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Aedes aegypti as a Vector of Flavivirus

Yimer Muktar*, Nateneal Tamerat and Abnet Shewafera

College of Veterinary Medicine, Haramaya University, PO Box 138 Dire Dawa, Ethiopia

***Corresponding author:** Muktar Y, College of Veterinary Medicine, Haramaya University, PO Box:138 Dire Dawa, Ethiopia, Tel: +82325607169; Fax: +251925920594; E-mail: yimermktr21@gmail.com

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Abstract

Aedes aegypti, is an invasive black and white striped day biting mosquito which bites human and animals with the potential to transmit various arboviruses including flaviviruses. It is believed to be originated from Africa before it spreads to other part of the world. Only the female mosquito is capable of transmitting these viruses, since it primarily feeds on human blood. Over the past decades, there is dramatic increment of these flaviviruses due to geographical expansion of *Aedes aegypti*. Flavivirus is a single-stranded, RNA virus genus involving dengue, zika and yellow fever viruses. These flavivirus are transmitted primarily by *Aedes aegypti*, consequently, the control and regulation of these mosquitos have paramount significance in the prevention of these diseases. These days, there are various mosquito controlling methods including chemical, physical and biological means, according to the regional context. However, the dispersed and transient egg laying pattern of the female *Aedes aegypti* mosquito and its effective adaptation to the urban habitat, make the control of these mosquitoes challenging. Therefore, further research should be conducted and encouraged to come up with innovative solution such as gene modification of vector mosquito while intensifying the battle against individual flavivirus through vaccine development.

Keywords *Aedes aegypti*; Control; Flavivirus; Vector

Introduction

Aedes aegypti is a small mosquito responsible for transmitting the Zika virus, dengue virus, yellow fever virus and chikungunya virus as a primary vector in certain parts of the world [1]. Mosquito-borne virus infections are on the raise, expanding its geographical range into new areas. The spread of infections from Africa and Asia to other continents is thought to be due to extensive travelling, trade, population growth in high-risk areas, globalization of vectors, urbanization, climatic change, as well as virus genome evolution [2].

Female autonomous *Aedes aegypti* mosquitoes need a blood meal from a vertebrate host to reproduce [3]. The nutrients taken up with the blood are used to synthesize large amounts of yolk proteins that are deposited in the eggs. Yolk delivers the energy and building blocks for embryogenesis. The need for blood in order to reproduce makes anautogenous mosquitoes effective disease vectors because they require at least one insect host contact for every batch of eggs they develop. During feeding, adult female *Aedes aegypti* can take up more than their own body weight in blood [4].

The feeding habits of *Aedes aegypti* is more likely anthropophilic, endophagic and endophillic which means they are biting mosquito, prefer to stay inside house and resting indoors after blood feeding while the meal is digested and the eggs mature, respectively [5,6]. As a result, they can serve as vectors for numerous pathogens, e.g., arthropod-borne viruses or parasites, responsible for both human and animal diseases. The most important mosquito-borne viruses include flaviviruses such as Zika virus, Dengue virus (DENV), Yellow fever virus (YFV) and West Nile virus (WNV) [3,7].

All of the above arboviruses are mainly transmitted by Aedes Species including *Aedes aegypti* and *Aedes albopictus*. In recent decades, the incidence of mosquito borne viral infections has grown dramatically. For instance, according to world health organization more than 2.5 billion people i.e. over 40% of the world's population are estimated to be at risk for DENV [3]. *Aedes aegypti* is also the primary vector of yellow fever which is a disease prevalent in tropical South America and Africa [8]. The other important flavivirus is Zika virus with the most frequently reported symptoms of maculopapular rash, fever, arthritis or arthralgia, headaches and non-purulent conjunctivitis [9]. Other severe manifestation of Zika virus includes Guillain-Barré syndrome (BCG), meningoencephalitis, autoimmune complications (thrombocytopenic purpura and leucopenia), microcephaly, other foetal malformations and optical lesions [10] .

