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RESEARCH ARTICLE

ZIKA VIRUS: EPIDEMIOLOGY, VECTOR AND SEXUAL TRANSMISSION, NEUROLOGICAL DISORDERS AND VECTOR MANAGEMENT- A REVIEW

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ABSTRACT

Although mosquitoes are the primary vectors of Zika virus (ZIKV) and are considered to be responsible for its major outbreaks worldwide, sexual transmission is also agreat concern. Another major concern is the neurological disorders of ZIKV infection of pregnant mothers on the newly born babies. The ZIKV is an emerging *Flavi virus* of the Spondwenisero complex, a mosquito-borne zoonotic pathogen that causes dengue-like syndromes and is described as a mild, self-limiting febrile illness with no known fatalities. ZIKV remained confined to a narrow equatorial band in Africa and Asia until 2014 when it spread eastward, first to Oceania and then to South America. The virus is vectored by mosquitoes but other modes of transmission are also common. Sexual transmission is a unique characteristic of this virus and increased travel and commerce movements have facilitated the spread of ZIKV to different parts of the globe where the vectors are either absent or not established to transmit the virus locally. ZIKV was limited to isolated cases in Africa and Asia, until the 2015 Brazilian epidemics when it rapidly spread throughout the Americas. Mostly ZIKV infections are characterized by mild subclinical illness but the severe neurological manifestations like Guillain-Barre syndrome in adults and microcephaly with other neurological disorders in babies born to infected mothers are serious public health concerns. Unfortunately, neither an effective treatment nor a vaccine is available to treat the infected patients and the public health response is focused on vector population management and transmission prevention, particularly in pregnant women. Information on growing knowledge about ZIKV regarding the vectors, reservoirs, modes of transmission, neurological disorders, microcephaly, and vector management with possible potential synergy of co-infection with other co-circulating viruses is very crucial to develop management strategies. This paper presents a critical review of the available literature on epidemiology, vector and sexual transmission and neurological disorders of ZIK Valong with the vector management.

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INTRODUCTION

There are numerous arboviruses belonging to different families and genera capable of causing human diseases throughout the world (CDC 2016, Arbocat website). The most historically important one is yellow fever, the first recognized viral fever causing deadly epidemic hemorrhagic fever (Fauci and Morens, 2016). The arboviruses of the Flaviviridae family transmitted by ticks and mosquitoes can infect humans (Chastel, 2012; Choumet and Desprès, 2015). Members of this family belong to the genus, Flavivirus (Heang, 2012). The Zika virus (ZIKV) is an emerging Flavi virus of the Spondwenisero complex (Berthet *et al*., 2014), a mosquito-borne zoonotic pathogen that causes dengue-like syndromes (Burke *et al*., 2016) and is described as a mild, self-limiting febrile illness which lasts four to nine days with no known fatalities (Marcondes and Ximenes, 2016; CDC, 2017). ZIKV remained confined to a narrow equatorial band in Africa and Asia until 2014 when it spread eastward, first toward Oceania and then to South America (Chang *et al*., 2016). Since its global emergence, the virus has infected millions of individuals mostly in South America and for the first time, ZIKV infection in pregnant women was noticed to result in microcephaly and other neuro-developmental disorders in their offspring (Mlakar

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et al., 2016). Another disease manifestation that had never been noted before is the virus-associated Guillain-Barré syndrome in adults (Roth *et al*., 2014). The neurological complications and the multiple vectors resulting in rapid spread of the virus throughout the globe prompted the World Health Organization (WHO) to issue a global health emergency (WHO, 2016; Higgs, 2016). Symptom based identification of ZIKV is extremely difficult because of its cross-reactivity with Dengue and Chikungunya and only serological testing can distinguish this virus form the others (Aubry *et al*., 2015). ZIKV was known to be associated with only mild illness prior to the large French Polynesian outbreak when severe neurological complications were reported, and a dramatic increase in severe congenital malformations (microcephaly) in Brazil were suspected to be associated with ZIKV (Musso and Gubler, 2016). Factors such as changes in populations and climate have played a role in the potential threat to the global community due to uprising infection rates of mosquito-borne diseases like Zika (Chen and Wilson, 2010; Dhama *et al*., 2013; Lee *et al*., 2013; Fauci and Morens, 2016). Caminade *et al*. (2016) suggested that the large outbreak of ZIKV was not the result of mere introduction of ZIKV in the new area, but the changes in climatic conditions due to 2015 El Niño were conducive for vector-borne transmission of ZIKV in South America. *Aedes aegypti* and *Ae. albopictus* are the principal vectors for dengue and ZIKV. The geographic distribution of *Ae. albopictus* and dengue transmission has been extending steadily toward East Asia (Hales *et al*., 2002, Benedict *et al*., 2007). ZIKV outbreak is considered to be unpredictable and spreads rapidly, therefore, its management and control are very challenging (Hayes, 2009; Gautret and Simon; 2016; Gatherer and Kohl, 2016; Gulland, 2016). Some agents of vector-borne diseases, such as West Nile virus, required to be maintained in enzootic transmission cycles, whereas, others like ZIKV or DENV can amplify in transmission cycles involving only a single arthropod vector and human host (Weaver and Reisen, 2010). About 5,158 laboratory-confirmed symptomatic ZIKV cases were reported to ArboNET by States and Territories-United States, 2015–2017 (CDC, 2017). ZIKV is primarily transmitted by mosquitoes, but sexual transmission has also been reported (Foy, 2011; Musso *et al*., 2015). This is also true for perinatal transmission (Besnard *et al*., 2014) and for blood transfusion (Musso *et al*., 2014). Because of the serious outbreak of ZIKV in the America's during 2015 and 2016, many research articles were published in 2016. This comprehensive review covers the published literature on the epidemiology, vectors and sexual transmission and neurological disorders in babies born to ZIKV infected mothers along with the vector management.

Epidemiology

ZIKV is an emerging vector-borne pathogen that was originally isolated in 1947 from a rhesus monkey from a forest called Zika near Kampla, Uganda (Dick *et al*., 1952). It was named ZIKV after the locality from where it was first isolated. The chronological events related to ZIKV epidemiology are shown in Table 1. The second isolation was made from *Ae. africanus* mosquitoes collected in January, 1948, from the Zika forest. It was first isolated from humans in 1952, in Uganda and in Tanzania (Dick, 1952). ZIKV infections were detected in some patients while searching for yellow fever during the epidemic of jaundice in Eastern Nigeria in 1954 (Macnamara, 1954). The patients infected with ZIKV were not infected either with yellow fever or malaria. Weinbren and Williams (1958) isolated and identified two new strains of ZIKV from mosquitoes collected from Lunyo forests and reported the pathogenic properties in mice. Marchette *et al*. (1969) isolated ZIKV from *Ae. aegypti* in Malaysia, while Olson and Ksiazek (1981) reported the virus cases from Central Java Indonesia. McCrae and Kirya (1982) described that the evidence of an epizootic of ZIKV occurred in two stages, the first in 1969 following the build-up of non-immune monkey populations after the previous epizootic of 1962–1963 and the second in 1970 when *Ae. africanus* bite densities increased. Initially, ZIKV was not considered a significant human pathogen because only a few human cases with a self-limiting febrile illness were reported (Filipe *et al*., 1973; Fagbami, 1979; Olson and Ksiazek, 1981) until 2007 when the first outbreak was identified in Yap State in the Federated States of Micronesia (Duffy *et al*., 2009). During the last decade, ZIKV has been reported from several African (Hayes, 2009) and Asian countries (Lanciotti *et al*., 2008). Although the number of cases was few, studies suggested that the ZIKV was endemic to Africa and Southeast Asia. In 2007, it caused an epidemic on the island of Yap, Micronesia, and another in Gabon (Grard *et al*., 2014). In 2013, another outbreak was reported in French Polynesia. From 2012 to 2014, some cases of ZIKV were identified in Thailand (Buathong *et al*., 2015). Introduction of ZIKV in Easter Island in 2014 was thought to originate from French Polynesia (Tognarelli *et al*., 2016). Whereas, the extent of the disease in Cambodia was not confirmed (Heang, 2012), recently, several important outbreaks of ZIKV were reported from the Pacific (Yap, 2007, Duffy *et al*., 2009; French Polynesia, 2013;Cao-Lormeau *et al*., 2014, Cambodia, 2010; Heang, 2012) as well as from the Americas, Brazil and Colombia, 2015 (Porrino, 2016) and Africa, Cape Verde, 2015; (Dick *et al*., 1952; ProMed-mail., 2015). Based on phylogenetic analysis, there are two major lineages: the African lineage which includes African strains and the Asian lineage that was found in the Pacific and the Americas (Saiz *et al*., 2016).

