

Zika Virus Disease

Adel I. Al-Afaleq

Department of Environmental Health, College of Public Health, University of Dammam, Dammam, Saudi Arabia

Correspondence: Prof. Adel I. Al-Afaleq, Department of Environmental Health, University of Dammam, P.O. Box 1982, Dammam 31441, Saudi Arabia. E-mail: aalafaleq@uod.edu.sa

ABSTRACT

The Zika virus is an arbovirus belonging to the virus family *Flaviviridae*. The virus was isolated in 1947 from a rhesus monkey in the Zika Forest of Uganda. The virus causes sporadic mild human infections in Africa and later in Asia. However, by 2007 a major shift in its infection pattern was noticed and thousands of human infections were reported in the State of Yap and Federated States of Micronesia. In the last 3 years, major outbreaks have continued to occur and the virus has spread to several Pacific and American countries. These outbreaks were mostly asymptomatic; however, there were more severe clinical signs associated with the infections. Those signs included microcephaly and Guillain–Barre syndrome. It is believed that various species of mosquitoes can biologically transmit the virus. However, *Aedes aegypti* is most widely associated with the Zika virus. Recently, new modes of virus transmission have been reported, including mother-to-fetus, sexual, blood transfusion, animal bites, laboratory exposure and breast milk. Differential diagnosis is very important as some other arboviruses such as yellow fever virus, West Nile virus, dengue virus, and chikungunya virus have similar clinical manifestations to the Zika virus infection as well as relating serologically to some of these viruses. Established laboratory diagnostic tests to detect the Zika virus are limited, with reverse transcription polymerase chain reaction being the most widely used test. Taking into consideration the quickness of the spread of infection, size of the infected population and change of the infection severity pattern, the Zika virus infection merits collective efforts on all levels to prevent and control the disease. Limited research work and data, concurrent infection with other arboviruses, involvement of biological vectors, mass crowd events, human and trade movements and lack of vaccines are some of the challenges that we face in our efforts to prevent and control the Zika virus infection.

Key words: Arbovirus, microcephaly, review, Zika virus, zoonotic

ملخص البحث:

تهدف هذه المراجعة إلى تسليط الضوء على فيروس زيكا والذي اكتشف سنة 1947 من قرد الريبوس في غابة الزيكا في أوغندا. يسبب هذا الفيروس عدوى منقطعة لدى الإنسان في بعض الدول الإفريقية والآسيوية. وخلال السنوات الثلاثة الأخيرة حدث انتشار واسع في عدة مناطق أخرى وخاصة في دول أمريكا الوسطى والجنوبية وكان هذا الانتشار مصحوبا ببعض العلامات السريرية الخطيرة كصغر رأس الجنين ومتلازمة غيان بارى (Guillain – Barre syndrome). تقوم بعوضة تدعى (*Aedes aegypti*) بنقل هذا الفيروس إلى البشر، كما يمكن نقله من الأم إلى الجنين وعن طريق التواصل الجنسي، نقل الدم ومشتقاته وحليب الأم. يناقش الكاتب كيفية التصدي لهذا الفيروس الذي يتطلب تكاتف جماعي وعلى كل المستويات.

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INTRODUCTION

In 1947, an unknown virus was reported. This occurred during a study on yellow fever virus (YFV), where a sentinel rhesus macaque was placed in the Zika Forest in Uganda, which is where the name of the virus originated.^[1] The Zika virus is a member of genus *Flavivirus* of the virus family *Flaviviridae* with a single-stranded RNA genome. The virus is mosquito-borne, with *Aedes aegypti* reported to be the primary vector.^[2] The virus has been reported to cause sporadic asymptomatic infections in humans with mild signs of fever and headache in a small number of the infected population.^[3-6] The infection spread to Asia and then to the Pacific Islands and Americas.^[7-15] In the last decade, different patterns of the virus infection, transmission, and virulence have been reported in some of these areas.^[15-19] Outbreaks of the disease have involved hundreds of thousands of people in Brazil. Although most infections were asymptomatic with a few reports of mild symptoms of fever and headache, severe clinical signs including babies born with microcephaly and mother-to-fetus transmissions were reported.^[18,20-23] This major shift has prompted world attention. The aim of this review is to present the latest information on the Zika virus in an informative, concise form. The paper has also made some preventive and control suggestions and presented the challenges.

