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Epidemiological and Zoonotic Importance of Zika Virus

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Summary:

Zika virus disease is caused by genus Flavivirus, that transmitted mostly by Aedes mosquitoes and it was first isolated from a rhesus monkey in the Zika forest of Uganda in 1947. This review was made to document the distribution of Zika virus. Zika virus is the major human and non human diseases found in tropical regions of the world. Epidemiology of the disease depends on whether a condition of which is suitable for vector reproduction. The virus transmission depends on the numbers of primates and mosquitoes. Zika virus diseases can also transmit by non-vectors such as sexual transmission, blood transfusions and mother to child during pregnancy. The clinical signs of the disease include acute fever and skin rashes. However, 80% of infected patients are asymptomatic and it became a public health problem at the end of 2015, when an outbreak in Brazil was associated with a microcephaly cases in fetus and newborns. Diagnosis is either direct detection of the virus or antibody responses to infection in body fluids. The serological evidence of infection was identified in a few animals in Indonesia, including horses, cows, goats and bats. There is no specific treatment and vaccine of Zika virus infection. But there are supportive care which consists of rest, fluids, and symptomatic treatment. Prevention and control relies on reducing mosquitoes breeding sites; contact between mosquitoes and people should be implemented.

1. **Keywords:** Control; Prevention; Transmission; Zika Virus; Zoonoses

2. Introduction

Zika virus (ZIKV) disease is caused by an arthropod-borne virus of family Flaviviridae genus Flavivirus **[1]**. It is an arbovirus which can transmit the disease to humans through a mosquito vector that was a daytime-active *A. aegypti* and *A. albopictus* mosquitoes. These mosquitoes are also important in transmitting viruses such as dengue virus (DENV), yellow fever virus (YELLOW FEVER VIRUS) and chikungunya viruses (CHIKKV). It was first isolated from a rhesus monkey in the Zika forest in Uganda in 1947 [**2**].The virus is most prevalent and emerging pathogen that has recently causing serious disease around the world. Cases of ZIKV disease were reported in Micronesia in 2007 and then in French Polynesia in 2013. In Brazil the virus was introduced and associated with cases of microcephaly **[3]**. The virus has the potential to spread anywhere the day time active mosquitoes capable of spreading this virus are found, but there is no case report about ZIKV disease in Ethiopia **[4]**. They are highly sensitive to climate **[5]**. Temperature and rainfall influence the abundance and seasonality of mosquitoes. Furthermore, temperature has a major effect on the population of mosquitoes to transmit virus. The risk of transmission can be vectors **[6]**.

The most common symptoms reported in confirmed ZIKV infections are fever, headache, maculopapular rash, fatigue or myalgia, arthritis and arthralgia **[7]**. The virus RNA can be detected in blood, urine and saliva during the acute phase of the disease, in seminal fluid after acute illness and also in semen for two to ten weeks **[8]**. After recover from clinical symptoms of virus, there were probable cases of sexual transmission **[6,9,10]**. In non-human primates (NHP), antibodies against ZIKV have been reported both in wild and experimental animals in Borneo and Uganda **[11,12]**. The disease is relatively mild and has no specific treatment. Prevention and control relies on reducing mosquitoes through reduction of breeding sites and reducing contact between mosquitoes and people. This can be done by using insect repellent, wearing clothes preferably when light-colored, and using physical barriers such as window nets, closed doors and windows and additional personal protection **[13]**. There is no case report of Zika virus disease in Ethiopia, Even though some studies and literatures review have been conducted on the ZIKV disease, the viral pathogen is re-emerging and spread into different countries of the World. Therefore the objects of this review are to review the epidemiology and public health importance of Zika virus disease.

3. Epidemiology and Zoonotic Importance of Zika Virus Diseases

3.1. Etiology

ZIKV is a mosquito-borne disease caused by single strand, non-segmented, positive-sense RNA virus of family Flaviviridae genus flavivirus. The virus infects and cause disease in humans and non-human primates (NHP). No other animals have been found to develop disease. Although, serological evidence of infection was identified in a few animals from one study in Indonesia, including horses, cows, water buffalos, goats, ducks and bats. However, these animals are not believed to play a role virus transmission to humans **[14]**.