Currently, there are no effective vaccines for a number of important human-infecting arboviruses including DENV and Zika virus. Therefore, the control of mosquito vectors is still the main tool to eradicate, or at least reduce, the incidence of arboviral diseases [5]. However, in addition to adult day time biting, larval small habitat and wide transient dispersion makes the control of these mosquitos difficult [11]. Thus, the objective of this manuscript is to review the biology, control of *Aedes aegypti* while highlighting the transmission and vector role of *Aedes aegypti* for alarmingly concerning flavivirus.

Literature Review

Description of *Aedes aegypti*

The adult *Aedes aegypti* is a small to medium-sized mosquito, approximately 4 to 7 millimeters. To naked eye, adult yellow fever mosquitoes resemble the asian tiger mosquito with a slight difference in size and thorax patterns.

Figure 1: *Female Adult Aedes aegypti*

Adults *Aedes aegypti* has white scales on the dorsal surface of the thorax that form the shape of a violin or lyre as shown in Figure 1, while adult *Aedes albopictus* have a white stripe down the middle of the top of the thorax. The abdomen is generally dark brown to black, but also may possess white scales [12]. Females are larger than males, and can be distinguished by small palps tipped with silver or white scales. Males have plumose antennae, whereas females have sparse short hairs. When viewed under a microscope, male mouthparts are modified for nectar feeding while the female mouthparts are modified for blood feeding. The proboscis of both sexes and the tip of the abdomen come to a point, which is characteristic of all Aedes species [13,14].

Distribution and Taxonomical Classification of *Aedes aegypti*

Aedes aegypti most likely originated from Africa, since then these mosquitoes has been transported globally throughout the tropical, subtropical, and parts of the temperate world, through global trade and shipping activities [15,16]. Taxonomical classification of *Aedes aegypti* is as follows.

Kingdom	Animalia
Sub kingdom	Bilateria
Phylum	Arthropoda
Class	Insecta
Order	Dipteria
Family	Culicidae
Genus	Aedes
Species	Aegypti

Table 1: Taxonomic classification of *Aedes aegypti.*

Habitat and Feeding of *Aedes aegypti*

This mosquito usually live between the latitudes of 35°N and 35°S below an elevation of 1000m [5]. *Aedes aegypti* utilizes both natural and artificial habitats including either terrestrial or aquatic. Their adaptations to urban domestic habitats have led to the exploitation of a range of artificial containers frequently associated with human habitation which include vases, water tanks and tyres as shown in Table 1. *Aedes aegypti* larvae require standing water for the completion of their growth cycle. As a result a potential breeding habitats are those places that contain standing bodies of water [17].

The female *Aedes aegypti* feed almost exclusively on human blood, however, it can also feed on other hosts including bovine, swine, cat, rat, and chicken which represents < 1% of blood meals [18]. Athough females *Aedes aegypti* are particularly active biters and feed readily and consistently under favorable circumstances, it can maintain existence for long periods on food other than blood [19]. Feeding on humans generally occur at one to two hour intervals, preferring to bite typically from below or behind, usually the feet and ankles [20].

Reproduction and life cycle of Aedes aegypti

Aedes demonstrate wide behavioral flexibility that allows them to mate in single pairs or in aggregations. Once compatible partners are found, the mating couple forms a union known as a copula. Aedes males usually first grasp the female dorsally and then rapidly change to the ventralposition.

The 180° rotation of mosquito genitalia allows the claspers to be ventrally oriented and this position allows them to grasp the females' cerci. Copulation lasts less than one minute In fact; it was found that 6 seconds was sufficient for insemination [21]. *Aedes aegypti* is holo metabolous i.e. it goes through a complete meta morphosis comprises of an egg, larva, pupa and adult stage. Its entire aquatic cycle can occur in roughly 7-8 days [22,23].