THE VIRUS

The genome of the Zika virus contains 10,794 nt encoding 3,419 aa. In addition, the Zika virus contains several proteins, namely capsid, precursor of membrane, envelope and seven nonstructural proteins.^[24] The virus originated in East Africa and spreads to Asia, Pacific Islands and the Americas. It has been noticed that Zika virus isolates from Asia, Pacific Islands and the Americas have a distinct lineage from the African isolates. Thus Zika strains are grouped as African and Asian strains. This may indicate the occurrence of some viral evolutions during Zika virus spread.^[25-27] So far, all strains detected in Asia, Pacific Islands and the Americas showed nearly 99% nucleotide homology.^[28] Overall, strains of the Zika virus have <12% divergence at the nucleotide level which indicates that the virus has strong conservation among its strains.^[29] These findings have an impact on some diagnostic tests as well as vaccine production.

EPIDEMIOLOGY

After the Zika virus was first recognized, it was isolated from *Aedes africanus* mosquitoes.^[2] A serosurvey study

on humans in Uganda indicates 6.1% prevalence of antibodies against the Zika virus.^[30] Following further surveys, the Zika virus was found in wider areas, including Egypt,^[31] East Africa,^[32] Nigeria,^[33] India,^[34] Thailand, Vietnam,^[35] the Philippines^[36] and Malaysia.^[37]

The first report of human illness caused by the Zika virus was recorded in Nigeria in 1953 and involved three persons.^[33] During the following years, cases in humans were rarely reported.^[3-6] It was surprising to notice the string of several Zika virus infection outbreaks which occurred in the State of Yap, Federated States of Micronesia in 2007,^[38] French Polynesia in 2013 and 2014,^[7-9] New Caledonia in 2014,^[39] Easter Island in 2014,^[40] Cook Islands in 2014, Samoa in 2015 and American Samoa in 2016.^[41] Some of the outbreaks reported above involved thousands of human infection cases in Yap and French Polynesia.^[7,9,38] In the last 7 years, however, the pattern of the Zika virus infection in Thailand,^[10,42] East Malaysia,^[43] Cambodia,^[44] the Philippines^[11] and Indonesia^[45,46] is different as only sporadic cases have been reported.

The Zika virus spreads to the Americas through the Pacific Islands; this became evident when in March 2015 the virus was identified in an exanthematous illness outbreak in Bahia, Brazil.^[12,47] By October of the same year, the virus had spread to another 14 states in the country with estimated 1.3 million suspected cases.^[13,14] Colombia witnessed the first report of autochthonous transmission of the Zika virus outside Brazil.^[15] It is estimated that a total of 51,473 suspected cases of the Zika virus had been reported in Colombia by March 2016.^[15] The Zika virus has now spread to more than 33 countries and territories in the Americas.^[14,15]

TRANSMISSION

The Zika virus is a mosquito-borne disease. It appears that several *Aedes* spp. can probably support virus transmission, including *aegypti*, *hensilli*, *africanus* and *albopictus*.^[1,48-50] However, *Aedes aegypti* is reported to be the major vector in Asia.^[5] It is likely that a mosquito becomes infected with the virus during a blood meal, followed by virus replication and then passes the virus to a reservoir animal at the next blood meal.^[51] It has been suggested that the Zika virus has multiple animal reservoirs as it has been isolated or anti-Zika virus antibodies detected in several primates and other wild and domestic animals.^[29] In a pathogenesis study conducted on *A. aegypti*, the Zika virus content was high on the day of inoculation and decreased by day 10 to an

undetectable level. By day 15, the virus content increased and remained high for 20–60 days.^[52]

