Review Article

Zika Virus: A Global Public Health Menace: A Comprehensive Update

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Abstract

Zika virus (ZIKV) is a RNA virus and belongs to genus *Flavivirus* and family *Flaviviridae*. The virus was first discovered from a febrile primate from the Zika forests of Uganda in 1947 and the first human case was documented in 1954. The nonspecific clinical manifestations of ZIKV pose diagnostic dilemmas and delays early and effective treatment. Dental professionals should have a thorough knowledge about the virus and should follow standard infection control measures as the virus has been demonstrated in various body secretions (including salivary secretions). The disease is managed by symptomatic and supportive care and no vaccine exist till date. Recent ZIKV outbreaks and increase association of microcephaly with congenital ZIKV and neurological complications (Guillain-Barré syndrome) has drawn global public health attention. The World Health Organization declared it a public health emergency of international concern in 2016. This review article provides a detailed overview on ZIKV; it is clinical and oral manifestations, diagnostic aids, differential diagnosis, preventive aspects, and management protocol.

Keywords: *Guillain-Barré syndrome, microcephaly, pregnancy, public health menace, zika virus*

Introduction

Zika virus (ZIKV) is a single-stranded RNA virus and belongs to the *Flavivirus* genus and *Flaviviridae* family.[1,2] Phylogenetically, ZIKV is linked to African and the Asian lineage, with the latter related to the recent Latin American epidemic.[3,4] The year of 1947 marks the isolation of ZIKV from a surveillant macaque in the course of yellow fever surveillance in Uganda's Zika forests, thus, deriving the name of the virus.[5] Soon after, the virus was isolated in the same forest in *Aedes africanus* mosquitoes.[6]

In Africa, the life cycle of ZIKV usually involves propagation between the various simian species (such as apes and monkeys) and mosquito vectors, with humans being the infrequent accidental hosts. However, in the Asian subcontinent, humans have probably become the main host.[7,8] Infrequently, ZIKV transmission may also occur through various nonmosquito modes such as perinatal,[9] congenital,[10] and sexual.[11] There have also been reported the incidence of the spread of ZIKV by blood transfusion,[12,13] animal bites,[14] and laboratory exposure.[15]

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The two major forms of ZIKV infection are-Zika fever and congenital ZIKV syndrome. Zika fever has nonspecific manifestations ranging from asymptomatic infections (80% of cases) to a self-limiting febrile sickness. The sign and symptoms mimic a "dengue-like" syndrome with low-grade fever, bilateral nonpurulent conjunctivitis, maculopapular exanthem, retro-orbital pain, headache, arthritis/arthralgia with small joint edema, myalgia, asthenia, and vertigo. Congenital Zika syndrome most frequently manifest as microcephaly.[16-20]

The laboratory diagnosis of ZIKV infection is confirmed by the demonstration of viral RNA using reverse transcriptase-polymerase chain reaction (RT-PCR) and viral detection.[5]

Until date, there exists no definitive treatment or vaccination for ZIKV. The principal preventive methods

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for ZIKV spread are as avoidance of insect bites along with abstinence and barrier protection to avoid ZIKV dissemination through sexual mode (especially during pregnancy).[21] Universal precautions are an absolute mandate, particularly necessary until the time a complete knowledge is attained regarding the possible means of ZIKV dissemination.[22]

ZIKV has emerged as a public health menace owing to its implacable geographic dissemination, along with a distressing increased incidence of congenital ZIKV infections (manifesting as microcephaly), and serious neurological complications.[23]

Various schemes and policies are being implemented by Government and Public Health Agencies to combat ZIKV infection and possible complications. The "World Health Organization (WHO) Zika App" has been launched of late by the WHO to enhance the awareness and understanding of this public health disaster.[24]

Transmission

In urban and suburban settings, ZIKV dissemination involves human – mosquito – human cycle, with *Aedes* species mosquitoes as the most important vectors.[12] *Aedes* species are primarily daytime biting mosquitoes. The viral dissemination occurs through the blood-sucking mosquitoes which have a predilection for salivary glands. The virus multiplies in the salivary glands and persists there all its life. Few other mammals, such as elephants, zebras, and rats, may also serve as the likely ZIKV pool.[25]

ZIKV has a predisposition to occur in any natural habitat of the *Aedes* mosquito vector.[5,26] The virus has been identified in various mosquito species namely - *Aedes aegypti*, *Aedes albopictus*, *Aedes furcifer*, *Aedes africanus*, *Aedes apicoargenteus*, *Aedes luteocephalus*, and *Aedes vittatus*.[27-30]

Table 1 depicts the various mosquito species and their peculiar features.[7,31-37]

Table 1: Various mosquito species associated with Zika virus

Mosquito species	Features
Aedes hensilii	Yap island Zika virus epidemic (2007)[31]
Ae. Aegypti	Brazil Zika virus epidemic (2015)[32]
Aedes africanus	Uganda Zika virus epidemic[33,34]
Aedes. aegypti and Aedes albopictus	Zika virus vector in Asian continent[7]
Ae. Albopictus	Invasive mosquito species as it can be easily carried to other geographic regions[35]
	Adaptable to both urban and sylvatic habitats[36]
	Alleged linkage for yellow fever virus in Brazil[37]

Nonmosquito Transmission

Although mosquitoes serve as the primary vector agency for ZIKV spread, various nonvector means of virus spread have also been proposed.

