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Review Article

The Epidemiology of Zika Virus in the World: A Comprehensive Review Study

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ABSTRACT

Zika virus is an emerging public health threat. The large outbreak related to this infection was first reported in 2007 in Yap Island. This virus is associated with microcephaly, Guillain Barre syndrome and some of the presentations of Zika infection include fever, maculopapular rash, arthralgia, bilateral conjunctivas, headache, arthritis/arthralgia with edema of tiny joints of feet and hands, retro-orbital pain, myalgia, asthenia and vertigo. In most of the cases, the infection is asymptomatic and self-limited. One of the largest known outbreaks of the virus was reported in French Polynesia, south pacific in October 2013. At the beginning of 2016, more than 52 countries have had reported the active transmission of the Zika virus. In general, there are two transmission modes for the Zika infection: Vector-borne transmission and Non-vector-borne transmission. Some diagnostic tests for Zika infection are RT-PCR, ELISA, and PRNT. Up to now, there is no specific antiviral medicine for the treatment of Zika infection and also no vaccine is available for immunization. As far as we know, more than half of the world's people live in areas where the *Aedes* mosquito lives. There is a probability occurrence of the Zika virus epidemic at any time and in any place without prior notice in today's "global village". Therefore, health systems in all the involved countries should implement better triage and early warning surveillance systems for morbid cases of Zika to prevent large epidemics and the spread of the virus among mosquitoes and finally to avoid its disastrous consequences.

Introduction

High impact viral infections, especially those transmitted by arthropods, have become more relevant in the last decade. The global spread of arboviruses must be considered as a threat to global health security. Zika virus is a new emerging viral disease with high fatality and mortality rates especially in fetal [1, 2]. Zika virus as an emerging mosquito-borne virus belongs to the Flaviviridae family. Genus Flavivirus is phylogenetically close to West Nile Virus (WNV), Dengue Virus (DV), Japanese Encephalitis Virus (JEV), and Yellow Fever Virus (YFV) [1, 3-6]. The first case of infection in humans was detected in a 10-year-old female from Nigeria in 1954. Its strains can be grouped into three main lineages: Asian, East African and West African [4]. The first large outbreak was reported in 2007 in Yap island [3]. It emerged outside Africa in Asia after 1960, reached to Latin America in 2013-2015 and it has circulated on all continents except Europe [7].

During the Zika epidemic in Brazil, an increase was reported in number of newborns with microcephaly. Thus, the World Health Organization (WHO) indicated scientifically that the Zika virus was a cause of microcephaly and Guillain Barre Syndrome. In continue, the results of some epidemiological studies in Brazil showed that there is an association between Zika infection in pregnant women and developmental disorders such as microcephaly in fetuses and newborns [7, 8]. Zika infection characterized by self-limiting symptoms including exanthema, fever and non-purulent conjunctivitis although many cases were asymptomatic [9, 10]. The rate and importance of the virus in the development of microcephaly and Guillain Barre syndrome were so high that WHO on the 1st of February 2016 introduced Zika virus infection

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as a public health emergency in the whole world with a potential threat for the next generations [7, 11-13].

After the outbreak of Zika virus in Brazil, the virus was able to spread rapidly and right now more than 70 countries have reported cases of this infection [12]. Some potential factors that facilitate the rapid spread of Zika virus are high densities of human-biting mosquitoes, high human density, and suitable environmental conditions [7]. In the present review study, we comprehensively intend to have the most updated look to an epidemiological picture of Zika virus infection and demonstrate the current status of this infection in the world.

Epidemiology

Zika virus was identified in 1947 from a rhesus monkey during routine surveillance for yellow fever in the Zika Forest near Entebbe, Uganda and it was subsequently isolated from *Aedes africanus* mosquitoes [14, 15]. Since then, several outbreaks of Zika virus have been reported [16]. In literature, there are few reports about human infection from Zika virus in Asia and Africa before 21st century [3, 17]. Although the virus was isolated from *Aedes aegypti* mosquito in Malaysia in 1966 and the first human infections were reported in central Java of Indonesia in 1977, the ZIKV is suspected to circulate from 1954 in Malaysia, Philippines, Thailand and Vietnam. In most of tropical counties, the mosquito *Aedes aegypti* has colonization and is endemic in Asian countries [4]. *Aedes* mosquitoes as a carrier of Zika and other viruses are likely to live year-round across much of Central America, northern South America, West Africa, Central Africa and South-East Asia [18, 19]. In the places where non-human hosts are not available, humans become the primary host [20].

