Zika virus – An Overview

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ABSTRACT: Zika virus a Flavivirus transmitted through the bite of a mosquito, has been considered as a neglected tropical disease for decades, until now. Due to its multiple outbreaks in the various regions of the world it has attained a significantly prominent position. The disease can be transmitted by various means, predominantly the common vector “Aedes aegypti” contributes to its high geographical distribution. The virus is important as it is responsible to cause permanent damage to infants and fetuses, e.g., microcephaly, cranial calcification and multiple neurotic abnormalities. The review comprehensively covers the epidemiology, distribution, transmission of the virus along with the measures that can be adopted to prevent its further dissemination.

Key words: Zika virus, Aedes, Prevalence in Pakistan

INTRODUCTION

Zika virus is a virus of family Flaviviridae belonging to genus Flavivirus and is enveloped, icosahedral, with single strand of RNA of positive polarity (Gubler et al., 2007; Focosi et al., 2016), capable of causing asymptomatic to mild disease (Duffy et al., 2009; Iloso et al., 2014). Its genome is comprised of 10,794 nucleotides encoding 3,419 amino acids and has a single reading frame that encodes for a polyprotein [with 3 structural components that includes capsids (C), premembrane (prM) and the envelope (E)] and 7 non-structural proteins, namely: NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5 (Baronti et al., 2014). Antigenically it is closely related to other arboviruses of the family and has been grouped into 3 genotypes: East Africa, West Africa and Asia (Robert et al., 2016). The virus is closely related to Spondweni virus. These viruses are the only members of their clade with mosquito-borne cluster (Kuno et al., 1998; Cook and Holmes, 2006). The NS1 codon usage adaptation in the human population is the main reason behind the spread of pandemic Zika lineage (Faye et al., 2014; Freire et al., 2015).
Replication of Virus

The replication cycle has been poorly studied. In a study conducted in 1988, the detection of the virus specific antigens was reported by indirect immunofluorescence in the nuclei of infected Vero cells (Buckley and Gould, 1988), prior to this study the replication of this arbovirus was thought to be exclusively cytoplasmic (Westaway et al., 1985).

History, Distribution and Epidemiology

Zika virus strain MR766 was first isolated from Zika forest, Uganda (Dick et al., 1952) in from a Rhesus Monkey in 1947, when a Rhesus Monkey was placed on a tree platform cage in the Zika forest. The Rhesus Monkey named as Rhesus 766 was a sentinel animal for research on jungle yellow fever in Rockefeller Foundation’s Program. The animal was carried to the Foundation’s laboratory after 2 days in febrile state and the serum of the monkey was inoculated into mice. It was after 10 days, that all 10 inoculated mice receiving the serum intra-cerebrally, were observed to become sick and the transmissible agent was isolated (filterable), from the mice brains. Through serological testing it became evident that it can be transmitted and can infect human beings (Dick, 1952).

Studies on transmission of Zika by “artificially fed” Aedes aegypti mosquitoes to mice and monkeys were conducted in a laboratory in 1956. Boorman and Porterfield (1956) demonstrated the transmission of zika virus to mice and monkeys by Aedes aegypti in the laboratory. In the study, it was reported that, the virus content was high at the day of artificial feeding and dropped to an undetected level on day 10, after which on day 15, increase in the virus was reported which remained high from 20 to 60 days. The extrinsic incubation period was therefore suggested to be approximately 10 days. Their results along with phylogenetic study and isolations of the virus from wild mosquitoes and monkeys make it reasonably conclusive that Zika virus is transmitted through mosquito bites.

Solid evidence is yet needed to confirm presence of non-primate reservoirs of Zika virus. One study did found an antibody against Zika virus in rodents (Darwish et al., 1983).