Sexual mode of ZIKV spread has been suggested by Foy *et al*. in 2011. The patient contracted the infection in Senegal and got his wife infected via unprotected sex on his visit to the US.[38] Sexual mode of ZIKV spread has been reinforced by the fact that the viral RNA can be detected in the semen even after 17 days of acute illness and 62 days after the symptoms sets in.[11,39] ZIKV demonstration from the semen emphasize the avoidance of unprotected sexual practices and necessitates condom usage (primarily throughout pregnancy), thus preventing ZIKV spread by sexual mode.[40]

ZIKV spread via perinatal route has attracted significant attention due to an alarming increase in microcephaly cases in congenital ZIKV-infected newborns. Isolation of ZIKV RNA from the maternal serum up to 5 days following childbirth and in the young infant up to 6 days, reinforce the perinatal mode of ZIKV spread.[10]

Transfusion with contaminated blood and blood products has also been suggested as a likely mode of ZIKV spread. Demonstration of ZIKV RNA in roughly 3% of asymptomatic blood donors during the French Polynesian outbreak, have supported this mode of disease transmission.[12]

Till date, there is no published literature reporting ZIKV spread through saliva. However, the viral RNA has been demonstrated in saliva during the acute infectious phase. 20 ZIKV RNA concentration was found to be greater in saliva than in blood[20,41] and was equal to that present in urine.[41] Salivary detection of ZIKV requires considerable attention, especially in dental clinics, where salivary contact is frequent with droplets and aerosol generation during varied dental procedures.[42]

ZIKV RNA has also been identified in breast milk, amniotic fluid, placental or fetal tissues; although, there has been no published evidence of ZIKV spread via these routes.[24]

Figure 1 depicts the possible modes of ZIKV transmission.

Epidemiology

History of ZIKV isolation and detection goes back to the year 1947, where a febrile sentinel monkey acquired this virus during the surveillance of yellow fever virus in Zika forests of Uganda.[5,43,44]

The first human case of ZIKV infection was documented in Nigeria and Tanzania during 1952–1954. Further,

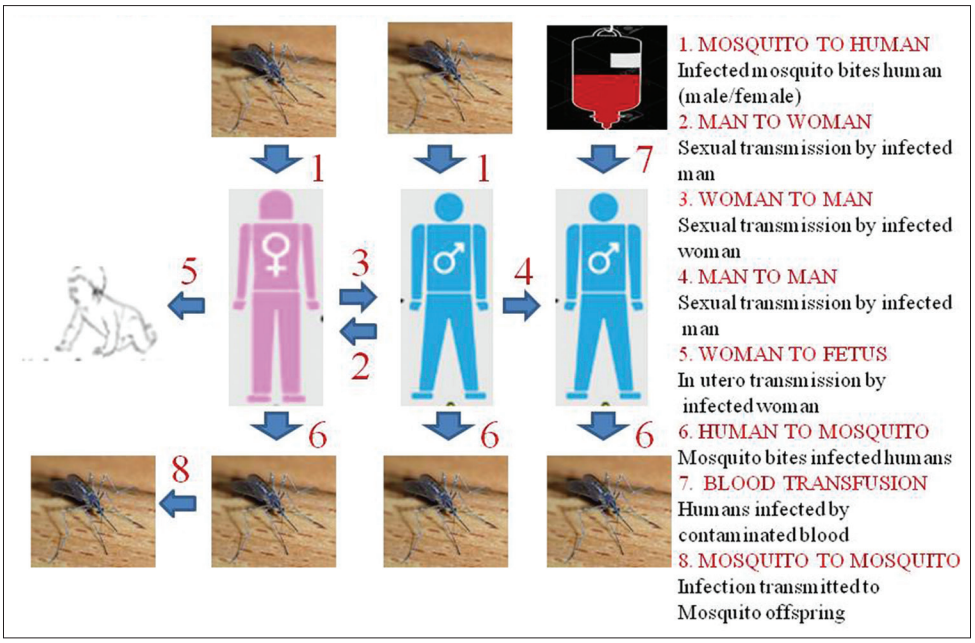

Figure 1: Possible modes of Zika virus transmission

ZIKV dissemination to the Asian subcontinent alarmed the public health officials about the impending likelihood of ZIKV epidemics.[44,45]