Moreover, 13 countries in the Americas have registered sporadic ZIKV infections, highlighting its rapid geographic expansion (WHO 2016; Petersen *et al*., 2016). Zika has been considered as an emergent disease since 2007 and only a few cases were described or reported until the 2013 major epidemic in French Polynesia and the first autochthonous cases in New Caledonia in January 2014 (Dupont-Rouzeyrol 2015). Ioos *et al*. (2014) reviewed the literature on epidemiology and epidemics of ZIKV. Its presence in Italy was reported in 2015 when 2 cases were diagnosed in individuals showing low-grade fever, malaise, conjunctivitis, myalgia, arthralgia, ankle edema, axillary and inguinal lymphadenopathy (Zammarchi *et al*., 2015a). One of these individuals also showed leukopenia, with monocytosis and thrombocytopenia after a 12-day stay in Salvador, Bahia. ZIKV was suspected to be introduced in Brazil in 2014, when many tourists visited various Brazilian cities during the Soccer World Cup who possibly were infected by *Aedes* (*Stegomyia*) mosquito bites (Marcondes and Ximenes, 2016). However, similar clinical presentation between Zika and other viruses like Dengue and Chikungunya support that Zika has been circulating and spreading inadvertently. This hypothesis gained strength when rates of laboratory confirmation diagnosis for Dengue were observed in Brazil and Colombia, two of the most affected countries by ZIKV infection (Porrino, 2016). In the USA, local Zika transmission occurred in southern Florida, southern Texas, Puerto Rico, the US Virgin Islands, and American Samoa, and travel-associated cases in 49 states (CDC, 2016).The first US

case of microcephaly was reported from Hawaii in January 2016 (Basarab *et al*., 2016; O'Dowd, 2016). In February 2016, four cases were documented in the UK. Symptoms of ZIKV, i. e. chills, fever, headache, muscular pain, arthralgia, and periorbital pains are similar to DENV. However, the symptoms are very mild and no cases of permanent body damage or fatalities have been observed (Marcondes and Ximenes, 2016). The symptoms of ZIKV can vary from very mild as was reported in infected Rhesus monkeys to quite visible symptoms showing high fever, malaise, chills, anorexia, vomiting, diarrhea, stomach aches, dizziness, leg pain (Olson and Ksiazek, 1981). In addition to a ZIKV-associated case of Guillain-Barré syndrome (tetraparesis) predominantly in the lower limbs, paresthesia of the extremities, a bilateral but asymmetric facial palsy, with abolition of deep tendon reflexes (Oehler, Watrin *et al*., 2014), another 40 cases of this syndrome were described in French Polynesia (Ioos *et al*., 2014). Zanluca *et al*. (2015) and Marcondes and Ximenes (2016) described ZIKV and suggested that it may not be referred to as a mild cousin of dengue, because the symptoms of the disease are more prominent, especially in non-immuno competent patients. ZIKV local transmission (autochthonous) has been reported from 61 countries or territories worldwide (Zanluca *et al*., 2015; Calvet *et al*., 2016). The future of the ZIKV epidemic is unpredictable, but the worldwide spread of DENV and CHIKV over time suggests that the virus has the potential to become a globally important disease (Chan *et al*., 2016). ZIKV infection in humans has changed from an endemic arbovirus causing mild illness to outbreaks in new unexposed populations that are linked with Guillain-Barré syndrome and congenital malformations during geographical expansion (Kindhauser *et al*., 2016). The future transmission of ZIKA infection will depend on the global distribution of their mosquito vectors, some of which are invasive and their range is expanding fast. Vertical person-to-person transmission, mother to fetus, and horizontal through sexual transmission, are likely to continue, and spread through international travel.

Vector Transmission

ZIKV is mainly considered a vector-borne disease, although sexual and congenital transmission (Foy, 2011) have also been reported. Natural transmission and onset of ZIKV disease follows the bite of an infected mosquito and predominantly involves the *Aedes* species (Hayes, 2009). Primarily maintained in a zoonotic cycle involving non-human primates, ZIKV was first isolated in 1947 from a febrile rhesus monkey (Dick, 1952; Dick *et al*., 1952; O'Dowd, 2016). Alternatively, humans may be implicated as amplification and reservoir hosts in regions not inhabited by primates (O'Dowd, 2016). The first isolation of ZIKV from mosquito samples was made in 1948 from *Ae. africanus* (Dick, 1952). In 1956, Weinbren and Williams (1958) isolated two other ZIKV strains from *Ae. africanus* specimens. Out of 1,355 samples collected from the forest, ZIKV was isolated from two pools, containing 206 and 127 specimens, respectively. Increased travel and commerce movements to world urban centers facilitated rapid movement of infected mosquitoes and infected humans to uninfected regions of the world which resulted in ZIKV dissemination to a new location. When established in new areas, the vectors can become a source of viral transmission, resulting in random outbreaks. Since the vectors are from the same genus *Aedes*, infections of DENV, CHIKV, and ZIKV (Asian strain) were observed in the Pacific region from 2011 – 2014 (Roth *et al*. 2014). Mild clinical symptoms of ZIKV makes the virus identification difficult during multiple infections. ZIKV was found in *Ae. aegypti* and *Ae. Africanus* (Dic *et al*., 1952); Haddow *et al*., 1964), *Ae. luteocephalus*, *Ae*. (*Fredwardsius*) *vittatus*, *Ae*.(Stg.) *apicoargenteus*, *Ae*. (*Diceromyia*) *furcifer* in Senegal (Diallo *et al*., 2014) and *Ae. albopictus* in Gabon (Grard *et al*., 2014), representing the first report of ZIKV transmission by this mosquito in urban areas. ZIKV was also isolated from 31 pools of several species of genus *Aedes*, *Mansonia uniformis*, *Culex perfuscus*, *Anopheles coustani*, *Ae. vittatus* and *Ae. Furcifer* (Diallo *et al*., 2014). However, their vectorial role was not clearly established. Transmission of ZIKV by *Ae.aegypti* was first reported by (Boorman and Porterfield, 1956). On the contrary, ZIKV was not detected in Ae. (Stg.) hensilli in Yap Island, Micronesia, where an outbreak occurred in 2007 (Lanciotti *et al*., 2008). However, frequent presence of ZIKV in *Aedes* species in the collections and high susceptibility of this vector to experimental infections indicated that members of this genus are the vectors (Ledermann *et al*., 2014). Berthet *et al*., (2014) isolated 3 strains of ZIKV from *Ae*. *africanus* and *Ae. opok*. Phylogenetic analysis based on the amino acid sequence of the polyprotein showed a cluster of three ZIKV strains and the molecular data suggested the presence of different subtype of West African ZIKV strains circulated in *Aedes* species in Central Africa. Diagne *et al*. (2015) reported that all of the populations of *Ae. aegypti*, *Ae. unilineatus*, *Ae. vittatus*, and *Ae. luteocephalus* were susceptible to oral infection of ZIKV, but only *Ae. vittatus* and *Ae. luteocephalus* with the presence of the virus in saliva had the potential to transmit the virus. Since the status of these species as vectors is not clear, Diagne *et al*. (2015) suggested further studies to establish the vector competency of the other species to understand the ecology and epidemiology of ZIKV in Senegal.

