



Historical Trend and Epidemiology of Zika Virus

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ABSTRACT

Zika virus (ZIKV) is a flavivirus related to yellow fever, dengue, West Nile, and Japanese encephalitis viruses. In 2007 ZIKV caused an outbreak of relatively mild disease characterized by rash, arthralgia, and conjunctivitis on Yap Island in the south western Pacific Islands. Zika virus trend infection have been confirmed in several infants with microcephaly and in fetal losses in women infected during pregnancy. The virus can be prevented and control by sleeping under treated mosquito net to protect you from Mosquito bite. This was the first time that ZIKV was detected outside of Africa and Asia. The history, transmission dynamics, virology, and clinical manifestations of ZIKV disease are discussed, along with the possibility for diagnostic confusion between ZIKV illness and dengue. The emergence of ZIKV outside of its previously known geographic range should prompt awareness of the potential for ZIKV to spread to other Pacific islands and the America.

Key words: Zika virus, disease, microcephaly, dengue, Africa, Asia, and Southern Pacific Islands

INTRODUCTION

Zika is a mosquito-borne infection caused by Zika virus, a member of the genus flavivirus and family Flaviviridae. It was first isolated from a monkey in the Zika forest in Uganda in 1947 (Heang *et al.*, 2010). The infection, known as Zika fever, often causes no or only mild symptoms, since the 1950s, it has been known to occur within a narrow equatorial belt from Africa to Asia. In 2014, the virus spread eastward across the Pacific Ocean to French Polynesia, then to Easter Island and in 2015 to Mexico, Central America, the Caribbean, and South America, where the Zika outbreak has reached pandemic levels (WHO, 2015). Zika virus is related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses (ECDC, 2015). The illness it causes is similar to a mild form of dengue fever, is treated by rest, and cannot yet be prevented by drugs or vaccines. There is a possible link between Zika fever and microcephaly in newborn babies by mother-to-child transmission (Mallet *et al.*, 2015, ECDC, 2015).

It is difficult to assess the significance of the increase in the incidence of microcephaly in Brazil in the absence of the number of births in the affected areas in the affected time period (Olson *et al.*, 2012). Zika virus disease is caused by an RNA virus transmitted to humans by *Aedes* mosquitoes, especially by the *Aedes*

egypti species. Up to 80% of infections are asymptomatic (Duffy, 2009). Symptomatic infections are characterized by a self-limiting febrile illness of 4-7 days duration accompanied by maculopapular rash, arthralgia, conjunctivitis, myalgia and headache. Zika virus has not been noted to cause death in the past, nor has it been linked to intra-uterine infections and congenital CNS anomalies (Duffy, 2009). There are two lineages of Zika virus, the African lineage and the Asian lineage (Kuno *et al.*, 1998, Faye *et al.*, 2014 and Haddow, 2012). Phylogenetic studies indicate that the virus spreading in the Americas is most closely related to the virus from the Asian lineage isolated in French Polynesia in 2013-2014. Presently, only two full genome sequences of Zika virus from Brazil and Suriname have been published (Haddow *et al.*, 2015). Sexual transmission of Zika virus is possible, and is of particular concern during pregnancy. Current information about possible sexual transmission of Zika is based on reports of three cases. Men who reside in or have traveled to an area of active Zika virus transmission who have a pregnant partner should abstain from sexual activity or consistently and correctly use condoms during sex (i.e., vaginal intercourse, anal intercourse, or fellatio) for the duration of the pregnancy (Ministério da Saúde Brazil., 2015).

