*Review Article*

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# Dengue Fever: A Unique Challenge for Treatment, Prevention & Prophylaxis

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**Abstract**

Dengue is the most common arthropod-borne viral (Arboviral) illness in humans also known as breakbone fever an infectious tropical disease caused by the dengue virus transmitted by the bite of an *Aedes* mosquito. There are four distinct, serotypes of the virus that cause dengue (DEN-1, DEN-2, DEN-3 and DEN-4). Symptoms appear 3-14 days after the infective bite. About half of the world's population is now at risk. Classic dengue fever is marked by rapid onset of high fever, headache, retro-orbital pain, diffuse body pain (both muscle and bone), weakness, vomiting, sore throat, altered taste sensation, and a centrifugal maculopapular rash. There is no vaccine available against dengue, and there are no specific medications to treat it. Bed rest and mild analgesic-antipyretic therapy are often helpful in relieving lethargy, malaise, and fever associated with the disease. Prevention is mainly by means avoiding mosquito bites or travel to an endemic area. Several vaccine candidates are currently being evaluated in clinical studies. Different attenuation mechanisms have been used to develop three of the leading candidates: 1) Chimerization with yellow fever 17D vaccine strain, 2) Combinations of defined mutations/deletions and chimeras, 3) Chimerization with dengue 2 PDK53 virus, attenuated by cell culture passage. Dengue prevention and management can now exploit opportunities presented by promising advances in vector control technology interventions, evidence-based clinical interventions and candidate vaccine developments.

**Keywords:** Dengue; Dengue fever; Breakbone fever; Dengue hemorrhagic fever; Dengue prophylaxis; Dengue vaccines.

## Introduction

Dengue is the most common arthropod-borne viral (Arboviral) illness in humans. Globally, 2.5-3 billion individuals live in approximately 112 countries that experience dengue transmission.[1]

Dengue fever, also known as breakbone fever, is an infectious tropical disease caused by the dengue virus. Symptoms include fever, headache, muscle and joint pains, and a characteristic skin rash that is similar to measles. In a small proportion of cases the disease develops into the life-threatening dengue hemorrhagic fever, resulting in bleeding, low levels of blood platelets and blood plasma leakage, or into dengue shock syndrome, where dangerously low blood pressure occurs.[2]

Dengue is transmitted by the bite of an *Aedes* mosquito infected with any one of the four dengue viruses. It occurs in tropical and sub-tropical areas of the world. Symptoms appear 3-14 days after the infective bite. Dengue fever is a febrile illness that affects infants, young children and adults.[3]

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The infection causes flu-like illness, and occasionally develops into a potentially lethal complication called severe dengue. About half of the world's population is now at risk. Dengue is found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas. Severe dengue is a leading cause of serious illness and death among children in some Asian and Latin American countries. There is no specific treatment for dengue/ severe dengue, but early detection and access to proper medical care lowers fatality rates below 1%. There are four distinct, but closely related, serotypes of the virus that cause dengue (DEN-1, DEN-2, DEN-3 and DEN-4).[4]

*Global Burden of Dengue*

According to the World Health Organization, dengue ranks as the most important mosquito-borne viral disease in the world. In the last 50 years, the incidence of dengue has increased 30-fold worldwide.[1]

The incidence of dengue has grown dramatically around the world in recent decades. Over 2.5 billion people – over 40% of the world's population – are now at risk from dengue. WHO currently estimates there may be 50–100 million dengue infections worldwide every year. An estimated 5,00,000 people with severe dengue require hospitalization each year, a large proportion of whom are children. About 2.5% of those affected die.[4]

The mortality is 1–5% without treatment, and less than 1% with adequate treatment; however severe disease carries a mortality of 26%. Dengue is endemic in more than 110 countries. It infects 50 to 390 million people worldwide a year, leading to half a million hospitalizations, and approximately 25,000 deaths.[2]

Among an estimated 2.5 billion people at risk globally, about 1.8 billion (more than 70%) reside in the Asia Pacific Region.[5]

In India 11,465 cases were reported in 2012, with 83 deaths (CFR 0,7%) compared to 55 deaths (CFR 1,3%) in the corresponding period of 2011. Most cases in 2012 were reported from southern states and West Bengal.[6]

