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RESEARCH ARTICLE

THE EPIDEMIOLOGICAL REVIEW OF ZIKA VIRUS

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ABSTRACT

Zika virus (ZIKV) infection is one of the re-emerging infectious diseases that are of public health important considering its short-term and long-term effects. Aedes mosquitoes are widely distributed globally, and native habitats of most species are warm tropical and subtropical regions. Zika virus, a mosquito-borne disease that belonged to the genus flavivirus and flaviviriae family was discovered during a study of yellow fever in Uganda in Zika Forest (Ioos *et al*., 2014). The Zika Virus has been described as having two lineages, the African and Asian lineages. Human illness caused by Zika virus was first recognized in Nigeria in 1953, when viral infection was confirmed in three ill persons (Hamel, Liégeois, *et al*., 2016). Despite recognition that Zika virus infection could produce a mild, febrile illness, only 13 naturally acquired cases were reported during the next 57 years. Zika virus was first identified in the Americas in March 2015, when an outbreak of an exanthematous illness occurred in Bahia, Brazil (Musso, 2015). Epidemiologic data indicate that in Salvador, the capital of Bahia, the outbreak had begun in February and extended to June 2015. No Zika virus vaccine exists; thus, prevention and control measures center on avoiding mosquito bites, reducing sexual transmission, and controlling the mosquito vector (Baden *et al*., 2016). The rapid spread of Zika infection raises new challenges for the health authorities and researchers about the magnitude and possible complications in future outbreaks (Plourde & Bloch, 2016).

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INTRODUCTION

Zika virus (ZIKV)infection is one of the re-emerging infectious diseases that are of public health important considering its short term and long-term effects. Zika virus, a mosquito-borne disease that belonged to the genus flavivirus andflaviviriae family was discovered during a study of yellow fever in Uganda in Zika Forest(Ioos *et al*., 2014). It was isolated from a rhesus monkey in 1947 and later in Aedes africanus in 1948(Baden, Petersen, Jamieson, Powers, & Honein, 2016). The Zika virus infection was not seen as a global health issue for almost 70 years until the recent outbreak in French Polynesia and Brazilconsidering its link toGuillain-Barre syndrome and microcephaly in fetuses and newborns. Although, these current re-emergences have in part being attributed to global warming, epidemiologist and other public health professionals are currently most concernedwith addressing thecurrent trend and spread of Zika virus to avert its consequential health implications. The potential of the Zika virus to spread globally to areas that favors themosquito'sspecies that carries the infectious agent is high due to globalization (Zanluca, Duarte, & Santos, 2016).