The year of 2007 marks the documentation of the first epidemic outburst of ZIKV from Yap State, Federated States of Micronesia. More than 49 confirmed ZIKV infected patients presented maculo-papular exanthema (rash), bilateral nonpurulent conjunctivitis and arthralgia over the 13 weeks duration of the epidemic.[31] An additional ZIKV epidemic outburst was recognized in the French Polynesian population in 2013, marking the first documentation of ZIKV and Guillain-Barré syndrome (GBS). However, majority of the affected population presented with mild manifestations.[46,47]

Soon, the ZIKV cases were noticed in Canada, Germany, Japan, Italy, Australia, the United States, and Easter Island (Chile-Pacific Ocean).[45] The virus got introduced to Brazil and Latin American sub-continent in April 2015, marking the third reported epidemic of ZIKV.[48,49]

The first incidence of microcephaly with ZIKV was documented in October 2015 in Brazil. ZIKV was affirmed a public health emergency of international concern by the WHO in February 2016 due to alleged linkage with microcephaly and varied neurologic complications.[50]

Data till February 2, 2017, revealed that vector-borne transmission of ZIKV has been documented in 70 countries.[51]

Figure 2 shows geographical representation of areas ZIKV dissemination.

Table 2 depicts summary of the historical milestones of ZIKV discovery and epidemics.[52]

Pathogenesis

Although the exact pathogenetic mechanism is not clearly elicited, the general consensus proposes that replication of ZIKV takes place in skin dendritic cells after inoculation following the mosquito bite.[26]

The infection further gets disseminated through the bloodstream to the adjacent lymph nodes and other body organs such as myocardium, central nervous system, skeletal muscles, and to the fetus. Viral replication in astroglia and neuronal cells of infected mice brain causes neuronal degeneration, cellular infiltration, and alleviation in the brain, thus explaining ZIKV neurotropism and the related neurological complications (microcephaly in congenital ZIKV infection).[17]

Viremia usually occurs within 3–4 days of the onset of symptoms. 26 Viral RNA can be demonstrated in the bloodstream from the day of disease onset and may remain present till the 11th day of illness.[53]

Figure 3 shows the pathogenesis of ZIKV.

Clinical Features and Differential Diagnosis

The clinical spectrum of ZIKV infection mimics that of dengue and Chikungunya viral infection (especially during the acute phase), thus necessitating differentiation between these three entities.[54]