*Definition*

Dengue fever is most commonly an acute febrile illness defined by the presence of fever and two or more of the following, retro-orbital or ocular pain, headache, rash, myalgia, arthralgia, leukopenia, or hemorrhagic manifestations (e.g., positive tourniquet test, petechiae; purpura/ecchymosis; epistaxis; gum bleeding; blood in vomitus, urine, or stool; or vaginal bleeding) but not meeting the case definition of dengue hemorrhagic fever.[7]

*Reservoir*

Humans are the only vertebrate hosts of the virus. There is a jungle cycle between monkeys and mosquitoes, but this plays no role in human disease.[8]

*Transmission*

Dengue fever is transmitted to humans through the bites of female *Aedes* mosquitoes. When a patient suffering from dengue fever is bitten by a vector mosquito, the mosquito is infected and it may spread the disease by biting other people.[9]

*Communicability*

There is no evidence of person to person transmission.[8]

*Incubation Period*

The incubation period ranges from 3 – 14 days, commonly 4 – 7 days.[9]

*Susceptibility & Resistance*

Infection with a serotype of dengue virus does not necessarily confer immunity.[8]

*Clinical Manifestations*

Initial dengue infection may be asymptomatic (50-90%), may result in a nonspecific febrile illness, or may produce the symptom complex of classic dengue fever. Classic dengue fever is

marked by rapid onset of high fever, headache, retro-orbital pain, diffuse body pain (both muscle and bone), weakness, vomiting, sore throat, altered taste sensation, and a centrifugal maculopapular rash, among other manifestations.[1]

*1. Dengue Fever (Break Bone Fever)*

Dengue fever classically presents as an acute febrile illness of sudden onset. It is extremely debilitating with fever lasting three to five days, myalgia (particularly backache), arthralgia, retro-orbital pain, anorexia, gastrointestinal disturbance, rash and increased vascular permeability. There is a high subclinical rate of milder disease in children compared to adults and a low fatality rate. Recovery from infection with one serotype of the dengue virus results in homologous immunity but does not provide protection against infection with other serotypes.

*2. Dengue Haemorrhagic Fever*

Dengue haemorrhagic fever (DHF) is a severe complication of dengue virus infection. It occurs mainly in children and is characterised by abrupt onset of fever, haemorrhagic phenomena and thrombocytopaenia. In its severest form it may result in shock (dengue shock syndrome [DSS]), which has a high fatality rate. The rate of death from DHF without DSS is usually quoted at 1–5%. This is believed to be caused by immune enhancement when a person with dengue antibodies due to a previous infection is subsequently infected by a dengue virus of a different serotype.[8]

*Laboratory Criteria for Diagnosis for Case Definitions*

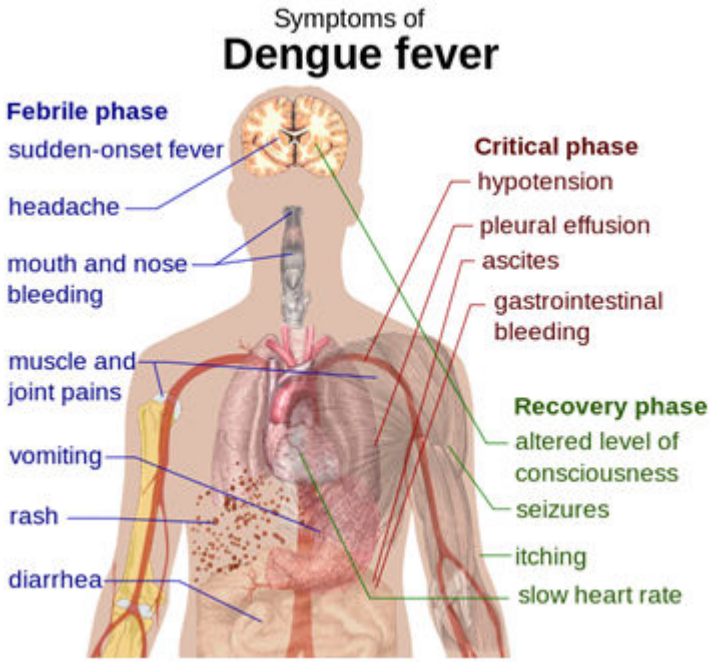
1. *Confirmatory*
   - Isolation of virus from or demonstration of specific arboviral antigen or genomic sequences in tissue, blood, cerebropspinal fluid (CSF), or other body fluid by polymerase chain reaction (PCR) test, immunofluorescence, or immunohistochemistry, *or*
   - Seroconversion from negative for dengue-specific serum IgM antibody in an acute phase ( ≤ 5 days after symptom onset) specimen to positive for dengue-specific serum IgM antibodies in a convalescent-phase specimen collected ≥ 5 days after symptom onset, *or*
   - Demonstration of a ≥ 4-fold rise in reciprocal IgG antibody titer or hemagglutination inhibition titer to dengue antigens in paired acute and convalescent serum samples, *or*
   - Demonstration of a ≥ 4-fold rise in PRNT (plaque reduction neutralization test) end point titer (as expressed by the reciprocal of the last serum dilution showing a 90% reduction in plaque counts compared to the virus infected control) between dengue viruses and other flaviviruses tested in a convalescent serum sample, *or*
   - Virus-specific immunoglobulin M (IgM) antibodies demonstrated in CSF.
2. *Presumptive/Probable:*
   - Dengue-specific IgM antibodies present in serum with a P/N ratio ≥ 2.
3. *Criteria for Epidemiologic Linkage:*
   - Travel to an dengue endemic country or presence at location with ongoing outbreak within previous two weeks of dengue-like illness, *OR*
   - Association in time and place with a confirmed or probable dengue case.[7]