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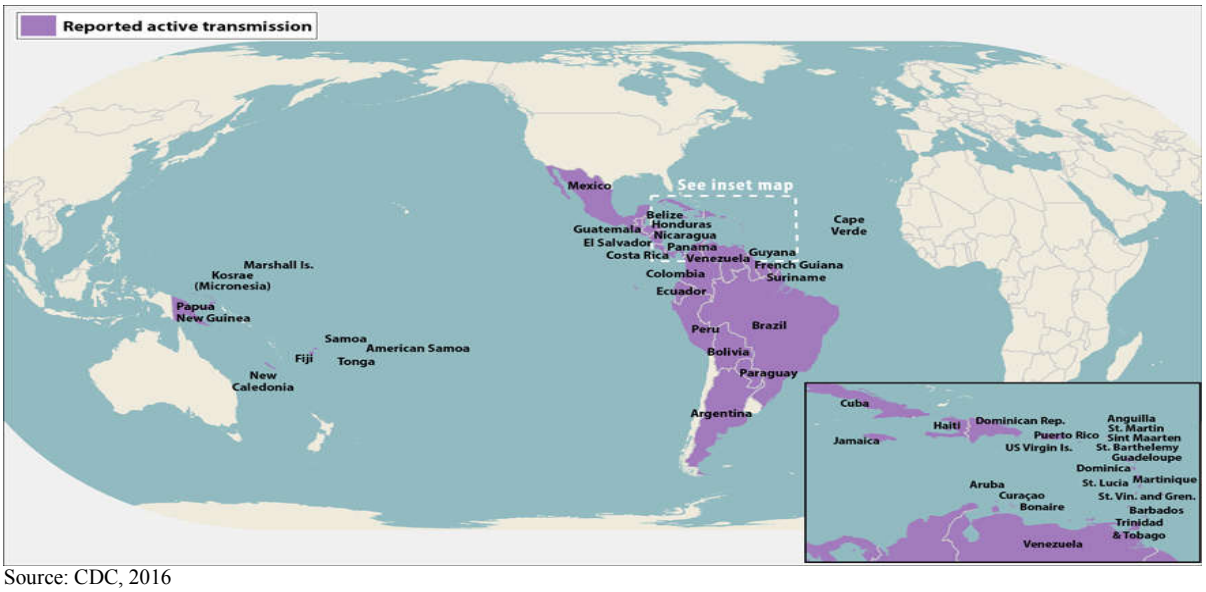
Due to recent adverse health outcomes associated with Zika virus infection, public health professionals have increased their interest in Zika virus research to device preventive measures and promote policies that would decrease its spread and address its health implication(Barton & Salvadori, 2016). Considering its recent occurrence in countries such as Yap Island of the Federated state of Micronesia in 2007, French Polynesia in 2013 and Brazil in 2015, the pathogenesis of Zika virus infection in respect to the differences existing among the different discovered strains have ensued (Hamel, Liegeois, *et al*., 2016). From 2007 to 2015, cases of Zika virus infections have been associated to more adverse health compared to what was experienced among cases in the years preceding 2007-2015. The first described strain, the African strain MR766 was reported to cause mild symptoms compared to subsequent incidences of Zika virus infections in Yap Island of the Federated State of Micronesia in 2007, French Polynesia in 2013 and Brazil in 2015. The effect of Zika virus infection outbreak in French Polynesia and Brazil resulted to increases cases of Guillain-Barre syndrome- an autoimmune disease and Microcephaly in fetus and newborns(Hamel, Liégeois, *et al*., 2016). These recent reported adverse health effect of Zika virus infection have led the World Health Organization to declare Zika virus infection a Public Health Emergency of International Concern(Heymann *et al*., 2016).

Pathophysiology of Zika Virus: The Zika Virus has been described as having two lineages, the African and Asian lineages. Like other mosquito borne viruses, Zika virus is a positive-sense single-stranded RNA virus in the family Flaviviridae, which includes several other species of clinical importance (e.g., DENV, WNV, and yellow fever virus(Plourde & Bloch, 2016). Zika virus have the capacity to be well adapted in various host ranging from arthropods to vertebrates (Zanluca *et al*., 2016). As with other flaviviruses, Zika virus genome encodes three structural proteins: the caps-id, the envelope glycoprotein and membrane (Zanluca *et al*., 2016). After being bitten by an infected mosquito, the virus penetrates the skin cells by attaching to a receptor, it then migrates to the lymph nodes and blood stream (Ramos da Silva & Gao, 2016). The attachment of the Zika virus to a cellular receptor (AXL) is mediated by the envelope glycoprotein, followed by endocytic uptake and then uncoating of the nucleocapsid and eventual release of the viral RNA into the cytoplasm (Baden *et al*., 2016). In the cytoplasm, virial polyproteins are produced through RNA replication and modified by the endoplasmic reticulum. These immature virions collects both in the endoplasma reticulum and the secretory vesicles before there are released into the system (Ramos da Silva & Gao, 2016). Structural differences discovered between Zika virus and other Flaviviruses in the amino acids around the glycoprotein have shown to affect their viral assembly and exist and level of infectivity (Ramos da Silva & Gao, 2016). Structural difference recently discovered in Zika virus NS1 protein showed different electrostatic potentials among the different Flaviviruses (Dengue viruse, West Niles viruse, Zika Virus) and might be essential to clarification of the differences existing among them in terms of pathogenicity (Ramos da Silva & Gao, 2016).

