



## A Survey on Zika Virus Infection as a Global Emergency, a Mosquito-Borne Flavivirus

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### ABSTRACT

**Introduction and Objectives:** The spread of the Zika virus throughout Africa, the Americas, Asia, and Oceania and the reported outbreaks of the Zika virus disease has turned this virus into a public health emergency of international concern. Given the significance of this disease and its spread across the world, this study investigated the history, epidemiology, symptoms, vectors, reservoirs, transmission methods, virus characteristics, and control, and its status in Iran and the rest of the world. **Materials and Methods:** Some keywords such as Zika virus, neurodegenerative disorders, global distribution, vector and control were used to search the Internet and authentic medical journals in scientific databases for papers submitted from 2009 to 2019. Seventy-one articles were found of which 52 were selected considering the objectives of the study. These researches were studied and criticized while introducing the Zika virus disease. **Results:** This virus is broadly similar to the Dengue virus in terms of epidemiological indicators and transmission cycle in urban areas. It causes mild illness in most cases, but infection during pregnancy can lead to congenital birth defects. Several mosquito species have been identified as vectors for the Zika virus. It is also transmitted through breast milk, blood transfusion, sexual intercourse, and from mother to child during pregnancy or delivery. The virus is also transmitted transovarially to the eggs of the infected mosquitoes. There is currently no vaccine to prevent Zika and no medicine to treat it. **Conclusions:** Travels to regions where there is an active Zika virus and its transmission is common can increase the risk of transmission of this virus to Iran. Consequently, careful supervision along the borders and the airports when foreigners enter the country is essential.

**Keywords:** Zika virus, Control, Distribution, Epidemiology, Arbovirus, Iran

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### INTRODUCTION:

The arbovirus Zika virus (ZIKV) was first identified in Uganda in 1947 through a monitoring network of sylvatic yellow fever in rhesus monkeys. In 1952, the virus was

identified in humans in Tanzania and Uganda. Before the large ZIKV epidemics occurred in 2007 and 2013, only 20 cases of Zika were reported across the world. Researchers believe that ZIKV entered Brazil during the 2014 FIFA World Cup. ZIKV outbreaks have been recorded

in Africa, Asia, the Americas, and Oceania [1, 2]. From 1960 to 1980, human infection with this virus was reported across Asia and Africa. The World Health Organization (WHO) attracted global attention to the abnormal increase in the incidence of congenital anomalies (microcephaly) and neurological disorders (Guillain-Barré syndrome) caused by the increased prevalence of Zika virus in the region of Pan-American Health Organization. [3, 4].

ZIKV emerged for the first time in 2007 in Yap Island in Micronesia followed by another outbreak in French Polynesia in 2013 [5]. In July 2015, the association of Guillain-Barré syndrome with the ZIKV was reported in Brazil. The high humidity of some seasons in Brazil puts people at greater risk of mosquito bites and disease transmission. These seasons are the worst time for outbreaks or epidemics of a viral disease. There is still very little knowledge available on the disease and the Brazilian government is trying to control the disease in the short term by raising awareness and fighting mosquitoes because infected tourists can easily transmit the virus to other countries. If an infected person travels to a country where *Aedes* vectors exist, the mosquito can bite the infected person and thus spread the virus to an area where it did not previously exist [6]. In October 2015, the association of ZIKV infection with microcephaly was reported in Brazil. Brazilian local health authorities reported that the mosquito was linked to an increased incidence of microcephaly (a condition in which the head circumference is smaller than normal-small head and brain) syndrome in infants. Also, the virus may cause stillbirth and long-term health problems for the survivors. It is associated with the risk of neurological diseases in adults as well [7].