Aedes aegypti was considered a possible vector of ZIKV in Malaysia which had high population densities during the rainy season when the virus was reported as well as *Ae. albopictus* which was reported as a vector in the outbreaks of dengue fever in 1976 at a location near the study area of ZIKV (Sunarto *et al*., 1979) and is known to be another major mosquito present throughout rural parts of Indonesia (Sulianti Saroso 1978). Isolation of ZIKV from a number of *Aedes* species including subgenus *Stegomyia* indicated that *Ae. albopictus* might also be a vector. ZIKV transmission was reported in Gabon (central Africa) in urban cycle, supporting the potential of urbanization for spread of these diseases as was suggested by Weaver and Reisen (2010). Among the mosquito species captured in traps and tested for the presence of ZIKV, only *Ae. albopictus* pools were positive for ZIKV (Leroy *et al*., 2009). It may be because *Ae. albopictus* was the dominant species in the suburbs where ZIKV cases were detected, suggesting its major role in ZIKV transmission. The ratio of ZIKV-positive *Ae*. *albopictus* pools was similar to that reported for DENV-positive pools, suggesting its potential to transmit both DENV and ZIKV in equal proportions. Yap Island outbreak prompted some researchers to re-examine the susceptibility of *Ae*. *aegypti* to ZIKV infection (Li *et al*., 2012) but the vector was not properly identified because a prominent species, *Ae. hensilli*, remained negative (Duffy *et al*., 2009) and the virus was found only once from *Ae. aegypti* in Asia (Marchette *et al*., 1969) and its vector status in nature was not confirmed. Based on the earlier serologic studies carried on or angutang, a ZIKV enzootic transmission cycle involving non-human primates and sylvatic vectors was not ruled out (Wolfe *et al*., 2001; Kilbourn *et al*., 2003).

Table 1. Sequence of important events in ZIKV epidemiology as related to epidemics

Dates	Locations	Events	References
April 1947	Uganda	The first isolation of ZIKV from a febrile sentinel rhesus monkey.	Dick *et al.* (1952)
1947–1948	Uganda	The first detection of neutralizing antibodies to ZIKV in sentinel rhesus monkeys.	Dick, (1952); Dick *et al.* 1(952)
January 1948	Uganda	The first isolation of ZIKV from *Ae. africanus*; Mice inoculated with ZIKV-infected *Ae. africanus* became sick.	Dick *et al.*(1952); Smithburn (1952); Haddow *et al.*(1964)
1952 (archived samples)	Uganda	The first report of serum neutralizing antibodies to ZIKV were detected from a man.	Dick (1952).
1954	Nigeria	The first isolation of ZIKV from human serum.	Macnamara (1954)
1956	Nigeria	ZIKV was successfully transmitted from artificially fed *Ae. aegypti* mosquitoes to mice and a monkey in a laboratory.	Boorman and Porterfield (1956)
1964	Uganda	The first well-documented report of occupationally-acquired (medical entomologist) human ZIKV infection.	Simpson (1964)
1981	Indonesia	ZIKV cases were reported from Central Java, Indonesia	Olson and Ksiazek (1981)
1960–2006	Africa and Asia	<20 sporadic cases reported in the literature; all in African and Asian countries.	Moore *et al.*(1975); Fagbami (1979); Olson and Ksiazek (1981); Heang (2012)
2007–2008	Yap Island, FSM	The first major ZIKV epidemic in an urban region with ~73% of the Yap population being infected in 4 months.	Duffy *et al.*(2009.)
2009	Senegal	The first case of probable sexual transmission was reported in 2008 when an entomologist acquired ZIKV in Senegal and infected his wife via unprotected sexual contact in the USA.	Foy (2011)
August 2010	Cambodia	ZIKV infection was confirmed in a patient by using PCR, sequencing, serology, and virus isolation.	Heang (2012)
2009–2012	Africa, Asia, Europe, North America, and Australia	A few cases including travel-related ZIKV infection were reported.	Kwong *et al.* (2013)) Fonseca, *et al*. (2014); Kutsuna et al. (2014); Wæhre *et al.* (2014); Summers et al. (2015); Heang (2012); Duong *et al.* (2011)
2013	Australia	A case of ZIKV infection in an Australian traveler who returned from Indonesia with fever and rash was reported in Australia.	Kwong *et al.* (2013)
2013	Thailand	In 2013 and 2014, many ZIKV cases were diagnosed in Thailand.	Buathong *et al.*(2015)
October 2013	French Polynesia and other Pacific islands	The second major outbreak reported in the Pacific region with an estimated 30,000 people being infected; subsequently spread to other Pacific Islands including New Caledonia, Cook Islands, Vanuatu, Solomon Islands, and Easter Island.	Roth *et al.* (2014); Duong *et al.* (2011); Cao-Lormeau *et al.* (2016); Musso *et al.* (2014).
December 2013	Tahiti	ZIKV infection was reported in a patient.	Wæhre *et al*. (2014)
December 2013	USA	ZIKV was reported in an American traveler who returned to New York after visiting French Polynesia.	Summers *et al.* (2015).
December 2013 - January 2014	Japan	Two cases of ZIKV were reported in Japan in patients who returned after visiting Bora Bora, French Polynesia.	Kutsuna *et al*. (2014).
2014	Canada	First case of ZIKV infection reported in a returning Canadian traveler from Thailand.	Fonseca *et al*. (2014).
2014	Easter Island, S. Pacific	First outbreak of ZIKV was reported in Easter Island, South Pacific.Genetic analysis indicated that the strains identified in Easter Island were related to the strains of French Polynesia.	Tognarelli *et al*. (2016).
January 2014	New Caledonia	First autochthonous case of ZIKV was reported in New Caledonia.	Dupont-Rouzeyrol (2015).
October 2014	Germany	An acute ZIKV infection was reported in a traveler who returned from Malaysian Borneo to Heidelberg, Germany.	Tappe *et al.*(2015)
March 2015	Brazil	The first autochthonous case of ZIKV virus was reported from Brazil. Total estimated cases in Brazil were ~500,000–1,500,000.	Campos *et al.* (2015); Campos *eta l*. (2015); Zanluca *et al.*(2015); Dyer (2015); Bogoch *et al*. (2016).
2015	Italy	Presence of ZIKV was reported from Italy.	Zammarchi *et al.* (2015a); Zammarchi *et al*. (2015b).
2015	Colombia	Zika related Guillain-Barré syndrome was reported.	WHO (2016)
June, 2015	Finland	ZIKV infection in a patient with fever and rash were reported after returning to Finland from Maldives. The patient had DENV (DENV) IgG and IgM antibodies, but pan-flavivirus RT-PCR and subsequent sequencing showed presence of ZIKV RNA in urine.	Korhonen *et al*. (2016).
October 2015	Brazil	An unusual increase in cases of neonates with microcephaly in northeastern Brazil with ~3,000 cases including deaths (~20-fold increase in microcephaly rate from 2010).	Schuler-Faccini (2016).
October 2015	South America	Autochthonous cases reported in other South American countries.	PAHO (2015).
November 2015 - January 2016	Venezuela	Local mosquito transmission of ZIKV infection andZIKV related Guillain-Barré syndrome cases were reported in Venezuela.	WHO (2016)
January – April 2016	USA	9 cases of male-to-female sexual transmission of ZIKV were reported in the US. Information on both timing of exposure and symptoms of sexually transmitted ZIKV was also reported.	Russell *et al.*(2017)
February 2016	WHO	WHO declared ZIKV epidemic as a global public health emergency.	WHO (2016)
February, 2016	Global	More than 30 countries in Africa, Asia, Latin America, and Oceania/Pacific islands reported autochthonous cases; whereas imported cases were reported in Europe and North America.	PAHO/WHO (2016)
March 2016	Netherlands	First sexual transmission of ZIKV was reported.	Reusken *et al.* (2016)
February, 2016	United Kingdom	4 cases of ZIK were reported in the UK.	O'Dowd (2016)
March 2016	Spain	A case of ZIKV vertical transmission was reported in Spain. At 19 weeks of pregnancy, fetal malformations and presence of ZIKV were detected in the amniotic fluid of a pregnant woman.	Perez *et al.* (2016)
March 2016	France	First sexual transmission of ZIKV was reported in France.	Frank *et al.*(2016); Mansuy *et al*. (2016)
April 2016	Germany	First sexual transmission of ZIKV was reported in Germany	Frank *et al.*(2016)
02 Aug 2016	USA	First local transmission of ZIKV was reported in continental USA.	ECDC (2017).