3.1.1. Morphology and Life Cycle of the Virus

The structure of the Zika virus is similar to other Flaviviruses like the DENV, YELLOW FEVER VIRUS and WNV. A virion is about 40-60 nm in diameter, and has 5-10nm surface projections which arranged in an icosahedral symmetry. The protein is surrounded by lipid bilayer envelope. The other complex structure of the genome is terminus which is essential for causing disease in human. The protein composes the majority of the virion surface and is involved in the viral-host cell binding and membrane fusion during replication **[15] (Figure 1)**.

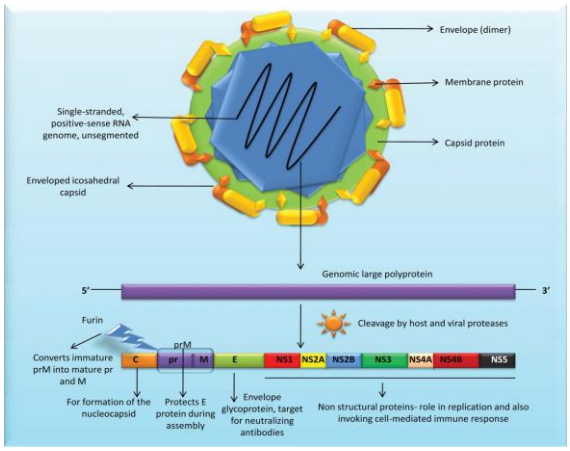

Figure 1: Structure of Zika virus and its genome **[16]**.

The natural cycle of ZIKV involves mosquito vectors and vertebrate hosts. In the current outbreak the vertebrate hosts are humans. The infected female *A. aegypti* and *A. albopictus* mosquitos transmit virus during their blood-feeds in primates and humans. Both lay eggs in stagnant water around the house and they are daytime biters, special during early morning and late afternoon (evening). After infected female mosquitoes bite human or non human primate, viruses bind to receptors at the cell surface and enter host cells by receptor-mediated endocytosis. Infection is initiated when the viral RNA is introduced into the cytoplasm of the target cell after fusion of the virion envelope with endosomal membranes. Cellular mechanisms translate the viral structural and nonstructural proteins from the viral RNA, and the RNA is replicated by the viral replicase in cellular factors **[17]**. The newly synthesized viral RNAs are then packaged with viral structural proteins into a noninfectious immature particle, which leaves the cell via a cellular secretor pathway. During this process, virion maturation and replication induces changes to both the cellular structure and cellular metabolic pathways to promote its own replication and subvert host innate immune responses **[18](Figure 2)**.

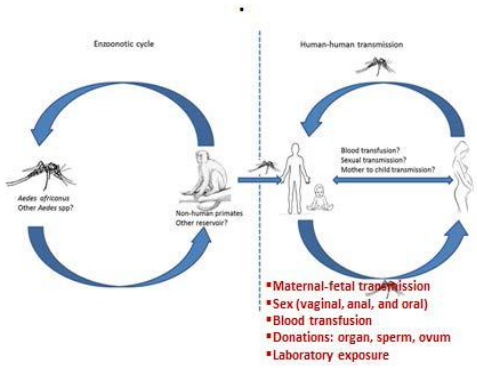

Figure 2: Zoonotic and life cyle of Zika virus **[19]**.

