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A REVIEW ON DENGUE AND CURRENT STATUS OF IT'S TREATMENT

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ABSTRACT

Dengue is of great concern in various parts of the world, especially in tropical and subtropical countries where the mosquito vectors Aedes aegypti and Aedes albopictus are present. The BMC reported 2322 cases of dengue during period of 1st sept to 15th sept 2018 and screen 3229 people across the city for dengue related symptoms. Attack of dengue produces immunity for lifetime to that particular serotype to which the patient was exposed. Even though a vaccine against dengue is now available but which is nonable achievement because it is not long term effective against dengue.[21] Only the female Aedes mosquito bites it needs the protein in blood to developed its egg. This review will highlights a brief account of the status of therapeutic research and development for dengue.

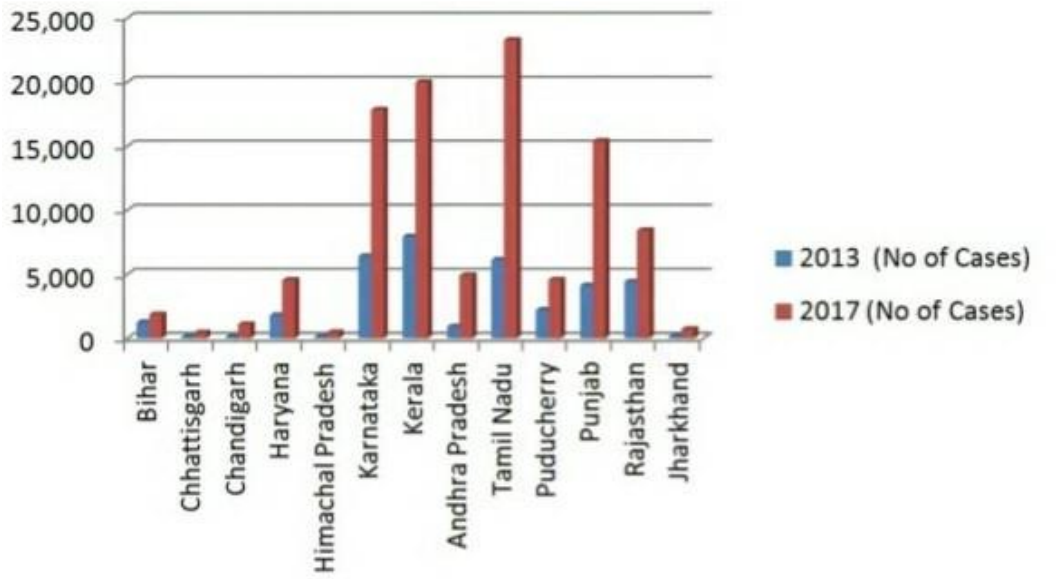
KEYWORDS: Dengue is of great concern Aedes albopictus for dengue.

INTRODUCTION

Dengue is an acute systemic viral disease that has established itself globally in both endemic and epidemic transmission cycles. Dengue fever and dengue hemorrhagic fever (DHF) are acute febrile diseases, found in the tropics, with a geographical spread similar to malaria. The incidence of dengue has grown dramatically around the world in recent decades. Dengue fever also known as Breakdown fever, is a mosquito borne infection that can lead to severe flu-like illness. It is caused by 4 different viruses and spread by 'Aedes mosquitoes' i.e. Aedes aegypti, Aedes albopictus.[22] The transmission of this virus to humans, by what is known as horizontal transmission, occurs through the bite of infected females of one or other of the two mosquito species. Furthermore, an infected female or male parent, by what is known as vertical transmission, can transfer this arbovirus to some part of their offspring.[19] Dengue fever has been reported from India over long time, but dengue haemorrhagic fever was first

reported in 1963 from Calcutta city. On 16 March 2018, WHO was notified by the International Health Regulations (2005) National Focal Point for France through the European Commission (EC) Early Warning and Response System (EWRS) about a sharp increase in the number of dengue cases reported. Dengue is significant global health problem.

