

Overview of dengue and Zika virus similarity, what can we learn from the Saudi experience with dengue fever?

Sulaiman A. Alshammari¹,
Yousif S. Alamri²,
Fatimah S. Rabhan³,
Aljoharah A. Alabdullah³,
Noura A. Alsanie³,
Fatma A. Almarshad³,
Amal N. Alhaqbani³

¹Department of Family and Community Medicine, Research Chair of Health Education and Health Promotion, College of Medicine, King Saud University, Riyadh Saudi Arabia, ²Department of National Drug and Poison Information Center, Saudi Food and Drug Authority, Riyadh, Saudi Arabia, ³Department of Epidemiology, Princess Nourah Bint Abdulrahman University, Riyadh, Saudi Arabia

Address for Correspondence:

Sulaiman A. Alshammari, Department of Family and Community Medicine,
College of Medicine, King Saud University,
P.O. Box 2925 Riyadh 11461,
Riyadh Saudi Arabia.
E-mail: sulaiman@ksu.edu.sa

WEBSITE: ijhs.org.sa

ISSN: 1658-3639

PUBLISHER: Qassim University

ABSTRACT

There is high public health alert in the Kingdom of Saudi Arabia concerning Zika virus infection. So far, there is no reported outbreak. So are we at risk of this disease? Reviewing the literature of recent outbreaks of other infectious diseases in Saudi Arabia may clarify the situation. It is evident that there is some similarity between Zika and dengue regarding vector (*Aedes aegypti*) which is available in the Kingdom of Saudi Arabia. Furthermore, they have similar transmission process and the required environment for infection. It seems that the Kingdom has learned from previous outbreaks, so they are well prepared to face such challenges. The Saudi Ministry of Health built the command and control center to deal with the pandemic flues. Furthermore, they are trying to create a center for disease control, and they are recruiting local and international experts in monitoring the emerging infections.

Keywords: Aedes, Dengue, Zika, Saudi Arabia

Background

Zika virus became a global health emergency following the outbreak in Brazil in 2015. The emerging pathogen has recently been causing severe epidemics around the world. The Saudi health authority is trying to do their best to prevent any outbreak.

Below is a review of Zika virus in the context of lessons learned from dengue fever experience in Saudi Arabia. We reviewed vector (*Aedes aegypti*), mode of transmission, environmental factor, the clinical symptoms, and diagnosis. We tried to investigate the similarity between Zika and dengue and whether there a risk of Zika outbreak in Saudi Arabia.

Methods

Two independent researchers conducted an electronic search to find appropriate articles in PubMed, Google Scholar,

Ovid, World Health Organization (WHO), Cochran, and CDC website. The search terms were (Dengue, *A. aegypti*, Saudi Arabia, and Zika virus). The inclusion criteria for our search were studies or reviews conducted in Saudi Arabia in the English. There was no year restriction. These studies investigated dengue fever, Aedes mosquitoes, and Zika virus. The exclusion criteria were studies related to other infection diseases or conducted outside Saudi Arabia. Titles and abstracts were reviewed to scan for the inclusion and exclusion criteria. We found a total of 110 articles. These covered the infectious agent, the vector, transmission, incidence, and geographical distribution in Saudi Arabia. The investigators distributed this literature among them to read them in depth. Then, each one of the investigators presented their finding to the rest of researchers. We found forty articles, website documents, and reports relevant to our study. We excluded 70 articles because they were investigating other diseases or other vectors, and the studies were not done in Saudi Arabia. It contains original articles, case report, case series, randomized clinical trials, and systematic review.

Zika Virus

Recently, there were series of emerging infectious diseases worldwide. Zika virus is the last in this series of several outbreaks. There is a Saudi concern about this, so we conducted this literature review to find the possibility of having a risk of Zika virus in Saudi Arabia. Zika virus is a flavivirus, transmitted by *Aedes* mosquitoes. First discovered in 1947 in monkeys, and later, in humans in Uganda 1952.^[1] The WHO reported that 148 countries and territories had Zika virus transmission from 1 January 2007 to 10 March 2017, where Angola had the last reported Zika virus transmission.^[2] Zika is similar to dengue in symptoms of fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache. Furthermore, *A. aegypti* mosquitoes transmit both dengue and Zika.^[3] Zika has an added complication of microcephaly that leads to a smaller head circumference of babies and Guillain-Barré syndrome.^[4]

