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Complications Associated with Zika Virus Infection: A Systematic Review Study

Uyi Faluyi[a], Oyindamola Obadare[b], Aneela Sangem[c], Chinwendu Angel Onuegbu[d], Srinivas Medavarapu[e*]

[a,b,d]Medical Students, All Saints University School of Medicine, Hillsborough Street, P.o.box 1679, Roseau, Dominica

[c]Medical Scribe, Pediatrics 2000, 3332 Broadway, New York, NY 10031, USA

[e]Assistant Professor, All Saints University School of Medicine, Hillsborough Street, P.o.box 1679, Roseau, Dominica

[e]Email: srinivasmedavarapu@yahoo.co.in

Abstract

Zika virus an arthropod borne virus which causes dengue like symptoms is a global concern that has affected thousands of people with mild symptoms and causing more severe symptoms in neonates of infected mothers in recent years. It has been associated with Guillain Barre Syndrome and microcephaly. Guillain Barre Syndrome is an autoimmune disorder that causes demyelination of peripheral nerves and motor fibers causing symmetric muscle weakness which begins from the lower extremities towards the upper part of the body. Microcephaly is a condition in which a baby is born with a small head with incomplete brain development causing mental retardation.

Articles were selected from different databases like PUBMED, BioMed Central, Google Scholar, and Scopus were reviewed by the participants drawing out points relevant to this topic and combining them to describe the Zika virus infection, modes of transmission and complications associated with it.

Keywords: Zika virus; Guillain-Barre syndrome; microcephaly; Infection; All Saints University; Dominica.

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* Corresponding author.

1. Introduction

Zika virus (ZIKV) has drawn a global concern because of its emergence as a widespread pandemic, affecting thousands of people especially offspring of infected pregnant mothers in the Western hemisphere within the last decade [1]. To better deal with ZIKV pandemic, it is important to trace its sequence of events from its origin to the current state of affair. ZIKV was first isolated from Rhesus monkey in 1947 in the Zika forest of Uganda where it caused minor outbreaks with relatively few cases reported [2,3]. The first cases of ZIKV infection were reported in Nigeria, Uganda and Senegal in the 1960s [4]. Zika virus lineage was later identified in the Malaysia in 1966, and despite its continuous spread to more geographical areas, diseases reported from the viral infection was very rare [3].

Zika is an arthropod-borne virus because part of its reproductive cycle occurs inside the body of a host organism. They are classified under the *Flaviviridae* family and *Flavivirus* genus. Other viruses such as dengue, Japanese encephalitis, West Nile and yellow fever, are also *Flaviviruses* [1,2,5,6]. As of 2014, 58 species of mosquitoes are found to be present in the Zika Forest in Uganda, where Zika was first isolated. Majority of these species belong to the genus *Aedes* [7].

Transmission of ZIKV is primarily by the *Aedes aegypti* as well as *Aedes albopictus* (Asian tiger mosquito) mosquito vectors, which reside in tropical and European Mediterranean regions respectively [3, 6, 8, 11]. *A. aegypti* are day time biters that thrive in water holding containers [3]. Other arboviruses as stated earlier (dengue virus, West Nile, chikungunya virus, and yellow fever virus), are also transmitted by the vectors, *Aedes Sp* mosquitoes [12]. Besides *A. aegypti* mosquitoes, ZIKV has been reported to be transmitted perinatally [13] potentially through sexual intercourse [12, 14] and potentially through blood transfusion [15]. Infection leads to a lifelong immunity [13].

ZIKV infection is often referred to as a "dengue-like syndrome" because it has similar symptomatic manifestations as the dengue virus infection [4]. This can potentially result in the misdiagnosis of patients as either ZIKV infected or dengue-virus infected, especially in regions where these two types of viruses are prevalent. Symptoms of ZIKV infection ensue about 9 days after mosquito bite [15]. The most common symptoms include mild fever lasting one to two days, periarticular swelling, non-purulent conjunctivitis, arthralgia, and maculopapular rash [6, 16]. These symptoms serve as one of the basis for the diagnosis of ZIKV. However, the Standard diagnostic method for ZIKV is by reverse-transcriptase polymerase chain reaction (RT-PCR) that tests for viral RNA in serum [2].