The implication of *Ae. aegypti* in the urban transmission of ZIKV was first attributed to field evidence including the high prevalence of anti-ZIKV antibodies in the urban population of Nigeria (Musso *et al*., 2014), the coincidance of peaks of infections and *Ae. aegypti* population in Indonesia (Olson and Ksiazek 1981) and its isolation from a pool of *Ae. aegypti* in Malaysia (Marchette *et al*., 1969). Presence of ZIKV from *Ae. aegypti* in Malaysia provided the first evidence of its transmission outside Africa. Status of *Ae. aegypti* as a vector was confirmed by the studies which demonstrated its competence to transmit ZIKV (Boorman and Porterfield, 1956). ZIKV is known to have the ability to adapt to new vectors like *Ae. albopictus* especially in areas where populations of this species were very high. *Aedes albopictus* was first introduced in Africa in 1991 (Cornel and Hunt, 1991, Paupy *et al*., 2012) in tires imported from Japan to South Africa. However, whether the transmission of ZIKV in central Africa was linked to the adaptive mutation of the virus to *Ae. albopictus* was not confirmed (Grard *et al*., 2014.)They also reported that *Ae. albopictus* was the predominant species with 55.4% of the mosquito pools, while *Ae. aegypti* accounted for only 18.2% in the collections in Gabon (Central Africa). It was then reported for the first time as a breeding population from the Delta State region of Nigeria, Africa (CDC, 1991) and in Benue State in north-east in Delta State (Savage *et al*., 1992). In 1999, biting females of *Ae. albopictus* were found for the first time in Southern Cameroon, when a large-scale survey in 2000 found breeding populations and adults in five southern towns, breeding mainly in old tires. Tires are frequently imported from both the USA and Nigeria, which are infested with these mosquitoes (Fontenille and Toto, 2001).

The other mosquito species consisted of members of the *Ae. Simpsoni* complex, *An. gambiae*, *Ma. africana*, *Ma. uniformis*, *Cx quinquefasciatus*, *Eretmapodites quinquevittatus* and an unidentified *Culex* species. Positive mosquito pools were captured from two suburbs (Nzeng-Ayong and Alenkiri) where *Ae. albopictus* was the predominant species (Grard *et al*., 2014.). They provided the first direct evidence of human ZIKV infections in Gabon, and its first occurrence in *Ae. albopictus*. These data revealed an unusual natural life cycle of this virus, occurring in an urban environment, and representing an emerging threat due to this novel association with a highly invasive vector, *Ae. albopictus*, the geographic range of which is still expanding to new areas. Based on the literature, the general assumption is that only *Aedes* species are the vectors of ZIKV. However, a few publications have reported its presence in *Culex* species, which are abundant in the tropical areas where ZIKV has spread. Faye *et al*. (2013) reported the isolation of ZIKV strains from many species of Aedes and *An. coustani*. Diallo *et al*. (2014) reported the presence of ZIKV in ten *Aedes* species, *Ma. uniformis*, *An. coustani*, and *Cx. perfuscus* in Senegal which possibly contributed to the zoonotic cycle of the virus transmission. Although laboratory studies provide the basic data on whether an organism is capable to acquire, maintain and transmit a pathogen, it requires extensive field studies to establish a mosquito species as a primary vector. For example *Ae. aegypti* and *Ae. albopictus* are present in Brazil but only *Ae. aegypti* is considered as the primary vector (Zanluca *et al*., 2015). Therefore, a possible role of other mosquito species in transmission of ZIKV in urban areas may be established under different environmental conditions and full knowledge of the vector status of mosquito species will facilitate the effectiveness of control strategies against all potential vectors. Zanluca *et al*. (2015) reported the identification of ZIKV as the causative agent of an outbreak in northeastern Brazil. It represented the first autochthonous transmission of ZIKV in the country. Spreading of the disease in the country might occur by virtue of the large population mobility and the widespread occurrence of the transmitting vectors (Zanluca *et al*., 2015). Furthermore, the complex epidemiological context with the co-circulation of DENV, CHIKV and ZIKV cannot be neglected because DENV and ZIKV (Dupont-Rouzeyrol, 2015) or DENV and CHIKV (Caron *et al*., 2012) co-infections have already been reported.

To assume that the main vector is only *Ae.aegypti*, especially in areas where other mosquito species coexist is risky and dangerous if other species are found to have a major role in ZIKV transmission. Therefore, the researchers working on vector–pathogen interactions at various geographical locations must address this important issue to ensure directing of control actions towards the right targets so that the incidence of the drastic effects of ZIKV disease outbreaks could be avoided. ZIKV is mainly vectored by *Aedes* mosquitoes (Marcondes and Ximenes, 2016). The members of *Aedes* including *Ae. aegypti*, *Ae. albopictus* and *Ochlerotatus japonicas* are invasive and are constantly spreading across the continents (Becker *et al*., 2012; Melaun *et al*., 2015; Abdel-Ghaffar *et al*., 2015; Kampango and Abílio, 2016). Kampango and Abílio (2016) reported the first occurrence of *Ae. albopictus* in Mozambique. ZIKV was reported to be vertically transmitted in their insect vectors, facilitating the virus to persist during adverse climatic conditions or absence of suitable host. Wong *et al*. (2013) demonstrated that local populations of *Ae. albopictus* in Singapore were susceptible to ZIKV with more than 70% of orally infected mosquitoes that had the virus in their saliva and were capable to disseminate it. This study highlighted the potential of *Ae. albopictus* to transmit ZIKV. The local transmission of ZIKV in Singapore is plausible due to the presence of susceptible vectors, an immunologically naive and vulnerable human population, and the travel hub status of Singapore. Nonetheless, the threat of ZIKV can be mitigated by existing dengue and chikungunya control program being implemented in Singapore. Thangamani *et al*. (2016) reported vertical transmission of ZIKV in *Ae. aegypti* injected with the virus, whereas, its vertical transmission was not demonstrated in *Ae. albopictus*. *Aedes albopictus* is now established in large parts of the Mediterranean Sea and is considered to be the main vector in Europe for autochthonous human infections with chikungunya and DENV (Medlock *et al*., 2012) and introduced into Germany through cargo from southern Europe (Becker *et al*., 2013). In 2015/16, its successful overwintering was observed for the first time in southern Germany (Pluskota *et al*., 2016). The overwintering population showed considerable susceptibility to ZIKV at 27 °C and the transmission rate was higher than in the *Ae. albopictus* from the Calabrian region in Italy. Susceptibility of European strains of *Ae. albopictus* to ZIKV pose a high risk of epidemics but low temperature may limit its spread to short summer periods (Huber *et al*., 2014).

In 2015, ZIKV emerged in Columbia and Brazil and spread rapidly across the American continent and the Caribbean, causing an epidemic with notable numbers of associated clinical cases of microcephaly and Guillain–Barré syndrome (Musso and Gubler, 2016). *Aedesaegypti* and *Ae.albopictus* are considered the primary and secondary vectors of ZIKV (WHO/Europe, 2016). However, with transmission rates

below 50%, their vector competence for ZIKV in the laboratory was low (Chouin-Carneiro *et al*., 2016). The question therefore remains whether *Culex* spp. may play a role in the transmission cycle of ZIKV. The few studies conducted have provided inconclusive results and suggested that at least *Cx. quinquefasciatus* might be able to transmit ZIKV (Aliota *et al*., 2016; Amraoui *et al*., 2016; Boccolini *et al*., 2016; Fernandes *et al*., 2016; Guo *et al*., 2016; Huang *et al*., 2016). *Culex* species: *Cx. pipienspipiens* biotype *pipiens*, and *Cx. torrentium* collected in Germany as well as laboratory-reared *Cx. pipienspipiens* biotype *molestus* artificially infected with ZIKV at 18 °C or 27 °C did not show vector competence, whereas, *Ae. albopictus* was susceptible for ZIKV only at 27 °C, with transmission rates similar to laboratory-reared *Ae. aegypti* (Heitmann *et al*., 2017).