The first isolation of Zika virus from mosquito sample was done in 1948, from Zika forest in Uganda whereas Aedes africanus was reported to be the mosquito serving as the vector (Haddow et al., 1964). In 1954, the first 3 human infection cases were reported during an epidemic of jaundice from Nigeria (Macnamara, 1954). Two more strains of the virus were isolated from the same mosquito species in 1956 (Weinbren et al., 1958). The species was thought to be the sole vector responsible for the outbreak and investigations neglected the other mosquito species until in 2007, when Aedes albopictus was included under the status of “vector for Zika virus” (Grard et al., 2014). In 2007, an outbreak with symptoms of rash, conjunctivitis and arthalgia was characterized and reported on Yap Island in the Federated States
of Micronesia. The patients in the acute phase of their illness were tested and the serum samples obtained showed the presence of Zika virus, exhibiting the presence of Zika virus outside its usual geographical range (Lanciotti et al., 2008, Duffy et al., 2009). The emergence of Zika virus in this decade has been reported in areas of Pacific and Americas (in 2007, 2013 and 2015 respectively) (Duffy et al., 2009; Musso et al., 2014; Campos et al., 2015; ProMED-mail, 2015a&b; WHO, 2015; Zanluca et al., 2015).

Autochthonous human infections have been reported in regions of Africa (ProMED-mail, 2015b), Americas (WHO, 2015), Asia (Olson et al., 1981) and Oceania (Musso et al., 2014). While during its geographical study, the co-circulation of the virus along with other arboviruses such as Dengue virus, Chikungunya virus and West Nile virus have also been reported, including regions of Africa, Americas and Asia (Olson et al., 1981; ProMED-mail, 2015b). The ratio of symptomatic / asymptomatic infections was reported by Musso and Gubler in a publication in 2016 to be 1/5-1/6 (Aubry et al., 2015a; Aubry et al., 2015b; Musso and Gubler, 2016).

Reservoir / Host

For the survival and maintenance in nature, the virus is dependent on its “non-human animal species” and cause zoonoses (Gubler, 2002; Novella et al., 2011). There are many animal species that are host reservoirs upon which the agent is dependent for its survival, humans in few exceptional cases serve as “dead end” or accidental hosts, i.e., the transmission of the agent from which is not usually seen to affect other susceptible host (Kenney and Brault, 2014). The virus can also spread through mosquito-human-mosquito cycle and thus, do not require a non-human reservoir for this type of transmission (Gubler, 2002).

Vectors

An arthropod that has ability to transmit the virus from one individual to another, mostly by biological means i.e., by biting is termed as a vector of Arboviruses. It transfers the infected blood to the healthy individual (WHO, 1961). *Ae. Africanus* and *Ae. Albopictus* were the first two mosquito species to be identified as the vector of Zika virus. *Ae.albopictus* has been reported to act as vector in Gabon (Grard et al., 2014) while, *Ae.hensilii* (Duffy et al., 2009; Ledermann et al., 2014). Mosquito Species reported to have Zika isolates/ strains have been reported in the literature from time to time, a few of the species reported in the literature have been listed below: *Ae.africanus* (Dick et al., 1952; Weinbren and Williams, 1958; McCrae and Kirya, 1982; Berthet et al., 2014), *Ae.apicocargentensis* (McCrae and Kirya, 1982), *Ae. luteocephalus* (Diallo et al., 2014), *Ae. furci-fer-taylori* (Diallo et al., 2014), *Ae. gambiae* (Diallo et al., 2014), *Ae. aegypti* (Marchette et al., 1969; Berge, 1975), *Ae. dalzieli* (Monlun et al., 1993), *Ae. vitatus* (Duffy et al., 2009), *Mansonia uniformis* (Duffy et al., 2009), *Ae. opok* (Berthet et al., 2014), *Ae. neoafri-
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eri (Monlun et al., 1993), Ae. minitus (Monlun et al., 1993), Ae. albopictus (Grard et al., 2007), Ae. hirsutus (Diallo et al., 2014), Ae. metallicus (Diallo et al., 2014), Ae. unileaetus (Diallo et al., 2014), M. uniformis (Diallo et al., 2014), Culex perfuscus (Diallo et al., 2014) and Ae. coustau (Diallo et al., 2014).