In 2007, Micronesian Island of Yap experienced the first ZIKV epidemic [3]. It then spreads across the Pacific to the West, including South and Central America and the Caribbean. But the largest ZIKV outbreak was recorded in French Polynesia between October, 2013, and April, 2014, where 32,000 people were suspected for ZIKV infection [2, 12]. As of July, 2016, 65 countries and territories have reported cases of ZIKV transmission since 2007. 15 countries and territories worldwide have reported cases of Guillain-Barre syndrome caused by ZIKV [17].

Previous studies have reported the potential for ZIKV to cause Guillain-Barre syndrome [18]. However, a recent case-study is the first to provide sufficient evidence for and confirm Guillain-Barre syndrome caused by ZIKV infection [2]. The study reports the complications of Guillain-Barre syndrome from ZIKV infection, following a 20-fold increase in the incidence rate of Guillain-Barre syndrome among ZIKV patients in Micronesia and French Polynesia. Data gotten from this study will be used as a basis for our review study in confirming the complications of Guillain-Barre syndrome from ZIKV infection [2].

Guillain-Barre syndrome is an autoimmune disease that results in the destruction of Schwann cells, causing inflammation and demyelination of peripheral nerves and motor fibers. In Guillain-Barre syndrome, antibodies against neuronal myelin sheath are formed [6]. Symptoms of Guillain-Barre syndrome include symmetric muscle weakness or paralysis beginning in lower extremities and ascending to the upper body, often resulting in facial paralysis [19, 20]. Guillain-Barre syndrome is known to be the leading cause of non-traumatic paralysis, with men more likely to be affected than women [21].

Microcephaly is a rare condition in which a baby is born with small head or in which a baby's head stops growing after birth. In microcephaly, the occipito-frontal circumference measurement of the head is greater than two standard deviations below the mean for age and gender [17, 22]. Microcephaly is classified into primary and secondary [6]. Primary microcephaly occurs during embryonic development and results in defect in neurogenesis or early degenerative processes, while secondary microcephaly occurs postnatally and resulting in abnormality in the development and function of the central nervous system [23]. Common symptoms of microcephaly include intellectual disability, developmental impairment, seizures, and hearing and vision impairment [6].

The aim of this study is to conduct a literature review about ZIKV infection and its neurological complications including Guillain-Barre syndrome and microcephaly, using recent research studies as template.

2. Materials and methods

40 articles published between 2007 and 2016 were carefully examined based on the relevance of their contents to the topic in study. Of these articles, 10 were selected to carry out this review study. Some of the references of these articles were also used in our work, based on their relevance to our topic. These articles were case-control studies, review studies, retrospective studies, survey studies and cohort studies. Articles and data collection was done using research journals and databases such as Google Scholar, BioMed Central, PubMed and Scopus. Some of the journals used were *Journal of Virology, Journal of Autoimmunity, Lancet, Emerging Infectious diseases, Neuroepidemiology,* etc. Key phrases used during the search were 'Complications associated with Zika virus', 'Guillain-Barre syndrome and Zika virus', 'Microcephaly and Zika', 'Mode of transmission of Zika' and 'Zika virus control and preventive measures'. There were 7 articles between 2012 and 2016, with data showing the prevalence and incidence rate of Microcephaly and Guillain-Barre syndrome linked with ZIKV. Of these articles, one was selected for our Guillain-Barre analysis based on the large number of cases reported (42 patients) [2]. Data from the other 6 articles were used for our microcephaly analysis. 18 articles were used to obtain information about the history of Zika, complications associated with ZIKV, potential vaccine and

treatment methods. According to the articles, the subjects used for data collection were patients who had ZIKV or are suffering from ZIKV infection within the past 5 years. Patient's age, sex, islands of residence, and clinical signs and symptoms were taken into account when collecting the data. The subjects were suffering from either Guillain-Barre syndrome or microcephaly, or developing the symptoms.