*Grading of Severity of DHF*

The severity of DHF has been classified into four grades according to two pathophysiological hallmarks – shock and bleeding.

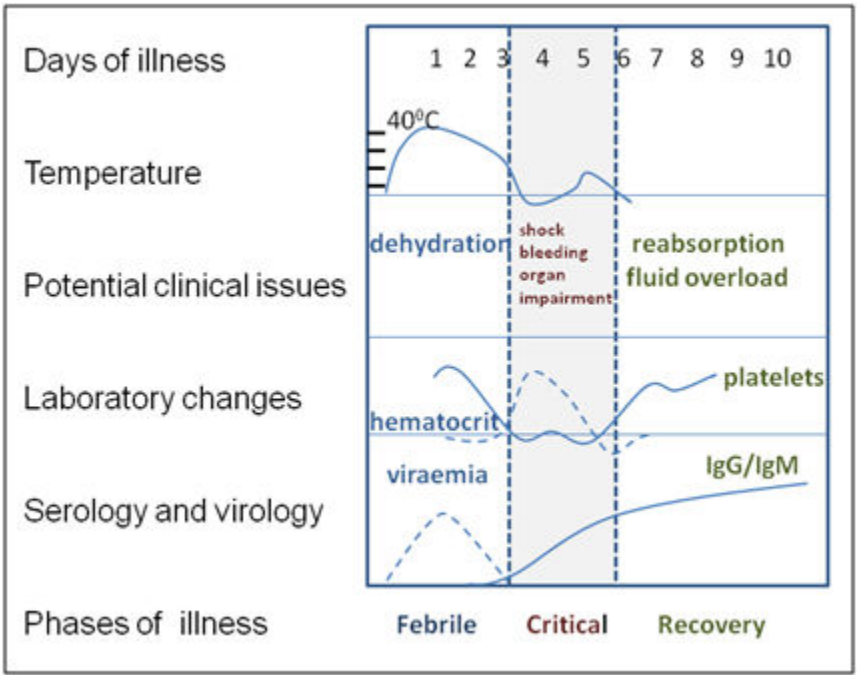
1. *Grade I:* Fever accompanied by non-specific constitutional symptoms. The only hemorrhagic manifestation is positive tourniquet test.

**Figure 1: Schematic depiction of the symptoms of dengue fever**




**Reference:** Dengue Fever. Wikipedia: The free encyclopedia. [Online] 2013 Jul 17 [cited 2013 Aug 14]. Available from URL:http://www.http://en.wikipedia.org/wiki/Dengue_fever.

**Figure 2: Clinical course of dengue fever**




**Reference:** Dengue Fever. Wikipedia: The free encyclopedia. [Online] 2013 Jul 17 [cited 2013 Aug 14]. Available from URL:http://www.http://en.wikipedia.org/wiki/Dengue_fever.

