# Dengue Fever

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**Dengue Virus (DenV)**

DenV is a single stranded RNA virus that exhibits four distinct serologic types known as D1, D2, D3 and D4. It is a flavivirus.

**Other pathogenic flaviviruses**

In addition to Dengue Fever (DF) flaviviruses can cause yellow fever (YF), West Nile Fever (WNF), Japanese Encephalitis (JE), Tick Borne Encephalitis (TBE), St Louis Encephalitis (SLE), Murray Valley Encephalitis (MVE) and the recently discovered Zika Fever.

**Arboviruses**

An arbovirus is an arthropod-borne virus. DF and YF are the two most important and best known arboviral diseases . Both are carried by mosquitoes but DF is unusual in that humans are the natural host.

**Arthropods**

are the largest and most diverse phylum in the animal kingdom and include crustaceans, insects, centipedes, and millipedes. They are characterized by a segmented body, a disposable exoskeleton and jointed appendages. Most arboviral diseases are carried by insects e.g. mosquitoes, ticks, sandfiles, midges.

**Epidemiology of Dengue**

Dengue fever is an emerging pandemic which has spread globally during the past 30 years as a result of changes in human ecology.

*Around 2.5 billion people in >100 tropical & subtropical countries are exposed.*

The disease burden occurs chiefly in Asia and the Pacific followed by the Americas, the Middle East and Africa. It is now also found in Queensland in Australia. In endemic areas over 50% of the population is seropositive. WHO estimates that there are 50 million cases each year.

**Seasonality**

DF occurs all year around in the tropics and in the wet seasons in sub tropical regions.

**Travellers at risk**

More and more cases are being reported in travellers and we can be sure there is gross under-reporting because most initial cases are asymptomatic. Reports on returned Israeli travellers who spent >3 months in SE Asia show that 1 in 1000 have the clinical disease and that about 7% are seropositive for DV. An estimated 200-400 imported cases occur annually in the USA while about 200 cases occur annually in the UK. A retrospective study in Leicester, England showed that DF accounted for 6.4% of hospitalized febrile returned travellers. Twenty five per cent of those admitted as malaria turned out to have dengue. Dengue hemorrhagic fever (see below) occurred in almost 20% of the dengue cases in this group. It is worth noting that there is a high Asian population in Leicester so one would expect many travel on holidays from Leicester to endemic areas in Asia.

**The mosquito vectors**

***Aedes (stegomyia) aegypti***

Dengue is mainly transmitted by aedes *(stegomyia) aegypti*. This is a small peridomestic mosquito that breeds in and around houses particularly in clean water. *A aegypti* rests in dark areas within houses and bites the human occupants mainly towards dawn and in the early morning. The bite is painless and it needs only one bite to transfer the virus to its human host. In fact one mosquito can infect many people living in the same house causing a mini epidemic of dengue in a particular family. *A aegypti* has spread widely in recent times due to the enormous increase in air travel, urbanization and drainage schemes constructed for land reclamation. *A aegypti* has now spread to most parts of the USA and we await reports of autochthonous spread of dengue that country.

***Aedes (stegomyia) albopicta***

The dramatic spread of the Asian tiger mosquito, *A albopictus*, from SE Asia to the New World, Europe (Italy, south of France) and Africa is well documented in the literature. This mosquito is an aggressive daytime biter that carries at least 24 types of virus including DenV.

It is easily distinguished by and gets it name from the presence of white stripes on its back. When it enters a new area *A albopictus* mates with the local mosquitoes rendering them infertile so that only its own type multiplies. This has been likened to a blitzkrieg but more nearly resembles genocide! Its entry to the USA is attributed to the importation of tyres, in which the mosquito was breeding, into Houston in 1985. *A albopictus* lives and generally bites outdoors and is believed to prefer biting towards dusk.

One of the frightening features of the Asian tiger mosquito is its ability to survive in a relatively cold environment. This means that it can take up winter quarters in a suitably insulated spot and emerge to transmit disease in Spring. The current milder winters in temperate zones favour this.