Before 2007, a few sporadic cases of human infection of this virus were reported in Africa and Asia [21]. The Asian genotype of Zika virus emerged out of Africa about 180 years ago. This genotype is responsible for the recent outbreak in the Caribbean, South America, Central America, and the Pacific islands [22]. In Africa, the ZIKV was detected in the west and east countries including Angola, Benin, Burkina Faso, Cameroon, Central Africa Republic, Chad, Guinea Bissau, Gabon, Liberia, Mali, Niger, Nigeria, Republic of Congo, Senegal, Sierra Leone, and Togo [7]. In north and south America, including the united states, the epidemic of Zika virus is a growing concern for public health [16]. The first morbid cases were reported in the United States in 2014 in those who came from the northeast of Brazil [13]. The largest known Zika outbreak reported started in October 2013 in French Polynesia and affected more than 28000 individuals [3]. Brazil is another country that experienced the large-scale spread of the virus. Since November 2015, 18 of Brazil's 27 states had reported new cases of Zika infection and all morbid cases were estimated to be approximately 500000 and 1500000 [11, 17, 23].

The peak of the Zika epidemic was in November 2015. Then, in 2017, the virus has spread to the Caribbean, Latin America, and the United States [24]. At the beginning of 2016, 52 countries had reported active viral transmission of Zika virus and on 31st August 2016, 72 countries and territories had observed the transmission of Zika virus [11, 13]. In different regions of the world, there is a clear difference in the landscape of the virus transmission. Climate factor is an important determinant for its occurrence as a mosquito-borne disease [4, 25]. Since January 2015, over 41000 cases of Zika infection have been reported within the United States and its territories of which 3461 cases were pregnant women [16]. Up to now, Zika was hardly a cause for global panic. From August 2015, doctors in North East of Brazil began to notice a trend: many mothers who had recently experienced symptoms of the Zika virus were giving birth to babies with microcephaly [13, 26]. After the risk assessment and management of infection of the virus, it has attracted global attention, especially after the announcement and warning on behalf of the WHO. This organization formerly declared that the Zika virus epidemic should be considered as a public health emergency and also as an international concern [1, 27].

Pathogenesis and Clinical Presentation

The pathogenesis of the Zika virus is unknown, but several studies have shown that Mosquito-borne flaviviruses initially duplicate in dendrite cells. Then, they spread in blood and lymph nodes. Although replication of flaviviruses occurs in the cytoplasm, it has been observed in some studies that Zika virus antigens were found in the nucleus of the cells. Also, it has been observed in human blood before the onset of the symptoms [28].

Clinical presentation of the Zika virus infection varies. Based on the clinical manifestations, the Zika infection has been categorized into two types of Zika fever and congenital infections [29]. The most common symptoms of Zika virus infection are fever, maculopapular rash, arthralgia, bilateral conjunctivas, headache, arthritis/arthralgia with edema of tiny joints of feet and hands, retro-orbital pain, myalgia, asthenia, and vertigo [29-32]. In some cases, sore throat, cough, and loose bowels are reported [33]. Also, a series of symptoms, known as gastrointestinal symptoms, include: nausea, vomiting, diarrhea, abdominal pain, constipation, and aphthous ulcers have been reported [29]. Occasionally, eye infections caused by the Zika virus cause uveitis, a potentially blinding inflammatory disease [11, 21]. In general, the clinical picture of natural human Zika virus infection is a self-limiting, short duration, mild fibril illness that is accompanied by a maculopapular rash [34]. The incubation period of Zika is estimated to be 2-14 days [29]. Most patients with Zika virus infection are asymptomatic (about 80%). Even if the symptoms appear, they dissolve so fast that the patient does not feel a need to visit the doctor. In some patients the severe neurologic complications such as Guillain Barre and microcephaly have been described [3, 4, 11, 20, 21].

Comorbidity of the virus in patients with the suppressed immune system makes them more vulnerable to a severe type of the infection [29]. During pregnancy, the Zika virus infection can cause microcephaly and other manifestations that are categorized as Zika congenital syndrome. Furthermore, the infection in adults is linked to Guillain Barre syndrome [34]. The recent epidemic of Zika virus in 2015 in America have revealed more severe clinical manifestations associated with Zika with high congenital defects in neonates and neurological complications in adults in the involved countries worldwide [21]. It is difficult to clinically differentiate Zika virus infections from another arboviral disease such as Chikungunya and Dengue [4]. In French Polynesia, the co-infection of Zika virus has been reported with the Dengue virus. Also, in Colombia, the co-infection of the Chikungunya virus with the Dengue

virus has been reported [27]. Symptoms such as conjunctivitis, edema of extremities and absence of leucopenia/thrombocytopenia are more common in the Zika virus infection [4]. About 15 to >28 days after symptom onset, the viremia could persist in whole blood of patients infected with Zika virus [27]. It can be said that the Zika virus, with Chikungunya and Dengue, is the same for their effect on microcephaly in neonates [23]. However, the long-term effects of Zika virus are providing the microcephaly in infants and Guillain-Barre syndrome in adults [16].

