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Dengue and dengue fever: A mosquito (*Aedes aegypti)* vector borne human killer

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Abstract

The past two decades mankind faced many viral infections amongst them the most dangerous and lethal infection was dengue fever. It is a mosquito vector borne disease transmitted from person to person. Dengue viral infection may be symptomatic or asymptomatic associated with fever, dengue fever, dengue hemorrhagic fever (DHF), or dengue shock syndrome (DSS). Every year, around 100 million people got affected and the cases are reported and half a million cases of DHF occur around the world. The untreated patients infected by dengue virus are left to a painful death. This deadliest disease was spread by mosquito species called *Aedes aegypti* and it serves as one of the host and carrier of the dengue virus from person to person. The current work is aimed to give a detailed report on the morphology of the mosquito *Aedes aegypti*, its life cycle as a vector of dengue fever, pathogenesis of dengue infection, symptoms, diagnosis, treatment and prophylactic measures to control dengue viral infections. This study report will serve as the supporting resource for the researchers working on the development of novel biomolecules to control dengue viral infections and to the entomologists to in the eradication of the dengue virus vectors. This review covers the important aspects of the etiology of dengue infections, the dengue virus and its mosquito vector, clinical features and pathogenesis of dengue infections, and the prevention, control of Dengue viral infections.

Keywords: virus; *Aedes aegypti;* vector; dengue; dengue fever; dengue hemorrhagic fever

Introduction

Dengue viral disease was classified under communicable systemic disease transmitted through a mosquito vector called *Ae. aegypti* [1]. In some affected individual it becomes a lethal [2]. Till today there were no official drugs or vaccines are available to combat this disease. Even after the implementation of tremendous efforts were undertaken to control the mosquito vector the global spread have not stopped [3]. Nineteenth century the world faced a sporadic endemic disease called dengue viral infection. The frequency of the infection had quite a long interval. At present the mosquito borne dengue viral infections was considered to be the most important amongst the vector borne viral diseases. A 30 fold increase in the total reported positive cases has dramatically risen to 30-fold with a tremendous and frequent outbreaks occurred around the continents. A report says that 5 of the 6 regions monitored by WHO (World health Organisation) are heavily affected by this infection. More than 100 countries around the world were affected by the dengue viral infections [4] [5].

The prime targets of this disease were identified as the people residing in the urban areas of the tropical and subtropical countries. Every year around 100 million dengue fever cases were getting reported and 50% of the cases were dengue Hemorrhagic Fever (DHF). The fatally rate was high in the Asian countries in the range of 0.5% - 3.5%. The majority of the DHF cases the most affected people were the children's of the age group of less than fifteen years Dengue virus exist in 4 sero types namely DENV1–DENV4. DHF was caused by all the four serotypes of dengue virus [6]. Amongst the serotypes the predominant serotype in the early 80s and the early 90s was DENV-2. DENV-3 serotype infection oversees DENV-2 in recent years [7] [8]. The evolution of DENV-3 serotype was first identified in Indian subcontinent and later got spread to other continents [9]. Less immunogenic people are affected by the DENV-3 serotype and became the reason for the outbreak of this disease and became a pandemic. Currently, dengue is endemic in more than 100 countries in the world. No vaccine is available for preventing this disease. Till today no drugs or vaccination is available for control and prevention this lethal disease. The mortality and morbidity of the disease can be reduced to promising level is the disease is identified in the earFly stages.

Dengue epidemiology

Dengue and dengue fever was found in the medical encyclopedia of China. The transmission of the disease might have happened through ships, because the mosquito vector uses and breeds on the stagnant and stored water in the ship and continues to transmit the virus.

Reasons for the dengue pathogenesis:

The major reasons for the spread of dengue infection were enlisted below:

- Uncontrolled population growth
- Unplanned and uncontrolled urbanization
- Inadequate wastewater management 0

- Lack of effective mosquito control

The distribution, spread and density of dengue virus can be controlled by solving the above-mentioned facts [10] [11]. Dengue viral infections are the widely spread among the five arboviral diseases. Mosquito vector-borne transmission of the DENV disease was reported from around 111 countries [12]. The global occurrences of dengue vector *A.aegypti* and *A. albopictus* were reported by Kraemer *et al* [13] [14] the study delivers all the information related to global occurrences of Aedes borne dengue diseases. The distribution pattern of dengue mosquito vector *Ae. aegypti* with the dengue epidemic activity is depicted in Fig 1. The suitability range for the mosquito vectors *A. aegypti* and *A. albopictus* based on Country-wise were shown as 0 (white) to 100% (deep red) occurrences. (Fig. 2) Kraemer and his fellow researchers developed a vector growth suitability maps based on the global occurrences both *A. aegypti* and *A. albopictus* vectors (Fig. 3).

The global burden of dengue infection grows drastically every year. As per the WHO reports, the occurrences and incidence of dengue has increased 30-fold over the last 50 years. Around 100 million DENV infections were estimated to occur around the world every year. This is the 50% of the world population is at life-threatening risk. The global status of dengue occurrences are clearly shown in the Fig.4. Autochthonous transmission of dengue occurrences were severely noticed in South America, Asia, Africa and in Australia. The countries in these continents are at are high risk of dengue infection. Another study by Brady *et al* around *4* billion from 128 countries are at risk [15].