Current status of dengue



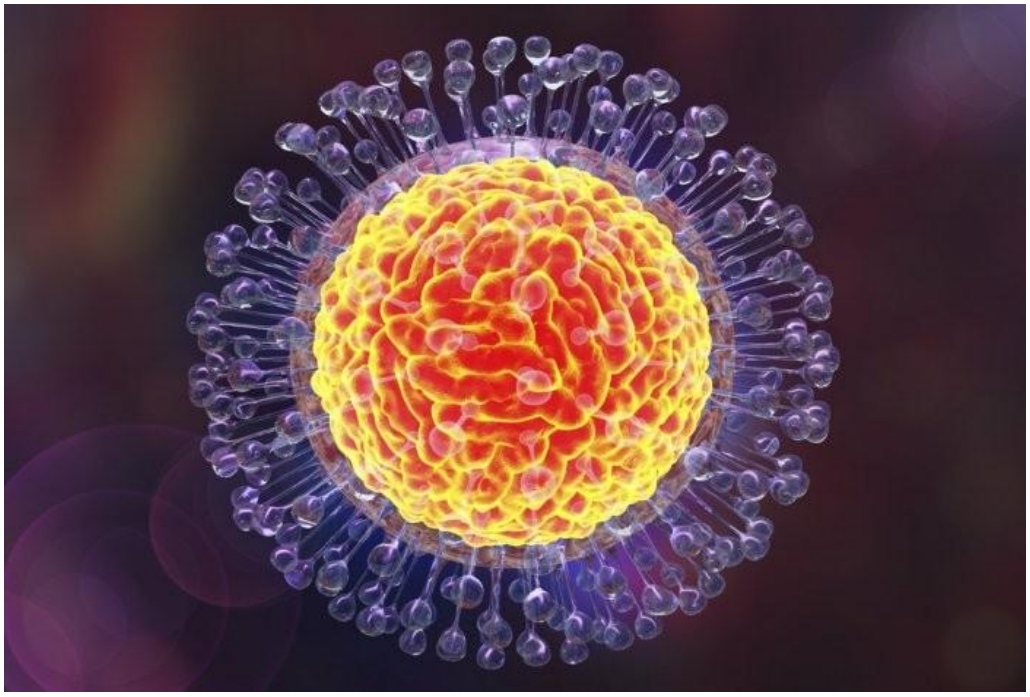
Graph shows the number of cases of dengue patients in 2017 as compared to the 2013 (statewise)

Causes

Globalization, urbanization, demographic changes and warning temperature are some of the causes associated with increase number of mosquitoes.[22]

Dengue chiefly occurs during the rainy season. The proposed etiologies for dengue virus infection are-

1. Viral replication, primarily in macrophages.
2. Immunological and chemical-mediated mechanism induced by host-viral infection.
3. Direct skin infection by the virus.



Dengue virus. (DENV is a 50nm virus enveloped with a lipid membrane).

Transmission & Life Cycle of Dengue Mosquito

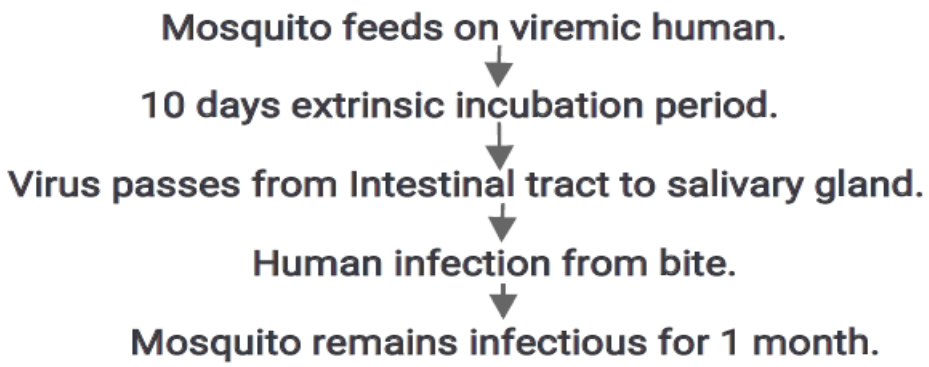
Dengue virus is an arbovirus. It has 4 different Serotypes: DENV-1, DENV-2, DENV-3, DENV-4. DENV is a 50 nm virus enveloped with a lipid membrane. Though vertical transmission of the virus has been reported, mosquitoes mainly acquire DENV by feeding on the blood of an infected human. DENV first infects and replicates in the mosquito midgut epithelium. It subsequently spreads through the hemolymph to replicate in other organs such as the fat body and trachea, finally infecting the salivary gland approximately after 10–14 days. Once in the saliva, DENV can be inoculated into human host when the mosquito acquires blood meal, thus spreading the disease.