In cases with sickle cell disorder and Guillain-Barre syndrome, the Zika virus infection can lead to death [20]. The maximum likelihood estimate of R0 was 4.5 and 5.8 for the assumed 4 and 5 weeks of exponential growth period [1]. Based on findings of a study conducted in Brazil, the estimated case fatality rate of Zika infection in morbid cases with microcephaly or other comorbidities was 8.3%. In morbid cases that did not have a comorbidity, the Zika infection has no risk of mortality [20].

I Microcephaly

Microcephaly is a rare congenital defect in which the baby's cranium with a significantly decrease in the occipitofrontal head circumference of greater than two standard deviations below the normative mean [35]. This defect can be divided in generally primary microcephaly (apparent congenitally) and secondary microcephaly (develops postnatally). Some literature mentioned that the causes of microcephaly can also be under the influence of potential factors such as genetic or even environmental factors [36].

The incidence rate of neonatal microcephaly differs from 1.3 to 150 per 100000 live births. Although the incidence rate of this defect is low, since 2015 in Brazil, the incidence rate of it has increased remarkably (approximately 3000 cases with microcephaly have been reported) [35]. This sudden and unexpected increase provided a platform for further studies in this scope. The consequences of microcephaly include seizure, developmental deficiency, functional motor deficiency, and learning disability abnormalities [37]. Recently, epidemiological studies have reported that new morbid cases of microcephaly arise from a mosquito-transmitted flavivirus (Zika virus). Therefore, the re-emerging of Zika virus and its association with microcephaly created a new challenge in gynaecology [17]. Zika virus is responsible for severe neurological complications in fetal and also an important potential agent in the development of microcephaly, especially in neonatal. Obviously, several infections, including the pathogens associated with the teratogenic effect summarized by the TORCH syndrome, may also be identified as the cause of microcephaly [27].

II Guillain Barre Syndrome (GBS)

GBS is a rare autoimmune disorder that body's immune system attacks the peripheral nerves. The exact cause of it was unknown before but now it has been identified that GBS is often preceded by an infectious disease such as gastrointestinal infection or acute respiratory tract infection [38, 39]. Early symptoms of this disorder were weakness and tingling sensation in the legs. During the outbreak of Zika virus in French Polynesia, 42 cases of GBS were also reported. Among the cases of GBS, those who had Zika virus infection simultaneously, had a more severe type of clinical symptoms resulting from this infection [17]. It can be said that the association between the Zika virus and the GBS is another important challenge and concern for public health, which requires further research in this regard.

Virology

Arboviruses belong to four main viral families including Togaviridae, Flaviviridae, Bunyaviridae and Reoviridae. Arboviruses are comprised of a very diverse group of viruses that are transmitted by arthropod vectors, including mosquitoes, ticks, and midges. Arboviruses can have various economic and social impacts on the community. They also can create a variety of severe illnesses and involve a different range of human and animal hosts [34]. Zika virus is one of these viruses that has been isolated in *Aedes apicoargenteus*, *Aedes luteoceplus*, *Aedes aegypti*, *Aedes vitattus*, and *Aedes furcifer* [11]. Zika virus is a positive, single strand-enveloped RNA virus with 10794 nucleotides that encoded 3419 amino acids. Zika virus belongs to the Flavivirus genus of the Flaviviridae family that includes several human pathogens. This virus is a 50-nm enveloped virus with an inner nucleocapsid and outer lipid bilayer. The inner nucleocapsid is composed of a single strand RNA. The outer lipid bilayer derived from the host cell is covered by 180 copies of two proteins include the viral member M protein and envelope E protein [7]. The E protein plays an important role in receptor binding and membrane fusion. Therefore, it must be considered as a key element in the virus [29].

The Zika virus genome consists of two noncoding regions, and one region encoding a polyprotein that is cleaved into ten proteins, including capsid, membrane, precursor, envelopes, and seven nonstructural protein (NS1, NS2A, NS3, NS4A, NS4B, and NS5) [13]. It should be noted that one of the potential challenges for Zika vaccine design is the focus on NS1, the unique protein of this virus. Also, focusing on Zika virus, NS1 protein becomes an interesting drug target [40].