Characteristics of dengue virus

Dengue virus (DENV) is a RNA virus morphological it is single stranded. It belongs to the belonging flaviviridae family [16]. Based on its biological and immunological characteristics it was classified in to four serotypes namely there are four serotypes DENV-1, DENV-2, DENV-3 and DENV-4. The viral genome is approximately 11 kb in length. The mature virion consists of three structural (core, membrane associated, and envelope) and seven non-structural proteins they are denoted NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5. The biological functions of the DENV is dependent on the envelop protein. These protein structures help the virus to bind to the host cells followed by viral entry in to the human cell. Further they induce neutralisation of antibodies and human immune responses. It causes agglutination of erythrocytes and platelets [17]. Non-structural proteins (NS1–NS5) expressed as both membrane associated and secreted forms have also been implicated in the pathogenesis of severe disease. NS1 dengue viral glycoprotein was not the part of dengue virion but upon viral adsorption on the infected cell it gets expressed. It was evident that it was involved in the replication of dengue virus [18] and the levels of NS1 were higher in patients affected by dengue hemorrhagic fever (DHF) [19]. Moreover, elevated free sNS1 levels within 72 hours of onset of illness identify patients at risk of developing DHF.

Aedes mosquito

The vector of dengue viral infection

Mosquitoes belonging to the Aedes are involved in the major spreading of dengue. Genus plays an important part in transmission of dengue. The three Aedes species are:

1. *Aedes aegypti*
2. *Aedes albopictus*
3. *Aedes polynesiensis*

Ae. aegypti is the prime vector responsible for transmission of dengue transmission and epidemics [20]. Amongst the three species *e aegypti* acts as the primary and most important vector in the transmission of dengue but *an albopictus* and *a polynesiensis* spreads the disease which is based on different geographical locations. *Ae. aegypti*, a container breeding, day biting mosquito is found in tropical and subtropical areas (Fig. 5).

Ae. aegypti is a small, dark mosquito that can be identified by the white bands on its legs and a silver-white pattern of scales on its body (Fig. 5). *Ae. aegypti* was found predominantly in the tropical and subtropical regions all over the world. Where the temperature during winter is not more than 10ºC. *Ae. aegypti* cannot survive in cold climate because it requires a warm climate; they typically do not live at altitudes above 1000 m, where the temperature is colder [21]. *A. agepti* mosquitoes hatches the eggs and lives closely associated with humans. They usually spend their complete lives in the houses where they hatched their eggs [22]. They rest indoors, mainly in living rooms and bedrooms. This maximises man-vector contact and minimises contact with insecticides sprayed outdoors, hence contributing to difficulty in controlling this vector [23].

Life cycle of *Ae. aegypti*

Polluted or stagnant water and water collected in utensils, tyres, flower vases, and coconut shells are the areas where *Ae. aegypti* breeds. The mosquito eggs can be viable in high and low temperature and survives for a prolonged period. During rainy season the larval population tends to increase drastically. This might be the reason there were frequent occurrences of dengue fever epidemics during the rainy season [24]. Furthermore, ambient temperature and relative humidity affect viral propagation in mosquitoes; rates being highest in climates resembling the rainy season [25]. Acute viremia s affected by the environmental temperatures. It falls shorten in the female Aedes mosquitoes [26]. The first step in the dengue transmission begins with biting an infected adult human by a female Aedes mosquito. The dengue virus from the infected adult gains entry in to the mosquito.

The life cycle of *Ae.aegypti* mosquito starts with eggs, secondly larval stage, followed by pupa and finally to grown up adult mosquitoes. (Fig. 6)

Eggs

- Eggs look like black dirt.
- Adult, female mosquitoes lay eggs on the inner walls of containers with water, above the waterline.
- Eggs stick to container walls like glue. The survival time might lead up to 8 months.
- Mosquitoes only need a small amount of water to lay eggs.
- Water stored in utensils and waste cups, tires, and any other container serves them as a grater nourished store for them

Larvae

- Hatching of larva occurs when the eggs are covered by

water, E.g. Rain.
- Larvae live in the water. They hatch from mosquito eggs.
- Larvae can be seen in the water and called as wigglers.

Pupae
- Pupae live in the water. Pupa gives rise to adult mosquito.

Adult
An adult mosquito bites a person.
- The prime targets for mosquitoes were humans and animals. Mosquitoes need blood to produce eggs.
- After feeding, female mosquitoes look for water sources to lay eggs.
- *Ae. aegypti* and *Ae. albopictus* don't fly long distances.
- The adult mosquitoes fly within restricted areas throughout their life period.
- They live in closer to the human and bite them.
- *Ae. albopictus* mosquitoes bite animal and human and live in homes or in the forest.
- *Ae. aegypti* mosquitoes live indoors and outdoors, while *Ae. albopictus* live outdoors.