3. Results and Discussion

Of all the complications related to ZIKV, microcephaly has been found to be the most common and most dangerous. In Central America alone, 25 countries and regions have had cases of ZIKV as of February 2016, with reports of a significant increase in microcephaly among neonates caused by ZIKV in Brazil [24]. Following ZIKV outbreak in the northeastern region of Brazil in 2015, the Ministry of Health in Brazil (MOH) released a bulletin that confirms the relationship between ZIKV infection and microcephaly [6]. There was a significant increase in the number of newborns suffering from microcephaly through fetal transmission of the ZIKV from affected mothers. Another study also reports a significant rise in the suspected cases of microcephaly associated with Zika patients in Brazil from 739 people in November 2015 to 4783 people in January 2016 [6].

Microcephaly is a medical condition present at birth, resulting in a small head and decreased brain development leading to poor motor function and decreased intellectual ability. Microcephaly can be caused by factors like alcohol, tobacco and radiation during pregnancy [25]. In the last few years, Zika virus epidemic has led to an increased number of cases of microcephaly in countries like Brazil, French Polynesia, Central America, Southeast Asia, Yap Island and Columbia. Zika virus as said earlier is from the family Flaviviridae, transmitted by the vector Aedes aegypti and Aedes albopictus [25]. Zika virus can directly cause damage or abnormality to fetal brain through the placenta, due to its neurotropic characteristics [25]. A testable hypothesis states that Zika virus affects neuroepithelial cells of the fetus at an early stage of development which might not be so because the direct exchange of maternal blood to the placenta begins at the 10^{th} week of gestation [25]. Other modes of transmission of Zika virus can be by leakage of the virus through trophoblast cells by exocytosis, uterine secretion, and diffusion into the amniotic fluid [25]. The transfer of Zika virus during fertilization by infected semen allows access to the early embryonic development of the fetus [25].

Another hypothesis was suggests that Zika virus is transmitted at about 12 week of gestation where direct exchange of maternal and fetal blood begins [25]. This occurs during the last stage of embryonic development [25]. This is also when infected pregnant women show signs of zika virus infection proving the evidence of direct viral transmission [25].

When testing for Zika virus, the highest amount is mostly found in the fetal membrane, placenta and umbilical cord [24]. It is suggested that the virus can cross the placental barrier as a result causing microcephaly or the placenta mounts an immune response against the exposure, which contributes to causing the brain defect [25].

The role of zika virus in the pathogenesis of microcephaly in fetuses could be attributed to nutrient deficiency [26]. GLUT1, the main glucose transporter across the blood brain barrier and placental barrier. A genetic GLUT1 deficiency is associated with microcephaly. Researchers are yet to confirm the effect of ZIKV on

GLUT1 however inhibition of protein kinase C, an enzyme involved with GLUT1 functionality, has been reported to be involved in the replication of dengue virus which is in the same genome as zika virus [27].

It is assumed that the viral effect of zika on GLUT1 could inhibit access of the placenta to the glucose needed for rapid endothelial growth of fetus thereby causing microcephaly [26].

During the week of symptomatic infection, RNA detection in serum or blood is considered to be the diagnostic method of choice [28]. ZIKV RNA can be detected in urine for some days longer [29, 30]. ZIKV is also present in semen for an unknown length of time, and reports of sexual transmission of ZIKV have emerged [12, 14, 31].

Table 1: Maternal symptoms, fetal abnormality, and final diagnosis.