Sexual transmission

Initially, most of the ZIKV infections resulted from bites of infected *Aedes mosquito* vectors. One of the major difference between ZIKV and other infective viruses is that it has been documented to be sexually transmitted. The first case of probable sexual transmission was reported in 2008 when an entomologist acquired ZIKV in Senegal and infected his wife via unprotected sexual contact in the USA (Foy, 2011). The second probable incidence of potential ZIKV sexual transmission was during the outbreak in French Polynesia when a Tahitian man with symptoms was found to have ZIKV RNA in his semen and urine (Fréour *et al*., 2016). Since the large ZIKV outbreak in the Americas, there have been many documented sexual transmission cases of male-to-female (Venturi et al., 2016; Arsuaga *et al*., 2016; Brooks, 2016; Russel *et al*. 2017); male-to-male (Deckard, 2016; Hills, 2016) and female-to-male (Davidson, 2016; Hamer *et al*., 2017). ZIKV was isolated from semen in a patient from French Polynesia (Musso *et al*., 2015) and non-vector-borne, probably sexual transmission was observed in humans in the US (McCarthy, 2016). Atkinson *et al*. (2016) reported the presence of ZIKV in the semen of a 68-year-old man who had onset of fever, marked lethargy, and an erythematous rash 1 week after returning from the Cook Islands, a ZIKA infected area. Musso *et al*. (2015) reported the isolation of ZIKV from the semen of a patient in Tahiti who sought treatment for hematospermia. Nicastri *et al*. (2016) reported a case where a man in his early 30s reported a history of fever, asthenia and erythematous rash during his stay in Haiti and ZIKV RNA was detected in his urine and saliva 91 days after symptoms onset, and in his semen on 188 day after onset of symptoms upon returning to Italy. These findings support the possibility of sexual transmission of ZIKV and highlight the importance of research to investigate non-vector-borne transmission. Reusken *et al*. (2016) reported the longitudinal follow-up of ZIKV RNA in the semen of a traveler who developed the disease after returning to the Netherlands from Barbados. Persistence of ZIKV RNA was followed until the virus load reached undetectable levels in blood, urine and saliva. RNA levels were higher in semen than in other sample types and reduced to undetectable level at day 62 post onset of symptoms. D'Ortenzio *et al*. (2016) reported that their data supported the hypothesis of sexual transmission (either oral or vaginal) of ZIKV and did not rule out the possibility of transmission through other biologic fluids, such as pre-ejaculate secretions or saliva exchanged through deep kissing. ZIKV has been detected in saliva, but no cases of transmission through saliva were documented. Fréour *et al*. (2016) and Frank *et al*. (2016) reported sexual transmission of ZIKV in France and Germany, where the vectors were not active. In a French couple who traveled to ZIKV infected areas of Martinique, the man tested negative for ZIKV RNA in blood, but positive in urine and seminal plasma. Detection of ZIKV RNA in the man's semen supported the hypothsis of sexual transmission from the man to the woman between 21 – 36 days of infection. The woman was found to be viraemic in blood 39 days after her return, which strongly suggested the transmission of ZIKV through sexual intercourse because if the transmission had occurred before sexual contact, it would have corresponded to at least 20 days longer than the maximal time of viral clearance. The woman tested positive for ZIKV RNA in blood and urine samples. Serological analysis for the man indicated the presence of anti-ZIKV IgM (absence of anti-dengue IGM) and anti-flaviviruses IgG. Both of these individuals reported having no clinical symptoms of ZIKV infection during and after their visit to Martinique.

Infectious organisms, especially sexually transmitted microorganisms are known to be etiologic agents of hematospermia (Stefanovic *et al*., 2009). However, Foy (2011) and Musso *et al*. (2015) reported arbovirus infections in humans to be associated with hematospermia, and no arboviruses were isolated from human semen. Musso *et al*. (2015) detected a high ZIKV RNA load and replicative ZIKV in semen samples, at the times when ZIKV was not detectable in the blood samples of infected patients and suggested viral replication in the genital tract. Lack of symptoms in the patient and acute infection concomitantly to hematospermia suggested the occurrence of an upstream viremic phase during mild ZIKV symptoms. This detection of ZIKV in both urine and semen is consistent with the results reported in a study of effects of Japanese encephalitis virus on boars (Suzuki *et al*., 2009). The virus was isolated from urine and semen of experimentally infected animals, and viremia developed in female boars artificially inseminated with the infectious semen (Habu *et al*., 1977). Barzon *et al*. (2013) reported the presence of flaviviruses in the urine of infected persons. Similarly, in YFV, RNA was present in urine of vaccinated persons but the virus isolated from the infected patients were also not infective (Domingo *et al*., 2011) and the Saint Louis encephalitis viral antigens were also infective (Foy, 2011). Musso *et al*. (2015) hypothesized that ZIKV can be transmitted by sexual intercourse. The detection of ZIKV RNA in urine samples with no presence in blood samples suggested that like other viral infections, urine samples can yield evidence of ZIKV for late diagnosis (Musso *et al*., 2015). During laboratory investigations, (Harrower *et al*., 2016) reported negative RT-PCR results for ZIKV RNA from the serum at 19 days and from urine at 21 days after symptoms onset in patient 1, whereas, serologic testing on day 21 detected Zika IgM and IgG (IgG titer 1:320). Semen collected on day 23, 35 and 76 tested positive, whereas, semen samples collected on days 99 and 117 tested negative for ZIKV RNA. However, virus isolation from the semen sample collected on day 23 failed to cultivate infectious particles. Similarly, transmission of ZIKV to patient 2 may not have occurred through a mosquito bite because neither of the *Aedes* species of mosquito capable of transmitting ZIKV infection was established in New Zealand (Ministry of Health of New Zealand, 2016). Hills (2016) reported a patient with fever, arthralgia, bilateral conjunctivitis, and a maculopapular, pruritic rash who returned to the US after a 10-day trip to the Caribbean. Because of sexual intercourse during initial days of his illness, his female partner developed a

febrile illness with rash, conjunctivitis, and myalgia in 13–14 days with detectable levels of ZIKV RNA in the woman's serum. Another patient who traveled to Central America developed symptoms of ZIKV and after sexual intercourse with his female partner, also developed ZIKV like symptoms. Since these women did not travel outside USA, local transmission of ZIKV was not possible because vectors were not present or active where they all lived. These cases suggested that the sexual transmission of ZIKV is more common than previously reported. All the reported cases of sexual transmission of ZIKV were from asymptomatic males, whereas, sexual transmission of the virus from asymptomatically infected females to their sexual partners has not been reported.

Baud *et al*. (2016) reported that the majority of sexual transmission occurs from a symptomatic male to a female and more importantly, ZIKV RNA can persist for at least 6 months in semen with urogenital tract serving as a reservoir. Detection of ZIKV RNA in a cervical swab of a patient 3 days after the classic symptoms suggested a potential tropism for the female genital tract. It is not known whether genital ZIKV infection might have a deleterious effect on the fertility of the couples. Mansuy *et al*. (2016a) reported that the rapid spread of the virus in South America and increasing reports of congenital abnormalities associated with ZIKV infections led WHO to declare a Public Health Emergency of International Concern. ZIKV was a neglected tropical disease before 2015 with no known natural history. Male to female sexual transmission is possible (Foy, 2011) and ZIKV was detected in the semen from a patient with haematospermia during the 2013–14 French Polynesia outbreak (Musso *et al*., 2015). Mansuy *et al*. (2016b) described a case of a 32-year-old man who tested positive for ZIKV at Toulouse University Hospital (Toulouse, France) and showed typical clinical symptoms of an arbovirus infection 2 days after returning from Brazil and French Guyana. He completely recovered in few days, but the samples of blood, urine, and semen taken 2 weeks after diagnosis showed presence of ZIKV RNA. The viral load in the semen was roughly 100,000 times more than blood or urine after 2 weeks of onset of symptoms. This infectious viral load in semen suggested that ZIKV is sexually transmitted but the retention period was not known.