Dengue virus replication in *Ae. aegypti*
Replication of virus occurs in the midgut, then it reaches the haemocoel and haemolymph, finally it gets distributed to different tissues of the mosquito. The virus loaded salivary secretion of mosquito transmits the virion to another human. Ultra structural studies show viral particles within the nervous system, salivary glands, foregut, midgut, fat body, epidermal cells, ovary and internal body wall lining cells of the mosquito. Controversially, the virion is found absent in muscle, malphigian tubules and hind gut. The infected mosquito which carries the virion takes considerably longer time to digest the blood meal sucked from the humans (Fig. 6) [26] Research reports predict that infected mosquitoes allows propagation of virus to their progeny. Such a process would allow it to act as a reservoir for virus maintenance during interepidemic periods (without human or other vertebral host participation) [27]. Reports also suggest that dengue viruses may be transmitted sexually from the male to female mosquitoes, but not vice versa [28].

Dengue virus transmission cycle
The dengue virus infection is a communicable disease spread by mosquito vector. The disease transmission sequence begins with an infected human to *A.aegepti* mosquito to health human as a continuous cycle (Fig. 7). After an incubation period of four days from the day bitten by the infected Aedes mosquito enormous level of virion in the blood occurs. This condition is called as viremia. This stage is asymptomatic and there were no signs or symptoms of infection. The viremia stage proceeds for a period of four to twelve days. No symptoms are noticed on the first day of viremia. After a period of five days of viremia the infected individual shows the symptoms of dengue fever and it exists for another seven days. When a mosquito bites an infected human with dengue virus it gets infected and becomes a dengue vector for their entire life. A period of eight to twelve days time is the lag period where the virus gets spread throughout the body of the vector. This infected mosquito loaded with the virion transmits the viruses to a healthy individual through biting. It continuously transmits the dengue virus to healthy people for the rest of their life. Female mosquitoes requires blood for the production of eggs, hence they bite humans for blood. During their life time *Aedes* mosquitoes consumes many blood meals before laying eggs and they lays multiple batches of eggs in their life span. The infected mosquito carries dengue virus, in its salivary glands. The Aedes mosquito injects the saliva while biting a healthy human to prevent blood clotting and moreover its makes the feeding easy. So the injection of saliva becomes the reason for the infection of the host with the dengue virus [29].

Clinical manifestations of dengue infections
Dengue infections may be asymptomatic or give rise to undifferentiated fever, dengue fever, DHF, or dengue shock syndrome. Dengue viral infections and its associated diseases occur within five to seven days of incubation period [30] [31].
The dengue infection might lead to various complication and they are listed below:
1. Undifferentiated fever
2. Dengue Fever
3. Dengue hemorrhagic fever (DHF)
4. Dengue Shock Syndrome (DSS)

1. Undifferentiated fever
The cause of this fever occurs after a primary infection. But there is a possibility of the occurrence of the disease even after a secondary infection. It is hard to differentiate and distinguish between other infections caused by virus.

2. Dengue fever
The etiology of dengue fever is due to primary or secondary viral infections. The onset of dengue infection is sudden with the following symptoms:
- High fever
- Severe headache (especially in the retro-orbital area)
- Arthralgia
- Myalgia
- Anorexia
- abdominal discomfort
- Dermal rash.

The fever may be biphasic and tends to last for 2–7 days. The face, neck and chest appears flushed, which is the characteristic feature of this phase [32].Younger children tend to present with coryza, diarrhoea, rash and seizure, and less commonly with vomiting, headache, and abdominal pain. Although, hemorrhagic manifestations are uncommon in dengue fever, petechiae/pupura, gastrointestinal bleeding, epistaxis, and gingival bleeding have been observed in some individuals. [33]. A positive tourniquet test has been reported in many individuals with dengue fever possibly due to reduced capillary fragility [34] [35]. Recovery from dengue fever is usually uneventful, but may be prolonged especially in adults.

3. Dengue hemorrhagic fever (DHF)
DHF usually follows secondary dengue infections, but may sometimes follow primary infections, especially in infants. In such infants, maternally acquired dengue antibodies are presumed to enhance primary infections. Such a phenomenon has not been described in human infections other than dengue [36] [37]. DHF is characterized by high

fever, hemorrhagic phenomena, and features of circulatory failure [38] [39]. Those who remain ill despite their temperature subsiding are more likely to progress to DHF [40] [41].

4. iv. Dengue shock syndrome (DSS)

The dengue infected person with severe plasma leakage leads to dengue shock syndrome. A high death rate of 9.3% to 47% was notices in severe shock instances [42]. The symptoms of DSS are cold blotchy Skin, circumoral cyanosis, and circulatory disturbances. Short term pain in the abdominal region and frequent vomiting are early signs of DSS. Sudden fall in blood pressure is the clear indication of the beginning of profound shock [43]. Metabolic acidosis is the major complication of the prolonged shock, which may precipitate disseminated intravascular coagulation or enhance ongoing disseminated intravascular coagulation, which in turn could lead to massive hemorrhage. DSS causes Dengue shock causes encephalopathy due to electrolyte and metabolic disturbances.