Transmission

Zika is an arthropod-borne virus (arbovirus) that has been isolated in Asia and Africa from several different mosquitoes which can potentially act as vectors for viral transmission in a given environment of those endemic area's species in the genus *Aedes*. Thus, it is naturally transmitted to humans through the bite of an infected mosquito [41]. In general, there are two transmission modes for the Zika infection that each of them has its own cycle.

I Vector-Borne Transmission

Aedes mosquito will be infected when bites a ZIKV virus polluted human or warm-blooded mammal. Then, infected mosquitoes can spread the virus to other people through bites [42, 43]. In this mode, two cycles of transmission have been defined so far: first is the sylvatic cycle and the second is an urban cycle.

i. Sylvatic cycle: Include the transmission of ZIKV between arboreal mosquitoes in forests and non-human primates.
ii. Urban cycle: Include the transmission of ZIKV between humans and urban mosquitoes in towns [44].

In the urban cycle, mainly two types of mosquitoes will be involved in the transmission of Zika virus infection: *A. aegypti* and *A. albopictus* [45]. The virus infection can also spread to distant parts of the globe by traveling off the infected passenger; for instance, vector mosquitoes with Zika virus can come along with the travelers by the vehicles and with the luggage [46].

II Non-Vector-Borne Transmission

Direct human-to-human transmission of ZIKV virus can occur perinatally, sexually, and through breastfeeding or blood transfusion [3, 47].

i. Zika virus can be transmitted from infected mother to fetus during pregnancy. RNA of Zika virus was detected in the amniotic fluid, urine or serum of mothers whose fetuses had brain abnormalities [47].
ii. Sexual transmission is another non-vector-borne way to transmit the Zika virus from an infected person to his or her partner. Sexual transmission occurs between both sexes, but the male-to-female transmission occurs more frequently than female-to-male or male-to-male transmission. In addition to transfer through semen, ZIKV virus has been detected in urine, saliva, and nasopharyngeal swabs [20, 48, 49].
iii. Breastfeeding is another way that has a potential risk of transmission in this infection. ZIKV virus was identified in the breast milk [12, 50].
iv. Virus transmission through transfusions of blood from donors who were infected with the virus can also be another type of non-vector-borne transmission [42, 43, 51].
v. As of other hypotheses have been proposed for the transmission of Zika virus is the direct transmission from the skin and mucous membranes, but such transmission is not common [52].

Diagnosis

The infection of Zika virus in most cases (about 80%) is asymptomatic. The similarity of clinical symptoms related to this infection with other flaviviruses infections such as dengue virus is high and also their diagnosis is complicated [32]. Currently, there are two direct and indirect ways to diagnose Zika:

i. Direct method includes isolation and detection of the viral genome by RT-PCR in blood, saliva, urine, and other body fluids (cerebrospinal fluid, amniotic fluid, semen, vaginal fluid, breast milk, pharyngeal secretions).
ii. Indirect methods based on the identification of Zika antibodies in the blood [53-55].

In the indirect method, antibodies against Zika virus were detected by ELSA, then confirmed by PRNT (plaque reduction neutralization test). The RT-PCR method is often considered as the gold standard for a definitive diagnosis. Diagnosis, due to the high cost and lack of experienced professional laboratory experts often is not available [56-59]. The viremia in Zika virus is usually low and limited to the third and fourth days after the disease onset. For this reason, often the ability of the RT-PCR method to detect ZIKV RNA in the blood is limited. It has been recommended that serum samples are better to be collected for the detection of RNA in the first five days of disease onset. Because in this period the chance of detecting the virus in serum samples is high [55, 60].

Sample saliva can be used as a good alternative when the blood sample is not available. When taking samples from infants and young children in some cases the urine sample is more applicable, since urine samples contain more viral load and have longer lifespan [32]. For this reason, in the acute phase of the disease, the detection and identification of the virus increase in urine compared to serum [61]. Some studies have also detected Zika virus infection 14 days and its genome 28 days after onset of symptoms in semen of infected person [3, 62]. Zika virus can remain detectable in urine for more than 10 days after the onset of the disease [63]. The Zika virus antibodies are detected by the ELISA method and then confirmed by the PRNT (plaque reduction neutralization test). There is a lack of a laboratory network with ZIKV diagnostic capacities and access to standardized reagents remains difficult in various countries [54, 64]. PRNT is used to differentiate antibodies of closely related viruses. Although this test is efficient, it is costly and time-consuming, often unavailable and cannot be done on a massive scale [65, 66].