Dengue Fever

Dengue is a mosquito-borne viral disease that has rapidly spread in all countries. The infected *A. aegypti* and the *Aedes albopictus* transmit dengue fever. It has widespread disease throughout the tropics. Dengue hemorrhagic fever was first known in the 1950s during dengue epidemics in the Philippines and Thailand. There are four different serotypes of the virus that cause dengue (DEN-1, DEN-2, DEN-3, and DEN-4). Recovery from infection provides lifelong immunity against that particular serotype.^[5] The first recorded case of dengue fever was written in the Chinese medical encyclopedia in 1992.^[6] Dengue fever had become a global pandemic after World War II in Southeast Asia.^[7] The viral etiology and the transmission of mosquitoes were recognized in the 20th century. At the moment, about 4 billion of the world's population live in high-risk areas of dengue transmission. The number of new cases is significantly increased. Every decade, the reported cases are doubling.^[8,9] The WHO has reported that the global prevalence of dengue fever has increased dramatically, and the disease became endemic in more than 100 countries which are severely affected by the illness. Dengue virus can cause dengue fever, to dengue hemorrhagic fever or dengue shock syndrome.^[5]

Dengue fever in Saudi Arabia

On October 1993, dengue hemorrhagic fever first appeared in Jeddah City. On March 1994, the Disease Control Division in Jeddah initiated surveillance of dengue hemorrhagic fever to detect any new cases.^[10] The number of recorded cases were 289 by disease control division in Jeddah.^[11] In 1995, the outbreak of dengue fever in Saudi Arabia was reported from the western and southern cities and regions, following the heavy rainfall and agricultural activities.^[12] After 2001, dengue fever in Makkah region has become endemic,^[13] “study provides systematic evidence that Alkhurma, Crimean-Congo

hemorrhagic fever, dengue, and Rift Valley fever viruses are endemic to western if not all provinces of Saudi Arabia.^{[14]”} A systematic review published in 2015 found a prevalence of dengue between 31.7% and 56.9%.^[15]

Until 2013, there are 2,219 reported cases of dengue fever in Jeddah with an increasing cases day-by-day.^[11] At that time, 37% of patients included construction workers at different places in Saudi Arabia.^[12] Since first cases reported in Saudi Arabia, the observed incidence of the diseases undergoes various increase and decline.^[11] There was a case report study about Alkhurma hemorrhagic fever.^[16]

Mosquitoes

Mosquitoes can transmit several diseases and parasites to humans. There are over 3000 species of mosquito in the world. The most common are the various species of the *Culex*, *Anopheles*, and *Aedes* mosquito. *Aedes* mosquito is known as floodwater because it lays their eggs in moist soil or in containers that periodically catch rainfall. There are two main species of mosquitoes that cause many diseases such as dengue fever and Zika virus. These are *A. albopictus* and *A. aegypti*. These can bite people in tropics and cooler area.^[17] *A. albopictus* was known as Asian tiger mosquito. *A. albopictus* has migrated globally throughout the tropical, subtropical, and temperate area. These mosquitoes live close to people but less so than *A. aegypti*. *A. albopictus* transmits dengue fever and eastern equine encephalitis.^[18] *A. aegypti* also known as yellow fever mosquito. *A. aegypti* is a small and dark mosquito with white lyre-shaped markings and banded leg. They prefer to bite indoors and primarily bite humans.^[18] *A. aegypti* originated in Africa mostly; the mosquito has migrated globally throughout the tropical countries. *A. aegypti* mosquitoes have a high vectorial capacity transmits for DENV, CHIKV, ZIKV, and YFV.^[17,18] A study was conducted in Makkah, Saudi Arabia, after the increase of cases of dengue fever. The researchers investigated the abundance of container breeding mosquitoes with preeminence on *A. aegypti*, mosquitoes habitats indoors, and nearby homes and some environmental factors related to occurrence dengue fever in Makkah. Furthermore, Makkah has a highly fluctuating human population, so it is at risk to spread *A. aegypti*.^[19] Furthermore, there are many types of mosquitoes found in the Western region, Saudi Arabia, according to a study conducted in 2014. They identified four different types of *Aedes* mosquitoes, namely, *Aedes* (*Stegomyia*) *aegypti*, *Aedes* (*Ochlerotatus*) *caspius*, *Aedes* (*Aedimorphus*) *vexans* var. *Arabiensis*, and *Aedes* (*Aedimorphus*) *vittatus*.^[20]