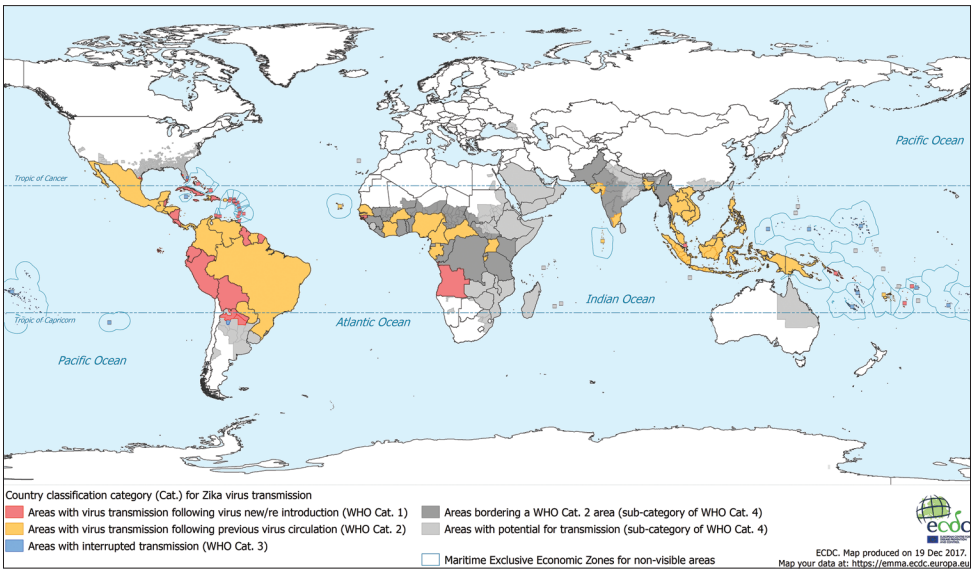

Figure 2: Geographical distribution of Zika virus

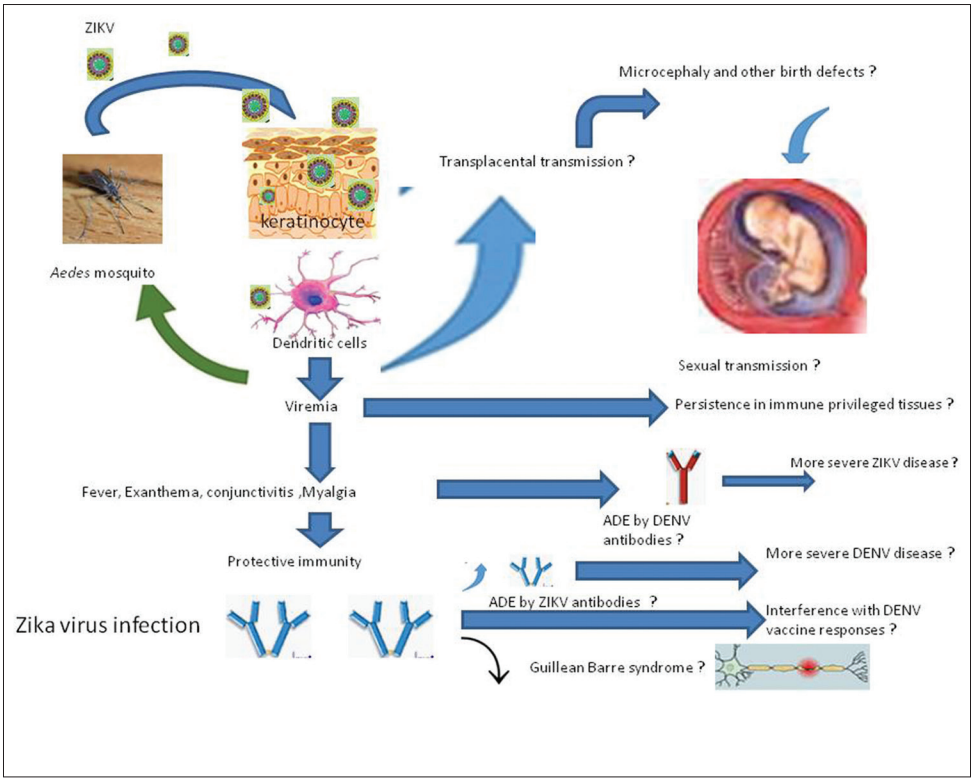

Figure 3: Pathogenesis of Zika virus

About 80% of infections are asymptomatic, thus, posing a diagnostic dilemma and a barrier to the prevention of disease transmission.[55] In general, clinical symptoms appear within 3–12 days of insect bite and resolves in 2–7 days.[31] About 20% of cases present with mild, bizarre, self-limiting manifestations, mimicking other arbovirus infections, thus delaying the accurate diagnosis and treatment protocol.[56]

The most frequently manifesting feature is a macular or maculopapular exanthema (seen in 90% of cases). The rash has a characteristic centrifugal pattern (extends from the trunk to the extremities), often pruritic and persist for a period of 4–5 days.[31,56,57] The typical rash of ZIKV is usually seen within the 1st or 2nd day after the symptoms sets in. This is in contrast to the rash in dengue and Chikungunya,

Table 2: Historical milestones of Zika virus

Year	ZIKV feature	Affected population
1947	ZIKV was first discovered in Zika forests of Uganda	
1952	ZIKV first human infection in Nigeria	
2007	First epidemic in Yap island, Micronesia	49 confirmed cases
2008	First Sexually transmitted case of Zika virus	
2013	Second epidemic in French Polynesia	>400 cases
2013	First reported case of Zika virus with Guillain-Barré syndrome	
2015	Third epidemic in South America	>1.5 million cases
October 2015	First incidence of microcephaly with ZIKV	
February 2016	WHO declared ZIKV a public health emergency of International Concern	

ZIKV=Zika virus, WHO=World Health Organization

which usually appears after 4 days of clinical symptoms.[58] Other uncommon cutaneous features are as follows: subcutaneous hematomas, ecchymosis, petechiae, aphthous ulcers, and other ulcerative oral mucosal lesions.[58]

Low-grade fever (usually lower than 38°) and fatigue may precede the cutaneous exanthema (rash) in about 65%–70% of cases. The fever usually persists for 1–4 days to a maximum of 7 days.[57,59] Arthralgia accounts for the third most frequently occurring manifestation (seen in 65% of cases). About 20%–45% of patients present with periarticular edema, especially of small joints (hands and feet, and less frequently knees and wrists) in association with Arthralgia, which may last for a week up to a month.[57]

About 55%–60% of patients may present with bilateral, nonpurulent conjunctivitis, which usually shows resolution within 1–2 weeks.[31,57]

ZIKV may also present with uncommon manifestations such as a headache, retro-orbital pain and myalgia.[57] ZIKV is associated with less intense muscle and joint pain as compared to severe intense myalgia of chikungunya infection.[31] Localized or generalized lymphadenopathy may also be seen in a few cases of ZIKV infection.[57]

Criteria defining the suspected and confirmed cases of ZIKV infection by the Brazilian health ministry are:[60]

- Suspected case: patients presenting with pruritic maculopapular exanthema, in addition to two or more of the following features:
  a. Fever
  b. Nonpurulent conjunctivitis and pruritus
  c. Arthralgia of multiple joints (polyarthralgia)
  d. Periarticular edema.
- Confirmed case: features of a suspected case along with either one of the following positive test or demonstration of a particular response for ZIKV evaluation:

a. Viral RNA identification
b. RT technique demonstrating ZIKV RNA
c. Immunoglobulin M (IgM) serological reaction (may exhibit false positive reaction if a dengue virus infection co-exists)
d. Confirming ZIKV acute cases by incorporating various clinical-epidemiological measures.