Phases of dengue viral disease

All the dengue viral diseases follow a scripted pattern in developing the disease. The infection develops through three phases, [44] they are:

1. Febrile Phase
2. Critical Phase
3. Convalescent Phase

1. Febrile phase

- Fever typically lasts 2–7 days and can be biphasic.
- Other signs and symptoms may include severe headache; retro-orbital eye pain; muscle, joint, and bone pain; macular or maculopapular rash; and minor hemorrhagic manifestations including petechia, ecchymosis, purpura, epistaxis, gums tends to bleed, and bloody urine.
- Some patients have injected or pharynx and facial erythematic in the first 24–48 hours after onset.
- Frequent vomiting, abdominal pain, edema, internal bleeding in the mucosal lining, difficulty in breathing, restlessness, hypotension, hepatomegaly, and gradual increase in hematocrit.

2. Critical phase

- The critical phase of dengue begins at effervescence and typically lasts 24–48 hours.
- Most patients clinically improve during this phase, but those with substantial plasma leakage can, within a few hours, develop severe dengue as a result of a marked increase in vascular permeability.
- Initially, physiologic compensatory mechanisms maintain adequate circulation, which narrows pulse pressure as diastolic blood pressure increases.
- Patients with severe plasma leakage may have pleural effusions, ascites, hypoproteinemia, or hemoconcentration.
- Patients may appear to be well despite early signs of shock.
- Patients can also develop severe hemorrhagic manifestations, including hematemesis, bloody stool, or menorrhagia, especially if they have been in prolonged shock. Uncommon manifestations include hepatitis, myocarditis, pancreatitis, and encephalitis.

3. Convalescent phase

- As plasma leakage subsides, the patient enters the convalescent phase and begins to reabsorb extravasated intravenous fluids and pleural and abdominal effusions.
- As a patient's well-being improves, hemodynamic status stabilizes (although he or she may manifest bradycardia), and diuresis. The patient's hemo concentration declines dilution of blood components.
- A rise in WBC begins which is followed by normalization of platelet count.
- The convalescent-phase rash may desquamate and be purity.
- Laboratory findings commonly include leukopenia, thrombocytopenia, hyponatremia, elevated aspartate aminotransferase and alanine aminotransferase, and a normal erythrocyte sedimentation rate.

Complications of Dengue

Severe dengue infections may give rise to many complications such as liver failure, disseminated intravascular coagulation, encephalopathy, myocarditis, acute renal failure, and hemolytic uremic syndrome.

Liver failure

Since hepatocytes and Kupffer cells support viral replication, liver involvement is common in all forms of dengue infection; its severity varies with the overall severity of the dengue infection. DENV-3 or DENV-4 serotypes produce greater liver involvement (liver enzymes higher compared with infection with the other two serotypes) [45]. Liver failure can arise due to hepatitis or focal necrosis of the liver leading to hepatic encephalopathy, and even it becomes lethal. Convulsions or disturbances in the consciousness level are associated with liver failure. Jaundice may be present. Neurological examination may show hyper-reflexes or an extensor plantar response. Electrolyte imbalance and decrease in blood glucose may get associated with the abnormal liver enzymes.

Encephalopathy

Encephalopathy has been reported in 0.5% of patients with DHF, and has a mortality rate of 22%.67 Many factors contribute towards development of encephalopathy including: hepatic dysfunction, electrolyte imbalances, cerebral oedema (caused by vascular changes leading to fluid extravasations), hypo perfusion (due to circulatory disturbances), and dengue encephalitis [46]. Furthermore, in mice, breakdown of the blood-brain barrier and direct viral infection of the brain has been shown to occur. There is suggestion that histamine might have a critical role in this process. Other neurological manifestations such as altered consciousness, seizures, spasticity of limbs, hemiplegic, and a positive Kernig's sign have also been reported in 5.4% of patients with dengue [47] [48].

Myocarditis

Patients suffering from severe dengue infections experiences acute reversible myocarditis. ST segment and T wave changes in the electrocardiogram together with low ejection fractions and global hypokinesia on radionuclide ventriculography have been found. No myocardial necrosis was detected in any of the patients [49]. In another study, 16.7% of children had left ventricular dysfunction when assessed by two-dimensional and colour Doppler

echocardiography. The left ventricular failure may contribute to hypotension seen in DHF/dengue shock syndrome and may have implications in fluid management as fluid overload may worsen the condition [50]

Laboratory diagnosis of dengue infections

Dengue viruses are isolated from blood during the early febrile phase of the disease. During autopsy specimens were collected from Cerebrospinal fluid (CSF), and the visceral organs liver, lung, kidney and spleen. The dengue infected patients were screened by adopting various methods for the diagnosis of dengue viral infections, they are:

a. Virus isolation
b. Serological Diagnosis
c. Reverse transcriptase-polymerase chain reaction (RT-PCR)

a. Virus isolation

Virus can be isolated during the febrile phase of the illness. It can be isolated from plasma, serum, plasma, and leucocytes. It has also been isolated from visceral organ specimens during postmortem namely lung, liver, thymus, spleen, cerebrospinal and pleural fluids. The samples were collected before the formation of neutralising antibodies. For short periods of time (less than 24 hours) serum can be kept at 4–8˚C, but for longer periods should be stored at 270˚C. Newborn mice or cell cultures are traditionally used to isolate dengue virus. However, mosquito cell lines have replaced these methods as they are more sensitive, relatively easy to maintain at room temperature, and can be kept for at least 14 days without change of medium. Currently, inoculation of C636 mosquito cell lines (obtained from an albopictus) is the method of choice [51].