Week of zika associated symptoms + source	**Mothers' symptoms**	**Week of first abnormal fetal ultrasound**	**Fetal head circumference**	**Fetal weight**	**Associated fetal defect**	**Diagnosis**
18 week [32]	Cutaneous rash with itching	21 weeks	30cm	-	Dilation of ventricle, hypoplastic cerebellum, absence of cerebral vermis	Microcephaly
- [33]	-	18 weeks	21.5cm	930g	Intracranial calcification, reduced cortical parenchyma, lesion of posterior fossa, hydrothorax, subcutaneous edema	Microcephaly, hydranencephaly and still birth
11 week [34]	-	20 weeks	24cm	-	Severe brain abnormality, reduced head circumference	Microcephaly

13 week [35]	Musculoskeletal and retroocular pain, itching, maculopapular rash	29 weeks	26cm	1470g	Calcification in cortex, Wallerian degeneration	Microcephaly
- [35]	-	38 weeks	33cm	3500g	Lower limb spasm at birth, calcification in basal ganglia, ventriculomegaly, chorioretinal scar	No microcephaly but presents with ophthalmic disorder
26 week [36]	Maculopapular rash	35 weeks	29cm	2000g	Abnormal umbilical artery flow, intrauterine growth restriction	Microcephaly
8 week [35]	Maculopapular rash	35 weeks	24cm	2300g	Cerebral calcification, abnormal middle cerebral artery, intrauterine growth restriction.	Microcephaly
22 week [36]	Maculopapular rash	27 weeks	25cm	1400g	Placenta insufficiency, oligohydramnios, intrauterine growth restriction.	Microcephaly
25 week [36]	Maculopapular rash	30 weeks	26cm	1500g	Fetal death detected at 36 week after repeated ultrasound	Stillbirth
Unknown [37]	Maculopapular rash	30.1 weeks	24.6cm	1179g	Brain atrophy, coarse calcification involving white matter of the frontal lobe	Microcephaly

					including cerebellum, enlarged cisterna magna	

The articles used in the table above [32 -37] are collected from different countries to prevent selection bias. The data includes the maternal symptom associated with Zika virus infection, the week of symptoms, the first gestational week of detecting fetal abnormality, the circumference of the fetus head, weight of the fetus, related defect of fetus and the final diagnosis.

From our data in the table, pregnant women present with a maculopapular rash and fever which is a common symptom of ZIKV infection. Since most ZIKV infection are asymptomatic [35], most of the pregnant women did not show any symptoms which led to late detection of fetal abnormality. The fetuses presented in the table were tested positive to having being infected by ZIKV. The weight of the fetus was not present in some result because the fetus were terminated before birth and all maternal family history revealed no genetic disease relating to microcephaly, still birth, and visual defect. Cerebral Cortex calcification was the most common effect of ZIKV related microcephaly with normal cerebellum, brain stem and spinal cord and the PCR assay test was negative for all other Flaviviruses and non flavivirus (e.g. HIV, HPV etc.) in each fetus. All fetus presented in the table suffered severe brain damage an eye defect associated with ZIKV infection because they all tested positive to ZIKV infection [37]. Tests showed that all other organ present in the fetus was normal meaning the eye and brain is the main target for defects associated with ZIKV infection [37]. The most common abnormality seen is the calcification of the fetal cerebral cortex which is mostly identified at the late stage of gestation [37].

Apart from microcephaly and eye defect, ZIKV infection has also been known to cause the premature death of the fetus and hydrops fetalis [33]. The absence of symptoms in infected pregnant women may lead to hydrocephalus in the fetus and the strain of ZIKV that lead to fetal demise and hydrocephalus was the same as the ZIKV outbreak in America and the Caribbean [33]. Ocular defect can be seen in fetus that have been infected by ZIKV but does not present with microcephaly [35]. ZIKV can be transferred to the fetus by the placenta through blood exchange [35]. It goes to the central nervous system and affects neural cells [32].