3.1.2. Geographical Distributions

Some literatures documented that during scientists conducting Yellow fever virus study in Uganda at the Zika forest in 1947 accidentally they observed a fevered rhesus monkey placed in a cage. The monkey that kept for the purpose of Yellow fever virus study developed a fever, and researchers isolate a transmissible agent from its serum that was first described as zika virus **[20]**. Following the virus isolation, there was first virus case reported in human being in Uganda and Tanzania in 1954. Before 2007, there were reports of confirmed cases of Zika virus infection from the Africa and Southeast Asian continent. Later on in 2007, major epidemic occurred in Yap Island (Micronesia) in which about 5000 person affected and also case report in Gabon **[12,21]**. In late 2015, the virus was reported for the first time in a number of countries in Central and South America with symptoms of microcephaly in affected parts of Brazil and now includes many Caribbean nations. However, the epicentre of the virus was Brazil and the virus soon spread to El Salvador, Honduras, Colombia, Venezuela and Costa Rica. The relationship of mosquito number with increased temperature is biological, that means it favors mosquitoes reproduction and increase their chance of contact with humans (for blood meal in case of female A. aegypti), which favor Zika transmission **[22]**. Aedes mosquitoes are found in many parts of the world, as result the outbreaks of the virus can be occurred to new areas **[23]**. The outbreak on the Island of Yap in 2007 was the first outbreak occurred outside of Africa and Asia. Outbreaks in French Polynesia occur in 2013, in which clinicians recognized an increase in the incidence of (GBS) **[24,25]**. The out breaks of Zika virus was reported in October 2015 in Brazil with a significant increase in the incidence of microcephaly among newborn infants [26,27]. The outbreak of virus outside of Africa and Asia was that occurred in April 2015, in Brazil that is suspected to linked with 2014 FIFA World Cup, which coupled with large population of vectors such as A. aegypt (main vector) and A. albopictus (Asian tiger) mosquitoes that inhabit the region. Currently, increased global travelling of peoples will also contribute for infection [28]. Moreover, after health authorities in Brazil warned of an increase in the prevalence of microcephaly in newborns might be associated with Zika Virus infection in mothers during pregnancy, health authorities in French Polynesia confirmed that neurologic congenital abnormalities also have been associated with Zika outbreak **[29]**.

The last outbreak occurred in Brazil in early 2016 which were associates with El Niño phenomena that happened in the Pacific Ocean. Recent study in Brazil showed that, urbanization contributes for the large outbreak of Zika virus. That means, in urban areas where dense population living in close proximity and a lot of vector mosquito present, the efficiency of Virus to pass from infected person to healthy is high. Due to the world population increases in alarming rate,

now days it is common to see rapid urbanization in which people found in remote area moved to highly vector infested place which predispose people to infection **[28]**.

3.2. Risk Factor

3.2.1. Host Related Risk Factors

The virus reservoir host is not completely identified and isolated, some studies suggests that, the reservoir host of Zika virus was primates. The other authors indicate the presence of anti-Zika antibodies in various animals including big mammals such as Zebras, Elephants and rodents in Pakistan **[30]**. The virus has been shown to infect and cause disease in humans and non-human primates (NHP). However, serological evidence of infection was identified in a few animals from one of study conducted in Indonesia, including horses, cows, water buffalos, goats, ducks and bats. Considering the current epidemiological situation of the Zika virus, Brazil has a large number of non-human primate (NHP) population **[31]**.The driving forces in the spread of diseases, include anthropogenic activities, introduction of in vasive species and wildlife trafficking, These show that, many of the emerging and re-emerging infectious diseases like Zika virus are reserved in the wild and domestic animals **[32]**.

3.2.2. Vector Related Risk Factors

Aedes mosquito is a common vector that transmits viruses which cause disease such as Dengue virus (DENV), Chikungunya virus(CHIKV), West Nile Fever(WNV) and Zika virus(ZIKV) disease. The species of genus Aedes include *Aedes aegypti*, *Aedes polynesiensis*, *Aedes albopictus and Aedes hensilli*, which were identified during Zika outbreak on the Island of Yap in 2007, in Micronesia [**33]**. The main source of ZIKV is infected mosquitoes, mainly *Aedes* and secondary source is in fected humans **[34]**. Regarding the vector distribution, there was an increase in the number of the mosquito vector, such as *A. aegypti* and *A. albopictus*, when compared to the previous vector presence. The movement of mosquito is directly related with ZIKV infection Aedes mosquito can be identified by white mark on its legs and upper surface of the thorax **[35](Figure 3)**.