Attack of dengue produces immunity for lifetime to that particular serotype to which the patient was exposed. Life cycle of Dengue virus involves endocytosis via a cell surface receptor. The virus uncoats intracellularly via a Specific process.

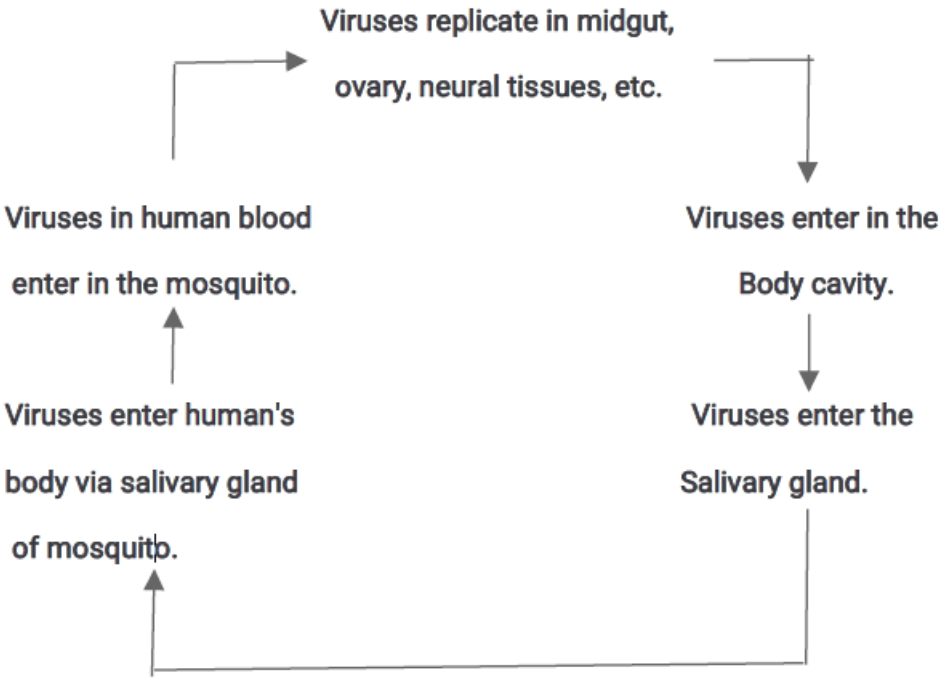
When virus is carried into the cell and into lysozomes, the acidic environment causes the protein into a different shape, assembling to trimeric spike. Several hydrophobic amino acids at the tip of this spike insert into the lysozomal membrane and cause the virus membrane to fuse with lysozome. This releases the RNA into the cell and infection starts.

Dengue virus gains entry into the host organism through the skin following an infected mosquito bite. Alteration in endothelial microvascular permeability and thromboregulatory mechanisms lead to an increased loss of protein and plasma.

Endothelial cell activation caused by monocytes, T-cells, the complement system and various inflammatory molecules mediate plasma leakage. Platelet dysfunction, damage/depletion, leading to significant hemorrhages.