ZIKV infection is usually mild and severe forms are rarely encountered from earlier reported epidemics. This supports the infrequent rate of hospitalizations and death rates with ZIKV.[31,61]

Table 3 depicts differentiating features of Zika, dengue, and chikungunya.

The oral manifestations in ZIKV are not a frequent occurrence; although, Foy *et al*. have reported oral aphthous ulcers on the lip mucosa.[38] Aphthous ulcers were also a frequent oral feature during the 2013 French Polynesian epidemic. However, the data supporting other oral features in ZIKV infection is scarce.[62,63] Hyperemia and petechial lesions on the hard palate of ZIKV-infected patient were documented by Brasil *et al*.[64]

Lin H Chen and Derrington also described petechial palatal lesions; vesicles, or aphthous ulcerations in a ZIKV-infected patients.[65,66]

Thorough and advanced researches are necessary to demonstrate the various oral features of ZIKV. Saliva may have a significant function in the human-to-human spread of ZIKV and salivary diagnostics may serve as an important investigative tool for ZIKV infection.[67]

Table 4 depicts summary of reported orofacial features in ZIKV infection.

Congenital Zika Syndrome

ZIKV has drawn global public health attention due to its alleged linkage with the increasing incidence of microcephaly. In September 2015, increased frequency of microcephalic babies was documented in females residing in ZIKV endemic regions of Brazil, thus, raising the question of a probable association. Thereafter, a total of 2366 confirmed cases of microcephaly associated with ZIKV infection have been noted in Brazil.[68]

In cases of microcephaly, the headoccipto-frontal circumference dimensions are more than two standard deviations lower than the mean for age and sex. The proportionally smaller brain of these individuals account for the varying degree of intellectual disability.[69]

Table 3: Differentiating features of Zika, Dengue, and Chikungunya

Features	Dengue	Zika	Chikungunya
Incubation period	3-14 days	3-12 days	1-12 days
Etiology	RNA virus belongs to the genus *Flavivirus* of family *Flaviviridae*. (4 different serological types exists - DENV 1, 2, 3 and 4) Mostly, Infection with one serotype Leads to lifelong immunity against the same type. However, occasionally, exposure of the individual to a second type of dengue virus Leads to a very severe form of illness (dengue shock syndrome and dengue hemorrhagic fever)	RNA virus belongs to the genus *Flavivirus* of family *Flaviviridae*. Lifelong immunity after infection with one type has not been reported in Zika virus infections	RNA virus of genus *Alphavirus* of the family *Togaviridae*
Fever (duration)	Higher (≥40°) +++ Lasts for 4-7 days	Lower (≤38.5) ++ Lasts for 1-2 days	High fever++Lasts for 2-3 days
Rash (maculopapular exanthema)	Moderately elevated +	Elevated +++	Moderately elevated ++
Headaches	Frequent and high intensity +++	Frequent and moderate intensity +	Frequent and moderate intensity +
Arthralgia	Mild	Mild/moderate +	Frequent and in multiple joints +++
Nausea and vomiting	Seen	Unusual	Unusual
Blood dyscrasias (shock and thrombocytopenia)	+++	+/_	+/_
Non-purulent conjunctivitis	+	+++	++
Peripheral edema	_	+	_
lymphadenopathy	++	+	++
Neurological complications	Encephalitis	Guillain-Barré syndrome and encephalitis	Guillain-Barré syndrome and encephalitis (especially in neonates)
Course of disease	Mostly, dengue infection is benign and limited to fever during the acute phase followed by a Gradual return to normal. Occasionally, after exposure to secondary serological type of dengue, there are three distinct phases of disease: an acute febrile phase, a critical (plasma leak) phase where hematologic abnormalities, shock and death can occur, and a recovery phase	Usually self-limiting (2-7 days)	The illness is usually self-limiting and resolves with time. However, preexisting signs of chronic joint disease and other causes of chronic rheumatism predispose patients to chronicity of chikungunya infection
Hospitalization	Secondary dengue infection often requires hospitalization and 2.5% of infected individuals will develop a lethal illness	Most cases are managed on an outpatient basis	Patients with severe chikungunya fever requiring hospitalization tend to be older and have comorbidities such as cardiovascular, neurologic, and respiratory disorders or diabetes
Role of NSAIDS	NSAIDS can increase risk of bleeding	Acceptable to use in Zika virus infection as long as dengue has been excluded	Taking nonsteroidal anti-inflammatory drugs may reduce the symptoms of fever and pain
Neutropenia	++	Not demonstrable	+
Lymphopenia	++	Not demonstrable	+++