b. Serological diagnosis

Methods used for serological diagnosis of dengue infections include: haemagglutination inhibition tests, enzyme linked immunosorbent assay (ELISA), complement fixation test and neutralisation tests. Immunoglobulin M (IgM) and Immunoglobulin G. On the fifth day of infection IgM antibodies are found in the infected individuals. But 30–60 days of infection it becomes undetectable. Antigen capture ELISAs have also been developed. The serotype of the infecting virus can also be identified using conventional or capture ELISAs [52] [53]. A fourfold or greater rise in antibody titers is suggestive of a flavivirus infection (and not diagnostic of dengue infections). However, a single antibody titre >1/2560 is accepted as indicating secondary dengue infection if supported by a clinical history suggestive of dengue.

c. Molecular detection

RT-PCR is more sensitive than virus isolation, allows for rapid detection of dengue infections. The results can be derived within in 24 hours and the DENV strains are easily identified. RT-PCR could also be used for detecting dengue viruses in infected mosquito cell culture supernatants or mosquito larvae. The PCR techniques have also been able to detect dual viraemia in some patients from naturally acquired DEN-1 and DEN-3 infections [54] [56].

Prevention and Control of Dengue:

There were no official drugs and vaccines against dengue. The disease can be prevented and controlled by reducing or preventing man-mosquito vector contacts. Various methods, techniques strategies have been developed and utilised to prevent and control dengue infection [56].

They are classified as:

1. Environmental control
2. Biological control
3. Chemical control

While each of these methods have some effect, successful control programmes should incorporate all appropriate methods and also foster a strong partnership between the different dengue control agencies and the community.

1. Environmental control

Environmental control methods used to combat dengue infection includes

- Reducing Dengue vector breeding sites
- Solid waste Management.
- Controlling mosquito breeding sites
- Living house design.
- Public education programmes play a vital part if they are to be effective [56].
- Prevention of man-vector contact.

A thick dress material will reduce the contact of dengue mosquito vectors. Insecticidal and insecticide repellents like mats and vaporizers are effective in controlling the spread of the disease. Sometime natural repellants from plant source like chrysanthemum flower extract and oils extracted from lemongrass are used as mosquito repellants. Mosquito nets are ineffective in controlling dengue because the dengue mosquitoes have limited usage because as the mosquito is mostly bites during daytime.

2. Biological vector control

The mosquito larval stages of dengue vector are better controlled by biological control methods. The larva feeding fish species namely *Poecilia reticulate* and *Gambusia affinis* are used as biological control method. The carnivorous habit of these fish species is utilized to control the kill the dengue larva. Bacillus bacterial species such as *Bacillus thuringiensis* serotype and *Bacillus sphaericus* are used as a biological control method. These bacterial species produces endotoxin, which produced larvicidal activity. *An aegypti* the prime vector of spreading dengue was better controlled by *Bacillus thuringiensis* serotype H-14 with a very less mammalian toxicity. Hence, they can be used in the household water storage containers [57].

3. Chemical vector control

Chemical larvicidal insecticides are used by space spraying technique. Insecticides used for treating containers that hold water includes Temephos 1% sand granules and insect growth regulators. Regular monitoring of resistance patterns is essential as resistance to Temephos has been reported among some Aedes mosquito species in the South East Asian Region. Insect growth regulators interfere with the development of the immature forms of the mosquito and have extremely low mammalian toxicity. Space spraying may be applied as thermal fogs or as ultra low volume sprays. Although both methods are equally effective in killing adult mosquitoes, thermal fogging tends to be used more widely [58]. Although insecticides such as malathion 4%, fenitrothion 1%, or pirimiphos-methyl have proved to

be very effective in many control programmes, mosquito vectors develop different patterns of resistance to them [59] [60].

Current status of the Dengue Vaccine Research

Dengue vaccine research leads to the development of live attenuated vaccine, chimeric vaccine, Subunit and DNA Vaccine against the DENV1 to DENV4 serotypes. These vaccines exhibited noticeable results but none of the vaccines are enough immunogenic to control or eradicate DENV infections. Tetravalent vaccine recipients using dog kidney cells found to have DEN-3 viraemia, and subsequently develop DEN-3 neutralising antibodies [61]. Moreover the DENV-2, DENV-3, and DENV-4, and 60% of DEN-1 vaccine recipients developed IgM antibodies [62]. After the first dose 58% of the recipients found to produce neutralizing antibodies. It got a drastic increase to 76% after the second dose [63]. Both monovalent DENV-2 and the tetravalent vaccines show T-cell responses against all dengue serotypes [64]. However, proliferation responses are higher to DEN-1 and DEN-3 than to DEN-2 and DEN-4, whereas cytotoxic T-lymphocyte responses are higher to DEN-2 and DEN-3 than to DEN-1. Recently researchers utilized recombinant cloning technology to develop chimeric DENV-2 vaccine [65].