The adult *Aedes aegypti* life span can range from two weeks to a month depending on environmental conditions. *Aedes aegypti* comes in three polytypic forms: domestic, sylvan and per domestic. The domestic form breeds in urban habitat, often around or inside houses. The sylvan form is a more in rural form, breeds in tree holes and forests while the per domestic form thrives in environmentally modified areas such as coconut groves and farms [24,25].

After taking a complete blood meal, females produce on average 100 to 200 eggs per batch, however, the number of eggs produced is dependent on the size of the blood meal. Females can produce up to five batches of eggs during a lifetime [26]. Most often, eggs will be placed at varying distances above the water line and a female will not lay the entire clutch at a single site, but rather spread out the eggs over two or more sites [27].

Eggs of *Aedes aegypti* are long, smooth, ovoid shaped, and approximately one millimeter long. When first laid, eggs appear white but within minutes turn a shiny black. In warm climates, such as the tropics, eggs may develop in as little as two days, whereas in cooler temperate climates, development can take up to a week [27]. *Aedes aegypti* eggs can survive desiccation for months and hatch once submerged in water, these making the control of *Aedes aegypti* difficult [28]. Adults *Aedes aegypti* has white scales on the dorsal surface of the thorax that form the shape of a violin or lyre as shown in Figure 1, while adult *Aedes albopictus* have a white stripe down the middle of the top of the thorax.

The abdomen is generally dark brown to black, but also may possess white scales. Females are larger than males, and can be distinguished by small palps tipped with silver or white scales. Males have plumose antennae, whereas females have sparse short hairs.

Figure 2: Egg of *Aedes aegypti.*

Regarding *Aedes larvae*, it can be distinguished from other genera by the unaided eye due to their short siphon which is used to breathe oxygen and it is held above the water surface while the rest of the body hangs vertically. Larvae feed on organic particulate matter in the water [26]. Males develop faster than females, so males generally pupate earlier. If temperatures are cool, *Aedes aegypti* can remain in the larval stage for months so long as the water supply is sufficient [27]. After Laval stage, *Aedes aegypti* enters the pupal stage. Mosquito pupae are different from many other holometabolous insects in that the pupae are mobile as shown in Figure 2. Pupae do not feed and approximately after 2 days the adults emerge head first by ingesting air to expand the abdomen thus breaking the pupal case [26].

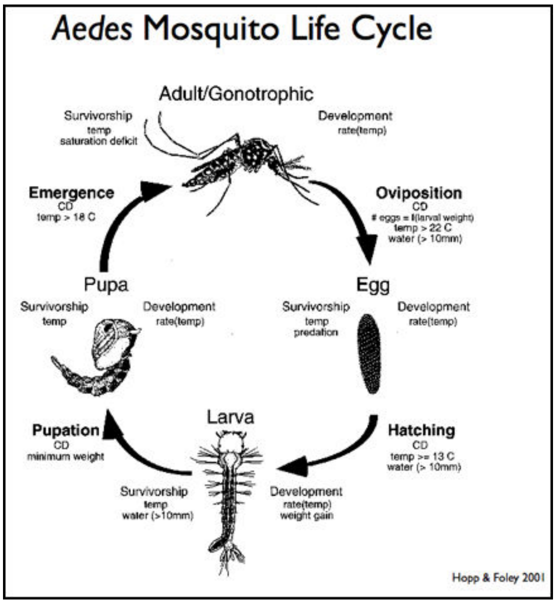

Figure 3: Lifecycle of *Aedes.*

Replication and dissemination of flavivirus in Aedes aegypti

The flavivirus genus group, dengue virus is comprised of four antigenically distinct serotypes (DENV-1, DENV-2, DENV-3 and DENV-4), multiple genotypes enclosed in each serotype [29,30]. The *Aedes aegypti* is the primary vector for all four serotypes and it becomes infected after feeding on a viremic individual, then a reported extrinsic incubation period of 7-14 days is required before the mosquitoes transmit the virus to a new host [31,32].