The presence of ZIKV in the semen is a significant challenge, as is the possible teratogenicity of the virus. First, more than 80% of infected people were probably asymptomatic (Duffy *et al*., 2009), making them an enormous potential reservoir. Pregnant women in infected areas should protect themselves not only from mosquitoes, but also from infectious virus in the semen of their partners. These findings confirm that infectious ZIKV is excreted into semen resulting in a high viral load that could lead to sexual transmission. Mansuy *et al*. (2016b) reported that the possible routes of transmission are via the blood, with the implied risk to blood transfusions; via semen, with the risk of sexual transmission; and via the placenta, with the risk of transmission to fetuses. Transmission via semen and the placenta are real challenges for women of reproductive age. Therefore, fertility preservation management is recommended by many agencies to delay pregnancy for up to 28 days after travel and the semen should be tested for ZIKV within 6 months of travel. The 6-month risk period after symptoms onset should be monitored for a ZIKV infection, as recommended by US Centers for Disease Control and Prevention and French guidelines, for patients returning from non-epidemic areas. It should also be regularly revised to keep pace with the evolution of scientific knowledge about the seminal shedding of ZIKV. Data on the ZIKV infected pregnant women who completed pregnancies in the USA indicated that 6% of fetuses or infants had evidence of ZIKV-associated birth defects, mainly brain abnormalities and microcephaly, whereas, 11%, of the women infected in first-trimester delivered the babies with effects of ZIKV-associated birth defects (Honein *et al*., 2017). These findings support the importance of screening pregnant women for ZIKV exposure. There is sufficient evidence that ZIKV is potentially sexually transmitted and persists in male genital secretions for a prolonged period after symptoms onset (Moreira *et al*., 2017). ZIKV RNA has been detected in vaginal secretions for 14 days and for longest reported time of 81 days in erythrocytes with development of rashes on the hands and feet of the patient, which was presumed to be related to her infection (Murray *et al*., 2017). This prolonged detection of ZIKV RNA in vaginal mucosal swab specimens and the blood from a US traveler who acquired virus during his visit to Honduras (Murray *et al*., 2017) is a cause of concern and requires further investigation. Recent evidence of presence of ZIKV in serum for a longer period than expected for other flavi viruses (e.g., dengue), have implications for diagnostic recommendations and prevention of transmission (Paz-Bailey *et al*., 2017).

Congenital Zika Syndrome and Neurological Disorders in New Born Babies

While ZIKV infection appears to be a mild disease in the general population, the potential consequences to the fetus and newborn could be profound (Citil Dogan *et al*., 2017).

There is a link between the populations of ZIKV infected vectors, spread of the disease, and an increase in cases of fetal abnormalities like microcephaly cerebral calcifications, abnormal brain structures, cataracts and calcifications of eye, and an association with Guillain–Barré syndrome (GBS) in adults (Oehler *et al*., 2014, Broutet *et al*., 2016, de Paula Freitas *et al*., 2016, Karwowski *et al*., 2016, Cao-Lormeau *et al*., 2016.). A temporal and geographic relationship has been reported between Guillain–Barré syndrome and ZIKV outbreaks in the Pacific and the Americas (Oehler *et al*., 2014; Broutet *et al*., 2016; Rozé *et al*., 2016; Thomas 2016). Miranda-Filho *et al*. (2016) reported that severe congenital abnormalities are linked to ZIKV infection. In Brazil, during the epidemics, 60 - 70% of the mothers reported rash mainly during the first trimester. Major outcomes of ZIKV infection were microcephaly, facial disproportionality, hypertonia/ spasticity, hyperreflexia, and abnormal neuro-images including calcifications, ventriculomegaly, and lissencephaly etc. Many cases showed severe abnormalities, and ZIKV infections may have resulted in marked mental retardation in babies. Local mosquito transmission of ZIKV was reported in Venezuela in November 2015 and January 2016 with total of 252 cases of Guillain-Barré syndrome showing a spatio-temporal association to the virus (Garcia *et al*., 2016). If a pregnant woman acquires ZIKV infection, the virus might cross placental barrier causing congenital infection. In this case, ZIKV RNA can be detected in amniotic fluid, confirming that ZIKV crossed the placental barrier. When this happens, the fetus might develop brain damage including microcephaly and, less frequently, calcifications, ventriculomegaly or hydrocephalus, and other congenital malformations (Schuler-Faccini, 2016). Mansuy *et al*. (2016b) reported that during the

2015 outbreak in Brazil, attention was focused on the impact of ZIKV on human health because new evidence was established that the virus can cause severe neurological injuries and adverse fetal outcomes.

Zika-specific RNA has been documented in brain and placental tissue (CDC, 2016; Driggers *et al*., 2016, Mlakar *et al*., 2016, Oliveira Melo *et al*., 2016). Mlakar *et al*. (2016) reported the association of ZIKV with microcephaly, a rare neurological condition where an infant's head is significantly smaller than the normal size babies. Microcephaly, usually is the result of abnormal brain development taking place in the womb or the brain not growing as it should after birth. The virus was isolated from the fetal brain tissues. Oliveira Melo *et al*. (2016) reported fetal microcephaly in two pregnant women from the state of Paraiba, Brazil and considered this as a part of the 'microcephaly cluster' because both women suffered from symptoms related to ZIKV infection. Blood samples from these women were negative for ZIKV but amniocentesis and PCR tests were positive representing the first diagnoses of intrauterine transmission of the virus. The sequencing analysis in both cases indicated a genotype of Asian origin ZIKV. Carvalho *et al*. (2016) reported 19 singleton pregnancies with microcephaly. Seven cases showed other CNS malformations and 7 had extracranial congenital anomalies. Symptoms were reported in 13/19 cases at a gestational age between 5 - 16 weeks. At a median gestational age of 31 weeks (range 28–38), 5 cases were positive for ZIKV. Three neonatal deaths and one stillbirth were also reported in these cases. These findings led to the conclusion that in the presence of fetal microcephaly associated with ZIKV infection, CNS malformations were frequently detected. Baud *et al*. (2016) while reporting the sexual and post-transfusion transmission of ZIKV during the outbreaks in French Polynesia and Brazil, noted that the virus infection was associated with microcephaly and Guillain–Barré syndrome. Since fetal infection includes other birth defects, congenital ZIKV syndrome was used to define in utero infection. Rasmussen *et al*. (2016) reported that the prenatal ZIKV infection is linked to adverse pregnancy outcomes like microcephaly and other serious brain anomalies.