Several other routes of transmission have been reported. These include sexual,^[53,54] perinatal,^[55] and congenital.^[22] Zika virus RNA was detected in amniotic fluid of two women who had experienced Zika virus disease symptoms during their pregnancy and both had babies with microcephaly.^[22] Viral RNA was also detected in tissues of fetuses of infected women during pregnancy. It was also detected in the brains of two newborn babies with microcephaly by women who were infected during pregnancy; both babies died within 20 h postdelivery.^[56-59] Intrapartum transmission was noticed when the Zika virus was detected in the blood of two babies within 4 days of their birth to infected mothers.^[55] The possibility of transmitting the Zika virus through sexual intercourse has been reported. The virus was detected in the semen of a 44-year-old man from Tahiti.^[54] Reports showed that viral RNA has been detected in sperm 62 days after the onset of symptoms.^[54,60,61] In another case, a man from the United States was infected with the Zika virus while in Senegal and following his return to the United States, his wife was infected.^[53] Another case of sexually acquired infection was reported in Texas, United States.^[62] Possible other transmission modes have been reported, including transfusion,^[63,64] animal bites,^[65] laboratory exposure^[6] and breast milk.^[55] More studies are needed to confirm the validity of these transmission routes.

PATHOGENESIS AND CLINICAL PICTURE

Research work on the pathogenesis of the Zika virus is limited. However, it is likely to resemble the case of other *Flaviviruses* where an initial viral replication takes place in certain skin cells including keratinocytes, fibroblasts and immature dendritic cells. This is followed by virus migration to the nodes and then to the bloodstream.^[66,67] Following skin entry, one study showed that the Zika virus antigen was detected mainly in the nuclei whereas typical *Flaviviruses* would be found in the endoplasmic reticulum.^[68] These findings deserve more investigations. Similar to other arboviruses of *Flaviviridae*, the incubation period for the Zika virus in humans is thought to be between 3 and 12 days.^[67]

Almost 80% of infected humans are likely to have an asymptomatic infection.^[38,51] If symptoms occur, they are normally mild and include headache, rash, mild fever, myalgia, arthralgia, fatigue and nonsuppurative

conjunctivitis. One of the prominent features is a rash and can be described as maculopapular and pruritic begins proximally and spreads to the extremities.^[6] Symptoms are normally resolved within 2 weeks; however, rare cases showed longer persistence.^[47,69] The above-mentioned clinical characteristics are similar to some other arboviruses such as dengue virus (DENV), West Nile fever (WNV) virus, chikungunya virus (CHIKV) and YFV; therefore, differential diagnosis is important.^[70]

Severe clinical and pathological features associated with the Zika virus infection have also been reported, especially in the last few years. Most prominently, infants born with microcephaly.^[71] In Brazil, this affection was noticed on an estimated 20 live birth cases per 10,000 compared to 0.5 per 10,000 in the previous year (2014–2015).^[71] During the Zika virus outbreak in French Polynesia in 2013/2014, an increase in congenital central nervous system (CNS) malformations was noticed.^[57] Studies on the outbreaks in French Polynesia and in Bahia, Brazil showed an association between first-trimester Zika virus infection and microcephaly risk.^[72] Those findings in Brazil and French Polynesia should be received with some caution, as it lacks high level of confirmation due to various factors including the absence of baseline rate of microcephaly in the relevant countries, laboratory confirmation, involvement of other existing infections and health problems.^[67] Involvement of the Zika virus in CNS malfunction is further supported by the findings of an experimental intraperitoneal inoculation of mice with the Zika virus which resulted in viral neurotropism.^[2] It has been hypothesized that the virus role in CNS is due to its effects on cell autophagy during replication.^[2] This affects the autophagy and centrosome stability in the cells resulting in an increase in centrosome number. It is important for brain development to have a normal number of centrosome.^[73] Microcephaly was reported in mice as a result of an increased number of centrosomes.^[73] Further investigations on this role of Zika virus are needed.

Adults are also reported to suffer from some severe neuropathological effects associated with Zika virus. These include Guillain–Barre syndrome, meningoencephalitis and meningitis.^[74] There was an increase in the number of Guillain–Barre syndrome cases during outbreaks of the Zika virus infection in Brazil, Venezuela, Colombia, Suriname, El Salvador and French Polynesia; however, laboratory confirmation of the Zika virus was not done in all cases.^[74]