The least common complication of ZIKV would be Guillain-Barre syndrome which is an attack on the nervous system leading to symptoms like symmetric muscle weakness or paralysis starting from the lower extremities to upper body often resulting in facial paralysis [20] as well as varying degree of sensory disturbances and movement of cranial nerves [19]. Paralysis caused by Guillain-Barre syndrome affects 1-4 persons per 100,000 populations every year, making it the leading cause of non-traumatic paralysis [2]. Besides ZIKV, other infections can lead to Guillain-Barre syndrome including Epstein-Barr virus infection, upper respiratory infections, cytomegalovirus infections and digestive tract infections [2]. Guillain-Barre syndrome has been reported to also be caused by other arboviral diseases including chikungunya, West Nile, dengue and Japanese encephalitis [2]. ZIKV and dengue virus have similar symptomatic manifestations, and both has been shown to cause Guillain-Barre syndrome [4]. So patients suffering dengue virus can often be misdiagnosed as having ZIKV if the standard diagnostic method is not used. According to the reference study used in this article, dengue virus was also prevalent at the time of ZIKV outbreak in French Polynesia. To ensure that Guillain-Barre syndrome is caused by ZIKV and not just dengue virus, a series of control subjects were used to confirm that ZIKV, with or without concurrent of dengue virus can cause Guillain-Barre syndrome.

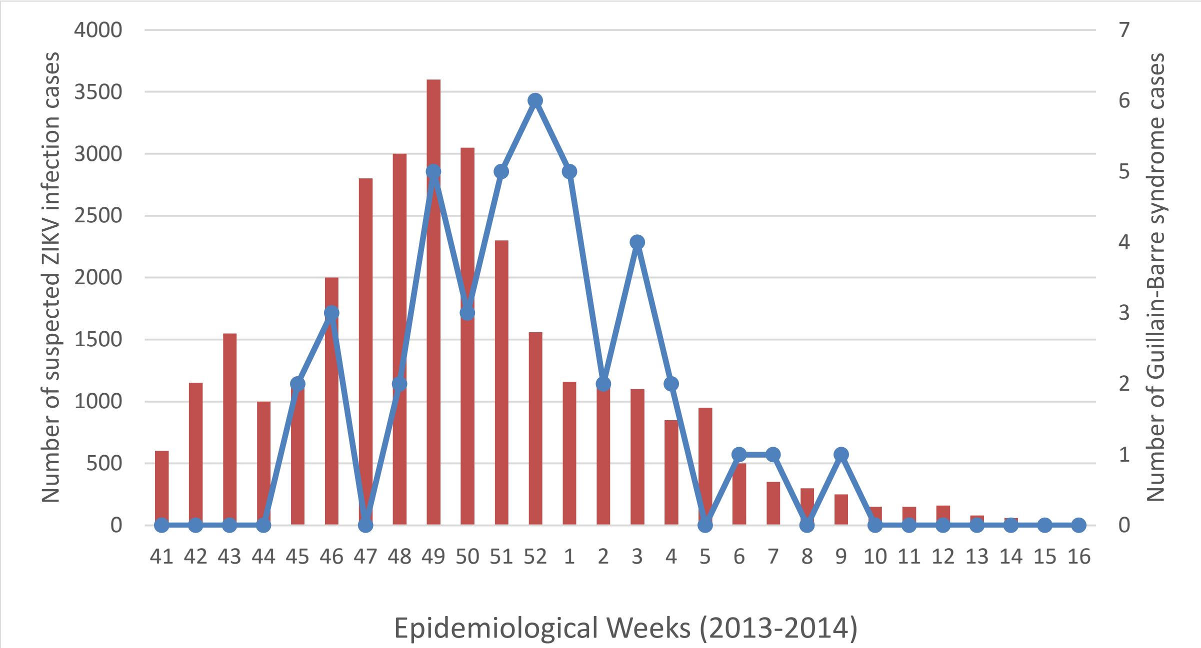

Figure 1: Graph showing the weekly cases of suspected ZIKV infection in French Polynesia between October 2013 and April 2014, obtained from Cao-Lormeau *et al* (2016).

