

## Review Article

---

# Recent Update on Management of Pregnancy with ZIKA Virus Infection

F.M ANAMUL HAQUE<sup>1</sup>, SARIA TASNIM<sup>2</sup>

### Abstract:

*Zika, an emerging Aedes-mosquito-borne virus are currently being identified with alarming outbreak is spreading throughout the America. Health expert warn that anytime virus could enter Bangladesh due to worldwide easy communication of the people. Concerns have grown even stronger in Bangladesh after news media in Thailand and Taiwan reported cases of the viral infection among locals. Both places are popular destinations for Bangladeshi travellers, increasing the risk of the virus also spreading here. Aedes aegypti, the carrier of the virus, is also responsible for spreading dengue fever throughout the Indian sub-continent region, especially in Bangladesh and India. Pregnant women are at increased risk of neonatal complication like microcephaly if infected with ZIKA virus. This review describes epidemiology, transmission of ZIKAV, clinical presentation and recommendations for pregnancy according to CDC, RCOG,SGOC and WHO guidelines.*

**Key words:** CDC, ZIKA virus, Pregnancy

### Introduction:

The Zika virus (ZIKV) first identified in monkeys in 1947, is the category of flavi viruses and later reported in humans in Uganda in 1952<sup>1</sup>. In Brazil first reported microcephaly in babies born to women who had a Zika infection. Viral RNA has been isolated in the brain tissue of a microcephalic infant<sup>2</sup>, and from the amniotic fluid in at least two cases where a microcephalic brain abnormality had been identified on ultrasound. The mosquito vector for Zika is a common mosquito in warmer climates that bites both day and night. The viral illness is brief, and approximately 80% will be asymptomatic. Sexual transmission of the virus has now been documented by men returning from endemic areas. Persons who have had Zika appear to be at increased risk of developing Guillain-Barre syndrome.

### Epidemiology

In 1947 ZIKV was first isolated from Ugandan monkeys. Human infections were detected in Uganda and Tanzania in 1952<sup>3,4</sup>. The first major outbreak of ZIKV disease was reported on the island of Yap (Micronesia) in the southwestern Pacific Ocean in

2007<sup>5</sup>. Between 2013 and 2015, several significant outbreaks occurred on islands and archipelagos from the Pacific region including a large outbreak in French Polynesia<sup>6,7</sup>. An outbreak was also reported in Cape Verde<sup>8</sup>. First report of local transmission in America was reported in Easter Island in 2014<sup>9</sup>. It has since spread to more than 20 countries and territories of south America<sup>10</sup>. The Brazilian Ministry of Health has estimated that 440,000 to 1,300,000 ZIKV infections occurred in Brazil in 2015. It is anticipated that ZIKV will continue to spread through the Americas, in particular in tropical and subtropical regions<sup>11,12</sup>.

### Mode of Transmission

The bite of an infected female Aedes mosquito is responsible for transmission of ZIKV. There are various species of Aedes mosquito, which may have the potential to transmit ZIKV, but Aedes aegypt is the most commonly associated with ZIKV<sup>13</sup>. When an infected mosquito bites a human, the first symptoms of ZIKV can develop in 3 to 12 days but it can be shorter or longer in some people. Human-mosquito-human, is the mode of transmission of the virus and direct human to human transmission does not occur.

---

1. Assistant Professor, Institute of Child & Mother Health, Matuail, Dhaka

2. Ex Professor (O & G ), Institute of Child & Mother Health, Matuail, Dhaka

Sexual transmission of the virus in human semen can occur<sup>14,15</sup> but more evidence is required to confirm whether or not this is possible. ZIKV can be transmitted by blood transfusion. Cases of maternal fetal transmission have been confirmed. ZIKV can not be transmitted to babies through breast milk and the advice to mothers to breastfeed remains unchanged<sup>16</sup>.