DENV is an single stranded RNA positive strand virus of the family- Flaviviridae, genus-Favivirus. The first infection cause mostly minor disease but secondary infections has been reported to cause severe diseases (DHF/DSS) in both children and adults. This phenomenon is called as Antibody-Dependent Enhancement.[20]



Symptoms

01) Intense headache.

02) Body rash that can disappear and then reappear.

03) Aching muscle and joints.

04) High fever.

05) Pain behind the eyes.

06) Vomiting and feeling nauseous.

07) Bleeding.

08) Low level of blood platelets.

09) Blood plasma leakage.

10) Low blood pressure.

11) Dengue Shock Syndrome (DSS)

12) Dengue Hemorrhagic Fever (DHF).

Relationship of Platelets with Dengue

Platelets are tiny, disc-shaped cell fragments present in large number in the bloods. Dengue is an acute viral disease that causes a rapid decline in a platelets counts leading to internal bleeding and death in extreme cases. In critical cases, patients with less than 20000/cubic mm platelet count may need urgent platelet transfusion to stop the bleeding. Unlike the blood, platelets can't be store for more than 5 days. Therefore getting a platelet donor on time becomes very critical to save the lives of dengue patients. Certain genes have been shown to influence platelet production and platelet aggregation, namely the Arachidonate 12-lipoxygenase (ALOX 12) also known as the Platelet-type Lipoxygenase as well as the Platelet-Activating Factor Receptor (PTAFR). An increase in activity of these genes is required for platelet production and activation. The ALOX-12 gene is strongly expressed in megakaryocytes and has been known to be responsible for the 12-Hydroxyeicosatetraenoic acid (12-HETE) production of platelets. The PTAFR gene was been found to be expressed in megakaryocytes indicating that it could be a precursor for platelet production in addition to its well known role in platelet aggregation.

Relationship of Obesity with Dengue

Patients with obesity were found to be at higher risks of developing complications and severe dengue infection compared to non-obese patients. This systematic review explore the relationship between obesity and dengue severity. Obesity might influence the severity of

dengue infection. Severe dengue infection often has unpredictable clinical progressions and outcomes. Obesity may play a role in the deterioration of dengue infection due to stronger body immune responses.[23]

Diagnosis

Serological Tests are most important method for confirmation of diagnosis of dengue. Most commonly used test are IgM, IgG antigen capture immunoenzymatic Non- structural Protein-1(NS1), which requires only one serum sample. IgA and IgM are immunoglobulins sensitive to infection such as Dengue and they have been used as a marker to diagnose the dengue infection.[22]

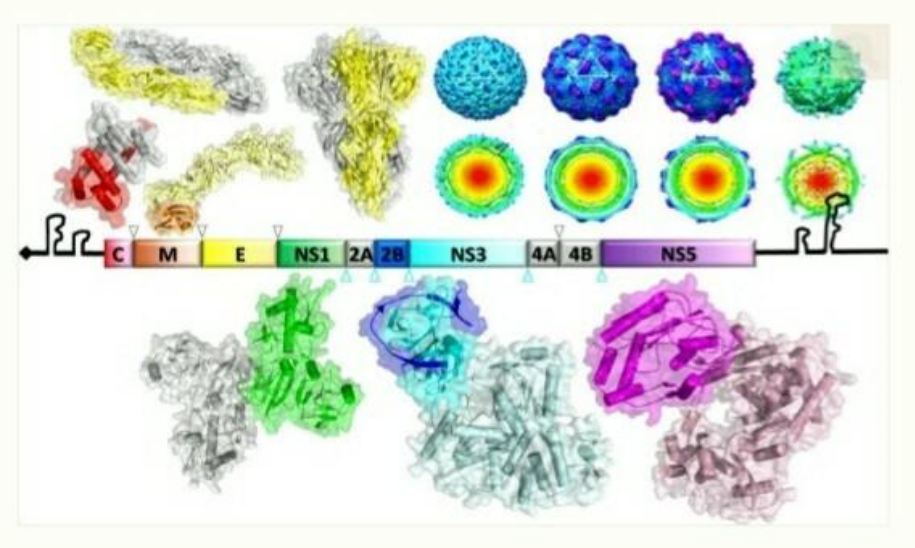
ICGEB Lab has developed a diagnostic kit for the disease called 'dengue day-1', it can detect the infection right on day 1. It is important to not only know if the patient is afflicted with dengue, but also whether it was a primary or a secondary infection. The 'dengue day 1 kit' helps in figuring this out. Blood serum of an infected person would have small pieces of the virus called NS1 from day one and immunity response of the body would release two type of antibodies IgM and IgG.