*The numbers of suspected ZIKV infection cases are approximated values.

In our Guillain-Barre syndrome analysis, we only used one study for analysis [2] because it is the only study with a large sample size (n=42) out of all related studies we looked at, where the sample sizes were less than 5. This allows for a significant analysis. Figure 1 shows the incidence rate of ZIKV infection and Guillain-Barre syndrome, recorded on a weekly basis from October, 2013 (41st week) to April, 2014 (16th week). From figure 1, we see the first case of ZIKV infection during the outbreak recorded in the 41st week of 2013, with over 500 suspected cases reported. The peak of the ZIKV epidemic was recorded on the 49th week with over 3500 suspected ZIKV cases and 5 cases of Guillain-Barre syndrome. The peak for cases of Guillain-Barre syndrome is seen at the 52nd week, which also had over 1500 suspected cases of ZIKV. In total, 42 cases of Guillain-Barre syndrome caused by ZIKV were recorded with or without the concurrent of dengue virus, which was also epidemic during the outbreak. Based on a calculated attack rate of 66%, the risk of developing Guillain-Barre syndrome following ZIKV infection in French Polynesia was estimated to be 0.48 per 2000 ZIKV infection.

Till date, there is no known treatment or vaccine for ZIKV [1]. Only some of the symptoms can be treated to provide comfort to patients, as well as by taking prevention measures. Implementation of control measures by individuals and government in regions or territories where ZIKV is an epidemic is needed to prevent and control the spread of ZIKV infection. For individuals, use of mosquito repellants, mosquito nets and air conditioning could help reduce risk for mosquito bites. For the government, implementation of policies that will limit or control the movement of pregnant mothers to regions/territories where ZIKV is an epidemic could be required. Programs to create public awareness of ZIKV epidemic and to educate citizens on possible precautionary measures and general mosquito management could also be implemented.

4. Conclusion

Zika virus is a mild viral infection that can result in serious complications including Guillain-Barre syndrome and microcephaly in neonates of infected mothers. Avoid travelling to endemic areas especially when you are trying to conceive. Although reportedly 80% of ZIKV are asymptomatic, severe neurological complications like microcephaly and Guillain-Barre syndrome makes it one of the most dangerous viral infection globally. Until effective treatments or vaccine for ZIKV is introduced, the best way to combat ZIKV outbreak is by taking preventive measures for protection against infected mosquitos especially in endemic areas and by treatments to alleviate some of the symptoms.

Further researches need to be done to further strengthen Guillain-Barre and microcephaly association with ZIKV and discover other new possible complications that can result from ZIKV infection.

References

[1]. Chang, C., Ortiz, K., Ansari, A., and Gershwin, M, E. (2016) The Zika outbreak of the 21st century. Journal of Autoimmunity. Vol 68: 1-13.

[2]. Cao-Lormeau, V-M, Blake, A., Mons, S., Lastere, S., Roche, C., Vanhomwegen, J., Dub, T., Baudouin, L., Teissier, A., et al. (2016). Guillain-Barre syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet. Vol 387: 1531-1539.

[3]. Krug, E, G. (2016). Zika virus and Guillain-Barre syndrome: Another viral cause to add to the list. Lancet. Vol 387: 1486-1487.

[4]. Duffy, M, R., Chen, T, H., Hancock, W, T., et al. (2009) Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. Vol 360: 2536-2543.

[5]. Choumet, V., and Despres, P. (2015) Dengue and other flavivirus infections. Rev. Sci. Tech. Vol 34: 473-478.

[6]. De Carvalho, N, S., De Carvalho, B, F., Fugaca, C, A., Doris, B., and Biscaia, E, S. (2016). Zika virus infection during pregnancy and microcephaly occurrence: a review of literature and Brazilian data. Braz I Infect Dis. Vol 20(3): 282-289.