### Symptom

- Among the ZIKV infected person only 20-25% will manifest symptoms<sup>17</sup>. The clinical manifestations are generally similar to dengue and chikungunya infection with considerable overlap in symptoms, although ZIKV infections usually have milder clinical illness, short lived, lasting only 2-7 days<sup>18</sup>.
- Incubation period 3-12 days<sup>19</sup>
- Typical symptoms may include: a low grade fever, maculopapular rash, which may be itchy, non-purulent conjunctivitis/red eyes, arthralgia (with possible swelling, mainly in the smaller joints of the hands and feet), myalgia, headache, and eye pain<sup>20</sup>.
- Serious complications from ZIKV are uncommon. However, an increase in cases of fetal microcephaly<sup>22</sup>, Guillain-Barresyndrome<sup>23</sup> and other neurological and autoimmune syndromes has been reported in areas where ZIKV outbreaks have occurred<sup>24</sup>.

### How to diagnose ZIKV

#### Indication of testing

Pregnant women with a history of travel to an area with Zika virus transmission and who report two or more symptoms consistent with Zika virus disease during or within 2 weeks of travel, or who have ultrasound findings of fetal microcephaly or intracranial calcifications, should be tested for Zika virus infection.

Testing is not indicated for women without a travel history to an area with Zika virus transmission.

- Reverse transcription polymerase chain reaction (RT-PCR) for ZIKV in maternal serum of symptomatic patients.
- Antibody testing is less reliable due to potential cross-reaction with antibodies against other similar viruses (e.g. dengue or yellow fever<sup>25</sup>).
- Amniotic fluid study for ZIKV RT-PCR can also be performed although it is currently not known how

sensitive or specific this test is for congenital infection, or the likelihood of an infected fetus being affected, i.e. subsequently developing a fetal abnormality<sup>26,27</sup>.

### Treatment

Treatment is supportive, no specific antiviral therapy for the treatment of ZIKV infection. The supportive treatment like antipyretics (acetaminophen in pregnancy), hydration and rest is recommended. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided until dengue can be ruled out to reduce the risk of hemorrhage<sup>25</sup>. Symptomatic disease typically lasts for up to 7 days. For any symptoms associated with GBS, urgent medical care is recommended. If during pregnancy, ZIKV infection is confirmed referral to a Maternal Fetal Medicine Specialist should be made. If microcephaly, intracranial calcifications or other abnormalities are identified, appropriate counselling by a Neonatologist and Pediatric Infectious Diseases Specialist on potential neurodevelopmental outcome should be offered to parents

### Preventive measures

CDC recommends that all pregnant women consider postponing travel to areas where Zika virus transmission is ongoing, because there is neither a vaccine nor prophylactic medications available to prevent Zika virus infection<sup>25</sup>. Pregnant women who are willing to travel to an area with Zika virus transmission, should strictly follow steps to avoid mosquito bites<sup>25,26</sup>.

The main vector for ZIKV, the Aedes mosquito is active predominantly during daylight hours. They commonly bite during mid-morning and late afternoon to dusk. On the other hand the Anopheles mosquito which transmits malaria is more active by night. Travellers should take all possible measures to minimise the chances of mosquito bites. This includes wearing light-coloured, loose-fitting clothes that cover as much exposed skin as possible, for example long trousers and long sleeves specially during the daytime as much as possible. Clothing can be treated with an insecticide (e.g. permethrin) which kills insects, including mosquitoes. 19N, N-diethyl meta toluamide (DEET) 50% based repellents are the most commonly available and are safe in pregnant and breastfeeding women (and in infants and children over the age of 2 months)<sup>27,28</sup>. Insect repellents should not be

ingested, and not come in contact with the eyes or mouth. Insect repellents should be re-applied regularly, particularly after swimming and in hot humid conditions when they may be removed by perspiration. When both sunscreen and insect repellents are required, the insect repellent should be applied over the sunscreen<sup>29</sup>.