Aedes albopictus

Aedes aegypt

Figure 3: a. aegypti and a. albopictus **[36]**.

3.2.3. Environmental Related Risk Factors

The infections is re-emerging throughout the world and occurred in epidemic form because of environmental changes, which may facilitate development, distribution and disease transmission on larger scale. The driving forces in the spread of diseases include climatic change, loss of biodiversity, habitat destruction, land use change and urban development **[37]**. Changes in climatic conditions, creates suitable conditions for mosquitoes by increasing its biting season and disease carrying mosquitoes will continue to bite as the climate warms. Weather conditions and global warming are important in occurrences and incidences of ZIKV. For instance, El Niño is one of the factors that bring heavy rain which result in creating good opportunity for mosquito reproduction and multiplication site **[38]**. Presence of high rainfall is a positive indicator of ZIKV infection. Therefore, increased temperature has risk of the potential increase in transmission of mosquito-borne diseases like ZIKV. The global warming attribute to the rapid spread of the virus, because it help virus to emerge, survive longer and even spread to cooler areas of the world; and also during warm condition, working hours will be changed and people will be forced to go early in the morning and stay until evening at night. In addition,

the type of clothing will also be changed and help mosquitoes to bite human **[28]**.

3.2.4. Transmission

The virus transmissions can be based on the numbers of primates and mosquitoes vectors **[39]**. The most common route of Zika virus diseases transmission is through the bite of mosquitoes of the family Culicidae and genus Aedes (hematophagous arthropods) during their blood meal **[40]**. Other modes of transmission are non-vector borne transmission through sexual intercourse, blood transfusion, organ transplantation and prenatal transmission has been reported. Sexual transmission of virus is a particular concern during pregnancy. Transmission of the virus from infected women to their sex partners has not been reported. However, transmission from infected men to women partner has been reported **[41]**. Transmission is possible through organ transplantation, mother-to-fetus during the period of pregnancy **[42]**. People traveled from areas with active ZIKV transmission to countries with free of zika virus can transmit the disease to their sex partners. Transmission in laboratory form A. aegypti mosquitoes to mice and a monkey was reported **[43,44]**.

3.2.5. Pathogenesis

Zika virus has affinity towards human immature dendritic cells, dermal fibroblasts and epidermal keratinocytes. The virus may replicate in the midget. ZIKV enters the cells through receptors that are found on the surface of skin and nerve cells. After entrance the virus replicate and distributed to muscles, heart, central nervous system (CNS), and to fetus by crossing the placental barrier through blood vessels and lymphatic **[45]**. Viral replication in the host cells causes the release of type I interferon **[46]**. Inside the cells, they use host mechanism and finally cause apoptosis and autophagy of the cells. It causes damage to the eye of infants **[47]**. ZIKV use certain means to defeat the host defense of the trophoblast and by attacking neuronal tissues, it cause neuronal abnormalities in the fetus **[48]**. Some study show that, the virus have affinity towards brain cells which was demonstrated when intraperitoneal injection of virus into mice the virus cross the blood brain barrier. Neurons and glial cells were infected by virus and producing intracytoplasmic inclusions called viral factories. One recent study revealed that, Zika virus and man have a peptide in common which cause microcephaly and Guillain-Barré Syndrome (GBS) **[49]**.