NSAIDS=Nonsteroidal anti-inflammatory drugs. +: Mild, ++: Moderate, +++: Severe, +/-: May or may not be present

Microcephaly occurs during the neuronal proliferation phase in the initial stages of pregnancy (3–4 months) and may correspond to the infectious symptoms in the mother. Various proposed mechanisms for microcephaly in ZIKV infection are: (1) Increased occurrence of microcephaly cases associated with ZIKV epidemics (2) 2 Documented cases of pregnant females with features coherent with ZIKV infection, fetal microcephaly, and RT-PCR showing ZIKV positivity in amniotic fluid.[70]

Neurological Complications

GBS refers to a polyneuropathy of acute onset. More than two-thirds of the reported cases have an underlying infectious etiology.[71] In July 2015, neurological features

Table 4: Summary of reported orofacial features in Zika virus infection

Author and year	Reported orofacial feature
Foy *et al*., 2011	Aphthous ulcers on lip mucosa
Brasil *et al*., 2016	Local hyperemia and petechiae on the hard palate
Derrington *et al*., 2016	Palatal petechiae
Mondolfi *et al*., 2018	Petechial lesions on the hard palate of a female patient with acute Zika virus

were documented in Brazilian patients with a recent history of ZIKV infection in the Bahia state. 26 patients out of the 42 established GBS patients had features coherent with ZIKV infection.[61]

Laboratory Diagnosis

As ZIKV infection presents with atypical features, mimicking other arboviral infections, clinical assessment alone is unpredictable and definitive diagnosis is based on laboratory parameters. Patients presenting with acute onset fever, cutaneous exanthema, myalgia, or arthralgia after recent (previous 2 weeks) trip to a ZIKV endemic region should be assessed simultaneously for ZIKV infection.[56]

Laboratory diagnosis of ZIKV infections mostly relies on molecular biology and serology.[53,72] Viral RNA isolation from clinical samples (blood, urine) forms the confirmatory laboratory diagnosis for ZIKV. Viral RNA may be demonstrated from blood samples up to 1–5 days after the onset of symptoms.[73,74] The diagnosis should not be excluded even in cases of negative results because the RT-PCR has a sensitivity of 40%.

As the virus remain present in the urine for a relatively long period, individuals examined after 5 days of infection must undertake RT-PCR test. The RT-PCR may be employed up to 15 days after the onset of signs and symptoms.[73,74]

ELISA technique (IgM and IgG) or plaque-reduction neutralization test constitutes the basic serological tests for ZIKV. These tests must be performed and interpreted with caution, particularly in previous dengue virus-infected individuals, possibly due to cross-reactive reactions.[53]

Serological assays may demonstrate IgM and IgG antibodies from the 4th to 12th day of ZIKV infection, respectively.[73,74]

Prevention of Zika Virus Infections

Mosquito control measures

Mass community education regarding the safety measures for insect bite and controlling mosquito vector is extremely essential. Involvement of the homeowners to minimize mosquito breeding environment may serve as an essential preventive method.[75]

Insect bite precautions

Preventive measures against mosquito bite should be employed in the natural habitats of Aedes mosquito species. Various precautionary measures to prevent day time insect bites are:

a. Preventing skin exposure (staying covered with long-sleeved shirts, pants, and hats)
b. Wearing light-colored clothing
c. Treat clothing with permethrin
d. Use of mosquito repellents-Icaridin has been used as the repellent of choice for adults and pregnant women (providing 10 h protection). Use of mosquito nets
e. The use of air-conditioning
f. Staying indoors with protective barriers against mosquito entry, especially during sunset and dawn.[24,45,76]

Vector source control

The prevention of accumulation of stagnant water in dark automobile tires and plants (preferred mosquito breeding sites); mosquito larvae areas to be sprayed and debris removal are the few vector source control measures that need to be undertaken.[77] Climatic changes (global warming and changes in humidity or rainfall) may also play a role in predicting vector abundance. Previous reported studies have suggested that rainfall had a positive and negative predilection on ZIKV and dengue isolation, respectively.[78]

Various preventive measures to mitigate the mosquito population are summarized in Table 5.[79]

Other preventive measures include avoiding a visit to Zika endemic areas and transfusion-related ZIKV spread, and adopting safe sexual practices using condoms.[24]

A thorough screening of donors should be done by employing a validated RT-PCR to demonstrate the ZIKV in semen.[80]

Table 6 shows the UK guidelines on preventing sexual transmission of ZIKV.[51]

