) and established that all strains have a common ancestor. However, all the recent strains present a minimum of 400 amino acid mutations when compared with P6-740, which can obstruct with the viral replicative efficiency, fitness and transmissibility[54].

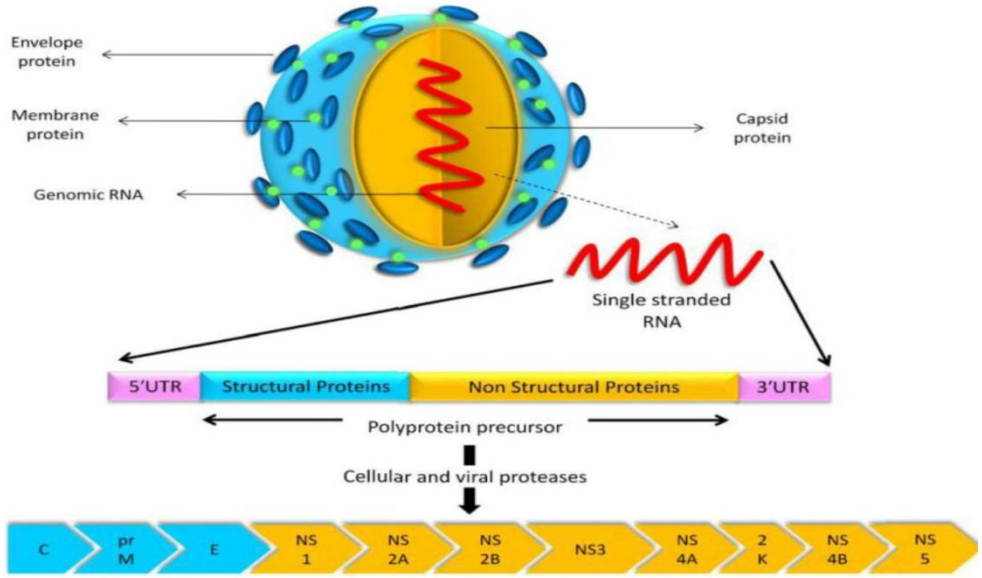

Figure 1: Structure and genome of Zika virus [81]

TRANSMISSION OF THE ZIKA VIRUS

ZIKV is transmitted to humans mostly through the bite of infected daytime active mosquitoes. The two main transmission cycles are (Fig. 2): (i) a sylvatic cycle between non-human primates and arboreal canopy-dwelling mosquitoes (Ae. africanus, Ae. bromeliae, Ae. dalzieli, Ae. furcifer, Ae. luteocaphalus, Ae. opok, Ae. taylori, Ae. unilineatus, Ae. vittatus) and (ii) an urban cycle with humans as both reservoir and intensification hosts, and anthropophilic mosquitoes as vectors (primarily, Aedes aegypti and secondarily, Aedes albopictus). The insinuation of Ae. aegypti as the main vector is supported by frequent isolation of ZIKV from field-collected mosquitoes[55-59] and experimental proof of ability to transmit ZIKV[60]. Ae. albopictus has been suggested to be involved in transmission as ZIKV has been detected in pools of mosquitoes collected in Gabon and Brazil[61,62] and transmission demonstrated in laboratory. ZIKV, as most arboviruses, has the potential to persevere in mosquito eggs. The virus can be acquired by the offspring by vertical transmission from infected mothers through (i) transovarial transmission when the virus infects germinal tissues in the ovaries and (ii) trans-egg transmission when infection occurs during fertilization[63]. VT has been demonstrated in Ae. aegypti and Ae. albopictus mosquitoes. This option has already been suggested by the detection of ZIKV from field-collected Ae. furcifer males in southeastern Senegal[55]. VT is another mechanism by which a virus can extend in a mosquito population. Males cannot get the

virus from a blood meal but can acquire virus by VT from an infected female parent. In trial studies, it has been shown that infected male Ae. aegypti can transmit the virus horizontally to non infected adult females during mating. Thus VT in Aedes mosquitoes may have a role in the preservation of ZIKV in nature. In addition to vector-borne transmission, direct human-to human transmission of ZIKV has been documented: in utero from infected mothers to fetus, sexually through secretions predominantly from male to female, blood transfusion, saliva, urine, through breast feeding[60]. The significance of these non-vector-borne ZIKV transmission routes is difficult to measure. However, these numerous modes of transmission are improbable to be as significant as mosquito-borne transmission, as suggested by their insignificant effect during seasons not permissive for mosquito activity. Beside kind symptoms, ZIKV can cause neurological disorders such as Guillain-Barre syndrome in adults[64,65] and microcephaly in newborns[66]. Zika has been then affirmed an emerging global health threat by the WHO.