### **Recommendations for Pregnant Women with History of Travel to an Area of Zika Virus Transmission**

Women who traveled to an area with ongoing Zika virus transmission during pregnancy should be evaluated for Zika virus infection and tested in accordance with CDC Interim Guidance<sup>30</sup>. Because of the similar geographic distribution and clinical presentation of Zika, dengue, and chikungunya virus infection, patients with symptoms consistent with Zika virus disease should also be evaluated for dengue and chikungunya virus infection, in accordance with existing guidelines<sup>31,32</sup>. Zika virus testing of maternal serum includes reverse transcription-polymerase chain reaction (RT-PCR) testing for symptomatic patients with onset of symptoms within the previous week. Immunoglobulin M (IgM) and neutralizing antibody testing should be performed on specimens collected  $\geq 4$  days after onset of symptoms. Cross-reaction with related flaviviruses (e.g., dengue or yellow fever) is common with anti-body testing, and thus it might be difficult to distinguish Zika virus infection from other flavivirus infections. Testing of asymptomatic pregnant women is not recommended in the absence of fetal microcephaly or intracranial calcifications. Zika virus RT-PCR testing can be performed on amniotic fluid (7,9). Currently, it is unknown how sensitive or specific this test is for congenital infection. Also, it is unknown if a positive result is predictive of a subsequent fetal abnormality, and if so, what proportion of infants born after infection will have abnormalities. Amniocentesis is associated with an overall 0.1% risk of pregnancy loss when performed at less than 24 weeks of gestation<sup>33</sup>. A positive RT-PCR result on amniotic fluid would be suggestive of intrauterine infection and potentially useful to pregnant women and their health care providers<sup>34</sup>.

### **Women reporting symptoms consistent with ZIKV disease**

If a pregnant women have a history of travel to an area with active ZIKV transmission and present with symptoms consistent with ZIKV disease during or

within two weeks of travel, should be tested for ZIKV infection and other travel associated infections(including malaria). If ZIKV is identified on laboratory testing, the woman should be referred to a fetal medicine service for further assessment. If the test for ZIKV is negative, serial (4-weekly) fetal ultrasound scans should be considered to monitor fetal growth and anatomy. Women whose symptoms have resolved by the time of presentation, ZIKV testing is not recommended but they too should be offered serial (4-weekly) fetal ultrasound scans. Routine testing of asymptomatic women (those who remained asymptomatic while travelling and for two weeks after their return from a ZIKV affected area) is not recommended. However, serial fetal ultrasound scans as above should be considered (as ZIKV infection is associated with minimal symptoms in the majority). Any woman in whom a small fetal head (Head Circumference more than 2 Standard Deviations below the mean for gestational age, i.e. below the 2.5<sup>th</sup> centile) or brain abnormality(such as intracranial calcifications) is diagnosed on ultrasound, and who has previously visited a ZIKV affected area during pregnancy, should also be referred to a maternal fetal medicine service for further assessment. If diagnosis of fetal microcephaly or intracranial calcifications is made but women who have not travelled to a ZIKV affected area during pregnancy do not need to be tested. If fetal microcephaly or brain abnormality, such as intracranial calcification, is diagnosed, consideration should be given to performing an amniocentesis to test for the virus using RT-PCR. Amniocentesis is associated with a small risk of miscarriage or preterm birth and should not be performed before 15 weeks of gestation. Even if ZIKV positive, it is not known how sensitive or specific this test is for congenital infection, nor the likelihood of an infected fetus being affected. Nevertheless, if there is fetal abnormality on ultrasound and ZIKV PCR on amniocentesis is positive, then it is highly likely that the abnormality is ZIKV associated and that the outcome is likely to be poor. When brain abnormalities are identified on ultrasound scan, consideration should be given to performing fetal brain MRI which may detect abnormalities that have not been detected on ultrasound. When a significant brain abnormality or microcephaly is confirmed in the presence of ZIKV infection, the option of termination of pregnancy should be discussed with the woman, regardless of gestation.