Border quarantine (screening of travelers at airports and the border) may serve as an important preventive tool for ZIKV infection import. However, border quarantine is associated with low detection rate as >80% of cases are asymptomatic.[81,82]

Implementation of universal infection control strategies may play an essential role in preventing the spread of ZIKV in healthcare background, including dental settings.[24]

Table 5: Summary of various preventive measures to mitigate mosquito population

	Method	Mechanism	Application method
1	Organophosphates	Larvicide; neurotoxic	Liquid or granules applied to aquatic habitat
2	*Bti*	Larvicide; larvae eat spores, cause larvae to stop eating	Liquid or granules applied to aquatic habitat
3	Surface oils (e.g., CocoBear™)	Larvicide; cuts off access to surface air	Liquid or granules applied to aquatic habitat
4	Hormone regulators (S-methoprene)	Larvicide; disrupts development	Liquid or granules/briquettes applied to aquatic habitat
5	Mosquitofish (*Gambusia*)	Larval predator	Fish released into mosquito producing water sources
6	Copepods	Larval predator	
7	Organophosphates	Adulticide; neurotoxic	Liquid spray, truck/aircraft/backpack
8	Pyrethroids	Adulticide; neurotoxic	Liquid spray
9	*Wolbachia pipientis*	Naturally occurring bacteria, renders mosquitoes unable to transmit RNA viruses or shortens lifespan	Release of treated mosquitoes with *Wolbachia* transmission to the offsprings
10	Sterile insect release	Laboratory-raised mosquito are sterilized via irradiation	Release of sterilized male mosquitoes
11	Genetically altered mosquitoes	Various mechanisms	Release of treated male mosquitoes
12	Traps	Oviposition or adult traps	Deploy traps with attractants
13	Reduction of breeding habitat (automobile tyres)	Reduce standing water	Reducing man-made containers, draining flood water, etc.

Bti=Bacillus thuringiensis israelensis

Table 6: UK guidelines on preventing sexual transmission of Zika virus

Population group exposed to ZIKV (by travel or sexual contact)	Recommended period of abstinence/safe sex practice
Pregnant women and their sexual partners	If both partners, or just the male, have travelled to an area with moderate or high risk of Zika transmission, barrier methods or abstinence should be practised for the duration of the pregnancy If only the female partner has been exposed, barrier methods or abstinence should be practiced for 8 weeks
Women planning pregnancy or of child-bearing age and their sexual partners	Avoid conception while travelling to an area with moderate or high risk of Zika transmission and: For 8 weeks from last possible exposure if the woman alone travelled (asymptomatic and symptomatic) For 6 months from last possible exposure if the male partner/both partners travelled (asymptomatic and symptomatic)

ZIKV=Zika virus

The center for diseases control has proposed intervening measures for assessment of newborns with congenital ZIKV infection. The guidelines comprise serial monitoring of fetal ultrasounds and the evaluation of mothers for ZIKV infection. ZIKV evaluation is suggested in following cases: (1) infants with microcephaly or intracranial calcifications born to women who traveled to or reside in an area with ZIKV transmission while pregnant or (2) infants born to mothers with positive or inconclusive test results for ZIKV infection.[83]

Pharmacological Intervention

One of the major challenges to combat ZIKV is the lack of a ZIKV vaccine. However, extensive researches are being carried out on ZIKV vaccine development by the Butantan laboratory in San Paulo, Brazil in collaboration with two other institutions of Brazil and US health ministry.[24]

Numerous candidate vaccines have progressed to the stage of clinical assessment. In brief, four types of vaccines, namely, three DNA, one modified RNA, four purified formalin-inactivated virus, and one live measles-vectored vaccine have advanced to phase 1 clinical trial.[84-86]

Genetic Adjustments to Diminish Vector Growth

The published research of 1991 dealt with genetic isolation of A. *aegypti* mosquito phenotype, showing resistance to flavivirus infection.[87] Detection of resistant versus susceptible mosquito phenotypes may demonstrate genetic disparity. The induction of strains that are nonsusceptible to infection and also do not cause viral dissemination into the mosquito breeding sites may serve as a probable mode to alleviate the ZIKV transmission. Although, this is still a conceptual idea, inherited adjustment of wild type *Aedes* species might show promising results to mitigate the universal dissemination of infection.