From 2007 to 2016, local transmission of ZIKV was reported in 52 countries. Among them, between 2015 and 2016, local transmission of the virus occurred in 40 countries, indirect evidence of viral circulation was observed in six countries, outbreaks of the disease were terminated in five countries and locally acquired infection in the absence of the vector was reported in one country. In the US, 664 cases of Zika infection were reported until late March 2016 (fifty-four cases in pregnant women, 6 cases of sexual transmission and two cases with

Guillain-Barré syndrome; muscle weakness that affects the legs and then progresses up to the arms). From January 2014 to February 2016, Zika became endemic in 33 countries [8]. With the new epidemics from 2015 to 2016, it appears that the virus is expanding its geographical range of activity [9]. Seroepidemiological research in Africa indicated that ZIKV existed in this continent before the outbreak on Yap Island in 2007, but few cases were reported due to unknown reasons [10]. In European countries, although there have been no reports of circulation and local transmission of the virus, as of April 4, 2017, 2130 cases were reported. ZIKV has been reported in 21 countries across Europe. All of these patients have traveled to infected areas and then they returned to their countries. Also, eight European countries reported ZIKV infection in pregnant women (108 cases). Of course, in 2019, the French authorities reported three probable autochthonous ZIKV cases in Hyeres, Var department, France [11].

*Aedes* mosquitoes bite mainly in the early morning or late afternoon and/or at night. *Ae. aegypti* and *Ae. albopictus* are the two dominant *Aedes* species. The virus is transmitted via *Ae. aegypti* in tropical regions [3]. In addition to *Aedes* vectors, ZIKV is transmitted via the placenta (from mother to fetus) during pregnancy. It is also transmitted via blood transfusion and sexual intercourse. Recently, the association between ZIKV in pregnant women with congenital birth defects has been confirmed. Now, it appears that ZIKV is associated with microcephaly. Microcephaly causes incomplete brain development and the head circumference is smaller than normal. Outbreaks of the Guillain-Barré syndrome associated with the ZIKV were reported in several countries. This syndrome is rarely a life-threatening autoimmune disorder in which the immune system attacks healthy nerve cells in the peripheral nervous system that can result in paralysis and, sometimes, even threaten the life of the individual. In addition to *Aedes* vectors, *Culex* mosquitoes are also able to transmit ZIKV. This increases the importance of Zika disease in Iran because both *Culex* and *Aedes* mosquitoes are found in this country [12-16].

Since there is no vaccine or medication for this disease, it is crucial to prevent mosquito bites.

Zika disease is a public health emergency of international concern, and the World Health Organization issued an International Emergency Declaration and guidelines on how to minimize the chances of exposure to the mosquito vectors and reduce the incidence of the disease. Therefore, this study investigated the history, epidemiology, symptoms, vectors, reservoirs, transmission methods, virus characteristics and control of the disease along with ways of coping with it.

#### **MATERIALS AND METHODS:**

This was a review study. Some keywords such as Zika virus, *Aedes*, *Culicidae*, microcephaly, congenital disorders, neurodegenerative disorders, global distribution, transmission methods, control, arbovirus, infants, pregnant women, and Iran were used to search the Internet and sites related to authentic medical and health journals in databases including Web of Science, Ovid, PubMed, SID, Iran Medex, Scirus, Google Scholar and Medline for papers in Persian and English submitted from 2009 to 2019. Seventy-one articles were found of which 52 were selected considering the objectives of the study. These studies and their applications in controlling Zika disease were examined while introducing the disease. Finally, the obtained data were used to prepare this review article. The study also describes transmission methods of ZIKV and prevention methods of the disease while considering the social, economic and cultural components.