NS1 test is the most reliable diagnostic test for dengue.[20] While IgM remains in the blood for a month so, IgG persists for life time. The kit can detect all of them-NS1, IgM, IgG. Consequently, it is able to not only diagnosis but also discriminate whether it is a primary/secondary infection.

Drug Target

The dengue virus has a genome of about 11000 bases that encodes a single large polyprotein that is subsequently cleaved into several structural and non-structural mature peptides.

The polyprotein is divided into three structural proteins C, prM, E. Seven Non- structural Proteins NS1, NS2a, NS3, NS4a, NS4b, NS5. The structural proteins are the capsid(C) protein, the envelope(E) glycoprotein and the membrane(M) protein, itself derived by furine mediated cleavage from a prM precursor.



The dengue genome and proteome. The 5' and 3' untranslated regions and the arrangements of the genes encoding 3 structural and 7 nonstructural proteins

The 'E' glycoprotein is responsible for virion attachment to the receptor and fusion of the virus envelope with the target cell membrane and bears the virus Neutralization epitopes.

The RNA genome of DENV is tranlated as a single polypeptide that is then cleaved into 3 structural proteins [Capsid(C), prM, E] and 7 non structural(NS) Proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) vy cellular protease and viral serine protease.[21]

Cellular α-glucosidases I and II are enzymes that sequentially trim the three terminal glucoses in the N-linked oligosaccharides of viral envelope glycoproteins. This process is essential for the proper folding of viral glycoproteins and subsequent assembly of many enveloped viruses, including dengue virus (DENV). Imino sugars are substrate mimics of α-glucosidases I and II. In this report, we show that two oxygenated alkyl imino sugar derivatives, CM-9-78 and CM-10-18, are potent inhibitors of both α- glucosidases I and II in vitro and in treated animals, and efficiently inhibit DENV infection of cultured human cells.[18]

Treatment

Treatment is easily possible if diagnosis occur before the patient develops DSS/DHF. Dengue is viral disease, so there is no specific treatment/cure.

Preventing the dehydration: A high fever and vomiting can dehydrate the body.

The person should drink clear water, ideally bottled rather than tap water. Rehydration salt

can also help to replace the fluids and minerals.[22]

The application of fluid therapy has become key in dengue management. In simple dengue, oral fluid replacement is sufficient there is no need for hospitalization. The basic recommendation for intravenous fluid replacement therapy is administration of 0.9% normal saline solution.[20]

The preferable new treatment for dengue would be antiviral drugs but specific antiviral drugs are not present on today's date also.