Transmission

The primary route of Zika infection is through the bite of infected Aedes species mosquitoes (Hayes, 2009), Horizontal transmission from infected human to mosquitoes and then to healthy individuals has also been observed. There is strong evidence that zika virus can be transmitted via trans-placental route (i.e., mother to child) (Bensard et al., 2014; Araujo et al., 2016). Other routes include blood transfusion, sexual contact, but are not very frequent and thus are considered as rare as compared to the former (Musso et al., 2014, 2015).

Vertical Transmission

The virus has been detected in the blood and the tissues of infants and fetuses (CDC, 2016a). Serious congenital anomalies can occur in fetus by trans-placental transmission of the virus thus, it poses a great threat to the child (CDC, 2016c), while pregnant women have been reported to be more vulnerable to the Zika virus. The transmission of the virus via breast milk has not been reported (WHO, 2016b).

Complications due to zika virus outbreaks such as foetal microcephaly, Gillian Barre Syndrome and various other neurological/autoimmune diseases have been reported in various countries around the world (Oeler et al., 2014). Perinatal deaths associated with microcephaly have also been reported (WHO, 2016a&c).

Sexual transmission of Zika virus

Zika can transfer through sexual activity from a person infected with zika virus to his or her partner. Transmission due to sex includes vaginal, anal, oral and use of sex toys. It can pass to the other partner even in a committed relationship. Zika virus can stay in the semen for a longer duration as compared to other body fluids, therefore; the actual time frame of passing the zika virus through can be different for men and women.

One problem addressed in the transmission of zika virus is that it is asymptomatic in people so, its transmission is possible while people are unaware of having the infection and even when it is symptomatic it has mild symptoms in the early stages of infection. It has also been highlighted by the CDC that zika transmission in the entire three situations is possible:

1. When the infection is in the asymptomatic stage
2. When the infection becomes symptomatic
3. When the display of symptoms ends
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Symptoms

Majority of the patients experience low grade fever, rash, headaches, joints pain, myalgia and flu-like symptoms (Abbasi, 2016; CDC, 2016b). Some of the symptoms reported during Zika infection are given in the Table 1.

Table 1.