After ingestion of DENV, mid guts were the first tissues to become infected. Infection spread laterally from this initial stage to the neighboring cells, probably due to virus release by budding as observed in invertebrate cells, frequently involving the entire organ by 7-10 days post infection as shown in Figure 3. For instance, DENV was detected in the salivary glands of 36% of blood fed *Aedes aegypti* at day 4 post infection. However, starting at day 10, but more noticeably at 14 day post infection, the amount of viral antigen in the midgut began to decline [33]. Interestingly, the virus seems to cause no harm to the mosquito which remains infected for life [34].

On the other hands, three strains of yellow fever virus i.e. Cenetrop-322, Jimenez and Asibi are determined by assay in mosquito cell cultures [35]. Determination of mosquito infection rates and dissemination showed that all YFV strains were able to infect *Aedes aegypti. A*lthough infection rates varied from 15.1% to 100%. The presence of YFV after 15 days is evidence of dissemination and replication in the *Aedes aegypti* [36].

Flavivirus

Flavivirus is a genus of a single-stranded RNA viruses in the family of Flaviviridae [37]. Flavivirus includes dengue virus, yellow fever virus, Zika virus and other virus [38]. The flavivirus is surrounded by a lipid bi-layer, which comes from the host cell. Within this bi-layer, the virion capsids exist. These capsids contain a single-stranded, positive-sense RNA molecule of approximately 10,700 base pairs. This genome is then surrounded by a nucleocapsid [39]. This genome consists of one open reading-frame that encodes a precursor polyprotein [40]. Overall, arthropod borne flaviviruses are responsible for significant human and animal disease worldwide [41].

Yellow fever virus

YFV is a mosquito-borne flavivirus, present in tropical areas of Africa and South America. It is related antigenic ally to West Nile virus, St. Louis encephalitis virus and Japanese encephalitis virus [42,43]. It has an incubation period of 3-6 days and possible symptom includes photophobia, myalgias, arthralgia, epigastric pain, anorexia, vomiting, hemorrhage and jaundice. Although, majority of YFV infections are asymptomatic, case-fatality ratio of severe yellow fever with hepato-renal dysfunction is 20%-50% .

At present, there is a very successful vaccine for yellow fever, in which Max Theiler won a Nobel Prize 1951, for his YF vaccine [44]. But the disease is still a challenge in tropical area, recently on 22 March 2016, Democratic Republic of Congo notified WHO a total of 151 suspected YF cases including 21 deaths [45].

Transmission of yellow fever

YFV is transmitted to humans primarily through the bite of an infected Aedes or Haemagogus mosquito species [46]. Mosquitoes acquire the virus by feeding on infected nonhuman or human primates and then can transmit the virus to naïve nonhuman or human primates. YFV has three transmission cycles: jungle (sylvatic), intermediate (savannah) and urban [47]. The jungle (sylvatic) cycle involves transmission of the virus between non human primates (e.g., monkeys) and tree-hole breeding mosquito species found in the forest canopy. The virus is transmitted via mosquitoes from monkey to human when the humans encroach into the jungle during occupational or recreational activities [48].

In Africa, an intermediate (savannah) cycle exists that involves transmission of the YFV from tree hole breeding *Aedes spp*. to humans living or working in jungle border areas [49]. The urban cycle involves anthroponotic transmission of the virus between humans and urban mosquitoes, primarily *Aedes aegypti*. Humans infected with YFV experience the highest levels of viremia and are infectious to mosquitoes shortly before the onset of fever and for 3-5 days thereafter [47].

Dengue virus

Dengue fever virus is another flavivirus which cause an estimated 50 to 100 million infections, a half-million hospitalizations and 22,000 deaths annually in more than 100 countries [50]. By 2085, an estimated 5.2 billion people 3 billion additional people worldwide are projected to be at risk for dengue because of climate change induced increases in humidity that contribute to increased mosquito presence [51].