Other reported effects associated with Zika virus infection are hypotension, transient hearing loss, hematospermia,

and genitourinary symptoms.^[43,44,53,54] The Zika virus was detected in semen from a 44-year-old man from Tahiti suffering from hematospermia.^[54] Deaths related to Zika virus infection are very rare.^[58] Four fatalities associated with the Zika virus infection have been reported. One of them was an infant and the others were a man and two girls aged 16 years. The man was suffering from rheumatoid arthritis, lupus erythematosus, chronic corticosteroid use and alcoholism; one of the girls was suffering from sickle cell disease. No history was provided for the second girl.^[58,75]

DIAGNOSIS

Due to the overlapping and similarities in clinical and pathological features of Zika virus infection to those of other arboviruses infections such as DENV, CHIKV, WNF and YFV, diagnosis of Zika virus disease based on the clinical findings is not reliable. Laboratory testing is the reliable way of diagnosing the Zika virus infection and should be evaluated concurrently with other arboviruses on all patients with fever, rash, myalgia, or arthralgia, especially those who have been in areas of ongoing Zika virus activity.^[70] Testing to detect the Zika virus should be performed in the viremic period within 7 days of the onset of symptoms. Some assays to detect the Zika virus from sera samples have been developed, such as reverse transcription polymerase chain reaction, and appear to be the most specific test.^[70] Serological assays have also been developed; however, they are less specific as cross-reaction with other *Flaviviruses* particularly DENV antibodies (IgM and IgG) have been reported.^[24,38,76] Therefore, another confirmatory serological test such as seroneutralization test on the positive samples is required.^[49] Cross-reaction with other *Flaviviruses* may also impose problems, especially in case of YFV-vaccinated patients.^[70] Although serum sample is the preferred sample to detect the Zika virus, other types of samples may be considered, especially when it has been reported that the virus RNA can be detected in urine up to 20 days after viremia had become undetectable.^[77]

Other laboratory biological tests gave an inconclusive diagnostic value for the Zika virus infection. Blood count was normal or nonspecific.^[76-79] Like other viral infections, a mild increase in serum lactate dehydrogenase, inflammatory markers, and liver enzymes was reported.^[39,43,69]

PREVENTION AND CONTROL RECOMMENDATIONS

No treatment or vaccines are available to prevent or treat the Zika virus disease. Patients may receive some

supportive measures and drugs including rest, hydration, and antipyretics. Analgesics may be given; however, blood-thinning drugs such as aspirin and nonsteroidal anti-inflammatory can only be given with caution and after excluding other hemorrhagic infections such as DENV disease.^[11] A number of measures can help prevent and control the Zika virus infection and these include the following:

- Avoidance of mosquito bites by wearing clothes that cover the skin, use of mosquito repellent and staying under a mosquito proof net especially at *A. aegypti* feeding times (late afternoon and early morning)^[80]
- Authorities should implement a strategy plan for mosquito control, including measures to dry up sites that could be suitable locations for mosquitoes to lay their eggs and bringing their population down by different chemical or biological means^[80]
- Pregnant women are advised not to travel to Zika virus infected areas^[81]
- Men returning from or those who reside in areas of Zika virus activities should use condoms during sexual intercourse with their partners, especially if their partners are pregnant^[62]
- Regular testing for Zika virus infection, fetal abnormalities and newborn babies should be available for infected or pregnant women and babies who may have the Zika virus infection^[82]
- Global efforts should be directed to closing major gaps in basic knowledge on all aspects of the infection

CONCLUSIONS

A considerable shift in various aspects of the Zika virus infection in the last 10 years has been noticed. Since its identification in 1947 in the Zika Forest of Uganda, the Zika virus has always been described as causing sporadic asymptomatic infection or in a few cases, mild symptoms of headache and fever. The shift of its infection pattern is believed to have started in 2007 where thousands of human infections were reported in the State of Yap and Federated States of Micronesia. In the following years, more outbreaks with even more severe clinical manifestations associated with the Zika virus were recorded in the Americas. Being an arbovirus disease, with new modes of viral transmission and recognizable clinical signs, it is important on individual, national, and international levels to support the efforts against the Zika virus disease in all aspects, control, prevention and spread of the disease. In addition, there are several challenges which include limited data on pathogenesis, transmission, diagnosis and differential diagnosis of the virus, vectors-reservoirs-human cycle, concurrent

infection with other arboviruses, vaccine development and human and trade movements.

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