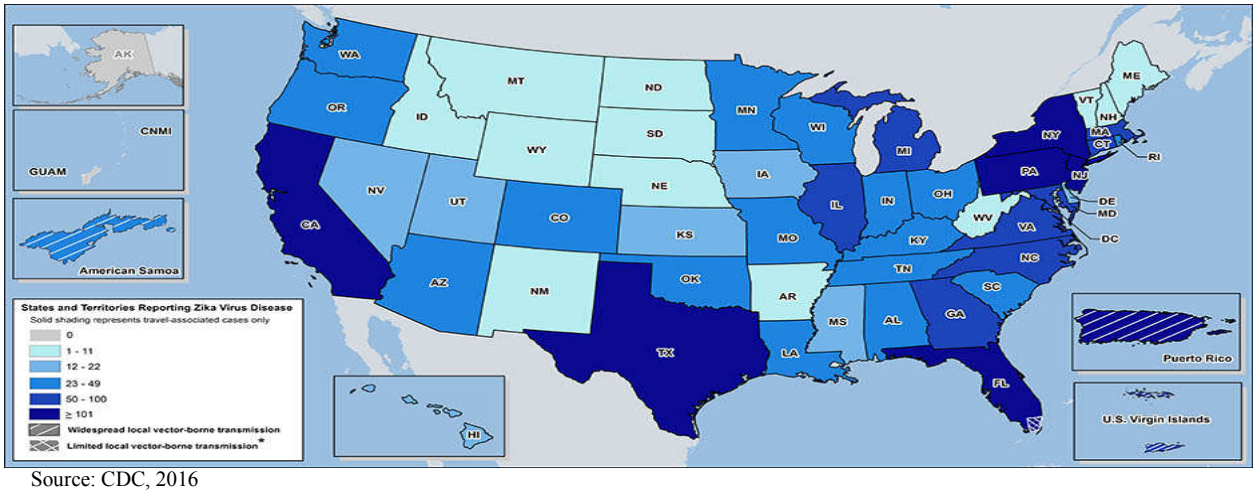
Epidemiology of Zika Virus: Although Zika virus was isolated on several occasions from Aedes africanus mosquitoes after its discovery in 1947 (Baden *et al*., 2016). In a bid to fully understand the epidemiology of the disease, aserosurvey involving residents of multiple areas of Uganda revealed a 6.1% seroprevalence of antibodies against Zika virus, which suggested that human infection has occurred. Further serosurveys indicated a much broader geographic distribution of human infection, including other parts of African, Asia and the Americans (Baden *et al*., 2016). After the report of the first human evidence of Zika Infection in 1952, serological evidence of Zika have been reported in other parts of the world including other parts of Africa, Asia, the pacific and in recent time the Americans(Paixão, Barreto, Da Glória Teixeira, Da Conceição N Costa, & Rodrigues, 2016). Human illness caused by Zika virus was first recognized in Nigeria in 1953, when viral infection was confirmed in three ill persons(Hamel, Liégeois, *et al*., 2016). Despite recognition that Zika virus infection could produce a mild, febrile illness, only 13 naturally acquired cases were reported during the next 57 years. Thus, it came as a great surprise when a 2007 outbreak on several islands in the State of Yap, Federated States of Micronesia, resulted in an estimated 5000 infections among the total population of 6700(Hamel, Liégeois, *et al*., 2016). Subsequently, an outbreak in French Polynesia in 2013 and 2014 is estimated to have involved 32,000 persons who underwent evaluation for suspected Zika virus infection(Musso, 2015). Although most of the illnesses appeared similar to those seen in Yap, cases of Guillain–Barré syndrome were also seen (Musso, 2015).Subsequent outbreaks occurred on other Pacific islands, including New Caledonia (in 2014), Easter Island (2014), Cook Islands (2014), Samoa (2015), and American Samoa (2016). Zika virus was first identified in the Americas in March 2015, when an outbreak of an exanthematous illness occurred in Bahia, Brazil(Musso, 2015).Epidemiologic data indicate that in Salvador, the capital of Bahia, the outbreak had begun in February and extended to June 2015. By October, the virus had spread to at least 14 Brazilian states, and in December 2015, the Brazil Ministry of Health estimated that up to 1.3 million suspected cases had occurred(Musso, 2015). In October 2015, Colombia reported the first autochthonous transmission of Zika virus outside Brazil, and by March 3, 2016, a total of 51,473 suspected cases of Zika virus had been reported in that country.By March 2016, the virus had spread to at least 33 countries and territories in the Americas(Baden *et al*., 2016). By September 2015, investigators in Brazil noted an increase in the number of infants born with microcephaly in the same areas in which Zika virus was first reported. The number continued to be on the rise. By mid-February 2016, more than 4300 cases of microcephaly had been recorded, although overreporting and misdiagnosis probably inflated the number(Brasil *et al*., 2016). Subsequently, French Polynesian investigators retrospectively identified an increased number of fetal abnormalities, including microcephaly, after the Zika virus outbreak in their country(Musso, 2015).