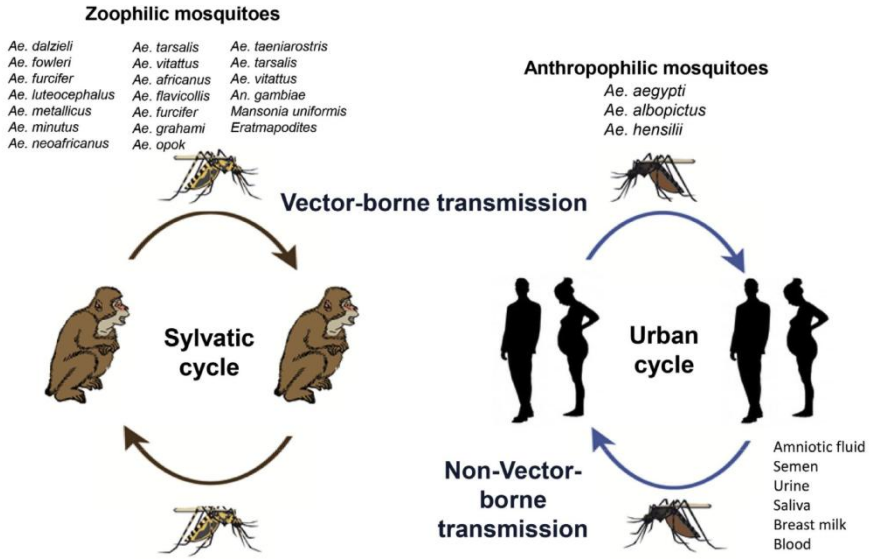

Figure 2: Transmission of Zika virus[60]

CLINICAL MANIFESTATION OF ZIKA VIRUS DISEASE

About 80% of ZIKV infections are asymptomatic[67]. Symptomatic infections are characterized by a self-limiting febrile illness which typically lasts 4-7 days and is connected with maculopapular rash, arthralgia, especially affecting the small joints of the hands and feet, conjunctivitis, back pain and mild headaches. Within 2 days, the skin rash begins to lighten spontaneously and within 3 days, fever starts to resolve and only few rash persists[68]. Other less common clinical features include nausea, diarrhoea, abdominal pain, ulcerations of mucous membranes, uveitis and palatal petechiae[68,69]. Harsh ZVD may be seen following in utero infection leading to neurological complications, notably microcephaly and Gullian-Barre syndrome. Meta-analysis showed that occurrence of ZIKV associated GBS and microcephaly (Fig. 3) among all pregnancies were 1.23% and 2.3% respectively[70,71]. Other neurological manifestation seen include spasticity, seizures, craniofacial disproportion, irritability and brainstem dysfunction, feeding difficulties and ocular abnormalities[72]. Neonates with ZVD usually have intrauterine growth restriction; other features may include a transient diffuse rash, conjunctivitis and conjunctival injection. Ocular abnormalities such as focal pigment mottling, chorioretinal macular atrophy, optic nerve abnormalities, cataract, intra-ocular calcifications, microphthalmia, conjunctival injections, optic disc cupping, lens subluxation in addition to bilateral iris coloboma, foveal reflex loss, macular hypoplasia and scarring[73]. Several foetal neuronal abnormalities have been demonstrated when ultrasound was done at 29 weeks gestation; this include brain atrophy, large cysterna magna, severe unilateral ventricular enlargement, corpus callosum and vermian dysgenesis, absence or redumentary thalamus, thin brainstem and pons calcifications involving frontal lobes white matter, caudate, lenticulostriatal vesssels and cerebellum[68]. Neuroimaging (computed tomography and magnetic reasoning imaging) characteristics commonly reported in newborns include enlarged cisterna magna, hypogenesis of corpus callosum, ventriculomegaly, delayed myelination, cerebellar and brainstem hypoplasia, calcifications in the junction between cortical and subcortical white matter and cortical malformations like polymicrogyria in the frontal lobes. Interestingly, abnormality of frontal lobe has not been reported in other congenital infections[68]. Congenital Zika syndrome refers to the range of abnormalities seen in neonates following Zika infection in pregnancy[74]. This includes visual, hearing and other neurological abnormalities (including neuroimaging findings) [75]. Complete cranial growth may be attained at 30 weeks[76]. Therefore, ZIKV infection in late pregnancy may not affect head size. The sensitivity of microcephaly in detecting probable or definite ZIKV infection is 83%. It has thus been suggested that microcephaly should not be a necessary criterion for diagnosis of CZS[74]. The Centres for Disease Control and prevention, the USA has described five features to define CZS which include: severe microcephaly with partially collapsed skull; specific pattern of brain damage including subcortical calcifications and decreased brain tissue; damage to the back of the eye, including macular scarring and focal pigmentary mottling of the retina; congenital contractures such as club foot or arthrogryposis and hypotonia which restricts foetal body movement soon after birth[77]. Regularly characterising this syndrome may be a challenge in resource constraint settings, with scarcity