Vaccine studies in monkeys have shown promising results, and currently chimeric vaccines encoding genes of the other three dengue serotypes have been constructed and are undergoing evaluation in animal models. The use of DNA based vaccines is another novel and promising immunisation approach. In-vivo screening of these vaccines on mice and monkeys are found immunogenic against DENV-[66].To improve immunogenicity, a DENV-2 candidate vaccine containing pre-membrane and envelope genes in which transmembrane and cytoplasmic regions of envelope genes were replaced by lysosome associated membrane protein has been constructed. Promising levels of neutralizing viral antibodies were noticed in immunised mice. Monoivalent and tetravalent vaccines with the recombinant proteins domains of DENV serotypes 1–4 were fused with the maltose binding protein of *Escherichia coli* on mice. Neutralising antibody titres to each individual serotype were significantly greater than any cross reactive neutralising titre induced by the monovalent vaccines. Thus, the tetravalent DENV recombinant subunit vaccine produces specific neutralising antibodies to all four DENV serotypes [67].

Conclusion

Ae. aegypti is a known vector of several viruses including dengue virus (DENV) and it is the primary vector for spreading *Dengue virus.* They prefer mammalian hosts, preferably human beings even if an alternative hosts were available. Dengue fever, Dengue Haemorrhagic Fever and Dengue shock Syndromes are the major diseases suffered by the human after an infection spread by the mosquito *Ae. aegypti*. The crucial factors which are to be better understood are the biological distribution, habitat, behaviour, transmission, living suitability, prevention and control method in relation to Aedes mosquitoes. We acknowledge that dengue is a threat to the mankind. The disease can be prevented only by creating awareness about the pathogenesis of this epidemic disease and ensure that humans are safeguarded against these bloodthirsty creatures. Dengue is the identified disease of the future where it will take a leap in the trend due to drastic urbanization, lack of consumable water and changes in the environment. In this review the morphology of dengue vector *A. aegypti*, its life cycle and the mode of viral replication and dengue transmission was better showcased. This current review on the mosquito *Ae. aegypti* the vector of dengue will be a supporting document for the researchers working in the field designing novel and potent Antidengue drugs. The referred control measures clearly indicate that killing the dengue vector will lead to complete eradication of dengue and dengue fever.

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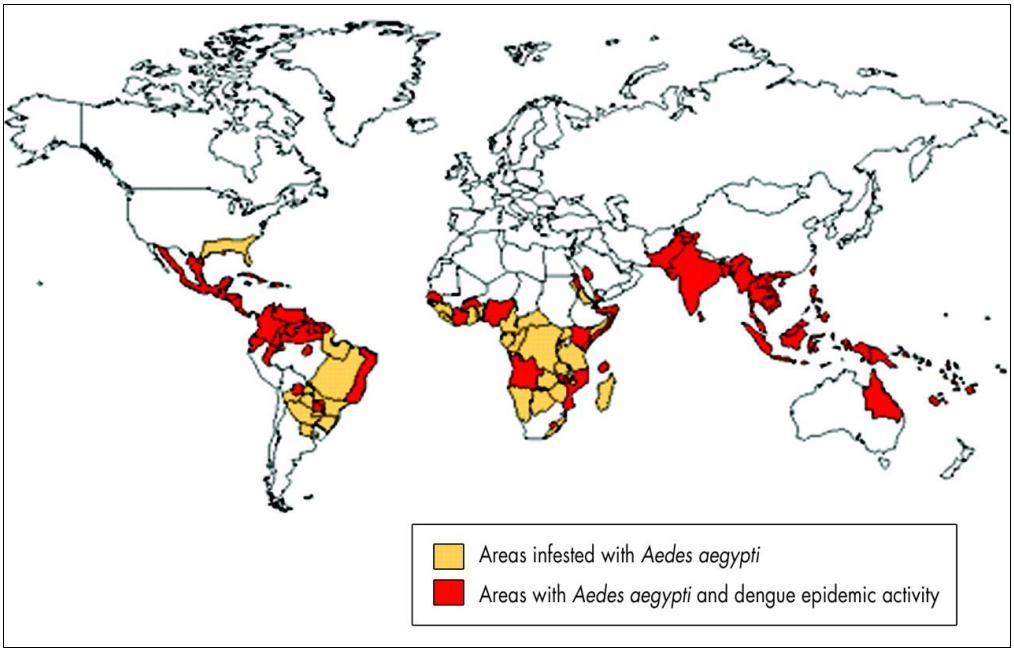

Fig 1: Shows the distribution pattern of dengue mosquito vector *Ae. aegypti* with the dengue epidemic activity [19].