#### **RESULTS AND DISCUSSION:**

ZIKV has been found in *Ae. africanus*, *Ae. apicoargenteus*, *Ae. leuteocephalus*, *Ae. vitattus*, *Ae. furcifer*, *Ae. aegypti*, *Ae. albopictus*, *Anopheles coustani*, and *Mansonia uniformis* [9, 17-21]. It is a mosquito-borne virus transmitted via infected *Aedes* bites, mainly *Ae. aegypti* followed by *Ae. albopictus* in tropical areas. These species also transmit dengue, chikungunya and yellow fever viruses. ZIKV is a flavivirus, a genus of viruses in the family Flaviviridae. It is an enveloped single-stranded RNA virus with a genome length of 10,794 nucleotides. Virus particles are about 40 nm in diameter. ZIKV reservoirs are still unknown. The Flaviviridae family contains

important human pathogens such as dengue fever, yellow fever, chikungunya, West Nile fever, and Japanese encephalitis. The virus is similar to dengue fever, yellow fever, and chikungunya viruses in terms of global distribution [22-28]. It is transmitted via blood transfusion, sexual intercourse, and from mother to fetus. Although ZIKV is detected in breast milk, virus transmission through breast milk has not been confirmed yet. Theoretically, virus transmission might occur via tissue or organ transplant [1-3]. As in the dengue fever virus, ZIKV is also transmitted transovarially to the eggs of the infected *Ae. aegypti* and *Ae. albopictus* mosquitoes [29].

The first outbreaks of ZIKV were reported from Yap Island in the Pacific Ocean and French Polynesia followed by outbreaks in the Americas (Brazil and Colombia) and Africa (Cape Verde). Also, more than 13 countries in the Americas have reported sporadic ZIKV infections indicating the rapid geographic distribution of ZIKV [4, 5, 8]. The virus can also be spread by sexual intercourse. Therefore, it is recommended that infected men and women intending pregnancy wait at least 6 months and 8 weeks, respectively, and use a barrier method during sexual intercourse (to prevent ZIKV transmission) [30, 31]. For this reason, and due to the deleterious effects of the disease, the WHO considers Zika a very important virus [3]. Zika epidemics are a far greater threat than Ebola [32] because they are characterized by microcephaly in newborns and by rapid distribution around the world [33]. This disease is considered the most dangerous threat to global health [34, 35].

ZIKV has caused serious concern in the world because it is expanding rapidly in Latin America since October 2015, and has caused the birth of more than 4,000 children with microcephaly. Only 20% of infected people present symptoms of Zika disease and no signs of the disease are observed in the remaining 80 percent [36]. The incubation period (the time from exposure to appearance of symptoms) of the disease in humans is not clear, but it is very probably 3–12 days. The clinical symptoms of Zika disease are similar to those of other arboviral infections such as dengue fever and include low-grade fever, maculopapular rash, conjunctivitis (swelling and itching), muscle and joint pain,

lethargy and headache. Furthermore, there are few reports of chills accompanying the fever. Symptoms occur 3-12 days after infected mosquito bites. One in four people develop symptoms but, in people who have the disease, the symptoms are usually mild (together with fever and pain) and last 2 to 7 days. The disease shows flu-like symptoms [2, 8]. The extrinsic incubation period in the mosquitoes is about 10 days, and then the vector can transmit the virus to a vertebrate host. The prerequisite for being a mosquito vector is that the virus should survive and reproduce in the body of the mosquito and, eventually, it should be able to transmit the virus to the human or vertebrate host through biting [18].

The definitive diagnosis of ZIKV infection can only be made through laboratory testing to confirm the presence of ZIKV RNA in blood or other body fluids such as urine or saliva. Also, possible virus infection can be detected via clinical signs or recent history (residing in or traveling to areas infected with ZIKV). Pregnancy is the most dangerous period for ZIKV infection because the virus can lead to neurological disorders during fetus development and may destroy the growing brain cells [12, 37]. The World Health Organization has urged Asian countries to be vigilant about the risk of being infected by ZIKV and take preventive measures to control it [38]. At present, China, the Philippines, Thailand, and Indonesia are the most vulnerable to the spread of the Zika epidemic. If it is not controlled quickly in these regions, over two billion and

600 million of the world's population will be at serious risk [39].