<table>
<thead>
<tr>
<th>S.NO</th>
<th>SIGN &amp; SYMPTOMS</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Puriritis</td>
<td>Ameline et al., 2014; Dupont-Rouzeyrol et al., 2015; Gourinat et al., 2015; Zanluca et al., 2015; Korhonén et al., 2016; ProMED-mail, 2016</td>
</tr>
<tr>
<td>2.</td>
<td>Maculopapuar rash</td>
<td>Ameline et al., 2014; Dupont-Rouzeyrol et al., 2015; Gourinat et al., 2015; Zanluca et al., 2015</td>
</tr>
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<td>3.</td>
<td>Fatigue/ Lethargy</td>
<td>Kwong et al., 2013; ProMED-mail, 2013; Fonseccaet al., 2014; Grard et al., 2014; Dupont-Rouzeyrol et al., 2015; Atkinson et al., 2016; Calvet et al., 2016</td>
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<tr>
<td>4.</td>
<td>Arthritis</td>
<td>Olson et al., 1981; Grard et al., 2007; Cao-Lormeau et al., 2014; Campos et al., 2015; ProMED-mail, 2015d; Zammarchi et al., 2015a</td>
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<tr>
<td>5.</td>
<td>Myalgia</td>
<td>Waehre et al., 2014; Dupont-Rouzeyrol et al., 2015; Gourinat et al., 2015; ProMED-mail, 2015d; Promed-mail, 2016</td>
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<td>6.</td>
<td>Headache</td>
<td>Simpson, 1964; Fagbami, 1979 ; Pro-MED mail, 2015c</td>
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<tr>
<td>7.</td>
<td>Conjunctivitis</td>
<td>Burst et al., 2014; Waehre et al.,2014; Zammarchi et al., 2015a</td>
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<td>8.</td>
<td>Malaise</td>
<td>Bearcroft, 1956; Foy et al., 2011; Burst et al., 2014; Summers et al., 2014</td>
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<td>9.</td>
<td>Jaundice</td>
<td>Leung et al., 2015; Zanluca et al.,2015</td>
</tr>
<tr>
<td>10.</td>
<td>Chills</td>
<td>Olson et al., 1981; ProMED-mail, 2013</td>
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<tr>
<td>11.</td>
<td>Dizziness</td>
<td>Olson et al., 1981</td>
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<tr>
<td>12.</td>
<td>Joint pain</td>
<td>Tappe et al., 2014; Tappe et al., 2015</td>
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<tr>
<td>13.</td>
<td>Anorexia</td>
<td>Foy et al., 2011</td>
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<td>14.</td>
<td>Photophobia</td>
<td>Fonseca et al., 2014; Pyke et al., 2014; Zanluca et al., 2015</td>
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<tr>
<td>15.</td>
<td>Sore throat</td>
<td>Heang et al., 2012; Alera et al., 2015</td>
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<tr>
<td>16.</td>
<td>Cough</td>
<td>Heang et al., 2012 Kwong et al., 2013</td>
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<td>17.</td>
<td>Rhinorrrhea</td>
<td>Bauthong et al., 2015</td>
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<tr>
<td>18.</td>
<td>Hematuria</td>
<td>Olson et al., 1981</td>
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<tr>
<td>19.</td>
<td>Aphthous ulcer</td>
<td>Foy et al., 2011; ProMED-mail, 2013</td>
</tr>
<tr>
<td>20.</td>
<td>Prostatitis</td>
<td>Foy et al., 2011</td>
</tr>
<tr>
<td>22.</td>
<td>Prostatitics</td>
<td>Foy et al., 2011</td>
</tr>
<tr>
<td>23.</td>
<td>Sweating</td>
<td>Filipe et al., 1973</td>
</tr>
<tr>
<td>24.</td>
<td>Hypotension</td>
<td>Olson et al., 1981</td>
</tr>
<tr>
<td>25.</td>
<td>Hematospermia</td>
<td>Foy et al., 2011</td>
</tr>
<tr>
<td>26.</td>
<td>Lymphadenopathy</td>
<td>Filipe et al., 1973; ProMED-mail, 2016</td>
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Diagnosis

Testing the maternal serum via RT-PCR is the diagnostic method adopted to detect the presence of Zika virus during pregnancy. In case detected then a detailed anomaly scan is recommended in which brain abnormalities such as intra-cranial calcification and foetal microcephaly etc., can be diagnosed using ultrasound. While, MRI and amniocentesis after proper counseling, may be performed (Peterson et al., 2016).

Clinical Laboratory Testing

A. Detection of virus

The detection of virus is a critical step in diagnosis of any disease. PCR, immunohistochemistry analysis with monoclonal antibodies can be used while detection of antigen in autopsy tissues (Buckley and Gould, 1988; Hamel et al., 2015).

B. Culture

The isolation for the first time was done from serum samples collected from rhesus monkey in 1947, while the isolation of the virus from the mosquito (Ae. Aegypti) was achieved through mouse brain inoculation (Dick et al., 1952). Other methods include inoculation chicken embryo (yolk sacs, allantoic sacs and chorio-allantoic membrane). Inoculation using cell culture has also been reported (Taylor, 1952; Way et al., 1976, Digoutte et al., 1992).

C. Animal Studies

Animal studies involving Zika virus isolation and detection of the antibody have been conducted, since the discovery of the virus. Studies on the following animals have been conducted (Table 2).

Table 2.