Epidemiology of Zika Virus

Zika virus was first discovered in Africa in the 1940s. The virus circulates in Africa and Asia in humans, animals and mosquitoes but prior to 2015 few outbreaks have been documented. The first Zika outbreak reported outside Africa and Asia occurred on Yap Island in the Federated States of Micronesia in 2007. It was caused by the Asian strain of the virus. The same strain caused a subsequent outbreak in French Polynesia in 2013 and has since caused large outbreaks in other parts of the Pacific region including the first cases in the Americas on Easter Island (a Chilean island in the south east Pacific) in 2014. In May 2015, the first locally-acquired confirmed case of Zika infection was reported in Brazil (WHO, 2015). The Zika virus epidemic continues to spread in the Americas. Since the Rapid Risk Assessment on 10th December, 2015 and as of 19th January, 2016, 13 additional countries or territories have reported laboratory confirmed autochthonous transmission including 12 countries in the Americas: Barbados, Bolivia, Ecuador, France (French Guiana, Guadeloupe, Martinique and Saint-Martin), Guyana, Haiti, Honduras, Puerto Rico, and Suriname, as well as one country in Asia. In addition, autochthonous transmission was reported retrospectively in the Maldives through a travel-related case returning to Finland in June 2015 (WHO, 2015).

Zika virus disease typically produces mild and self-limiting symptoms. The proportion of

asymptomatic infections may be as high as 80%. This, paired with limitations in the diagnostic capacity, means that only a small fraction of Zika virus infections are likely to be laboratory confirmed (WHO, 2015).

It is difficult to assess the significance of the increase in the incidence of microcephaly in Brazil in the absence of the number of births in the affected areas in the affected time periods. Furthermore, the increased awareness about the possible link between intra-uterine Zika virus infections and microcephaly and the changes implemented in the case definition will influence the number of notifications compared to background rates (Olson *et al.*, 2015).

The epidemic is currently spreading in the Americas and Caribbean, but widespread transmission is not yet reported in the latter. Because *Aedes aegypti* mosquitoes are present in the EU Overseas Countries and Territories (OCT) and Outermost Regions (OMR) in the Americas and the Caribbean, it is expected that local transmission will occur once the virus is introduced. The risk of spread is significant but will depend of environmental conditions, early detection of cases and subsequent vector control activities. As surveillance for Zika improves, further cases of Zika are expected to be reported in these regions and previously unaffected countries, particularly in south and Central America and the Caribbean, where the *Aedes* mosquito vector is present (WHO, 2016).



Fig, 1: Countries and territories with active Zika virus transmission (CDC, 2016).



Figure, 2: Global distribution of countries that have past or current evidence of Zika virus transmission (as of 26th January, 2016). Adapted from (CDC, 2016).

The CDC has a comprehensive site describing countries and areas with active Zika virus transmission. In May 2015, the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed Zika virus infections in Brazil. According to the Brazilian Health Ministry, as of November, 2015 there was no official count of the number of people infected with the virus in Brazil, since the disease is not subject to compulsory notification. Even so, cases were reported in 14 states of the country. Mosquito-borne Zika virus is suspected to be the cause of 2,400 cases of microcephaly and 29 infant deaths in Brazil in 2015. The emergence of Zika virus in South America led to a rapid spread throughout South and Central America, reaching Mexico in November, 2015.

World Health Organization (WHO) Case Definition

The first meeting of the Emergency Committee (EC) convened by the Director-General under the International Health Regulations regarding clusters of microcephaly cases and other neurological disorders in some areas affected by Zika virus was held by teleconference on 1st February 2016, from 13:10 - 16:55 Central European Time. The WHO Secretariat briefed the Committee on the clusters of microcephaly and Guillain-Barré Syndrome (GBS) that have been temporally associated with Zika virus transmission in some settings. The Committee was provided with additional data on the current understanding of the history of Zika

virus, its spread, clinical presentation and epidemiology. The following States Parties provided information on a potential association between microcephaly and other neurological disorders with Zika virus: Brazil, France, United States of America, and El Salvador. The Committee advised that the recent cluster of microcephaly cases and other neurological disorders reported in Brazil, following a similar cluster in French Polynesia in 2014, constitutes a Public Health Emergency of International Concern.