Aedes mesquites life cycle

A. aegypti have complex life cycle first; female mosquitoes lay eggs inside containers holding water. Then, eggs are ready to hatch from a few days to several months after being laid. Eggs hatch when submerged in water. After that, larvae are aquatic and develop into pupae in as little as 5 days. At the last

stage, pupae develop into adult flying mosquitoes in 2–3 days to be *Aedes* mosquitoes.^[21] *A. aegypti* preferred habitat is in clean water such as water storage tanks and jars inside and outside houses. Similar to *A. aegypti*, it breeds in temporary containers but prefers natural and breeds more often outdoors and sometimes breed indoors.^[17]

A. *aegypti* habitat

Between 2007 and 2008, a study to analyze the relation between different climatic factors and abundance of *Aedes* population in time and space revealed that the spread of *A. aegypti* in Jeddah was related more to human behavior than to climate.^[22] In another study conducted in Almadinah Almounawarah, *Aedes* mosquitoes were collected in temperature 25C–30C.^[23]

Aedes mesquites in Saudi Arabia

A. aegypti distributed mostly in west and southeast of Saudi Arabia, especially in Jeddah, Jazan, and some region of Aseer. These are the places of most infected areas of dengue cases.^[24] There is a study conducted in Makkah from 2008 to 2009. Ten types of artificial containers were found with developing larvae and 70% of these habitats located indoors.^[19] There are four species of *Aedes* in the western area, and the most abundant species was *A. aegypti* 57%.^[20] A study from Al-Ahsaa district from the eastern region of Saudi Arabia identified mosquitoes and collected larvae's using long aquatic nets. They identified four mosquito species which are *Aedes caspius*, *Anopheles multicolor*, *Culex perexiguus*, and *Culex pipiens*. The results showed that the prevalence of mosquitoes was high in winter and spring and can be found in autumn and rare in summer.^[25]

Transmission

There are two types of transmission as follows:

- Vector-borne transmission: Zika is an arthropod-borne virus, the vector that of dengue, yellow fever, and chikungunya is the same vector that transmits ZIKV. The *A. aegypti* and *A. albopictus* mosquitoes transmit ZIKV with two distinct transmission cycles (sylvatic cycle and urban cycle). ZIKV infected people by mosquitoes bite.
- Non-vector-borne transmission: This type of transmission is direct human-to-human through a sexual contact, breastfeeding, or contaminated blood transfusion. Furthermore, the infected mother can pass ZIKV to her fetus during her pregnancy by RNA. Those mothers had a probability to had a fetus with abnormal brine.^[4,26]
- In a case of dengue fever, the study showed that the male, especially in the age between 15 and 30 years old, is at high risk to get infected more than female due to their work in farming and ship herding.^[27] Investigators attributed this observation to that the males are more likely to spend time outdoor. Furthermore, they observed that the number of dengue fever cases increased in the first quarter of the year.^[28]

Symptoms

Zika virus and dengue fever are sharing the same symptoms of fever, skin rashes, conjunctivitis, muscle and joint pain, malaise, and headache.^[29] There is an association between depression, hemorrhagic complications, and shock on one side and the symptoms of dengue fever and Zika virus on the other.^[13] Zika virus and dengue virus serotype 2 were isolated from a patient with travel to Haiti who developed fever, rash, arthralgias, and conjunctivitis. The infecting Zika virus was related to Venezuelan and Brazilian strains but evolved along a lineage originating from strains isolated in 2014 in the same region of Haiti.^[30]

Diagnoses

Both dengue fever and ZIKV found in whole blood, urine, cerebrospinal fluid, amniotic fluid, semen, and saliva. These samples were taken from patients for the test by two test methods as the WHO recommended:

- Specimens for nucleic acid testing: Whole blood, serum collected from patients presenting with onset of symptoms ≤ 7 days.
- Serology (IgM detection): Whole blood collected in a dry tube and serum obtained from patients presenting with the beginning of symptoms ≥ 7 days.^[31]