They concluded a causal relationship between prenatal ZIKV infection, microcephaly and other brain anomalies. The supporting evidence for this causal relationship included ZIKV infection during prenatal development that was consistent with the observed defects; a specific, rare phenotype involving microcephaly and associated brain anomalies in fetuses or infants with congenital ZIKV infection. These data also strongly support biologic plausibility, including the identification of the virus in the brain tissue of affected fetuses and infants. Severe cerebral damage in most of the children with congenital infection are associated with the ZIKV (Aragao *et al*., 2016). Common features reported were brain calcifications in the junction between cortical and subcortical white matter associated with malformations of cortical development, often with a simplified gyral pattern and predominance of pachygyria or polymicrogyria in the frontal lobes. In addition, these findings pointed to an enlarged cisterna magna, abnormalities of corpus callosum (hypoplasia or hypogenesis), ventriculomegaly, delayed myelination, and hypoplasia of the cerebellum and the brainstem as the causes of the ZIKV infection. During ZIKV outbreak in French Polynesia in 2013 – 2014, more than 66% of general population were infected with the virus (Cauchemez *et al*., 2016). Out of the 8 microcephaly cases identified, 7 occurred within 4 months of pregnancy. The timing of occurrence of this syndrome is best explained by a period of risk in the first trimester. In their model, the prevalence of microcephaly was in 2 cases, and the risk of ZIKV related microcephaly was in 95 cases where the women were infected in the first trimester and the increased risk of microcephaly from infection in other trimesters was not ruled out. Their data provided quantitative estimates of the risk of microcephaly in fetuses and neonates when the mothers were infected with ZIKV during the first trimester. In 2016,WHO Secretariat briefed the Committee on the clusters of microcephaly and Guillain-Barré Syndrome (GBS) that are associated with ZIKV transmission in some settings based on information from Brazil, France, United States, and El Salvador (WHO, 2016).Based on information from these countries, WHO constituted it as a Public Health Emergency of International Concern (PHEIC). The Committee gave advice to the Director-General for her consideration to address the PHEIC (clusters of microcephaly and other neurological disorders) and their possible association with ZIKV, in accordance with The International Health Regulations (IHR) (2005). França *et al*. (2016) reported that during investigations on 1,501 suspected ZIKV cases, Brazilian Ministry of Health in 2014 and 2015, 76 were definite, 54 highly probable, 181 moderately probable, and 291 somewhat probable of congenital ZIKV syndrome.

However, clinical, anthropometric, and survival differences were small among these four groups. In spite of normal sized heads, rashes in the third trimester of pregnancy were associated with brain abnormalities. One in 5 definite or probable cases presented normal head circumferences and for one third of definite and probable cases, there was no history of a rash during pregnancy. Based on this data, it was concluded that ZIKV congenital syndrome was a new teratogenic disease. Since many definite or probable cases present normal head circumference values in babies and the mothers did not report having a rash, they suggested to revise screening criteria to detect all affected newborn babies. In 9 cases, the mothers reported a rash in the third trimester. Review of records of these newborn babies indicated that 5 babies represented the typical ZIKV brain malformations, whereas, the physicians reported malformations without specifying their precise nature in 4 cases. Some Brazilian studies suggested that late pregnancy infections could lead to brain lesions in cohorts of affected fetuses born to mothers with a rash on gestational week 25 or later (Brito 2016). Cardoso *et al*. (2015) reported that a child infected at 26 weeks' gestation stage had the virus at 2 months of age; and Oliveira Melo *et al*. (2016) reported that 3 of 32 confirmed cases had a history of rash in the third trimester. To support their conclusions, Gérardin *et al*. (2017) cited a case series of 19 fetuses or newborn babies in Réunion, of whom 5 mothers reported a rash in the first trimester but none in the second or third trimesters. This small study did not exclude the possibility that neuroimaging findings might be found in the offspring of women with third-trimester rashes. The Brazilian studies strongly suggested that ZIKV infections in late pregnancy could lead to brain abnormalities. Victora *et al*. (2017) questioned that the calculations of positive predictive values by Gerardin-Laverge (2017) contained an error and reported that the receiver operating characteristic curve referred to definite and probable cases (including some that did not present rash), whereas, the average head circumference they referred to was for third trimester rashes. They then stated that a 67% infection rate was unlikely in Brazil, but 97% of

our cases were from a smaller region—the northeast. A case-control study showed 64% antibody prevalence among controls in Pernambuco state, where the epidemic was most intense. In addition, this state saw relatively few cases of infection in the summer of 2016 compared to the large number reported in 2015, suggesting that herd immunity might have been achieved—which is compatible with an incidence of around 60–70% in the first epidemic wave. In addition, they noted that the data showed a marked regional distribution of the epidemic when it started, and therefore, our results need to be interpreted considering this spatial distribution rather than extrapolated to the whole of Brazil. Isolation of the virus from fetal brain provided the evidence for the association between congenital ZIKV infection and the brain damage (Driggers *et al*., 2016).

These data provided tools for further studies of the pathogenesis of ZIKV-induced microcephaly. Future research on gestational ages will further clarify the role of ZIKV infection on brain abnormalities that can identify the new markers for its detection. Role of ZIKV in pathognomonic radiographic pattern of microcephaly is inconclusive (Carvalho *et al*., 2016), partial calcifications and disorderly distribution of subcortical transition and the basal ganglia, in association with lissencephaly were characteristics of this type of infection. They also reported that during the maternal infection, viremia with vasculitis in the carotid brain circulation and brain tissue necrosis occurs, with evidence of cell migration abnormalities. The coarse severe calcifications are considered to be part of the dysmorphic calcification from the healing phase. A correlation between ZIKV infection of mothers in the first trimester and microcephaly in new borns is documented (Garcez *et al*., 2016). Effects of ZIKV and DENV infections on human neural stem cells grown as organoids in in vitroindicated that the virus targeted brain cells reduce the cell size and viability. Using immunocytochemistry and electron microscopy, Garcez *et al*. (2016) reported that reduction in viability and growth as neuro-spheres and brain organoids due to ZIKV infection of human brain cells, suggested an abrogated neurogenesis during human brain development. Noronha *et al*. (2016) showed a temporal association between cases of microcephaly and the ZIKV epidemic during Brazil epidemics. Viral RNA was detected in amniotic fluid samples, placental tissues and newborn and fetal brain tissues. They provided evidence of the transplacental transmission of ZIKV by detecting viral proteins and viral RNA in placental tissue samples from the mothers infected at different stages of gestation. They observed chronic placentitis (TORCH type) with viral protein detection by immunohistochemistry in Hofbauer cells and some histiocytes in the intervillous spaces. They also demonstrated the neurotropism of ZIKV by detecting viral proteins in glial cells, endothelial cells and scattered foci of micro-calcifications in the brain tissues. Oliveira Melo *et al*. (2016) reported neurological impairments, including microcephaly, a reduction in cerebral volume, ventriculomegaly, cerebellar hypoplasia and fetal akinesia deformation sequence in infants with congenital virus infection. These data confirm that microcephaly is one of several neurological impairments observed in infants exposed to the ZIKV.

Since microcephaly is just one of the clinical signs of this congenital malformation disorder, the term congenital Zika syndrome is appropriate for these cases. Hanners *et al*. (2016) demonstrated that ZIKV isolate replicates in human fetal neural progenitors that are partially cytopathic and persist for weeks showing a limited immunogenic effect in fetal neural progenitors. Teixeira Costa *et al*. (2016) described the epidemic of microcephaly, its detection and control in Brazil, the suspected causal link with ZIKV infections, and possible future scenarios. In 2015 in Pernambuco, Brazil, ZIKV infected mothers reported rashes during pregnancy. Women delivering in October were in the first trimester during the peak of a Zika epidemic and 4,180 cases of suspected microcephaly were reported. Carvalho *et al*. (2016) and De Carvalho*et al*. (2016) reported that the Ministry of Health of Brazil published an announcement confirming the relationship between ZIKV and the microcephaly in the Northeast, suggesting the transmission of virus from infected pregnant women to their fetuses. They reviewed the literature on ZIKV infection and microcephaly, evaluated national and international epidemiological data, as well as the current recommendations for the health teams. The main symptoms of the infection were rashes, fever, non-purulent conjunctivitis, and arthralgia. Transmission was mainly through mosquito bites, but reports via the placenta were also published. Sáfadi and Nascimento-Carvalho (2017) reported that by October 2016, 2,106 confirmed cases of microcephaly and/or malformation of central nervous system were reported in Brazil with 405 laboratory-confirmed cases of ZIKV infections. These cases were from areas where incidents of ZIKV infection were highest in 2015. Recently, data suggested a relationship between timing of infection and fetal effects. Two recent studies (early March, 2016) provided information about the relationship between the onset of infection using statistical coincidence models.