Zika Virus in the United States: In the United States of America, the area of Zika transmission continues to expand with three counties in the state of Florida reporting autochthonous cases of Zika virus infection: MiamiDade, Palm Beach, and Pinellas(Schuler-Faccini *et al*., 2016). In 2016, Zika virus disease and congenital infections became nationally notifiable conditions in the United States. As of September 3, 2016, a total of 2,382 confirmed and probable cases of Zika virus disease with symptom onset during January 1–July 31, 2016, had been reported from 48 of 50 U.S. states and the District of Columbia(Schuler-Faccini *et al*., 2016). Most cases (2,354; 99%) were travel-associated, with either direct travel or an epidemiologic link to a traveler to a Zika virus-affected area. Twenty-eight (1%) cases were reported as locally acquired, including 26 associated with mosquito-borne transmission, one acquired in a laboratory, and one with an unknown mode of transmission. Half of all cases were reported from four states: New York (558 cases; 23%), Florida (483; 20%), California (147; 6%), and Texas (117; 5%). Overall, 1,495 (63%) reported cases were in females (Schuler-Faccini *et al*., 2016). The median age of Zika virus disease patients was 39 years (range = 1 month–86 years) with 80% aged 20–59 years(Schuler-Faccini *et al*., 2016).

Among the 28 cases reported as locally acquired, 26 were associated with local mosquito-borne transmission(Schuler-Faccini *et al*., 2016). All 26 local cases of mosquito-borne disease were reported from Florida; patients ranged in age from 19 to 54 years, and 18 (69%) were male(Schuler-Faccini *et al*., 2016). One case that was not mosquito-borne occurred in a researcher who had a needle stick exposure while working in a laboratory(Schuler-Faccini *et al*., 2016). The second case that was not mosquito-borne occurred in a patient for whom the mode of transmission is not yet to be determined but had close personal contact with a family contact with travel-associated Zika virus disease; the family contact had a level of viremia approximately 100,000 times higher than average and subsequently died (Schuler-Faccini *et al*., 2016).



Source: CDC, 2016



Source: CDC, 2016

Source: CDC. 2016

Zika Cases Reported in the United States: Laboratory-confirmed Zika virus disease cases reported to ArboNET by state or territory (as of September 21, 2016). Florida has confirmed that local transmission of Zika virus is occurring in about a 4.5 square mile area in Miami Beach within the boundaries of 8th and 63rd streets(Hills, Martin, Fischer, & Staples, 2016). Within the United States, mosquito-borne transmission of Zika virus infection has occurred in Florida; pregnant women are advised to avoid travel an area of Miami Beach; the Wynwood area of Miami was an active transmission area from June 15 to September 18, 2016; the advisory was lifted after three mosquito incubation periods passed with no new locally transmitted cases of Zika virus infection(Hills *et al*., 2016). In addition, mosquito-borne Zika virus transmission in Puerto Rico has been extensive and there is also mosquito-borne transmission of Zika virus in the United

States territories of the Virgin Islands and American Samoa(Hills *et al*., 2016).