Historical Trend of Zika Virus

In a cage on a tree platform in the Zika Forest in Uganda, rhesus monkey number 766 developed a fever. Its serum was inoculated into the brains of mice and they felt ill. Zika virus had been discovered. The sentinel monkey researchers were the Virologist George Dick and the Entomologist Alexander Haddow, based at the Rockefeller Foundation Yellow Fever Laboratories in Entebbe. Haddow went on to build a 120-foot steel tower in the forest to study high-flying mosquitoes and their viruses (Faye *et. al.*, 2014). The best time and place to find Zika virus was in the evening, 80 -100 feet above the forest floor.

The first human case to be described was in 1964 in Entebbe by other virologist, David Simpson; he had a 36-hour fever, some back pain, a headache and a rash. He was better by day three. Antibody studies in Nigeria in the early 1970s found that 40 % of people had been infected at some time in the past.

For many years, Zika virus resided quietly in the textbooks as a member of the Flavivirus family, a distant and unimportant relative of yellow fever, dengue and West Nile viruses. The books said that it caused only mild symptoms (or none at all), that it was spread by the bite of *Aedes* mosquitoes, that monkeys were an animal reservoir, and that it occurred in Africa, India and South East Asia. (CDC, 2015). An alarm bell rang in 2007 when an outbreak occurred on Yap Island in the southwestern Pacific. The infection was mild, with a rash, conjunctivitis and joint pains. But not only was the outbreak the biggest so far recorded - it was estimated that well over half the residents had been infected - the virus had travelled a long way to get to Yap. Perhaps it could spread to the Americas. The bell rang again in late 2013 when a large outbreak started in French Polynesia, with the first report of the Guillain-Barré syndrome associated with a number of cases. Guillain-Barré is a neurological illness with paralysis as its main feature (CDC, 2016).

In May, 2015 the first confirmed indigenous cases of Zika virus infection were reported in north-east Brazil. Since then it has spread across the country, and reached Mexico, Haiti, Puerto Rico, Barbados, Paraguay and other South American countries, though not Bolivia, Peru, Chile, Uruguay or Argentina (CDC, 2016). But it is the reports of an increase in the number of children born in Brazil in 2015 with abnormally small heads - microcephaly - that have driven Zika to the top of the news.

Microcephaly has many causes and is not new. The close relationship between dengue virus and Zika makes it virtually impossible to know which virus could have stimulated an immune response. And dengue is currently on the rampage in Brazil. In 2015 there were 1.6 million suspected cases and 839 deaths (Melo *et al.*, 2016).

Transmission of Zika Virus

Zika is primarily transmitted through the bite of infected *Aedes* mosquitoes, the same mosquitoes that spread Chikungunya and dengue. These mosquitoes are aggressive daytime biters and they can also bite at night. Mosquitoes become infected when they bite a person already infected with the virus. Infected mosquitoes can then spread the virus to other people through bites. It can also be transmitted from a pregnant mother to her baby during pregnancy or around the time of birth (Petersen *et al.*, 2016). The vertebrate hosts of the virus were primarily monkeys in a so-called enzootic mosquito-monkey-mosquito cycle, with only occasional transmission to humans. Before the current pandemic began in 2007, Zika virus "rarely caused recognized 'spillover' infections in humans, even in highly enzootic areas". Infrequently, other arboviruses have become established as a human disease though, and spread in a mosquito-human-mosquito cycle, like the yellow fever virus and the dengue fever virus (both flaviviruses), and the chikungunya virus (a togavirus) (Cardos, *et al.*, 2016).