According to this model, microcephaly is likely to be more strongly related to first trimester or at least early second trimester of ZIKV transmission. There is however no information about other associated congenital anomalies (Buathong *et al*., 2015; Tognarelli *et al*., 2016). Availability of sufficient evidence to support the linkage of ZIKV with microcephaly, suggests its impact on adverse pregnancy outcomes, and demonstrates evidence of the virus replication and persistence in fetal brain and placenta (Bhatnagar *et al*., 2017). These conclusions point to the importance of tissue analysis in improving the diagnosis of ZIKV congenital and pregnancy-associated infections and understanding of mechanism of intrauterine transmission and pathogenesis. In addition, the tissue-based RT-PCRs extend the time frame for ZIKV detection and establish the diagnosis that enables the healthcare providers to identify the cause of microcephaly or fetal loss. In situ hybridization localized replicative ZIKV RNA was found in brains of 7 infants and in placentas of 9 women who lost pregnancy during the first or second trimester. These findings supported the argument that ZIKV replicates and persists in fetal brains and placentas which provided a direct evidence of the virus association with microcephaly. Data on the women who completed pregnancies in the United States revealed evidence of Zika-associated brain abnormalities and microcephaly in 6% of the fetuses whereas, the virus infectionin first-trimester caused 11% of fetuses to develop birth defects (Honein *et al*., 2017). Moore *et al*. (2017) reported a distinctive phenotypiccongenital ZIKV syndrome and suggested the use of this phenomenon by clinicians in comprehensive clinical investigation of virus related anomalies in affected infants. Bhatnagar *et al*. (2017) confirmed the linkage of ZIKV with microcephaly and other virus associated

pregnancy outcomes and reported the evidence of virus replication and persistence in fetal brain and placenta and emphasized that tissue analysis may be a useful tool to diagnose ZIKV congenital syndrome.

Vector management

There is no direct control of ZIKV infection available. Some efforts have been made to evaluate the medicines that are being used for treatment of other viruses. Bullard-Feibelman *et al*. (2017) evaluated sofosbuvir, an FDA-approved drug for hepatitis C virus for its effectiveness against ZIKV infection and found that sofosbuvir efficiently inhibits replication and infection of several ZIKV strains in multiple human tumor cell lines. They also demonstrated oral treatment of ZIKV-induced death in mice with sofosbuvir. Further studies with this or other available drugs are needed to explore the potential of these antiviral drugs in curing ZIKV infections. Since no cure is available, vector management is the only practical solution to manage the spread of this disease. Mosquito control and protection from mosquito bites has been done by humans to prevent vector-borne diseases for centuries. The concept of control is changing with the development of new technologies and changes in vector and pathogens. The spread of ZIKV and other arboviruses that are transmitted by urban mosquitoes can also adapt to Neotropical mosquitoes and primates, challenging future control strategies. For example *Ae. aegypti* is considered an urban species and main vector of ZIKV, however, *Ae. albopictus* was the predominant species and played a major role in the spread of ZIKV infections in Gabon. These data revealed an unusual natural life cycle of ZIKV, occurring in an urban environment, and potentially representing a new emerging threat due to this novel association with a highly invasive vector whose geographic range is still expanding across the globe. ZIKV and other arboviruses transmitted by urban mosquitoes can also adapt to Neotropical species and primates that can make the vector control a big challenge for the future. Since there are no vaccines or any other specific treatments available for ZIKV, avoiding or preventing mosquito bites is the best way to minimize the disease incidence (WHO, 2016). Minimizing direct mosquito bites by using mosquito repellents (Mehlhorn *et al*., 2005; Amer and Mehlhorn, 2006) and treated mosquito nets (Benelli, 2015) are still the most effective personal protective measures to reduce the incidence of arbovirus transmitted diseases.

There have been new efforts to restrict the use of chemically derived repellents that pose threat to human health and non-target organisms especially by the European Community and number of repellents registered for use are either deregistered or use is restricted. The registered repellents include N,N-diethyl-3-methyl benzamide (DEET), IR3535, picaridin, and also an Eucalyptus citriodora, para-menthane-3,8-diol (PMD) (Abdel-Ghaffar *et al*., 2015). There are many recent research publications which report the repellent activity of the natural products (Cantrell *et al*., 2011; Ali *et al*., 2012; Tabanca *et al*., 2013; Ali *et al*., 2013; Ali *et al*., 2015a; Ali *et al*., 2015b). Source reduction is a widely used method to reduce the vector populations which involves minimizing the number of breeding sites and application of pesticides especially in areas where mosquito-borne diseases are endemic (Semmler *et al*., 2009; Benelli, 2015). Pesticides resistance has become a major issue and there is a need to pay attention in the selection of synthetic pesticides to avoid the development of mosquito-resistant and their side effects on human health and the environment (Hemingway and Ranson, 2000; Naqqash *et al*., 2016). Due to the problem with synthetic pyrethroids which are commonly used for mosquito control, there is a new focus on exploring the potential of sterile insect technique (SIT) for suppression of these vectors (Lees *et al*., 2014; Oliva *et al*., 2013; Bourtzis *et al*., 2016). This new control concept of "boosted SIT" that includes the auto-dissemination may be useful in area-wide eradication or reduction campaigns against these vectors (Bouyer and Lefrançois, 2014). Use of Wolbachia-induced phenotypes in combination with irradiation with reliable sexing mechanisms is another technique with a potential to achieve population suppression through cytoplasmic incompatibility and pathogen interference (Lees *et al*., 2014).

There has been extensive research conducted to explore the effective use of plant-based products, but serious efforts are needed tonarrow the gap between laboratory data and field application. More research is needed on the chemical characterization and standardization of natural compounds (Heng *et al*., 2013), field evaluation of natural compounds as repellents (Iovinella *et al*., 2014), and impact of oviposition deterrence (Xue *et al*., 2001; Benelli, 2015; Benelli *et al*., 2015). Nanotechnology is another new exciting area of research and acute toxicity and sub-lethal effects of nano particles have been tested on a wide range of non-target organisms (Oberdörster *et al*., 2006; Park *et al*., 2014). However, very few efforts have been made to determine the sub-lethal toxicity of plant-synthesized nanoparticles against aquatic organisms sharing the ecological niche with mosquito vectors (Baun *et al*., 2008; Fabrega *et al*., 2011). *Spergularia rubra*- and *Pergularia daemia*-synthesized silver nanoparticles were not toxic to *Poecilia reticulata* fish, when exposed to dosages equivalent to LC50 and LC90 of these products against IV instar larvae of *Ae.aegypti* and An. stephensi (Patil *et al*., 2012a, b). Subarani *et al*. (2013) did not find any toxic effects of *Vincarosea*-synthesized silver nanoparticles against *P. reticulata*, when exposed to dosages that were toxic to *An. stephensi* and *Culex quinquefasciatus*. Similarly, Haldar *et al*. (2013) found that the silver nano particles produced from green fruits of *Drypetes roxburghii* were safe against P. reticulate when applied at the dosages equal to LC50 of IV instar larvae of *An. stephensi* and *Cx. quinquefasciatus*. Rawani *et al*. (2013) showed that mosquitocidal silver nanoparticles synthesized using *Solanum nigrum* berry extracts were not toxic against two mosquito predators, *Toxorhynchites* larvae and *Diplonychus annulatum*, and *Chironomus circumdatus* larvae, exposed to lethal concentrations of dry nanoparticles calculated on *An. stephensi* and *Cx. quinquefasciatus* larvae.

Silver nanoparticles biosynthesized using the 2,7. bis[2-[diethylamino]-ethoxyfluorence isolate from the Melia azedarach leaves did not show acute toxicity against *Mesocyclops pehpeiensis* copepods (Ramanibai and Velayutham, 2015). Information on impact of low dosages of these mosquitocidals on behavioral traits of aquatic predators sharing the same ecological niche is poorly known (Murugan *et al*., 2015; Murugan *et al*., 2016). The available literature unveiled fascinating scenarios. For example, Kalimuthu *et al*. (2017) showed that very low doses (1 ppm) of lemongrass-synthesized gold nanoparticles may help to control malaria and dengue vectors boosting early instar mosquito larvae predation by copepods (*Mesocyclops aspericornis*).

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