A study determined the seroprevalence of dengue virus and its antibodies among Saudi donors, and another study was conducted in Jeddah to individuals who are suspected to be infected with dengue fever, both studies used IgM test as a measurement tool.^[32,33] Another study conducted to highlight some clinical and epidemiological features of dengue fever. They have been done laboratory investigations routine, and diagnosis was confirmed by polymerase chain reaction.^[34]

Recommended serological assays include enzyme immunoassays and immunofluorescence assays detecting IgM antibodies using viral lysate, cell culture supernatant, or recombinant proteins as well as neutralization assays such as plaque-reduction neutralization tests.^[30]

Dengue Fever Distribution in Saudi Arabia

Hot spots, where mosquitoes distribution is large, associated directly with the prevalence of dengue fever. Rainfall, high temperature, and humidity are the reasons for increasing the hot spots. Most of the warm places were identified in low-quality districts with limited access to water and crowded with people. The distribution of dengue fever and *Aedes* mosquitoes can be measured using different methods of light traps. A study investigated the dengue fever cases and mosquitoes that transmit dengue virus to human bodies. They collected mosquitoes using black hole traps. To locate spots with the risk of a higher number of dengue fever cases, they used

GetisOrd Gi statistical measurement. Furthermore, larvae can be collected from stagnant and slowly running water canals, dirty water pools, water storage tanks, salty and polluted water, and drainage water with algae; larvae distribution was not affected by temperature, PH, or salinity of the water.^[35,36] In another study, 384 adults mosquitoes have been collected by CDC lights traps and New Jersey lights traps. Adult *Culex* mosquitoes were the most collected species.^[23]

Management of Cases

Early discovery of cases in Saudi Arabia

The disease control division in Saudi Arabia initiated a surveillance in 1994 in Jeddah city. All physicians have been alerted to dengue fever symptoms. The suspected cases were isolated. A blood sample has been taken from suspected patients to do the virology tests to diagnose dengue fever by virus culture and serological methods.

Then, confirmed cases reported to the disease control division for further investigation. 2 weeks after the blood test, another blood sample has been taken to do the tests again.^[36,37]

The role of quarantine

Saudi Arabia has been taking preventive measures against the Zika virus, as it fast becoming a global concern. The Ministry of Health has alerted the quarantine departments at all entry points to monitor the incoming passengers.^[38]

As with all contagious infectious diseases, the question of when to use the public health tools of quarantine and isolation is critical. There is no scientific basis for this approach. As noted previously, Zika virus is not readily transmitted from person to person, either before or after symptom onset. Caution is needed to avoid negative psychosocial consequences like stigmatization such as was seen in the 2014 Ebola virus disease outbreak.^[39]

Treatment

Zika virus disease is considered as a mild virus, and currently, there is no particular treatment or vaccine.^[5] However, there are some tips should be taking into account, for example, bed rest and supportive care, including increased intake of fluids to prevent dehydration and administration of acetaminophen for relief of fever and pain. The Zika virus is transmitted by mosquitoes bites so to eliminate the spread of the Zika virus is to control vector (*Aedes* mosquito) growth.^[40]

Prevention and Awareness

As we know that, the vector of the dengue fever is the same vector of the Zika and the symptoms are similar. A study conducted in 2008 in Jeddah, Saudi Arabia, on female students, teachers, and supervisors in high schools to measure knowledge, attitudes,

and practices. The results showed that most of the participants' source of information are social media. Furthermore, they had a poor knowledge of dengue fever, and two-third of them did not know that dengue fever is an infection. Some of them knew that mosquitoes bites could transmit dengue fever.^[41] A review study published in 2014 advised improving public awareness for prevention and control of dengue fever through radio and television. Furthermore, they suggested workshop for health professionals.^[42] Implementation of these suggestions leads to a drastic reduction in the population of *A. aegypti*. Some areas having high mosquito activity were reduced to zero mosquitoes. Further proof was done by the reduced movement of dengue fever approved cases and claim made by the citizens.^[43]

The main tools to control Zika virus include space spraying, larval control, targeted residual spraying, and personal protection measures, WHO still recommends a need more evidence required before pilot deployment (sterile insect by genetic modification technique, vector traps, and attractive toxic sugar baits).^[44]