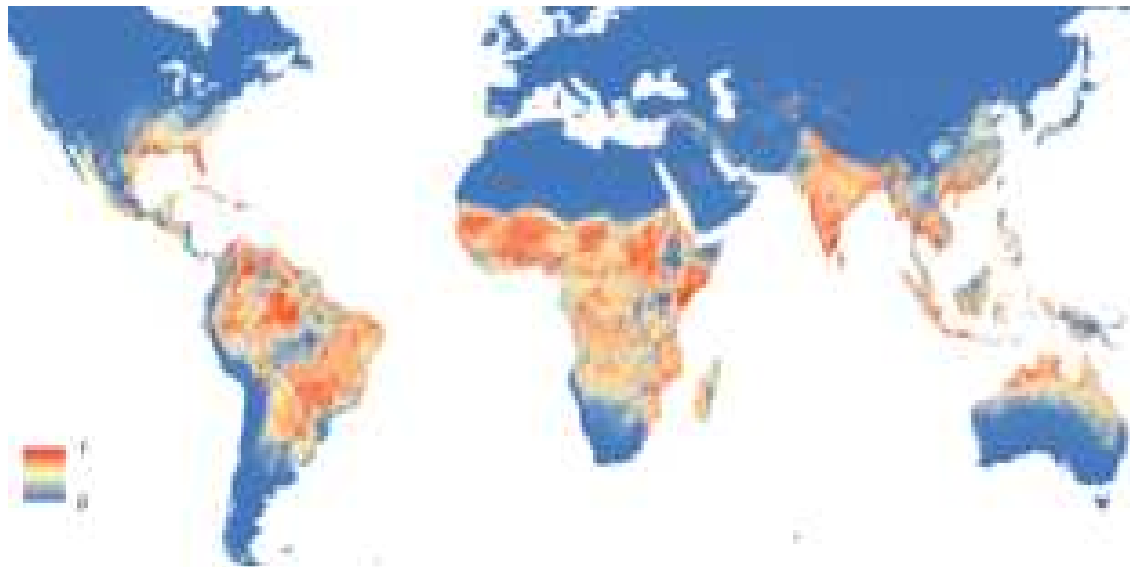


Fig. 3: Global *Aedes aegypti* predicted distribution. The map depicts the probability of occurrence (Petersen *et al.*, 2016).

Vector Transmission

The Zika virus is transmitted daytime by active mosquitoes as its vector. It is primarily transmitted by *Aedes aegypti*, but has been isolated from a number of arboreal mosquito species in the *Aedes* genus, such as *A. africanus*, *A. apicoargenteus*, *A. furcifer*, *A. hensilli*, *A. luteocephalus* and *A. vittatus* with an extrinsic incubation period in mosquitoes of about 10 days. (PAHO, 2015)

The true extent of the vectors is still unknown. The Zika virus has been detected in many more species of *Aedes*, along with *Anopheles coustani*, *Mansonia uniformis*, and *Culex perfuscus*, although this alone does not incriminate them as a vector (PAHO, 2015).

Sexual Transmission or Horizontal Transmission

As of February, 2016, three documented reported cases indicate that Zika virus could possibly be sexually transmitted. In 2014, Zika virus capable of reproducing itself was found in the semen of a man at least two weeks (and possibly up to 10 weeks) after he felt ill with Zika fever (Faye *et al.*, 2014; Hamel *et al.*, 2015). The second report is of a United States biologist who had been bitten many times while studying mosquitoes in Senegal. Six days after returning home in August 2008, he felt ill with symptoms of Zika fever but not before having unprotected intercourse with his wife, who had not been outside the US in 2008. She subsequently developed symptoms of Zika fever, and Zika antibodies in both the biologist's and his wife's blood confirmed the diagnosis (Faye *et al.*, 2014; Hamel *et al.*, 2015).

Transmission during Pregnancy or Vertical Transmission

Zika virus RNA was detected in the amniotic fluid of two pregnant women whose fetuses had microcephaly, indicating that the virus had crossed the placenta and could have caused a mother-to-child infection (Haddow *et al.*, 2012). According to the WHO a causal link between the Zika virus and microcephaly is "strongly suspected but not yet scientifically proven and the microcephaly cases in Brazil are spatio-temporally associated with the Zika outbreak, more robust investigations and research is needed to better understand this potential link (Wong *et al.*, 2013).