A) Treatment in Ayurveda

1) **Giloy:** Giloy is a very important herb in Ayurveda. It helps in maintaining the metabolic rate, strengthening the immune system and protects your body against infections. You can also add few Tulsi leaves in the drink.
2) **Papaya Leaves:** It helps in increasing the platelet count and reduces the symptoms of fever like body ache, chills, feeling low, getting tired easily and nausea. The enzyme in papaya leaf, 'chymopapainnd papain' help revive platelet count. It is reported that several dengue patients had remarkable platelet recovery after taking papaya leaf juice.[20] You can crush the leaves and consume or drink the juice which helps in flushing out the toxins. The papaya fruit is globally consumed either in its fresh form or the form of juices, jams, and crystallized dry fruit. The ripe fruit is said to be a rich source of vitamin A, C, and calcium.
3) **Fenugreek Leaves:** These leaves are known to reduce fever and act as a sedative to ease pain and promote more restful sleep for patients. You can soak the leaves in water and then drink it or you can get methi powder and mix it with water and have it.
4) **Goldenseal:** Goldenseal is a herb whose dried root is used to make medicine. It has the ability to clear up the symptoms of dengue fever very quickly and eliminate the virus from the body. It works like papaya leaves. You use it in the same way like papaya leaves either by crushing and chewing or by juicing it.
5) **Turmeric:** It is also known to boost metabolism and helps in making the healing process faster. You can consume turmeric along with milk.
6) Tulsi Leaves and Black Pepper
7) The war against dengue get new weapob. The scientists at the New Delhi based International Centre for Genetic Engineering and Biotechnology(ICGEB) are successful in developing a new antiviral that promises to tackle all the 4 types of dengue virus. The

new drug is derived from a plant called 'Cissampelos pareria Linn'. The researches selected a set of nineteen plants including neem, aloe and basil which were said to provide relief to symptoms to dengue. This new drug is world's first botanical drug against dengue.

B) Treatment in Homeopathy

Homeopathy provides a wide range of medicines for the treatment of the Dengue fever with respect to the symptoms. It has been proved much effective to relieve the patient from the disease. These medicines improve body's immune system enabling it to fight with dengue virus. These medicines also help in increasing the platelets count in human body very rapidly. The other symptoms like skin rashes, fever, tiredness and itchy skin are also controlled effectively by these medicines. The best part of treatment is that all this happens very quickly within few days and patient gets better and better after every passing day.

1) Eupatorium, Perfoliatum
2) Gelsemium
3) Belladonna
4) Ipecac and Arsenic

C) Treatment in Allopathy

Painkillers such as Tylenol and paracetamol. These can help lower fever and ease pain. An antiviral drug named 'Celgosivir' may be effective for treating dengue fever.

Drugs- In modern medicine

Ribavirin, glycyrrhizinnd-6-azauridinere NITD008 are also used.

A Study conducted by researchers in Singapore general hospital and Duke-NUS Graduate medical school aims to findout how celgosivir is effective against the dengue. Celgosivir is derived from the seed of Modern Bay Chestnut tree; Celgosivir is use for early stages of dengue fever.[20] Antibiotic and steroids shouldn't be used because they do not show any benefit.

Combination therapy of two broad-spectrum antiviral agents may provide a practically useful approach for the treatment of DENV infection. combination therapy of ribavirin with sub-effective dose of CM-10-18 demonstrated a significantly enhanced antiviral activity.[18]

Vaccine for Dengue

CYD-TDV is the first licensed dengue vaccine for individuals 9–45 years of age.

CYD-TDV is protective against serotypes 1, 3 and 4 regardless of baseline serostatus. CYD-TDV, the dengue vaccine developed by Sanofi Pasteur and now marketed as Dengvaxia. CYD-TDV is a live-attenuated recombinant tetravalent vaccine that uses the 17D yellow fever vaccine virus as a backbone and is administered in three doses given 6 months apart. The ability of CYD-TDV to elicit a strong DENV4 antibody response since the first vaccine dose, that was comparable to the immunity observed upon natural infections in all subjects, including those with no evidence of dengue exposure before vaccination. Pooled analysis of the results obtained in CYD14 and CYD15 showed that among children of 9–16 years of age, efficacy was 81.9%.