3.2.6. Clinical Signs

The virus has an incubation period of 3-12 days **[50]**. In confirmed case of ZIKV, clinical signs include acute fever, maculopapular skin rashes, nonpurulent conjunctivitis, arthralgia, headache, myalgia and asthenia **[51]**. There are also less evident signs like anorexia, abdominal pain, vomiting, diarrhea, burning sensation of sole and palm **[52,53]**. Symptoms are usually self-limiting and may last for 4-7 days **[54]**. The other complications are birth defects like microcephaly, neurologic complications like GBS **[43]**. Women in endemic areas who may become pregnant are very frightening about the disease. They do not know if they have ZIKV because they may not show any symptoms until later in pregnancy or after they have given birth. The disease of Zika virus is not a life threating, but it is serious because of its link to the birth defect like microcephaly, where babies born with abnormally small heads and GBS, in adults which cause neurological disorder. Even though the disease is not life threating the virus is spreading in alarming rate **[55]**.Unlike humans, wild mammals with ZIKV infection display few clinical signs. In a sentinel study in Uganda in 1947, primates showed only mild pyrexia. All monkeys inoculated virus developed neutralizing antibodies after 14 day of inoculation. In the same study, Swiss mice became ill and one animal died following intracerebral inoculation. Some authors point out that some species of wild and laboratory rodents are resistant to some Flavivirus infections, due to genetic resistance **[56]**.

3.2.7. Diagnosis

Diagnostic testing for Flaviviruses is either direct detection of the virus RNA or detection of antibody responses to viral infection. In this manner virus can be detected from blood, other body fluids and tissues depending on stage of infection. For ZIKV, urine appears to have a higher viral detection than blood **[57]**. Reverse transcriptase–polymerase chain reaction (RT-PCR) methods used to detect both intact viral particles and replicating viral RNA inside cells. Serological tests for Zika virus on immunoglobulins (IgG and IgM) can be done in order to confirm the presence of neutralizing antibody toward the infection **[58]**. ZIKV diseases can only be confirmed by laboratory testing for the presence of RNA in the blood or other body fluids, such as urine or saliva. Virus appears to circulate in the blood for the first 3-5 days after onset of symptom **[59]**.

3.2.8. Treatment

ZIKV disease is relatively mild and requires no specific treatment. People sick with this disease should get plenty of rest, drink enough fluids and treat pain and fever with common medicines like acetaminophen (paracetamol), and antihistamine for pruritic rash is necessary. Other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided until dengue can be ruled out to reduce the risk of hemorrhage **[58]**. It is also important to understand the link between microcephaly and the disease because the link is used to develop vaccine **[60]**.

3.2.9. Prevention and Control

Prevention and control relies on reducing mosquitoes through reduction of breeding sites and reducing contact between mosquitoes and people. This can be done by using insect repellent regularly, wearing clothes (light-colored preferable) that covers the body, using physical barriers such as window nets, closed doors and windows. Additional personal protection, like avoiding mosquito bites, reducing sexual transmission and avoiding travel to areas of ongoing Zika virus transmission. Sleep under mosquito nets during the day, clean or cover containers that can store water, and used for mosquito breeding sites **[12]**. Integrated management of the Aedes mosquitoes through biological and chemical control is safe and cost effective. Integrated vector management systems are the most important method. This includes chemical control and biological control **[22]**.In case of biological control, larvivorous fish are recommended for control of Aedes aegypti in large water bodies or large water containers. Endotoxin producing bacteria, Bacillus thuringiensis serotype H-14 has been an effective mosquito control agent. Moreover, chemical control measures are important in larvicides and adulticides, which are recommended in permanent big water containers where water has to be conserved or stored because of scarcity of supply **[23]**. Larvicides include temephos and organophosphate compound. Adulticide recommend for the control of adult Aedes mosquito is pyrethrum sprays. Applications of larvicides and insecticides to kill adult mosquitoes, has some limitations, in which communities are often mobilized to reduce A. aegypti breeding sites, but this strategy often fails, because of inconsistent participation among households and the presence of cryptic breeding sites in modern urban. But, there is no vaccine against ZIKV disease **[26]**. In conclusion, ZIKV disease is not a life threatening, but it is serious disease because of the birth defect. Prevention and control relies on reducing mosquitoes breeding sites and contact between mosquitoes and people. It is important to understand the link between microcephaly and the disease because the link is used to develop vaccine. Therefore, People should aware about the transmission, prevention and control of diseases to avoid exposure of pregnant women to the vector and community water gathering around the house**[61-66]**.

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