Signs and symptoms of Zika Virus Infection

The most common symptoms of Zika are fever, rash, joint pain, and conjunctivitis (red eyes). The illness is usually mild with symptoms lasting for several days to a week. People

usually don't get sick enough to go to the hospital, and they very rarely die of Zika (Musso *et al.*, 2015). Others include:

- Low-grade fever.
- Arthralgia, notably of small joints of hands and feet, with possible swollen joints.
- Myalgia.
- Headache, retro-ocular headaches.
- Conjunctivitis cutaneous maculopapular rash.

Risk Factors Predispose to Zika Virus Infection

Anyone who lives in or travels to an area where Zika virus is found and has not already been infected with Zika virus can get it from mosquito bites.

See your healthcare provider if you develop symptoms (fever, rash, joint pain, red eyes). If you have recently traveled, tell your healthcare provider.

Your healthcare provider may order blood tests to look for Zika or other similar viral diseases like dengue or chikungunya.

What should I do if I have Zika Fever?

- ✓ Treat the symptoms:
- ✓ Get enough of rest
- ✓ Drink fluids to prevent dehydration
- ✓ Take medicine such as acetaminophen to reduce fever and pain
- ✓ Do not take aspirin or other non-steroidal anti-inflammatory drugs

Protect others: During the first week of infection, Zika virus can be found in the blood and passed from an infected person to another person through mosquito bites. An infected mosquito can then spread the virus to other people. To help prevent others from getting sick, avoid mosquito bites during the first week of illness; See your healthcare provider if you are pregnant and develop a fever, rash, joint pain, or red eyes within 2 weeks after travelling to a place where Zika has been reported. Be sure to tell your health care provider where you travelled (WHO, 2016).

Clinical Descriptions of Zika Virus

A Polynesian woman in her early 40s, with no past medical history with the exception of acute articular rheumatism, was hospitalised in our institution for neurological deficits. She had been evaluated one day before (Day 0: onset of neurological disorders) at the emergency department for paraesthesia of the four limb extremities and discharged (Tourné *et al.*, 2009).

At Day 1, she was admitted to the department of neurology through the emergency department because paraesthesia had evolved into ascendant muscular weakness suggestive of GBS. At Day 3, she developed a tetraparesis predominant in the lower limbs, with paraesthesia of the extremities, diffuse myalgia, and a bilateral but asymmetric peripheral facial palsy. Deep tendon reflexes were abolished. There was no respiratory nor deglutition disorders. The patient developed chest pain related to a sustained ventricular tachycardia, and orthostatic hypotension, both suggestive of dysautonomia. The echocardiography was normal, without signs of pericarditis or myocarditis. The electromyogram confirmed a diffuse demyelinating disorder, with elevated distal motor latency, elongated F-wave, conduction block and acute denervation, without axonal abnormalities (Villamil-Gomez *et al.*, 2015).

Laboratory Diagnosis of Zika Virus

Direct detection of dengue virus (DENV) by non-structural protein 1 (NS1) antigen (SD Bioline Dengue NS1 Ag ELISA, ALERE Australia) and reverse transcription-polymerase chain reaction (RT-PCR) (ECDP, 2014) , and ZIKA by RT-PCR , were negative on blood samples eight days after the beginning of influenza-like symptoms (corresponding to Day 1), prior to the administration of intravenous immunoglobulin. Blood samples taken at eight and 28 days after the beginning of the influenza-like syndrome were both positive for ZIKA-specific IgM and ZIKA- and DENV-specific IgG, assessed by in-house enzyme-linked immunosorbent assays (in-house IgM antibody capture (MAC)- enzyme-linked immunosorbent assay (ELISA) and indirect IgG ELISA using inactivated antigen). On the last serum specimen sampled 28 days after the onset of influenza like syndrome, antibody specificity was determined by plaque reduction neutralisation test (PRNT) against serotype 1 to 4 DENV (DENV1-4) and ZIKA. A 90% neutralisation titre >1/320 for DENV1, 1/80 for DENV2, >1/320 for DENV3, 1/20 for DENV4 and >1/320 for ZIKA confirmed that neutralising antibodies against ZIKA and the four DENV serotypes were present in the sera of the patient. These serological analyses indicated a recent infection by ZIKA, and argued for resolute infections by DENV1-4 (ECDC, 2015). The symptoms of Zika are similar to those of dengue and chikungunya, diseases spread through the same mosquitoes that transmit Zika.