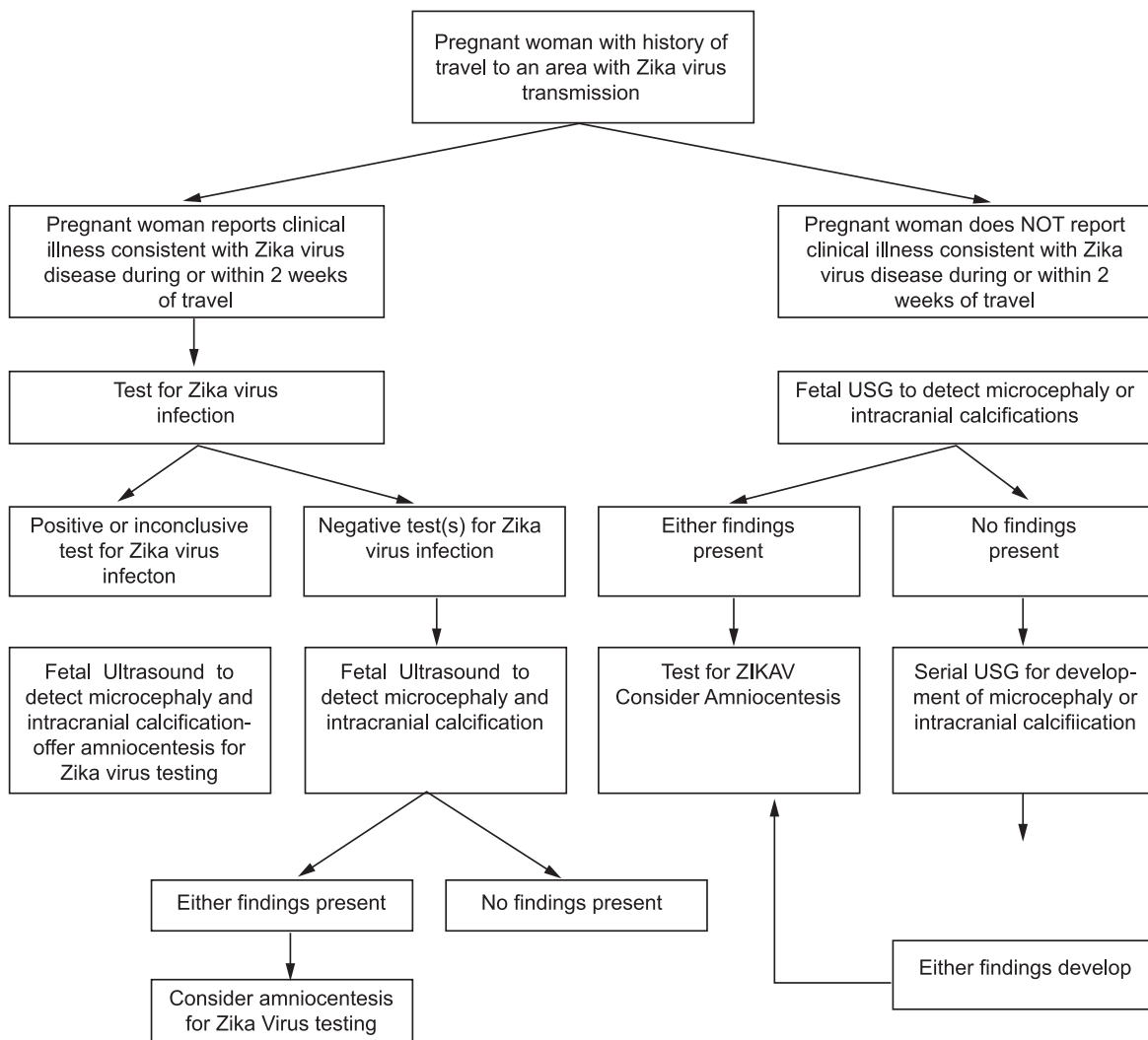
**Women planning pregnancy**

While travelling in an area with active ZIKV transmission, women should be advised to avoid becoming pregnant. They should avoid becoming pregnant for a further 28 days on returning to home; this allows for a maximum two weeks incubation period and possible two-weeks viraemia. Women whose partner has been to an area with ZIKV transmission, the risk of sexual transmission of ZIKV is thought to be very low. However, ZIKV has been identified in Semen of men who have had ZIKV infection, and it is not known how long this can persist. If a woman’s partner has travelled to a country with active ZIKV transmission, effective contraception is advised to avoid pregnancy (and the use of condoms could be considered to prevent against infection acquisition): for 28 days after his return home if he had no ZIKV symptoms, either whilst abroad or within 2 weeks of his leaving the affected country for 6 months following recovery if he did experience ZIKV symptoms during that period.