of high cadre health workforce. Therefore, it is needful to develop a simple algorithm that low cadre health worker can readily identify. This is further compounded by challenge of confirming maternal Zika infection.

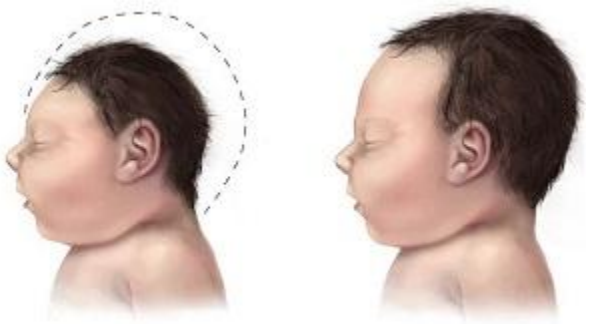

Figure 3: Congenital birth defects (Microcephaly) source: https://indianexpress.com

DIAGNOSIS

Although the diagnosis is difficult as the symptoms are gentle and not so accountable, some tests at molecular level are in present use. Diagnosis for ZIKV infection includes PCR tests to notice viral DNA as well as additional tests to detect ZIKV antibody (IgM) in serum[78,79]. IgM for ZIKV is typically detectable around 35 days following infection, but cross reactivity with closely related dengue, yellow fever, japanese encephalitis and west nile viruses are possible. These cross hasty results were more common in patients that denoted signs of previous flavi virus infection than patients with primary ZIKV infection. PCR tests should be conducted within 10 days of onset of illness. For best diagnosis practices, serum samples should be analyzed as early as possible with a second test 2 to 3 weeks after that[80]. Several methods can be used for diagnosis, such as viral nucleic acid detection, virus isolation and serological testing. Nucleic acid detection by RT-PCR targeting the nonstructural protein 5 genomic region is the primary means of diagnosis, while virus isolation is largely for research purposes. Saliva or urine samples collected during the first 3 to 5 days after symptom onset or serum collected in the first 1 to 3 days, are suitable for detection of ZIKV by these methods. It has been experiential that ZIKV can be detected for rapidly in saliva sample than in serum sample. Serological tests, including immune fluorescence assays and enzyme linked immune sorbent assays may indicate the presence of anti ZIKV IgM and IgG antibodies. Care should be taken with serological results as IgM cross reactivity with other flavi viruses has been reported in both primary infected patients and those with a probable history of prior flavivirus infection[81]. ZIKV can be detected from urine, serum and maternal milk during post partum period of new mother to identify whether the newborn baby she delivered has microcephaly or not[82]. It is also significant report about all the symptoms of present situation as well as the health issues of recent past to the medial stuffs to detect the coin fections which will further help in better diagnosis and treatment[82-84].

TREATMENT AND PREVENTION

At the instant, no preventive medicines or vaccines are available. Since zika presents asymptomatically or with mild symptoms, symptoms may be controlled with bed rest, intravenous fluids and acetaminophen[85]. The major challenge of zika is the difficulty of infection; effort should be placed on antiviral agents, vaccines and other preventive measures. About 30 FDA approved antiviral agents have been evaluated and were found to have important anti-Zika viral activity[86]. However, the antiviral effects were mainly determined using the Asian strains. It is therefore significant to determine this antiviral activity against African strains. The common preventive measures include preventing mosquito bites and sexual transmission. Measures of preventing mosquito bites include: wearing long sleeve shirts and long dresses, permethrin impregnated clothes, indoor residual spraying of insecticide, screening of doors and windows against mosquitoes and other environmental control measures meant at reducing or eliminating the breeding of mosquitoes[85]. Prevention of sexual transmission is particularly important when the sexual partner is pregnant. Sexual transmission can be prevented through abstinence or by using condom. Due to blood transfusion related transmission, it is needful to provide reasonable cost effective safe blood transfusion services in resource unnatural settings. This would include pre donation screening to rule out possible Zika infection and cost effective Zika serological test with high sensitivity. This is particularly important in pregnant women requiring blood transfusion. There are several candidate vaccines at various developmental stages, some are live attenuated, inactivated and others are genetically engineered vaccine constructs. Among these vaccines, there is one that targets both dengue and ZIKV[87]. It will be more helpful to develop multi flavivirus vaccine that can be used in resource limited settings with high and multiple flavivirus infections.