See your healthcare provider if you develop the symptoms described above and have visited an area where Zika is found.

If you have recently travelled, tell your healthcare provider when and where you travelled.

Your healthcare provider may order specialized blood tests to look for Zika or other similar viruses like dengue or chikungunya (ECDC, 2015).

Treatment of Zika Virus Infection

There is no specific medicine to treat Zika virus infections.

Treat the symptoms:

- Get enough of rest.
- Drink fluids to prevent dehydration.
- Take medicine such as acetaminophen to reduce fever and pain.
- Do not take aspirin or other non-steroidal anti-inflammatory drugs.
- If you are taking medicine for another medical condition, talk to your healthcare provider before taking additional medication.

Prevention and Control of Zika Virus

When traveling to countries where Zika virus or other viruses spread by mosquitoes are found, take the following steps:

- Wear long-sleeved shirts and long pants.
- Stay in places with air conditioning or that use window and door screens to keep mosquitoes outside.
- Sleep under a mosquito bed net if you are overseas or outside and are not able to protect yourself from mosquito bites.
- Use Environmental Protection Agency (EPA)-registered insect repellents. When used as directed, EPA-registered insect repellents are proven safe and effective, even for pregnant and breast-feeding women.
- Always follow the product label instructions
- Reapply insect repellent as directed.
- Do not spray repellent on the skin under clothing.
- If you are also using sunscreen, apply sunscreen before applying insect repellent.
- If you have a baby or child:
- Do not use insect repellent on babies younger than 2 months of age.
- Dress your child in clothing that covers arms and legs, or

- Cover crib, stroller, and baby carrier with mosquito netting.
- Do not apply insect repellent onto a child's hands, eyes, mouth, and cut or irritated skin.
- Adults: Spray insect repellent onto your hands and then apply to a child's face.
- Treat clothing and gear with permethrin or purchase permethrin-treated items.
- Treated clothing remains protective after multiple washings. See product information to learn how long the protection will last.
- If treating items yourself, follow the product instructions carefully.
- Do not use permethrin products directly on skin. They are intended to treat clothing. (ECDC, 2015).

DISCUSSION

Microcephaly usually results from abnormal brain development the long-term consequences of microcephaly depend on underlying brain anomalies and can range from mild developmental delays to severe motor and intellectual deficits, like cerebral palsy (WHO, 2016; CDC, 2016). In addition to congenital infections, microcephaly can result from chromosomal abnormalities; exposure to drugs, alcohol, or other environmental toxins; premature fusion of the bones of the skull (craniosynostosis); and certain metabolic disorders. The sudden increase in the number of infants born with microcephaly associated

REFERENCES

- "Brazil Health Minister. (2016). Zika epidemic worse than thought". ITV News. 28th January - 1st February.
- Centres for Disease Prevention and Control, (2016). Zika virus. Atlanta, GA: US Department of Health and Human Services, CDC. <http://www.cdc.gov/zika/index.html>.
- Centres for Disease Prevention and Control, (2016). CDC health advisory: recognizing, managing, and reporting Zikavirus: Infections in travelers returning from Central America, South America, the Caribbean and Mexico. Atlanta, GA: US Department of Health and Human Services, <http://emergency.cdc.gov/han/han00385.asp>.
- Centres for Disease Prevention and Control, (2015). Travelers' health. CDC issues

with cerebral damage characteristically seen in congenital infections in a region where an outbreak of a newly circulating virus has recently occurred is suggestive of a possible relationship (CDC, 2015).