**Following Birth**

For a live birth with evidence of maternal or fetal Zika virus infection, the following tests are recommended: histopathologic examination of the placenta and umbilical cord; testing of frozen placental tissue and cord tissue for Zika virus RNA; and testing of cord serum for Zika and dengue virus IgM and neutralizing antibodies. CDC is developing guidelines for infants infected by Zika virus. If a pregnancy results in a fetal loss in a woman with history of travel to an area of Zika virus transmission with symptoms consistent with Zika virus disease during or within 2 weeks of travel or findings of fetal microcephaly, Zika virus RT-PCR and immunohistochemical staining should be performed on fetal tissues, including umbilical cord and placenta

Interim guidance: testing algorithm for a pregnant woman with history of travel to an area with Zika virus transmission, with or without clinical illness consistent with Zika virus disease<sup>34</sup>



**Conclusion:**

The Bangladesh Institute of Epidemiology, Disease Control and Research tested blood samples from 101 patients previously thought to have dengue or other viral fevers, to see if any had been infected with Zika. It found one case in the samples, which dated back to 2014 - a 67-year-old from the city of Chittagong, who had not travelled abroad and was found to have the virus in his blood. He is the first known Zika virus-infected patient in Bangladesh. Zika virus continues to circulate and cause locally-transmitted disease in America. We should Consider the possibility of Zika virus infection in travelers with acute fever, rash, arthralgia, or conjunctivitis within 2 weeks after return. A substantial increase in rates of congenital microcephaly have been reported – Studies are underway to characterize the relationship between Zika and congenital microcephaly Pregnant women in any trimester should consider postponing travelling to areas of Zika virus transmission.

**Reference:**

1. Areas with Zika. Centers for Disease Control and Prevention 2016 [cited 2016 Feb 19]; Available from: URL: <http://www.cdc.gov/zika/geo/index.html>
2. Mlakar J, Korva M, Tul N, Popovic M, Poljsak-Prijatelj M, Mraz J, et al. Zika Virus Associated with Microcephaly. *N Engl J Med*. 2016; 10: page number
3. Dick GW. Epidemiological notes on some viruses isolated in Uganda; Yellow fever, Rift Valley fever, Bwamba fever, West Nile, Mengo, Semliki forest, Bunyamwera, Ntaya, Uganda S and Zika viruses. *Trans R Soc Trop Med Hyg* 1953;47(1):13-48.
4. Dick GWA. Zika virus (II). Pathogenicity and physical properties. *Trans R Soc Trop Med Hyg* 1952;46(5):521-534.
5. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *New Engl J Med* 2009;360(24):2536-2543.
6. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *New Engl J Med* 2009;360(24):2536-2543.
7. Musso D, Roche C, Nhan T-, Robin E, Teissier A, Cao-Lormeau V-. Detection of Zika virus in saliva. *J Clin Virol* 2015;68:53-55.
8. World Health Organization. Zika virus infection - Cape Verde; 2015. Available at: <http://www.who.int/csr/don/21-december-2015-zika-cape-verde/en/>. Accessed Feb 5, 2016.
9. Tognarelli J, Ulloa S, Villagra E, Lagos J, Aguayo C, Fasce R, et al. A report on the outbreak of Zika virus on Easter Island, South Pacific, 2014. *Arch Virol* 2015; epub:1-4.
10. Pan American Health Organization/World Health Organization. Epidemiological Update Neurological syndrome, congenital anomalies, and Zika virus infection; 2016. Available at: [http://www.paho.org/hq/index.php?option=com\\_docman&task=doc\\_view&Itemid=270&gid=32879&lang=en](http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=32879&lang=en). Accessed Feb 5, 2016.
11. European Centre for Disease Prevention and Control. Rapid risk assessment: Zika virus infection outbreak, French Polynesia; 2014. Available at: <http://ecdc.europa.eu/en/publications/Publications/Zika-virus-French-Polynesia-rapid-risk-assessment.pdf>. Accessed Feb 5, 2016.
12. Bogoch II, Brady OJ, Kraemer MU, German M, Creatore MI, Kulkarni MA, et al. Anticipating the international spread of Zika virus from Brazil. *Lancet* 2016;387(10016):335-336.
13. PAHO Statement on Zika Virus Transmission and Prevention. [http://www.paho.org/hq/index.php?option=com\\_content&view=article&id=11605&Itemid=11605](http://www.paho.org/hq/index.php?option=com_content&view=article&id=11605&Itemid=11605)
14. Hayes EB. Zika virus outside Africa. *Emerg Infect Dis* 2009;15:1347-50.
15. Musso D, Roche C, Robin E, et al. Potential sexual transmission of Zika virus. *Emerg Infect Dis* 2015;2:359-61.
16. Foy BD, Kobylinski KC, Chilson Foy JL. Probable non-vector-borne transmission of Zika virus, Colorado, USA. *Emerg Infect Dis*. 2011;17: 880-882.
17. Iosifidis S, Mallet H-, Leparac Goffart I, Gauthier V, Cardoso T, Herida M. Current Zika virus epidemiology and recent epidemics. *Med Mal Infect* 2014;44(7):302-307.
18. Villamil-Gómez WE, González-Camargo O, Rodríguez-Ayubi J, Zapata-Serpa D, Rodríguez-Morales AJ. Dengue, chikungunya and Zika co-