During the prevalence of Zika infection in the Yap Island, the tests used to confirm the diagnosis included RT-PCR and serological tests such as IgM, MAC-ELISA, and PRNT [24]. Interpreting the results of the tests was important for the diagnosis of Zika infection. Due to cross-reactivity in patients with previous flavivirus infections, particularly the Dengue virus, results need to be interpreted carefully [63]. Recently, with attention to the global response strategy outlined by WHO, the development of a reliable, affordable, and rapid diagnostic test is in priority. In this strategy, the EUROIMMUN produced a commercial kit for serological detection of Zika virus by ELISA and indirect immunofluorescence, also different commercial-diagnostic kits are under various quality control processes [67, 68]. Some of them entered the market, but the sensitivity and specificity of these kits are not yet completely confirmed [69].

Treatment

There is currently no specific antiviral medicine for the treatment of Zika infection. Also, no vaccine is available to prevent this infection. Now several research centers in Europe are trying to develop a vaccine against Zika virus [19]. Since most patients are asymptomatic or have mild symptoms, the specific drug for morbid cases with this virus is not necessary. In general, several treatment strategies for this infection are proposed. For example, some have suggested that it is better to treat morbid cases with Zika virus, doctors use the drugs that were previously prescribed for similar illnesses. Indeed, some of these drugs act as antiviral in the cell. Otherwise, for some morbid cases with Zika virus, physicians have proposed to use a fever and pain reducer such as acetaminophen [70].

Prevention

Since the vaccines have not been developed for immunization of this new viral infection, avoiding exposure to the virus is very important. In other words, protection against mosquito bites is a key measure to prevent Zika virus infection [20]. Centers for Disease Control and

Prevention and WHO have provided recommendations for preventing Zika virus infection, recommended measures include:

i. Patients that are living in endemic areas should wear full sleeve clothing to prevent mosquito bites.
ii. Using larvicide in areas where mosquito larvae exist.
iii. Committing people to use methods to eradicate mosquitoes.
iv. Using mosquito repellant spray or crème on the body skin which is not covered with the dress.
v. Using physical barriers such as window screens or closing doors and windows.
vi. Sleeping under mosquito nets.
vii. Covering, emptying or cleaning potential mosquito breeding sites around houses such as drums, buckets, pots, gutters and tires.
viii. Pregnant women should keep away from making contact with all potential vectors.
ix. In order to prevent sexual transmission of the virus, all patients (male and female) with Zika virus infection and their sexual partners (particularly pregnant women) should receive information about sexual transmission of the Zika virus, contraceptive measures, safer sexual practices provided with condoms [20, 71].

Flaviviruses can be effectively inactivated by temperatures above 56 0C UV light and gamma radiation for at least 30 min. Also, some disinfectants such as 1% sodium hypochlorite, 2% Glutaraldehyde, 70% ethanol, 3-6% hydrogen peroxide, and 3-8% formaldehyde can be used to inactivate the virus [15].

Updates

More than half of the world's people live in areas where the *Aedes* mosquito lives [72]. Consequently, WHO commits to long-term response to Zika as 'public health emergency' is lifted. There are 84 territories and countries in the world with evidence of vector borne Zika virus transmission. More than 60 local and global partners are participating in the Zika virus response until now. On the whole, the global risk assessment has not changed. Zika continues to spread geographically to areas where competent vectors are present. Although a decline in cases of Zika virus infection has been reported now in some morbid countries in the world, it should be noted that there is a probability occurrence of the Zika virus epidemic at any time and in any place without prior notice in today's "global village". Thus, health systems in all countries should implement better triage systems for potential imported cases of Zika virus to prevent large epidemics [73]. We will continue to monitor the epidemiology of Zika virus and its associated risk factors and add new information about its spread, trend, pathogenesis, and clinical outcomes as our knowledge about this emerging virus continues to evolve.

Conclusion

Since the Zika virus has emerged, several studies on the various aspects of the infection have been conducted around the world including identification of the virus, transmission routes, clinical signs of the disease, its effects on the fetus and prevention methods. Our comprehensive review is adding the most updated knowledge about Zika virus infection and its different epidemiological aspects. However, extensive field research is still needed to better understand this novel and emerging viral infection. We need more developed knowledge of virology and the mechanism of the virus to produce the vaccines in the future. As the disease can be a threat to the entire world, it is necessary to develop a vaccine with high effectiveness for this viral infection. It must be mentioned that the development of vaccines to prevent the next encounters with Zika virus is one of the most needs in medical sciences now.

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None.

Conflicts of Interest

None.

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