CONCLUSION

Zika virus trend infections have been confirmed in several infants with microcephaly and in fetal losses in women infected during pregnancy. Investigation is still going on to understand the full spectrum of outcomes that might be associated with infection during pregnancy, and the factors that might increase risk to the foetus. Healthcare providers are encouraged to report suspected Zika virus disease cases to their state health department to facilitate diagnosis and to mitigate the risk of local transmission.

Recommendations

- Zika virus infection should be considered in patients with acute fever, rash, arthralgia, or conjunctivitis, which travelled to areas predisposed with Zika virus infection and ongoing transmission in the two weeks prior to onset of illness.
- Pregnant women should consider postponing travel to any area where Zika virus transmission is ongoing. Foetuses and infants of women infected with Zika virus during pregnancy should be evaluated for possible congenital infection and neurologic abnormalities.

interim travel guidance related to Zika: Virus for 14 countries and territories in Central and South America and the Caribbean. Atlanta, GA: US Department of Health and Human Services,

<http://wwwnc.cdc.gov/travel/notices>.

Centres for Disease Prevention and Control, (2016). Travelers' health: avoid bug bites. Atlanta, GA: US Department of Health and Human Services, CDC; <http://wwwnc.cdc.gov/travel/page/avoid-bug-bites>.

Cardoso, C.W., Paploski, I, A., Kikuti, M. Rodrigues, M, S., Silva, M, M., Campos, G,S., (2015) Outbreak of Exanthematous Illness Associated with Zika, Chikungunya, and Dengue Viruses, Salvador, Brazil. *Emerging Infectious Diseases*. **December; 21 (12):2274-2276.**