Prevention of Dengue at Personal Level

1. Do not leave stagnant water lying anywhere in or around the house. It's very dangerous as these mosquotes lie on this stagnant water only, it doesn't matter if it is dirty or clean.
2. Spray the house with anti-mosquito sprays, like Kala Hit every day in the corners of your home to kill the hidden mosquitoes.
3. Keep your wet garbage separate and throw in a wet bin (which is kept covered)
4. In the rains, the chances of you getting infected by the Dengue/mosquito are extremely high due to the level of stagnant fresh water increase; at this point all measures of safety should be used.
5. Try to wear clothes that don't leave any skin areas exposed.
6. Wear a mosquito repellent cream and carry it with you at all times.
7. Keep the doors and windows of the house closed, mostly early in the morning and during the evening.
8. Change your hand towels after a day's use.
9. Keep your house clean and tidy.
10. Keep your wet and soggy clothes and shoes away from the dry garments. Also, try to dry the wet ones as soon as possible.
11. It's not only about our homes, we need to keep our area and city both clean.
12. The dengue mosquito typically attacks during the day and some experts say the favourite spots are below the elbow and below the knee. They are generally active between the time period of August- October and do not breed when the temperature falls.
13. You could turn to natural repellents like Lemon Eucalyptus Oil, Lavender, Neem Oil and

Cinnamon Oil to protect yourself against mosquito bites. There are a number of plants that have mosquito repellent properties like feverfew, citronella, catnip and lavender.

Diet for dengue patient

1. There is no recommendation regarding diet during dengue fever but then also eat foods which can be easily digested.
2. Patient's diet can include boiled vegetables, soup, rice.
3. Drink plenty of fluids such as oral rehydration solution, fresh juice, coconut water.
4. Tea made with fever reducing herbs such as gingernd cardamom.

CONCLUSION

Dengue is the most important epidemic infectious diseases caused by flaviviruses this century, causing immense public health problems with significant morbidity and mortality, particularly in resource-poor countries.[17] A vaccine that is not completely protective and vector-control measures that lack sustainable outcomes.

There is no specific medicine to treat dengue infection. If you think you may have dengue fever, you should use pain relievers with acetaminophen and avoid medicines with aspirin, which could worsen bleeding. Doctors can diagnose dengue infection with a blood test to check for the virus or antibodies to it.

People with weakened immune systems as well as those with a second or subsequent dengue infection are believed to be at greater risk for developing dengue hemorrhagic fever.

The government and pharmaceutical industry have been taking a initiative to develop new strategies to improve the treatment of dengue.

ABBREVATIONS

DENV- Dengue virus

ER- Endoplasmicreticulum FOS- Free oligosaccharide PK- Pharmacokinetic.

REFERENCES

1. Tricou V, Minh NN, Van TP et al. A randomized controlled trial of chloroquine for the treatment of dengue in Vietnamese adults. PLoS Negl Trop Dis., 2010; 4: e785.
2. McAuley DF, Laffey JG, O'Kane CM et al. Simvastatin in the acute respiratory distress syndrome. Engl J Med, 2014; 371: 1695–703.[PubMed]