Iran, as an Asian country, has different species of mosquitoes. Therefore, it can be faced with the risk of Zika transmission [40-43]. Sixty-nine species of mosquitoes belonging to the Culicidae family have been reported in Iran, 19 of which belong to the *Culex* genus and twelve to *Aedes* genus including *Ae. albopictus* (Table 1). This species is known as one of the vectors of ZIKV. Mosquitoes belonging to the subfamily Culicinae are the most important household and public health pests in Iran. These mosquitoes are scattered all over the country and deprive families of comfort more than other health pests. Studies suggest that there are 7 or 11 genera depending on the generic classification used for the tribe Aedini and 39 species of the subfamily Culicinae in Iran [14-16, 44-47].

Iran also has a suitable climate for endemic transmission of ZIKV [48]. Immigrants from neighboring countries for economic reasons and tourism could increase the risk of disease transmission in Iran [49]. The virus can be transmitted through sexual intercourse. Therefore, Iranians traveling to East Asia may boost the risk of disease transmission inside Iran [33]. The destination countries of Iranian tourists, especially in East Asia, are at risk of Zika and have cases of Zika [37]. Therefore, traveling to areas where active Zika virus exists and its transmission is common can potentially boost the risk of ZIKV transmission. The possibility of virus transmission is higher in summer and during vacations [37, 50-52].

**Table 1:** Mosquitoes belonging to the subfamily Culicinae in Iran

Species	Genus	Species	Genus
<i>Cx. modestus</i>	<i>Culex</i>	<i>Ae. vexans</i>	<i>Aedes</i>
<i>Cx. pusillus</i>		<i>Ae. vittatus</i>	
<i>Cx. pipiens</i>		<i>Ae. albopictus</i>	
<i>Cx. quinquefasciatus</i>		<i>Ae. echinus</i>	
<i>Cx. torrentium</i>		<i>Ae. geniculatus</i>	
<i>Cx. antennatus</i>		<i>Ae. unilineatus</i>	
<i>Cx. perexiguus</i>		<i>Ae. caballus</i>	
<i>Cx. theileri</i>		<i>Ae. flavescens</i>	
<i>Cx. laticinctus</i>		<i>Ae. caspius</i>	
<i>Cx. sinaiticus</i>		<i>Ae. pulcritarsis</i>	
<i>Cx. sitiens</i>		<i>Ae. detritus</i>	
<i>Cx. mimeticus</i>		<i>Ae. leucomelas</i>	
<i>Cx. pseudovishnui</i>			<i>Culiseta</i>
<i>Cx. tritaeniorhynchus</i>		<i>Cs. longiareolata</i>	
<i>Cx. arbieeni</i>		<i>Cs. morsitans</i>	
<i>Cx. deserticola</i>		<i>Cs. alaskaensis</i>	
<i>Cx. hortensis</i>		<i>Cs. annulata</i>	
		<i>Cs. subochrea</i>	

<i>Cx. territans</i> <i>Cx. bitaeniorhynchus</i>		<i>Cq. Richiardi</i>	<i>Coquillettidia</i>
		<i>Ur. Unguiculata</i>	<i>Uranotaenia</i>
		<i>Or.pulcripalpis</i>	<i>Orthopodomyia</i>

**CONCLUSIONS:**

Mosquitoes and their breeding sites will be an important risk factor for ZIKV infection. Prevention of the disease relies on decreasing mosquito populations by reducing their reproduction resources (such as eliminating and/or improving their breeding sites) as well as reducing contact between mosquitoes and humans. Proper mosquito control methods and personal protection are important principles in fighting against the disease. Since there is currently no vaccine to prevent Zika and no medicine to treat it, and given that the virus is sexually transmitted, close supervision over international arrivals seems necessary. It is also important to raise awareness and train people on disease transmission and prevention.

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All data were analyzed according to the relevant laws and guidelines of the ethical standards of the Declaration of Helsinki.

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The authors declare that they have no competing interests.

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