[7]. Kaddumukasa, M, A., Mutebi, J, P., Lutwama, J, J., Masembe, C., and Akol, A, M. (2014). Mosquitoes of Zika forest, Uganda: species composition and relative abundance. J. Med. Entomol. Vol 51: 104-113.

[8]. Carneiro, L, A., and Travasso, L, H. (2016) Autophagy and viral diseases transmitted by Aedes aegypti and Aedes albopictus. Microbes Infect. Vol 3: 169-171.

[9]. Grard, G., Caron, M., Mombo, I, M., Nkoghe, D., Mboui-Ondo, S., Jiolle, D., Fontenille, D., Paupy, C., and Leroy, E, M. (2014) Zika virus in Gabon (Central Africa) – 2007: A new threat from Aedes albopictus? PLoS Negl. Trop. Dis. Vol 8 (2): e2681.

[10]. Li, M, I., Wong, P, S., Ng, L, C., and Tan, C, H. (2012) Oral susceptibility of Singapore Aedes (Stegomyia) aegypti (Linnaeus) to Zika virus. PLoS Negl Trop Dis. Vol 6 (8): e1792.

[11]. Marcondes, C, B., and Ximenes, M, F. (2015) Zika Virus in Brazil and the danger of infestration by Aedes (stegomyia) mosquitoes. Rev. Soc. Bras. Med. Trop. Vol 49.

[12]. Musso, D., Roche, C., Robin, E., Nhan, T., Teissier, A., and Cao-Lormeau, V-M. (2015). Potential sexual transmission of Zika virus. Emerg Infect Dis. Vol 21: 359-361.

[13]. Besnard M, Lastère S, Teissier A, Cao-Lormeau VM, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. Euro Surveill 2014; 19: 8–11.

[14]. Foy, B, D., Kobylinski, K, C., Chilson-Foy, J, L., Blitrich, B, J., Travassos da Rosa, A., Haddow, A, D., Lanciotti, R, S., and Tesh, R, B. (2011). Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg Infect Dis. Vol 17: 880-882.

[15]. Musso, D., Nhan, T., Robin, E., Roche, C., Bierlaire, D., Zisou, K., Shan Yan, A., Cao-Lormeau, V-M., and Broult, J. (2014). Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. Euro Surveill. Vol 19 (14).

[16]. Smith-Sprangler, C, M., Bhattacharya, J., and Goldhaber-Fiebert, J, D. (2012). Diabetes, its treatment, and catastrophic medical spending in 35 developing countries. Diabetes Care. Vol 35: 319-326.

[17]. World Health Organization. Zika situation report. Zika and potential complication. Retrieved from WHO website. http://apps.who.int/iris/bitstream/10665/246222/1/zikasitrep14Jul16-eng.pdf?ua=1D Date Retrieved: July, 16th, 2016.

[18]. Oehler, E., Watrin, L., Larre, P., Leparc-Goffart, I., Lastere, S., Valour, F., Baudouin, L., Mallet, H, P., Musso, D., and Ghawche, F. (2014) Zika virus infection complicated by Guillain-Barre syndrome-case report, French Polynesia, December 2013. Euro Surveill. Vol 19 (9): pii 20720.

[19]. Wim, A, C., Jacobs, B, C., and Laman, J, D. (2004). The Guillain-Barre syndrome: a true case of molecular mimicry. Trends Immunol. Vol 25: 261-266.

[20]. Van den Berg, B., Walgaard, C., Drenthen, J., Fokke, C., Jacobs, B, C., and van Doorn, P, A. (2014). Guillain-Barre Syndrome: pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol. Vol 10: 469-482.

[21]. McGrogan, A., Madle, G, C., Seaman, H, E., and de Vries, C, S. (2009). The epidemiology of Guillain-Barre syndrome worldwide. A systematic literature review. Neuroepidemiology. Vol 32: 150-163.

[22]. Abuelo, D. (2007) Microcephaly syndromes. Semin Pediatr Neurol. Vol 14: 118-127.