- Duffy, M.R., Chen, T. Hancock, W. T., Powers, A, M., Kool, J. L., Lanciotti R. S., (2009) Virus outbreak on Yap Island, Federated State of Micronesia. *N Engl J Med.* ; **360**:2536 - 43
- European Centre for Disease Prevention and Control, ECDC. (2014). Rapid risk assessment: Zika virus infection outbreak, French Polynesia: updated Available from: http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad514aed4d32b960af70113dbb90&ID=1025-1028.
- European Centre for Disease Prevention and Control, (2015). Zika virus infection Outbreak, Brazil and the Pacific region: from: <http://ecdc.europa.eu/en/publications/Publications/rapid-risk-assessment-Zika%20virus-south-america>.
- European Centre for Disease Prevention and Control, (2015). Microcephaly in Brazil: potentially linked to the Zika virus epidemic Stockholm: ECDC; Available from: <http://ecdc.europa.eu/en/publications/Publications/zika-microcephaly-Brazil-rapid-risk-assessment>.
- European Centre for Disease Prevention and Control, (2015). Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barré syndrome Stockholm: Available from: <http://ecdc.europa.eu/en/publications/Publications/zika-virus-americas-association-with-microcephaly-rapid-risk-assessment>.
- European Centre for Disease Prevention and Control, (2015). Zika virus in Stockholm: Available from http://ecdc.europa.eu/en/professionals/Pages/factsheet_health_professionals.
- Faye, O., Freire, C.C., Iamarino, A., Faye, O. de Oliveira, J.V., Diallo, M., (2014). Molecular Evolution of Zika Virus during Its Emergence in the 20th Century. *PLoS Neglected Tropical Disease.*; **8(1)**:2636.
- Haddow, A.D., Schuh, A.J., Yasuda, C.Y., Kasper, M.R., Heang, V., Huy, R., (2012). Genetic characterization of Zika virus strains: geographic expansion of the Asian lineage. *PLoS Neglected Tropical Disease.*; **6(2)**:1477.
- Hamel, R., (2015). Biology of Zika Virus Infection in Human Skin Cells. *J. Virology* **89**, 8880-8896.
- Heang, V., Yasuda, C.Y., Sovann, L., Haddow, A.D., Travassos, da Rosa, A.P., Tesh, R.B., (2010). Zika virus infection, Cambodia, Emerging Infectious Diseases. ; **18(2)**:349-51. <http://dx.doi.org/10.3201/eid1802.111224>
- Kuno, G., Chang, G.J., Tsuchiya, K.R., Karabatsos, N., (1998) Cropp, C.B., Phylogeny of the genus Flavivirus. *J Virol.*: **73-83**.
- Melo, O.S., Malinger, G., Ximenes, R, Szejnfeld, P.O., Alves, Sampaio, S, Bispo, de Filippis, A.M., (2016). Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound Obstet Gynecol.*; **47(1)**:6-7.
- Ministério da Saúde, (2015). Confirmação do Zika Vírus no Brasil, [Internet Available from: <http://portalsau.de.saude.gov.br/index.php/cidadao/principal/agencia-saude/17701>].
- Musso, D., Roche, C., Robin, E, Nhan, T., Teissier, A, Cao-Lormeau, V.M., (2015). Potential sexual transmission of Zika virus. *Emerging Infectious Diseases.*; **21(2)**:359-361.
- Olson, O, Ken, E. Carvalho C, Danilo, O. (2015). Suppression of a Field Population of *Aedes aegypti* in Brazil by Sustained Release of Transgenic Male Mosquitoes *PLOS Neglected Tropical Diseases* **9(7)**:359-361.
- Pan American Health Organization, World Health Organization, Regional Office for the Americas. (2015). Epidemiological Alert: Neurological syndrome, congenital malformations, and Zika virus infection. Implications for public health in the Americas [Internet]. Washington: World Health Organization; Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&Itemid=&gid=32405&lang=en.
- Petersen, P. Emily, E., Staples, J., Erin, E. Meaney-Delman, M. Dana, D. Fischer, F. Marc, M. Ellington, E. Sascha R., Callaghan, C. William M., Jamieson, J. Denise J., (2016). "Interim Guidelines for Pregnant Women During a Zika Virus Outbreak - United States,". *Morbidity and Mortality Weekly Report* **65(2)**: 30-33.

- Tournebize, P., Charlin, C., Lagrange, M., (2009). [Neurological manifestations in Chikungunya: about 23 cases collected in Reunion Island]. *Rev Neurol (Paris)*; **165(1):48-51**.
- US Centers for Disease Control and Prevention. (2016). CDC issues interim travel guidance related to Zika virus for 14 Countries and Territories in Central and South America and the Caribbean [Internet].
- Villamil-Gomez, W., Silvera, L.A., Paez-Castellanos, J., Rodriguez-Morales A.J., (2015). Guillain-Barre syndrome after Chikungunya infection: A case in Colombia. *EnfermInfeccMicrobiolClin*.
- Wong, P.S., Li, M.Z., Chong, C.S., Ng, L.C., Tan, C.H., *Aedes (Stegomyia) albopictus*.(2013). (Skuse): a potential vector of Zika virus in Singapore. *PLoS Neglected Tropical Diseases*; **7:2348-2352**.
- World Health Organization.(2015). Disease Outbreak News :Zika virus infectionVenezuela. Availablefrom: <http://www.who.int/csr/don/-zika-venezuela/en/>. 59. NN. There have been 23 cases of zika at least six parishes in Maracaibo: El Venezolano; . Available from: <http://www.elvenezolano.com/2015/01/13/se-registrado-23-casos-zika-al-menos-6-parroquias-maracaibo/>. Availablefrom: <http://www.cdc.gov/media/releases/2016/s0315-zika-virus-travel.html>
- "Zika Fever". Centers for Disease Control and Prevention.CDCP. (2016). Retrieved 1st February