3. Whitehorn J, Van VC, Simmons CP. Dengue human infection models supporting drug development. J Infect Dis., 2014; 209(suppl 2): S66–70.[PMC free article] [PubMed]
4. Bhatt S, Gething PW, Brady OJ et al. The global distribution and burden of dengue. Nature, 2013; 496: 504–7. [PMC free article] [PubMed]
5. Simmons CP, Farrar JJ, Nguyen VV, Wills B. Dengue. N Engl J Med, 2012; 366: 1423–32. [PubMed]
6. Burt FJ, Rolph MS, Rulli NE, Mahalingam S, Heise MT. Chikungunya: a re-emerging virus. Lancet., 2012; 379: 662–71. View. ArticlePubMedGoogle Scholar
7. Lima-Camara TN. Emerging arboviruses and public health challenges in Brazil. Rev Saude Publica., 2016; 50: 1–7. Google Scholar
8. Zhang Q, Sun K, Chinazzi M, Pastore Y, Piontti A, Dean NE, et al. Spread of Zika virus in the Americas. Proc Natl Acad Sci USA., 2017; 114: 34. Google Scholar
9. Pinheiro VC, Tadei WP, Barros PM, Vasconcelos PF, Cruz AC. Detection of dengue virus serotype 3 by reverse transcription-polymerase chain reaction in Aedes aegypti (Diptera, Culicidae) captured in Manaus, Amazonas. Mem Inst Oswaldo Cruz., 2005; 100: 833–9. View ArticlePubMedGoogle Scholar
10. Romero-Vivas CM, Leake CJ, Falconar AK. Determination of dengue virus serotypes in individual Aedes aegypti+ mosquitoes in Colombia. Med Vet Entomol., 1998; 12: 284–8. View ArticlePubMedGoogle Scholar
11. Ahmad R, Ismail A, Saat Z, Lim LH. Detection of dengue virus from field Aedes aegypti and Aedes albopictus adults and larvae. Southeast Asian J Trop Med Public Health, 1997; 28: 138–42. Google Scholar
12. Lee HL, Rohani A. Transovarial transmission of dengue in Aedes aegypti and Aedes. albopictus in relation to dengue outbreak in an urban area in Malaysia. Dengue Bulletin., 2005; 29: 106–11. Google Scholar
13. Shroyer DA. Vertical Maintenance of dengue-1 virus in sequential generations of Aedes albopictus. J Am Mosq Control Assoc., 1990; 6: 312–4. PubMedGoogle Scholar
14. Joshi V, Mourya DT, Sharma RC. Persistence of dengue-3 virus through transovarial transmission passage in successive generations of Aedes aegypti mosquitoes. Am J Trop Med Hyg., 2002; 67: 158–61. View ArticlePubMedGoogle Scholar
15. Westaway EG, Blok J. Taxonomy and evolutionary relationships of flaviviruses. In: Gubler DJ, Kuno G, editors. Dengue and dengue hemorrhagic fever. Wallingford:CAB International, 1997; 147–73. Google Scholar
16. Sanchez-Rodríguez OS, Sanchez- Casas RM, Laguna-Aguilar M, Alvarado-Moreno MS,

Zarate-Nahon EA, et al. Natural transmission of dengue virus by Aedes albopictus at Monterrey, northeastern Mexico. BioOne., 2014; 39: 459–68. Google Scholar

17. Gubler DJ. Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic problem in the 21st century. Trends Microbiol, 2002; 10: 100–3. [PubMed]
18. Combination of alpha-glucosidase inhibitor and ribavirin for the treatment of Dengue virus infection in vitro and in vivo Jinhong Chang, Wouter Schul, Terry D. Butters.
19. Natural Verticle transmission of dengue virus in Aedes aegypti an Aedes albopictus: A Systematic Review.
20. A Review on dengue and treatments. JK Lalla, Sunita Oagle, Shraddha Seth.
21. Current Status of Dengue Therapeutics Research And Development Jenny G.H. Low, Subhash G. Vasudevon.
22. Everything you need to know about Dengue fever Reviewed by Jill Seladi-Schulman, PhD.
23. The association between obesity and dengue severity among pediatric patients: A systematic review and meta-analysis Mohd Syis Zulkipli , Maznah Dahlui, Nor'ashikin Jamil, Devi Peramalah , Hoe Victor Chee Wai, Awang Bulgiba , Sanjay Rampal
24. Bhatt S, et al. The global distribution and burden of dengue., 2013; 496: 504–507. doi: 10.1038 nature12060. [PMC free article] [PubMed]
25. World Health Organization. Clinical diagnosis, 16, 2011.
26. Carica papaya Leaves Juice Significantly Accelerates the Rate of Increase in Platelet Count among Patients with Dengue Fever and Dengue Haemorrhagic Fever Soobitha Subenthiran, Tan Chwee Choon.
27. FAOSTAT:Papaya marketing-general information. GFruit Web site, 2012.
28. Villegas VN. Carica papaya L. In: Verheij EMW, Coronel RE, editors. Plant Resources of South-East Asia 2: Edible Fruits and Nuts. Vol. 2. Wageningen, The Netherlands: PROSEA, 1997; 223–225.