Note: The title *albopictus* and *albopicta* are loosely interchangeable but grammatically agree with the gender of their preceding nouns. They can also be interpreted as male and female respectively.

***Mansonia species***

Female mansonia mosquitoes e.g. *Ma titilans,* Ma *dives, Ma annulata and Ma uniformis* are the major vectors of brugian filariasis in India and SE Asia. However they can also carry and transmit dengue. They are mainly swamp breeders and thrive in outside pools of water, blocked drains and neglected rivers and canals. They are nocturnal biters and are especially active around 0300h. They are predominantly rural mosquitoes and live outdoors. Although found in Central America e.g. Panama, they probably play little part in spreading dengue in that part of the world.

**The Disease**

***DF is no longer solely urban and solely daytime***

DF has traditionally been seen as a daytime urban disease in contrast to Japanese encephalitis which is has dusk/dawn transmission and occurs predominantly in a rural setting. However DF has now appeared in the suburbs of cities e.g. Bangkok, Hanoi and has been transmitted during the night. Its spread outside cities is partly due to an increase in mosquito breeding sites in suburbs because of open drains, garden ponds, animal troughs, plastic bags and discarded drink cans. It is also due to rural

electrification where artificial lights at night fool the mosquito into believing it is still daytime. Finally climate change with increased rainfall causing puddles and flooding favours mosquito breeding irrespective of the rural/urban divide.

**Transmission of DF**

***Mosquito to human to mosquito***

When someone acquires dengue infection there is a viraemia for about 5 days.
If, during this time, an uninfected female mosquito bites and takes a blood meal then the virus can be transferred to another person often someone living in the same house. The involvement of monkeys in this cycle is unusual and is of little epidemiological significance. There is NO human to human transmission.

**Asymptomatic dengue**

The vast majority of cases are asymptomatic or are associated with a very transient or trivial flu-like illness. Immunity against the specific infecting strain lasts for life. Some cross immunity is provoked against the other three strains and this appears to give protection against them for about 6 months.
In addition the infected person produces non-serotypic non-specific, non-protective anti-dengue virus antibodies and this ability is retained probably for a life itme. These antibodies appear to play an important role in the genesis of severe disease where there is reinfection by another strain of dengue (See ADE below)

**Classical Dengue Fever (DF)**

***General***

*Capillary leakage*: Dengue is classified as a **Viral Hemorrhagic Fever** (VHF) a title that has ominous implications both for health care workers and for the general public. Being a VHF means that DF is capable of producing severe hemorrhage and capillary leakage in any part of the body just like

§ Flaviviruses: Yellow Fever YF, Crimean-Congo Hemorrhagic Fever CCHF
§ Bunyaviruses: Rift Valley Fever RVF, Hantaan Fever
§ Arenavirus: Lassa Fever
§ Filoviruses: Ebola, Marburg Fever

Thus any sign of bleeding, bruising, petechiae or a postive tourniquet test must be viewed with alarm.
*FAR*: As with any VHF Dengue commonly presents with fever, arthralgia and rash, that is, the FAR syndrome.

***Clinical presentation***

1. Short incubation period. Normally about 2 – 5 days but may be up to 15 days
2. Acute high Fever ( may subside to normal in a day or so and then rise again – 'saddle back fever')
3. Arthralgia ( the old name for DF was breakbone fever. Not as pronounced as in Chikungunya)
4. Myalgia ( non specific but very common)
5. Severe headache
6. Retro-orbital pain is often very prominent
7. Rash which is usually confined to the trunk. A rash is present in up to 50% of cases. May blanch under pressure. The rash type varies but is often maculopapular and often very itchy.
8. Photophobia