All conventional system of medicine specifically homeopathy and ayurveda, may be attempted in ZIKV case, the cause is that homeopathic preparation has already shown effective in case of Japanese encephalitis virus which falls in the same genus like ZIKV.

POTENTIAL HOMEOPATHIC MEDICINES FOR ZIKV

Homeopathic prescriptions *Eupatorium perfoliatum*, *Atropa belladonna*, *Rhus tox* may be firmly utilized as a part of ZIKV treatment. These medications come the nearest in treating the symptoms of ZIKV infection disease. Homeopathy has been very effective in treating epidemic diseases such as cholera, dengue fever, yellow fever, typhus and conjunctivitis. In an outbreak when an immense number of individuals are beaten by acute and similar sufferings from similar cause, homeopathy may be an excellent prophylactic help. Records show that during epidemics, homeopathic pharmaceuticals are of huge help in diminishing the death when contrasted with those put under conventional system of medicines. *Atropa belladonna* is a medicinal plant categorized under Solanaceae family. This plant has huge commercial importance as it is a major source of pharmaceutical bioactive compounds like alkaloids mainly scopolamine and hyoscyamine and is native to Western Asia Europe and North Africa. Although, all alkaloids in *Atropa belladonna* are dispersed in the entire plant, but the majority of the alkaloid content is found in green leaves and ripe fruit. It has long been used in human medicine for the treatment of inflammation, headache, peptic ulcer, menstrual symptoms and histaminic reaction[88,89]. In our studies Belladonna treatment productively abridged the Japanese encephalitis virus infection[90]. This may be attempted in case of ZIKV after proper consultation with the physician, since they both belong to same family. In homeopathy, ultra-diluted concentration like 3, 6, 30, and 200 of above mention drugs are prescribed for the treatment of all infectious diseases. Therefore, homeopathy may have a enormous role to play as prophylactic when disease spreads suddenly over a substantial region. Additionally, homeopathic

pharmaceutical *Eupatorium perfoliatum* may be utilized as prophylactic as a part of ZIKV, as this drug has the nearest match to the symptoms displayed in ZIKV disease.

POTENTIAL AYURVEDA MEDICINES FOR ZIKV

Ayurveda is an ancient medical science which is based on naturally occurring herbal medicine and showed some efficient preventive and healing answers for most of the sicknesses. The most significant aspect of the ayurvedic system of medicine is that, they are completely based on naturally happening substances and therefore, totally secure for human consumption without showing any side effect. It has been asserted that *Tinospora cordifolia* is one of the effective natural solutions for the counteractive action of any sort of viral disease. It is considered as a potential immunomodulator. It is thought that, it reinforces the safe framework and assembles resistance in the body to battle infections. *Tinospora Cordifolia* is likewise an effective solution for treating fevers chiefly from unknown reasons. This herb, which has been utilized as a part of ayurveda, since hundreds of years, is extremely useful in boosting up immune function and the body's capacity to fight against infections. Ayurvedic herbs helps in enhancing the phagocytic capability of the immune cells especially macrophages. The astringent properties present in the medication show against infrequent and antispasmodic properties which are again useful in forestalling infectious sicknesses like intestinal sickness, dengue and swine influenza[91]. *Tinospora cordifolia* has also shown its effectiveness in case of other diseases like dengue fever, swine influenza and urinary tract infections hence may be an efficient remedy for ZIKV infection too.

FUTURE PROSPECTIVE AND CONCLUSIONS

As the number of cases of ZIKV infection is increasing radically, some necessary steps should be taken to eradicate this deadly infection and to inhibit the entry of it in future as well. 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 necessary. 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, RTLAMP, 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. We need to proceed with a sense of urgency in this context.

Conflict of interest statement

We declare that we have no conflict of interest.

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