Another prospective outlook is the introduction of genetically modified or genetically engineered male

mosquitoes lacking the potential to produce progeny in the insect infiltrated domains, thus reducing the mosquito population. For example, introduction of genetically engineered GE OX513A A. aegypti mosquitoes incapable to produce progency, thus, curbing their wildlife populations.[88]

Medications

Conducted researchers have demonstrated that Amotosalen and ultraviolet light A may inactivate ZIKV *in vitro*. The use of these medications may also result in a decreased amount of replicative virus, thus showing the way to the discovery of effective anti-ZIKV drugs.[89]

Treatment

The management of ZIKV mainly relies on the supportive and symptomatic therapy,[90,91] and till date, no antiviral medications for ZIKV exist. The management protocol entails complete bed rest, antipyretics for fever, hydration and nutritional therapy, along with monitoring the features of coagulopathies and multi-organ dysfunction.[92]

Acetaminophen is the preferred antipyretic for fever. Prescribing Aspirin and other nonsteroidal anti-inflammatory drugs in ZIKV is usually not acceptable, but may be prescribed cautiously after eliminating dengue virus infection (avoidance of hemorrhagic complications).[76] Aspirin should be avoided in pregnancy beyond the 32nd week of gestation due to possible premature arterial duct closure and young children (<12 years) to prevent the risk of Reye's syndrome.[76,93]

Antihistaminics may prove useful in controlling itching in patients with an exanthematous rash. Suspected cases of ZIKV infection must be shielded from additional insect contact through the initial infectious phase, thus, preventing other mosquito vectors from getting infected and limiting the local spread of disease.[76]

Few patients may require intravenous (IV) hydration therapy along with oxygen administration and monitoring of vital signs. Rarely, patients present with features of sepsis and multi-organ failure (coagulopathies, hepatic, and renal failure), thus necessitating intensive care admission.[47]

Pregnant female with a positive laboratory test for ZIKV should be immediately referred to an expert gynecologist or infectious disease specialist. Review of fetal ultrasounds to monitor fetal growth and malformations make an essential mandate of the high-risk prenatal care.[94]

GBS patients necessitate intensive care unit admission due to the possible development of paralysis of respiratory muscles. The management protocol for GBS involves the use of plasmapheresis or hyperimmune IV IG (hyperimmune). These modalities are costly but diminish the revival time.[95]

Figure 4 shows the evaluation of pregnant female with a travel history to regions with moderate-to-high risk of ZIKV transmission.[51]

Conclusion

ZIKV was a neglected tropical disease over the last 50 years (since its isolation in 1947). The disease is

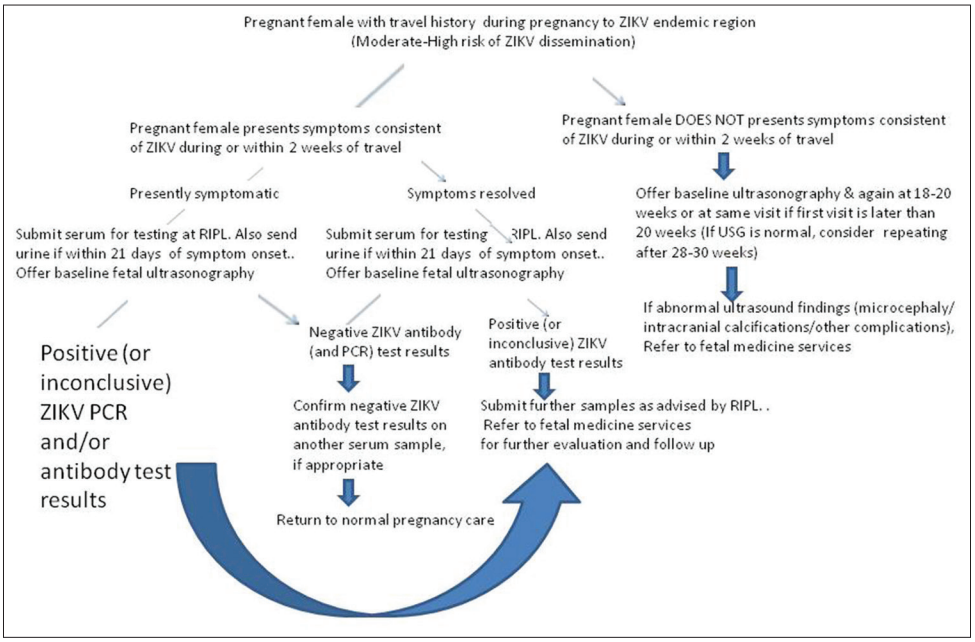

Figure 4: Evaluation of pregnant female with a travel history to regions with moderate-high risk of Zika virus transmission

mainly transmitted through mosquito vector, although, various nonmosquito modes of spread are also known, with the virus being detected in body fluids (semen, saliva, urine, and breast milk). Therefore, preventive measures including vector control, prevention of insect bite, abstinence and use of condoms, avoiding travel to ZIKV endemic regions play an important role. Adopting universal infection control methods may significantly prevent dissemination in oral health-care settings. Recent advancements are being carried out in the form of effective ZIKV vaccine and anti-ZIKV drugs. However, Rapid geographic dissemination, nonspecific clinical presentation, lack of vaccine, and specific diagnostic test are the possible challenges to combat this dreaded public health menace.

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Conflicts of interest

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