The characteristic symptoms of dengue are sudden-onset fever, headache, muscle and joint pains and a rash [5]. The name break bone fever was given to dengue, due to presence associated muscle and joint pains [52]. The course of infection is divided into 3 phases: febrile, critical, and recovery. The febrile phase involves high fever, potentially over 40°C (104°F) for 2-7 days. Then the critical phase commences characterized by considerable diffuse leakage of plasma for 1-2 days [5]. Then the recovery phase occurs with resorption of the leaked fluid into the bloodstream over a period of 2-3 days [53].

Transmission of dengue virus

Dengue virus is transmitted primarily by Aedes mosquitoes, particularly *Aedes aegypti*. These mosquitoes typically bite during the day, particularly in the early morning and in the evening. Other Aedes species that transmit the disease include *A. Albopictus*, *A. Polynesiensis*, and *A. scutellaris* [5]. Humans are the primary host of the virus and an infection can be acquired even in a single bite [54,55]. Dengue can also be transmitted via infected blood products, via organ donation and rarely person to person and and vertical transmission is possible during pregnancy [56,57]. Dengue genetic types are believed to be region-specific, suggesting that establishment in new territories is relatively infrequent. However, it has emerged in new regions in recent decades [58].

Zika virus

Zika virus is a flavivirus, closely related to dengue. It is transmitted to humans primarily through the bite of certain infected Aedes species like *Aedes aegypti* and *Aedes albopictus* mosquitoes. Outbreaks of Zika virus are previously reported in tropical Africa, Southeast Asia, South Americas and the Pacific Island [59]. Zika virus is considered to be an emerging pathogen. Although, it has been reported from Africa and Asia previously, it was in 2007 on Yap Island where an outbreak of Zika virus was reported with 185 confirmed cases which make it the first time the virus had been reported outside its usual geographical range [60].

These dayes the diseases is spreading beyounnd its natural geographical region. More recently, several zika cases have been reported even from America and Europe. For instance, four zika cases were reported from Florida and its likely caused by bites of local *Aedes aegypti* mosquitoes. These cases are probably the first known occurrence of local mosquito-borne Zika virus transmission in the continental United States [61]. In Europe, specifically, Spain the first zika infected infant with microcephaly has been born in Europe soil after the mother contracted the disease during previous travel to south America [62].

Zika virus causes a non-severe disease, with possible exception of its effects in fetus in pregnant women i.e. Microcephaly as a baby having a head circumference of less than 33cm with the possibility of Guillain-Barré Syndrome (GBS) which is an auto-immune disorder causing muscle weakness. Diagnosis of Zika virus infection will firstly be by exclusion, based on symptoms, travel history and exclusion of other diseases including measles and dengue [7]. The incubation period is typically 3-12 days. There is no specific therapy or vaccine for Zika virus infection [10].

Transmission of Zika

The transmission of ZIKV is predominately through vectors mosquitoes. However, a recent case shows that human to human contact is possible including sexual contact, which would make it the first time an insect-borne disease was passed via sexual contact [63]. Indeed, viral RNA has been detected in semen for up to 62 days after onset of febrile [64]. In nature, reservoirs for ZIKV virus are restricted to primates [60].

In addition to the arthropod vector bite, perinatal ZIKV transmission has been described and viral RNA has been detected in breast milk in two cases [65]. Caution should also be taken regarding the risk of contamination by blood transfusion [66]. Zika virus RNA and/or protein has also been detected in urine [67], saliva [68], amniotic fluid [69] and placental tissues [70] highlighting the possibility of other modes of transmission.