- infection in a patient from Colombia. *J Infect Public Health* 2015; epub.
19. Committee to Advise on Tropical Medicine and Travel (CATMAT). Canadian Recommendations for the Prevention and Treatment Of Malaria. 2014. Available at: <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/35s1/index-eng.php>. Accessed Feb 5, 2016.
  20. Committee to Advise on Tropical Medicine and Travel (CATMAT). Fever in the returning international traveller initial assessment guidelines. *Can Commun Dis* 2011;37(ACS-2): 1-24.
  21. Shinohara K, Kutsuna S, Takasaki T, Moi ML, Ikeda M, Kotaki A, et al. Zika fever imported from Thailand to Japan, and diagnosed by PCR in the urines. *J Trav Med* 2016;23(1):1-3.
  22. European Centre for Disease Prevention and Control. Zika virus infection: Factsheet for health professionals; 2015. Available at: [http://ecdc.europa.eu/en/healthtopics/zika\\_virus\\_infection/factsheet-health-professionals/Pages/factsheet\\_health\\_professionals.aspx](http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/factsheet-health-professionals/Pages/factsheet_health_professionals.aspx). Accessed Feb 5, 2016.
  23. Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastère S, Valour F, et al. Zika virus infection complicated by guillain-barré syndrome - case report, French Polynesia, December 2013. *Euro Surveill* 2014;19(9).
  24. Centers for Disease Control and Prevention (CDC). Clinical Evaluation & Disease; 2016. Available at: <http://www.cdc.gov/zika/hc-providers/clinicalevaluation.html>. Accessed Feb 5, 2016.
  25. Petersen EE, Staples JE, Meaney-Delman, D, et al. Interim Guidelines for Pregnant Women During a Zika Virus Outbreak —United States, 2016. *MMWR Morb Mortal Wkly Rep* 2016;65:30–31
  26. Oehler E, Watrin L, Larre P, et al. Zika virus infection complicated by Guillain-Barre syndrome—case report, French, Polynesia, December 2013. *Euro Surveill* 2014;19:4–6.
  27. Pan American Health Organization / World Health Organization. Epidemiological Update: Neurological syndrome, congenital anomalies and Zika virus infection. 17 January, Washington, D.C.: PAHO/WHO; 201
  28. Insect and tick bite avoidance. <http://travelhealthpro.org.uk/insect-tick-bite-avoidance/>
  29. CDC. Travelers' health: avoid bug bites. Atlanta, GA: US Department of Health and Human Services, CDC; 2013. <http://wwwnc.cdc.gov/travel/page/avoid-bug-bites>.
  30. CDC issues 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, CDC; 2016.
  31. Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. *Euro Surveill* 2014;19:13–6.
  32. Oliveira Melo AS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound Obstet Gynecol* 2016; 47:6–7.
  33. Centres for Disease Control and Prevention Morbidity and Mortality Weekly Report. Possible Association Between Zika Virus Infection and Microcephaly -Brazil, 2015. *Weekly / January* 29, 2016;65(3);59–62
  34. Interim Guidelines for Pregnant Women During a Zika Virus Outbreak — United States, January 19, 2016