Conclusion and Recommendations

So far, no reported cases of Zika in Saudi Arabia. However, it is evident that there is some similarity between Zika and dengue in many aspects as shown in Table 1. Furthermore, the Kingdom of Saudi Arabia is open for the visitors from the entire world, particularly during the religious occasions of Al-Hajj and Al-Omrah. The total number of Muslims, who visited the holy city Makkah in Al-Hajj, was 1,952,817 in 2015. The Brazilian Muslims, who performed Hajj, were 884 pilgrims during 2012–2015. This mass gathering represents a big challenge to the country annually where a huge mass gathering of people present in small space over a short period. Moreover, there are many expatriates, working in various projects and sectors in Saudi Arabia.^[45,46] There are no direct flights between Saudi Arabia and Brazil. However, there is an enormous import from different goods from Brazil to Saudi Arabia. In terms of weight, Saudi Arabia imports about 4.7 million tons which make Brazil in the second rank among 96 countries who export to Saudi Arabia.

Furthermore, the Saudis travel abroad as tourists, students, and businessmen. Theoretically, during the heavy travel forth and back to Saudi Arabia, people might catch the disease from other countries who are infected with Zika. However, we do not have the magnitude of those Saudi visitors to Brazil. Then, the endemic *Aedes* mosquitoes might transmit the virus to others by biting them in particularly the Southern and Western regions. The Saudi Health Authorities managed to control dengue fever by reducing the activity of *Aedes* mosquitoes, filling swamps and ponds. Furthermore, there was isolation for patients who carry this virus. For individual's protection, the WHO recommended spraying insecticide inside the houses that nearby mosquitoes sites, wearing clothes with long sleeves, closing the access to

Table 1: Similarity and dissimilarity of DENV & ZIKV

Variables	ZIKV	DENV
Definition	Zika virus is a flavivirus, transmitted by <i>Aedes</i> mosquitoes	Dengue is a mosquito-borne viral disease that has rapidly spread in all countries
Types	ZIK-1	DEN-1, DEN-2, DEN-3 and DEN-4
Symptoms	Fever, skin rashes, muscle and joint pain, headache, and malaise	Fever, painful muscle, bone, joint aches, headache, rash, and sweating
Borne-vector	<i>A. aegypti</i> , <i>A. albopictus</i>	
Environmental factor	Tropical, subtropical, and temperate area specially in floodwater	
Transmission	Through bites from female <i>A. aegypti</i> , <i>A. albopictus</i> . and sexual transmission	By female mosquitoes of <i>A. aegypti</i> and the <i>A. albopictus</i>
Treatment	At the present, there is no specific treatment, the best prevention is to protection from mosquito bites	There is no specific treatment, it's symptomatic measure such as using pain relief if needed
Biological structure	The virus stored in the digestive system of mosquito	
First reported case	First case reported 1952 in Uganda	in China (265–420 AD)
Recent outbreaks	In Aruba and Bonaire 2016	In Asian and Latin American countries
Complications	Guillain-Barré syndrome and microrcephaly, which is affect fetus	Hemorrhagic, shock syndrome, hypertension, dehydration, liver damage, and some cases death

A. aegypti: *Aedes aegypti*, *A. albopictus*: *Aedes albopictus*

the homes to protect from entry of the mosquitoes, cover the beds with mosquitoes nets, and get rid of water containers to prevent mosquitoes breeding. Furthermore, higher stages of preparedness must be taken in the rainy season, hot climates, and high temperature. Even though there is some similarity between Dengue and Zika in the disease symptoms, vector and the way of transmission, the precaution of reducing exposure to the mosquitoes, isolating cases, and continuous improvement of the public and professionals awareness might minimize the risk of Zika. Moreover, men and women who are travelling to the virus infected areas were advised by the WHO to adhere strictly to steps that can prevent mosquito bites during their trip. Furthermore, the WHO advises a pregnant woman who is planning to travel to Zika virus infected countries to seek medical advice and discuss their travel plans with their health-care provider and considering delaying their trip plans.^[47] The Ministry of Health, Municipality and Agriculture should collaborate to design, execute, and monitor control and prevention strategy.

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