2. *Grade II:* Patient with spontaneous bleeding usually in the form of skin and/or other hemorrhages in addition to the manifestations of grade I.
3. *Grade III:* Circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mm Hg or less) or hypotension with the presence of cold clammy skin and restlessness.
4. *Grade IV:* Profound shock with undetectable blood pressure and pulse.

The presence of thrombocytopenia with concurrent hemoconcentration differentiates Grade I and Grade II DHF from DF and other diseases.[10]

*Treatment*

No specific antiviral medication is currently available to treat dengue. The treatment of dengue fever is symptomatic and supportive in nature. Bed rest and mild analgesic-antipyretic therapy are often helpful in relieving lethargy, malaise, and fever associated with the disease. Acetaminophen (paracetamol) is recommended for treatment of pain and fever. Aspirin, other salicylates, and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided. Patients with dengue hemorrhagic fever or dengue shock syndrome may require intravenous volume replacement. Plasma volume expanders can be used in patients who do not respond to isotonic fluids.[1]

*Prevention*

There is no vaccine available against dengue, and there are no specific medications to treat a dengue infection. This makes prevention the most important step, and prevention means avoiding mosquito bites if you live in or travel to an endemic area.

- The best way to reduce mosquitoes is to eliminate the places where the mosquito lays her eggs, like artificial containers that hold water in and around the home.
- Outdoors, clean water containers like pet and animal watering containers, flower planter dishes or cover water storage barrels.
- Look for standing water indoors such as in vases with fresh flowers and clean at least once a week.
- The adult mosquitoes like to bite inside as well as around homes, during the day and at night when the lights are on. To protect yourself, use repellent on your skin while indoors or out.
- When possible, wear long sleeves and pants for additional protection.
- Also, make sure window and door screens are secure and without holes.
- If available, use air-conditioning.
- If someone in your house is ill with dengue, take extra precautions to prevent mosquitoes from biting the patient and going on to bite others in the household.
- Sleep under a mosquito bed net, eliminate mosquitoes you find indoors and wear repellent.[7]

*Dengue Vaccine Research*

While no licensed dengue vaccine is available, several vaccine candidates are currently being evaluated in clinical studies. The candidate currently at the most advanced clinical development stage, a live-attenuated tetravalent vaccine based on chimeric yellow fever-dengue virus (CYD-TDV), has progressed to phase III efficacy studies. Results from a phase IIb efficacy study in Thailand have been published in September 2012. Several other live-attenuated vaccines, as well as subunit, DNA and purified inactivated vaccine candidates, are at earlier stages of clinical development. Additional technological approaches, such as virus-vectored and VLP-based vaccines, are under evaluation in preclinical studies.

The WHO Initiative for Vaccine Research (IVR), in collaboration with a wide range of partners, aims to facilitate the development and future introduction of safe, effective and affordable dengue vaccines.[11]

Global strategy for dengue prevention and control, 2012–2020 aims to address all the

**WHO Classification & Grading of Severity of Dengue Infection**

Park K. Park's Textbook of Preventive and Social Medicine. 22th ed. Jabalpur, India: M/s Banarasidas Bhanot Publishers; 2013, 224-32.

challenges of Dengue outbreak. The goal of the global strategy is to reduce the burden of dengue. The specific objectives are to reduce mortality and morbidity from dengue by 2020 by at least 50% and 25% respectively (using 2010 as the baseline). These objectives can be achieved by applying existing knowledge.[12]

Different attenuation mechanisms have been used to develop three of the leading candidates:

- Chimerization with yellow fever 17D vaccine strain, developed by Sanofi Pasteur
- Combinations of defined mutations/ deletions and chimeras, developed by NIH
- Chimerization with dengue 2 PDK53 virus, attenuated by cell culture passage, developed by Inviragen.[13]

## Conclusion

Dengue fever is a real challenge for treatment, prevention and as well as for prophylaxis. Reversing the trend requires commitments and obligations from various organizations and countries, as well as leadership by WHO and increased funding. Dengue prevention and management can now exploit opportunities presented by promising advances in vector

control technology interventions, diagnostics, prognostic systems for triage, evidence-based clinical interventions and candidate vaccine developments. In order to realize these opportunities, we need to ensure they are implemented, coordinated and adequately resourced. Further research studies are essential in the trial and invention of Dengue treatment, its prophylaxis as well as its irradiation hardliner strategies.

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