[23]. Woods, C, G., and Parker, A. (2013). Investigating microcephaly. Arch Dis Child. Vol 98: 707-713

[24]. Samarasekera, U., and Trimfol, M. (2016). Concern over Zika virus grips the world. Lancet. Vol 387: 521-524.

[25]. Adibi, Jennifer J et al. "Teratogenic Effects Of The Zika Virus And The Role Of The Placenta". The Lancet 387.10027 (2016): 1587-1590. Web.

[26]. Zika virus and GLUT1 Blonz, Edward R The Lancet Infectious Diseases , Volume 16 , Issue 6 , 642

[27]. Noppakunmongkolchai W, Poyomtip T, Jittawuttipoka T, et al. Inhibition of protein kinase C promotes dengue virus replication. Virol J 2016; 13: 35.

[28]. Zika Virus Infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities R.W. Driggers, C.-Y. Ho, E.M. Korhonen, S. Kuivanen, A.J. Jääskeläinen, T. Smura, A. Rosenberg, D.A. Hill, R.L. DeBiasi, G. Vezina, J. Timofeev, F.J. Rodriguez, L. Levanov, J. Razak, P. Iyengar, A. Hennenfent, R. Kennedy, R. Lanciotti, A. du Plessis, and O. Vapalahti, N Engl J Med 2016;374:2142-51. DOI: 10.1056/NEJMoa1601824.

[29]. Gourinat AC, O'Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M. Detection of Zika virus in urine. Emerg Infect Dis 2015; 21: 84-6.

[30]. Korhonen EM, Huhtamo E, Smura T, Kallio-Kokko H, Raassina M, Vapalahti O. Zika virus infection in a traveller returning from the Maldives, June 2015. Euro Surveill 2016; 21.

[31]. McCarthy M. Zika virus was transmitted by sexual contact in Texas, health officials report. BMJ 2016; 352: i720.

[32]. Calvet, G., Aguiar, R, S., Melo, A, S, O., Sampaio, S, A., Filippis, I ., Fabri, A., Araujo, E, S, M., Sequeira, C, P., Mendonça, M, C, L., Oliveira, L., Tschoeke, D, A., Schrago, C, G., Thompson, F, L., Brasil, P., Santos, B, F., Nogueira, R, M, R., Tanuri, A., and Filippis, A, M, B.(2014). Lancent . Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study.Vol 16:653-660

[33]. Sarno ,M., Sacramento ,G,A., Khouri , R., Rosario ,S,M., Costa ,F., Archanjo , G., Santos, A,L., Nery, N., Vasilakis ,N., Ko ,A and de Almeida ,P,R,A.(2016). PLOS. Zika virus infection and still birth:A Case of Hydrops Fetalis, Hydranencephaly and Fetal Demise. Vol 10:1-5

[34]. Rasmussen , A,S., Jamieson,J,D., Honein , A,M., and Petersen, R,L.(2016).The new England journal of medicine .Zika virus and birth defect- Reviewing the evidence for casuality. Vol 20:1981-1987.

[35]. Ventura, C, V., Maia, M., Dias, N.,Ventura, O,L., and Belfort, R.(2016). Correspondence. Zika: neurological and ocular finding in infants without Microcephaly. Vol 387:2502

[36]. Brasil ,P., Pereira, J, P., Gabaglia, R, C., Damasceno, L., et al.(2016). The new England journal of medicine. Zika virus infection in pregnant women in Rio de Janeiro-Preliminary Report.DOI:10.1056

[37]. Mlakar, J., Korva, M., Tul, N.,Popovic, M., Poljsak-Prijatelj, M., Mraz, J., Kolenc, M., Rus, K,R., Vipotnik, T,V., Vodusek, F,V., Vizjak ,A., Pizem, J., Petrovec, M., and Zupanc, A, T.(2016).The England journal of medicine. Zika virus associated with Microcephaly. Vol 374:10:951-958.