9. Lymphadenopathy
10. Recovery in a few days is the rule. There is no specific treatment.

***Diagnosis***

1. History of travel or residence in dengue endemic area
2. Constellation of clinical symptoms and signs above
3. Viremia only lasts 5 days so unlikely to grow virus from blood
4. Leukopenia (greater than that of malaria)
5. Thrombocytopenia (marked. Usually < 150,000)
6. Eosinophilia ( > 500 this is not found in malaria or rickettsia)
7. ALT ( more elevated than in malaria)
8. IgM and IgG usually unhelpful in early cases. Higher in convalescent serum. False positives common because of cross reactions with other flaviviruses
9. Positive tourniquet test ($\geq$20 petechiae in 22.5cm$^2$ area of forearm after inflating BP cuff midway between systolic and diastolic pressure for 5 minutes)
10. A negative malaria slide in the presence of dengue like symptoms

***Traveller****s*: According to Stephenson and his colleagues in Leicester one should seriously consider dengue in anyone who has spent a long time in an endemic area, is a first time traveller, has a thrombocytopenia and whose symptoms (fever etc ) have begun a short time after return.

**Treatment**

There is no specific vaccine or treatement. Treat symptomatically and maintain the circulation. Avoid aspirin because of the bleeding tendency and the possibility of an associated Reye-like syndrome .

**Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS)**

According to a report from Taiwan about 5% of those living in endemic countries get classical DF and approximately 6% of these go on to DHF. Of these 92.2% will survive and 0.8% progress to DSS and die. These patients have a severe shock syndrome with multiple organ dysfunction and a hemorrhagic diasthesis.

**The Riddle of DHF**

Death from dengue was almost unheard of until after the second world war. Since then DHF and DSS have increased relentlessly and are now occurring in all dengue endemic countries from SE Asia to the Caribbean and to South and Central America. Several explanations for this have been put forward .

**1. *Immune Enhancement Hypothesis or Antibody Dependent Enhancement (ADE).***

Non specific antibodies mounted against a first attack by a specific strain of dengue are provoked by a second infection. These antibodies form a non-neutralising complex with the 'second' dengue virus and together they enter into macrophages allowing the new virus to multiply inordinately. As a result of the massive viral replication a huge immune response is provoked ( Systemic Inflammatory Response Syndrome, SIRS). This damages endothelial cells and provokes capillary leak throughout the body. This hypothesis is supported by the observation over many years that DHF is more likely to occur after a second than after a first infection.

A strong SIRS is typical of young healthy people and this may provide the basis of the old observation that well nourished children are more likely to display serious symptoms of dengue than malnourished ones.

Support for the ADE hypothesis may bave been provided by an outbreak of DHF and DSS in 6 -12 month old infants born in Bangkok in the 1960s. These children were born to mothers who were dengue immune and so were essentially having a second attack! The findings were ignored.

**2. *Geneticically different dengue virus***

There is a mass of epidemiological evidence to show that DenV3 subgroup 111 is associated with DHF and DSS far more often than the other types. Furthermore this subgroup of dengue is spreading in dengue endemic areas. It was introduced to Panama and Nicaragua in 1994 from India or SE Asia. It is appearing in Queensland since 2006 (Peter Legatt). The spread of DenV3 seems to follow the spread of *A aedes* and in particular the spread of *A albopictus*.

DHF and DSS can appear in travellers who have never been exposed to DenV before. Remarkably the rate of DHF in travellers is similar to that found in those living in endemic countries. This finding calls the ADE hypothesis into question.

DenV type 4 has been found to be associated with bone marrow damage and aplastic anaemia. Although this is a rare complication it may indicate that specific dengue serotypes can cause specific problems.

**3. *Racial genetic resistance***

Although DenV circulates widely in Africa, and although *A albopictus* is now in that continent, one does not find DF in the indigenous population. However it does occur in expatriates living in Africa. This difference, presumably genetic, was clearly seen in US miltary personnel in Somalia when DF antibodies were found all racial groups but DF predominated in Caucasians. This racial resistance to DF may be an adaptation to protect against DHF.

**Developments**

Immunoassay kits are now available to allow rapid diagnosis in the field. In addition live attenuated vaccines against all four types of Dengue are being developed.

**Prevention**

Personal protection against mosquitoes is recommended during the day time in dengue endemic areas. Mosquito control including spraying stored water with larvicide is essential. All potential sites where the *aedes* may breed must be eliminated if at all possible.