Active Zika Virus Transmission in Florida: Miami-Dade County, FL. Red shows areas of active transmission where CDC recommends adherence to travel and testing guidance for pregnant women, women of reproductive age, and their partners. Yellow shows areas where CDC recommends cautionary travel recommendations and strict adherence to precautions to prevent mosquito bites.

Transmission of Zika Virus: Theprimary mode of Zika virus transmission is through the bite of an infected female Aedes mosquito, mainly the Aedes aegypti(Baden *et al*., 2016). The mosquitoes that transmit the Zika virus usually bite in the day time either during the early morning hours or late afternoon. These species of mosquito are of the same specie with those that transmit deugue, chikungunya and yellow fever disease(Baden *et al*., 2016). In Africa, Zika virus exists in a sylvatic transmission cycle involving nonhuman primates and forest-dwelling species of aedes mosquitoes. In Asia, a sylvatic transmission cycle has not yet been identified(Ioos *et al*., 2014). Several mosquito species, primarily belonging to the stegomyia and diceromyia subgenera of aedes, including A. africanus, A. luteocephalus, A. furcifer**,** and A. taylori, are likely enzootic vectors in Africa and Asia(Baden *et al*., 2016). A. aegypti and, to a lesser extent, A. albopictus have been linked with nearly all known Zika virus outbreaks, although two other species, A. hensilli and A. polynesiensis**,** were thought to be vectors in the Yap and French Polynesiaoutbreaks, respectively(Baden *et al*., 2016).

A. aegypti and A. albopictus are the only known aedes (stegomyia) species in the Americas. Despite the association of A. aegypti and A. albopictus with outbreaks, both were found to have unexpectedly low but similar vector competence (i.e., the intrinsic ability of a vector to biologically transmit a disease agent) for the Asian genotype Zika virus strain, as determined by a low proportion of infected mosquitoes with infectious saliva after ingestion of an infected blood meal(Ramos da Silva & Gao, 2016). Aedes mosquitoes are widely distributed globally, and native habitats of most species are warm tropical and subtropical regions. Some species show a limited distribution (e.g., Aedes luteocephalus in Africa and Aedes hensilli in the Pacific Islands); others have a broad geographic span (e.g., Ae. aegypti and Ae. albopictus)(Plourde & Bloch, 2016). However, A. aegypti is thought to have high vectorial capacity (i.e., the overall ability of a vector species to transmit a pathogen in a given location and at a specific time) because it feeds primarily on humans, often bites multiple humans in a single blood meal, has an almost imperceptible bite, and lives in close association with human habitation(Ramos da Silva & Gao, 2016). Substantial evidence now indicates that Zika virus can be transmitted from the mother to the fetus during pregnancy(Hennessey, Fischer, & Staples, 2016). Zika virus RNA has been identified in the amniotic fluid of mothers whose fetuses had cerebral abnormalities detected by ultrasonography, and viral antigen and RNA have been identified in the brain tissue and placentas of children who were born with microcephaly and died soon after birth, as well as in tissues from miscarriages(Mlakar *et al*., 2016). Sexual transmission to partners of returning male travelers who acquired Zika virus infection abroad has been reported(Brooks *et al*., 2016). In one instance, sexual intercourse occurred only before the onset of symptoms, whereas in other cases sexual intercourse occurred during the development of symptoms and shortly thereafter. The risk factors for and the duration of the risk of sexual transmission have not been determined. Replicative viral particles, as well as viral RNA — often in high copy numbers — have been identified in sperm, and viral RNA has been detected up to 62 days after the onset of symptoms(Brooks *et al*., 2016). Although the transmission of Zika virus through a blood transfusion is yet to be reported, it is likely to occur, given the transmission of other, related flaviviruses through the sameroute. During the Zika virus outbreak in French Polynesia, 3% of donated blood samples tested positive for Zika virus by reverse-transcriptase polymerase chain reaction (RT-PCR)(Plourde & Bloch, 2016).