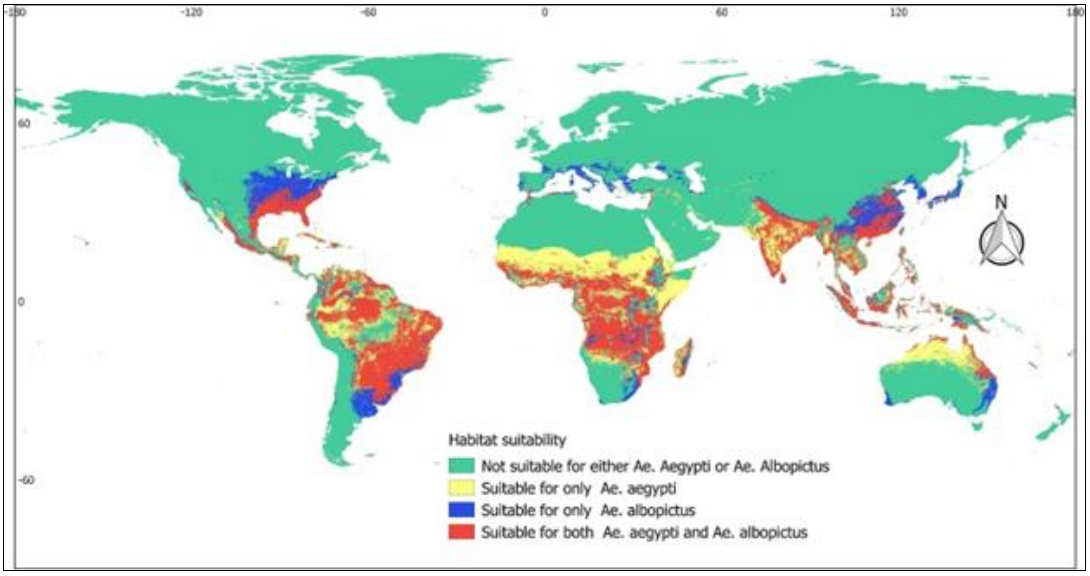

Fig 2: Shows the Country-wise suitability range for the mosquito vector [19]

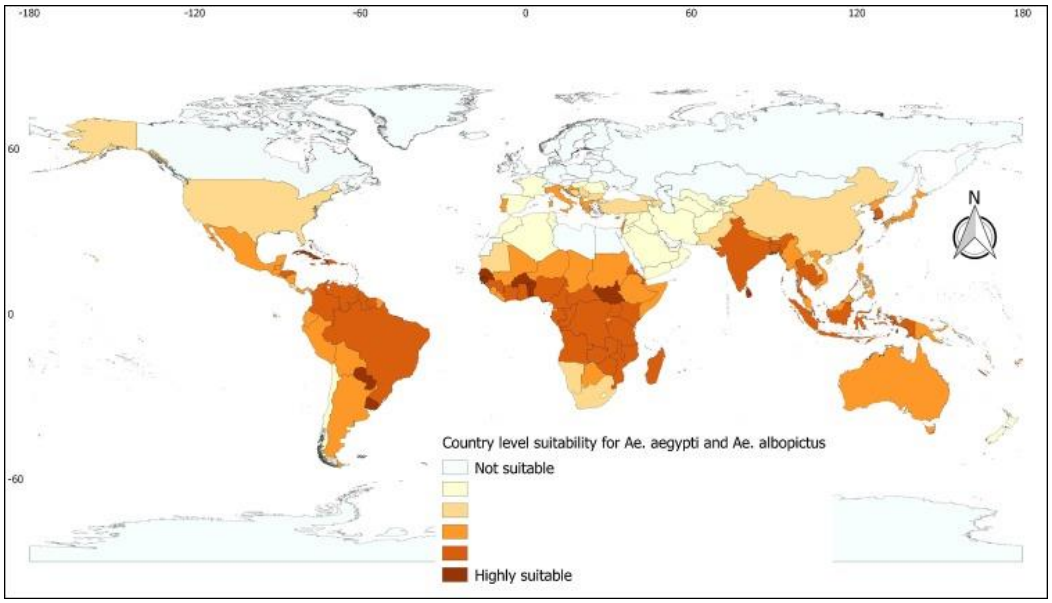

Fig 3: Shows the global suitability for the mosquito vector *Ae. aegypti* and *Ae. albopictus* [19].