<table>
<thead>
<tr>
<th>S.NO</th>
<th>ANIMAL USED FOR STUDY</th>
<th>REFERENCES</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Rhesus Monkeys (<em>Macaca mulatta</em>)</td>
<td>Dick, 1952</td>
</tr>
<tr>
<td>2</td>
<td>Grivets (<em>Cercopithecus aethiops</em>)</td>
<td>Dick, 1952 ; Chippaux -Hyppolite and Hannoun, 1965</td>
</tr>
<tr>
<td>3</td>
<td>Redtail Monkeys (<em>Cercopithecus ascanius</em>)</td>
<td>Dick, 1952</td>
</tr>
<tr>
<td>4</td>
<td>Abyssinian colobus (<em>Colobus guereza</em>)</td>
<td>Andral et al., 1968</td>
</tr>
<tr>
<td>5</td>
<td>Baboons (<em>Papio cynocephalus</em>)</td>
<td>Andral et al., 1968</td>
</tr>
<tr>
<td>6</td>
<td>Bats</td>
<td>Andral et al., 1968</td>
</tr>
<tr>
<td>7</td>
<td>Wild mammals</td>
<td>Bres, 1970</td>
</tr>
<tr>
<td>8</td>
<td>Mangabey (<em>Cercocebus</em>)</td>
<td>McCrae and Kirya, 1982</td>
</tr>
<tr>
<td>9</td>
<td>Mona Monkeys</td>
<td>McCrae and Kirya, 1982</td>
</tr>
<tr>
<td>10</td>
<td>Colobus Monkey</td>
<td>McCrae and Kirya, 1982</td>
</tr>
<tr>
<td>11</td>
<td>Vervets</td>
<td>Kirya and Okia, 1977</td>
</tr>
<tr>
<td>12</td>
<td>Rodents</td>
<td>Darwish et al., 1983</td>
</tr>
<tr>
<td>13</td>
<td>Domestic animals</td>
<td>Darwish et al., 1983</td>
</tr>
<tr>
<td>14</td>
<td>Orangutans (pongo) [Both semi-captive and Free ranging]</td>
<td>Wolfe et al., 2001; Kilbourn et al., 2003</td>
</tr>
</tbody>
</table>
Several blood disorders have been reported in the zika virus infection and are common in other viral infections as well (Table 3). The incidence of these complications is unknown, therefore for all suspected cases; a standard complete blood count is recommended for differentially diagnosing the Zika fever.

Table 3.

<table>
<thead>
<tr>
<th>S.NO</th>
<th>BLOOD DISORDERS AND COMPLICATIONS</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Leucopenia</td>
<td>Besnard et al., 2014; Fonseca et al., 2014; Kutsuna et al., 2014;</td>
</tr>
<tr>
<td>2.</td>
<td>Increased Lactate dehydrogenase</td>
<td>ProMED -mail, 2015c</td>
</tr>
<tr>
<td>3.</td>
<td>Thrombocytopenia</td>
<td>ProMED -mail, 2013; Fonseca et al., 2014; Zammarchi et al., 2015ab</td>
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<tr>
<td>4.</td>
<td>Albuminemia</td>
<td>Macnamara, 1954</td>
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<tr>
<td>5.</td>
<td>Presence of bile pigment in Urine</td>
<td>Macnamara, 1954</td>
</tr>
<tr>
<td>6.</td>
<td>Increase transaminase Levels</td>
<td>Ameline et al., 2014; Calvet et al., 2016</td>
</tr>
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</table>

Important Precautions for avoiding sexual transmission of Zika virus

Precautions from acquiring Zika virus by sexual activity can be taken by having the following measures:

1. Use of condoms (both for male and females) and dental dams (for certain type of oral sex) can reduce the chance of acquiring the Zika infection. They should be used from start to finish of the intercourse for effective results that is to avoid Zika virus infection.

2. Sharing and use of sex toys can also contribute in acquiring the infection so, it not be used or shared.

3. Not having sex during pregnancy eliminates the risk of getting Zika virus and ensures the birth of a healthy infant (CDC, 2017).

Status of Zika virus in Pakistan

Although there have been no reported cases have been notified of Zika virus in Pakistan. According to Butt et al. (2016), the first serological traces of this infection are stated to dates back to 1983 (Darwish et al., 1983). The factor involved in obscuring the detection of Zika virus is the lack of “National unified surveillance system for Arboviruses”. The patients exhibiting symptoms similar to those of arbovirus-acquired fever, they are likely tested for dengue fever and Zika virus diagnostic tests are also not being used currently by medical practitioners and these tests are not included in clinical protocols. There is more inclination to test for dengue and hence, this disease remains oblivious and poses menace to the human population. 61% of the Pakistani population lives in rural areas and symptoms like rash, fever and pain of joints is not considered as a red flag.
sign to have a visit to the hospital (Butt et al., 2016).