Control of *Aedes aegypti*

Control of immature stage of Aedes aegypti: Control of immature Aedes aegypti could be accomplished via three methods i.e. chemicals such as larvicides, biological or environmental sanitation methods. The first method is the use of chemicals or biological agents to prevent the development of mosquito immature stages. Biological larvicides includes products containing Bacillus thuringiensis var. israelensis, spinosad, and insect growth regulators such as juvenile hormone analogs (methoprene, pyriproxyfen) and chitin synthesis inhibitors (Diflubenzuron, Novaluron) [71]. On the other hands, biological control involves aquatic predators including copepods and larvivorous fish (Gambusiaaffinis). However, this biological control method may not be practical since Aedes aegypti often develop in small temporary containers [5]. Finally, environmental sanitation involves elimination of containers producing Aedes aegypti and Aedes albopictus by various means [71].

Control methods of adult *Aedes aegypti*

Chemical and physical control: Chemical control of adult mosquitoes includes space spraying, residual spraying, and barrier spraying, and using attractive toxic baits [72-74]. Using insecticides to control mosquitoes should always include insecticide resistance monitoring and management. Insecticide resistance has been demonstrated in almost every class of insecticide, including microbial pesticides and insect growth regulators [75]. Insecticide resistance, which is an inheritable trait, usually leads to significant reduction in the susceptibility of insect populations which renders insecticide treatments ineffective [5]. Regarding, physical control protecting oneself from aggressive biters by wearing light-weight, long-sleeved shirts and pants when working or playing outdoor is recommended. In addition, certain brands of clothing are pretreated with mosquito repellents such as permethrin [76].

Other method of controlling Aedes aegypti

Entomopathogenic fungi: To control adult mosquito vectors, a further alternative biological approach is the use of Entomopathogenic fungi such as *Metarhiziumanisopliae* (*M.anisopliae*) and *Beauveriabassiana* (*B. bassiana*). For a decade, these entomopathogenic fungi have been considered to be good candidates for decreasing pathogen transmission by mosquitoes mainly because of their ability to shorten the mosquitoes' life span or reduce the blood feeding success of female mosquitoes and in arboviruses vectors such as *Aedes aegypti* and *Aedes albopictus* [77,78].

Vector Gene modification and chromosomal translocation

Effort to has been made to genetically engineer Aedes mosquitos in order to suppress or replace vector populations. While population suppression aims to reduce the number of disease-transmitting mosquitoes, population replacement aims to substitute wild type mosquitoes with ones that have impaired vector competence in order to block pathogen transmission. Following the presence of complete genome of mosquitoes, potential targets on mosquito genes have been functionally characterized as influencing mosquito vector competence for arboviruses [79]. In fact, U.S. Food and Drug Administration approved recently, the trial application of genetically modified mosquitoes to combat and suppress the population of *Aedes aegypti* in florida as part of the effort to limit zika cases [80].

On the other hands, translocation is a chromosomal rearrangement resulting from the simultaneous breakage of two non-homologous chromosomes and the subsequent interchange of the broken segments. It can be induced in insects by irradiation. Among wild *Aedes aegypti* females mated to released males bearing translocations, the incidence of sterility was measured as the proportion of non-hatching eggs. For experiments conducted in Kenya, mating to single translocation heterozygote males yielded 50% infertile eggs and mating to double translocation heterozygote's produced approximately 75% non-hatching eggs [81,82].

Conclusions and Recommendation

Aedes aegypti is one of the world most important biological vector responsible to transmit a wide ranges of arbovirus, primarily flavivirus. These mosquito-borne virus infections are on the raise and extending to new geographical areas due to the increasing activities of globalization and climate change. These viruses are causing tremendous negative impact on the health of the global population. Since controlling the vector mosquitoes is a key for controlling these arboviruses various control method should be considered according to the regional context including chemical, biological and environmental means. Based on the above conclusion, further more the effort should be intensified to come up with more innovative ways of controlling the mosquito such as utilizing genetically modified vector mosquitoes, practically while research on the development of vaccines for individual flavivirus including dengue and zika virus should be encouraged.

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