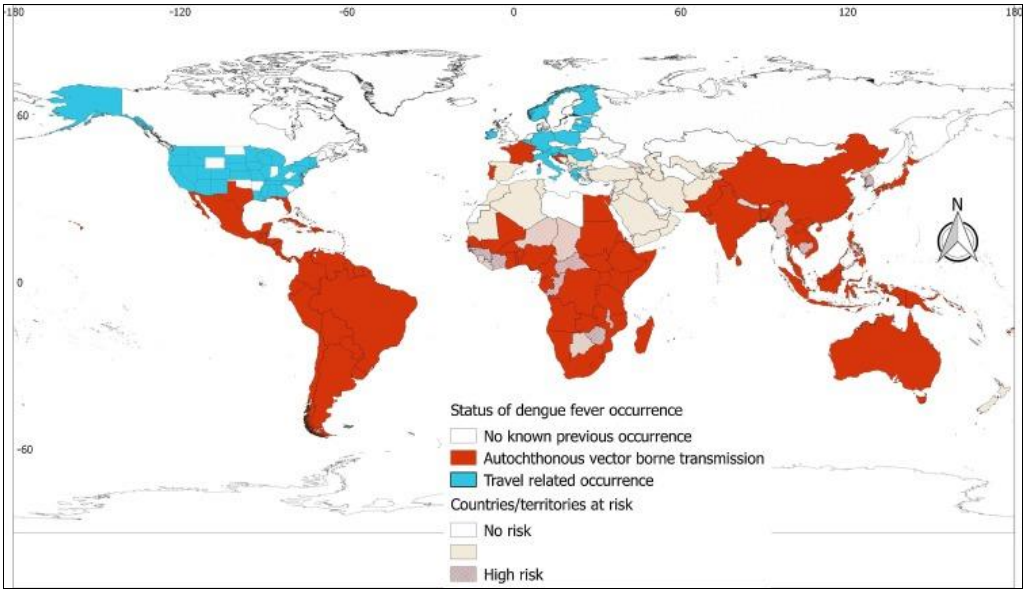

Fig 4: Shows global status of dengue fever occurrence [19].

Fig 5: *Ae. Aegyptii* Source: CDC, Source: CDC, NCEZID & DVBD [44]

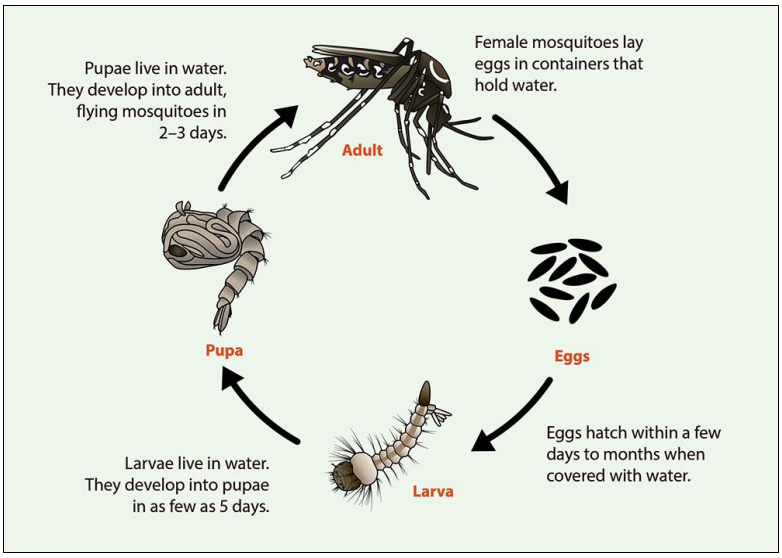

Fig 6: Life Cycle of *Ae. aegypti* mosquito Source: CDC, NCEZID & DVBD [44]

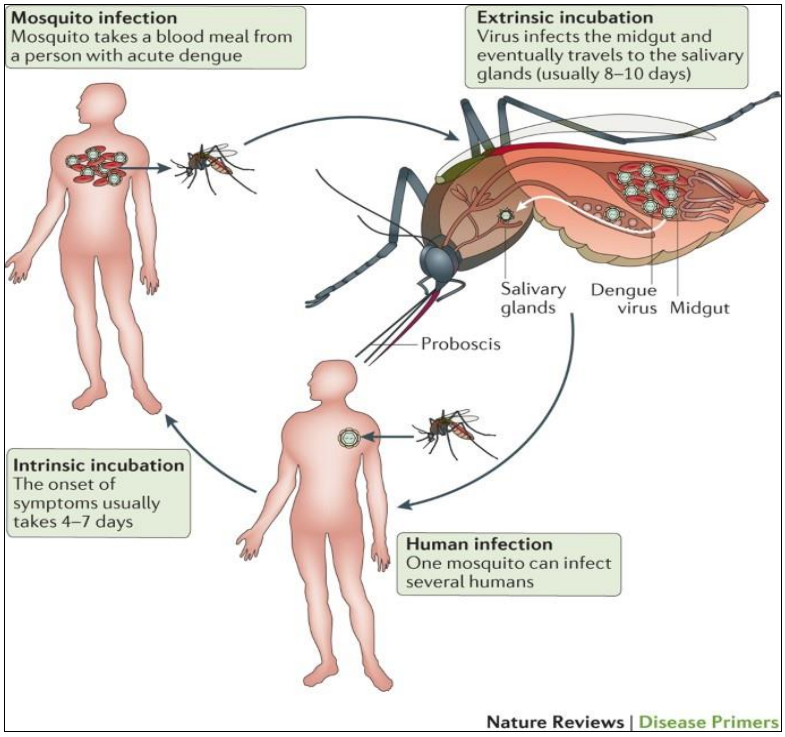

Fig 7: Shows the dengue virus transmission Cycle. The dengue virus is spread through a human-to-mosquito-to-human cycle of transmission. (*Source: Nature Reviews Disease Primers 2: 1–26*) [15]

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