Pakistan harbors the Aedes aegypti mosquito and according to the Ministry of Health Services Regulations and Coordination, Government of Pakistan from 2011-2014, more than 48000 laboratories have reported the confirmed cases of dengue virus in the country (Ministry of National Health Services, Regulations and Coordination, 2016). The clear indication of dengue, being rampant in Pakistan highlighted the high risk of transmission of Zika virus and its spread as an epidemic across the whole country (Khalid et al., 2016).

A study conducted by Butt et al. 2016, conducted a qualitative analysis for estimating the potential risk of Zika virus introduction into Pakistan. They used circular statistical package for R software to visualize the logarithm of relative passenger volume, that is the incoming traffic to Pakistani airports from different countries, that have been characterized and declared by the US Centers for Disease Control and Prevention (as of Sep, 2016) as the Zika virus infected countries. The infected areas were the only ones that were considered. The data of the incoming traffic and the passenger volume was obtained from International Air Transport Association for 2015 (in which all kinds of direct and indirect routes were included along with stopovers. The highest proportion of high risk travelers from the study conducted was conclusively described to be from Singapore. While, the countries like Brazil and USA (Miami, FL) were the next 2nd largest contributors. While there were 23 other Zika infected regions that have people that travelled to Pakistan. The location of these airports was explained to be situated in an area where, Aedes mosqitos breeds so the potential onward transmission is clearly expected concluding Airports to serve as entry routes for Zika virus.

Control Measures

Maintaining the standard control measures can help in preventing of the notorious virus from spreading in Pakistan. Some problems faced against Zika such as the lack of effective and efficient public health measures prominently suggest increased chances of Zika virus to travel into Pakistan. Containment efforts acting as cornerstone, primarily includes both community initiatives as well as social mobilization.

The potential role of media agencies can help in facilitating the efforts of the government in spreading the awareness to ensure the preparedness of the population against zika virus outbreaks in the years to come.

Awareness about Zika virus via SMS alerts, educational camps, and by distributing flyers are some good options that can be adopted for the implementations of preventive measures. The effective Public-private partnership and collaborations at international level with the National Programs can not only cease the proliferation of the potential travelers, but can also cut its roots by denying
visas all over the world. By revisions and improvements in the National Programs we will one day be successful in eradicating and diminishing it from the world.

CONCLUSION

Need for a regional approach is urgently required in order to harmonize the surveillance with the vector control approaches and to share the epidemiological information.

REFERENCES


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76. ProMED-mail (2013). Zika virus-Canada ex Thailand. ProMED-mail (29 May), archive no. 20130529.1744108.

77. ProMED-mail (2015a). Zika virus-Columbia ProMED-mail (18 October), archive no. 20151018.3723954.

78. ProMED-mail (2015b). Zika virus-Suriname Cape Verde. ProMED-mail (6 November) archive no. 20151106.3770696.
79. ProMED-mail (2015c). Zika virus –Netherland ex Suri name. ProMED-mail (13 December) archive no. 20151213.3858300.

80. ProMED-mail (2015d). Zika virus–Americas. Atlantic ocean. ProMED-mail (23 December), archive no. 20151223.3886435.

81. ProMED-mail 2016. Zika virus–Americas. ProMED-mail (8 January), archive no. 20160108.3921447.

82. Pyke AT, Daly MT, Cameron JN, Moore PR, Taylor CT, Hewitson GR, Humphrey’s JL and Gair R (2014). Imported Zika virus infection from the Cook Islands into Australia, 2014. PloS Curr 6: ecurrents. Outbreaks. 4635a54dbff-ba2156fb2fd76de49f65e.