Treatment of Zika Virus: As with the other mosquito-borne flaviviruses, treatment for uncomplicated Zika virus infection focuses on symptoms(Baden *et al*., 2016). No Zika virus vaccine exists; thus, prevention and control measures center on avoiding mosquito bites, reducing sexual transmission, and controlling the mosquito vector (Baden *et al*., 2016). Management is supportive and includes rest, fluids, antipyretics, and analgesics. Aspirin and other nonsteroidal antiinflammatory drugs should be avoided until dengue is excluded because of the risk for hemorrhage among dengue patients(Plourde & Bloch, 2016).

Prevention of Zika Virus: At present, effective methods of prevention focused on reducing infections among pregnant women include avoiding unnecessary travel to areas of ongoing Zika virus transmission, avoiding unprotected sexual contact with partners who are at risk for Zika virus infection,and using mosquito repellent, permethrin treatment for clothing, bed nets, window screens, and air conditioning(Petersen *et al*., 2016). The most effective A. aegypti vector control relies on an integrated approach that involves elimination of A. aegypti mosquito breeding sites, application of larvicides, and application of insecticides to kill adult mosquitoes(Petersen *et al*., 2016). However, each of these approaches could have substantial limitations associated with them. Pregnant women residing in countries that are not Zika virus–endemic should be advised against travelling to affected countries(Petersen *et al*., 2016). For early detection and management, testing should be offered to all pregnant women who have traveled to areas with ongoing Zika virus transmission(Petersen *et al*., 2016). Serial fetal ultrasounds should also be considered to monitor fetal anatomy and growth every 3–4 weeks in pregnant women with positive or inconclusive Zika virus test results, and the infant should be tested at birth(Petersen *et al*., 2016). Men who reside in or have traveled to an area of active Zika virus transmission and who have a pregnant partner should abstain from sexual activity or use condoms during sex; similar guidelines apply for men with a nonpregnant female sex partner who is concerned about sexual transmission of Zika virus(Petersen *et al*., 2016).

Summary

Zika virus has been declared a public health emergency. As many as 1.3 million persons have been affected in Brazil alone, and 20 countries or territories have reported local transmission of the virus during 2016(Baden *et al*., 2016). Because of the ease of air travel and international trade, further spread into regions where the virus is not endemic is likely, and

transmission is probable in locations with competent mosquito vectors(Baden *et al*., 2016). The rapid spread of Zika infection raises new challenges for the health authorities and researchers about the magnitude and possible complications in future outbreaks (Plourde & Bloch, 2016).The long-term outlook with regard to the current Zika virus outbreak in the Americas is uncertain, herd immunity sufficient to slow further transmission will undoubtedly occur, although this will not obviate the need for immediate and long-term prevention and control strategies (Paixão *et al*., 2016). Whether and where the virus becomes endemic and whether an enzootic transmission cycle will develop somewhere in the Americas are matters of conjecture, but they are of considerable importance for the long-term development and sustainability of countermeasures, such as a Zika virus vaccine (Baden *et al*., 2016). The current Zika virus epidemic requires the highest vigilance, especially since this disease is not well known and some questions stillremain unanswered, concerning the reservoir(s) and modes of transmission, the clinical presentation, and possible complications(Paixão *et al*., 2016). Some uncertainties remain on the outcome of co-infections with other arboviroses such as the dengue fever(Ramos da Silva & Gao, 2016). Identifying and addressing Zika virus research gaps would be beneficial to complete understanding of the frequency and full spectrum of clinical outcomes resulting from fetal Zika virus infection and of the environmental factors that influence emergence(Paixão *et al*., 2016). The resultant outcomewill be development of discriminating diagnostic tools for flaviviruses, animal models for fetal developmental effects due to viral infection, new vector control products and strategies, effective therapeutics, and vaccines to protect humans against the disease(Paixão *et al*., 2016).

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