Factsheet for health professionals

DENGE FEVER

Dengue is a mosquito-borne viral disease widely spread in tropical and subtropical regions. The disease is transmitted by *Aedes* mosquitoes, which breed in the peri-domestic environment. While most of the clinical cases present a febrile illness, severe forms including hemorrhagic fevers and shock with fatalities are reported. As dengue is a "viral hemorrhagic fever", the disease is under European surveillance. It is by far the most important mosquito-borne viral disease affecting humans worldwide; tens of millions of cases occur each year resulting in approximately 20,000-25,000 deaths mainly in children. There are four serologically distinct dengue viruses, so people living in a dengue-endemic area can have several dengue infections in their lifetime. There is currently no vaccine available for dengue. Dengue is endemic in most of the European Overseas Countries, Territories and Departments located in tropical areas. In continental Europe limited outbreaks may occur in areas infested by *Aedes albopictus*, an invasive mosquito species that spread over the past twenty years.

THE PATHOGEN

- Dengue is caused by a virus of the Flaviviridae family, *Flavivirus* genus which includes viruses such as yellow fever, West Nile and tick-borne encephalitis.
- There are four distinct dengue viruses without immunity. People can have up to four dengue infections in their lifetime. It is fairly widely accepted that all four viruses are of Asian origin.

CLINICAL FEATURES

- Up to 40% of all dengue infections are asymptomatic.
- Commonly reported clinical symptoms include sudden onset of high fever, severe headache and retro-orbital pain, myalgia, arthralgia, a maculopapular rash and minor haemorrhages. Fever and other symptoms often follow a 'saddleback' sequence, with a brief remission after the third day. Illness rarely lasts for more than ten days, but convalescence can be prolonged and debilitating.
- A portion of cases, usually < 5%, can be severe and a fraction of these may be fatal. Most severe cases and fatalities occur among children and adolescents. Severe dengue — commonly referred to as 'Dengue haemorrhagic fever/Dengue shock syndrome (DHF/DSS)' to distinguish it from 'classic' dengue fever (DF) — is characterised by an increase of vascular permeability that can lead to life-threatening hypovolemic shock.
- The causes of the severe dengue condition have been debated for decades, but remain unresolved. A highly contested hypothesis is that after a 'primary' infection with one serotype, 'secondary' infections by one or more of the other serotypes can precipitate 'antibody dependent enhancement' (ADE). Resolution of this issue is hampered by the absence of a reliable animal model. In addition, controversy remains with regards to the validity of a graded set of criteria to categorise severity. Both issues are of prime importance for the management and treatment of patients, and for future acceptance of dengue vaccines.

TRANSMISSION

- The incubation period ranges from 3 to 14 days, with an average of 4–7 days.
- Viraemia reaches high titer on the day before onset of symptoms and is generally high enough to infect mosquitoes for the next four days.
- Immunity to any of the four serotypes is probably life-long, but this does not confer protective immunity to the other three serotypes.
- Humans are the main amplifying host of the virus. In tropical and sub-tropical urban areas, the viruses are maintained in a human/mosquito cycle.
- Bites from infected mosquitoes are the mode of transmission.
- Mosquitoes acquire the virus when they feed on a viremic host, and this is found to be susceptible species. The virus infects many tissues, including the salivary glands. While it can be a matter of weeks (and many blood meals) to become infective, the mosquitoes are infected for life. New infections in humans can occur when a mosquito is infected into a non-immune host during subsequent blood meals. The 'extrinsic incubation period', the time required for the mosquito to become infective, is about ten days at 37°C.
- There is some evidence that forest monkeys infected with *Aedes aegypti* are involved in a 'jungle cycle' with forest mosquitoes serving as vectors in south-eastern Asia and western Africa. However, there is no evidence that these viruses are responsible for large epidemics.
- The virus circulates among humans in village and urban areas. Dengue is essentially a village and urban disease because its principal vector, *Aedes aegypti*, is abundant in the peri-domestic environment. The species is highly effective in transmission: it feeds almost exclusively on humans, breeds in small man-made articles that contain water, rests inside buildings, and is rarely found more than 10 meters from human habitation. As biting habits tend to be diurnal, it is primarily an urban vector.
- A second species, the Asian tiger mosquito, *Aedes albopictus*, can be common in the peri-domestic environment, particularly in urban areas with abundant vegetation. It is widely regarded, however, as a secondary vector because it is not host-specific; blood-meals are taken from animals that are not susceptible to the dengue virus and therefore do not participate in the transmission cycle. Nevertheless, epidemics have occurred in places where the mosquito was the only vector species present.
- *Aedes aegypti* was once present in Europe and responsible for large epidemics of yellow fever and dengue. Its disappearance after World War II has never been explained. Currently it is present in Madeira and it is conceivable that it could become re-established and widespread in Europe.
- The *Aedes albopictus* mosquito present in southern Europe is well adapted to warmer temperatures, and is likely to extend its range northwards. It is already a major nuisance in several Mediterranean countries, and was responsible for autochthonous cases of dengue in France and Croatia in 2010.

DIAGNOSTICS

- Dengue viral genome can be detected by RT-PCR in blood specimens up to day five of illness.
- Another approach is the detection of the non-structural-1 (NS1) dengue antigen up to day four post-onset. However sensitivity of the assay is depending on the serotype.
- Determination of the dengue serotype and genotype is important for epidemiological studies; co-circulation of different dengue serotypes during an outbreak is not uncommon.
- Serological diagnosis can be performed by detection of dengue IgM antibodies in serum specimens from day 5–6 of illness, or detection of a four-fold rise of specific IgG antibody titre on a pair of sera (acute and convalescent specimens).
- In secondary dengue infection, dengue IgM antibodies usually appear earlier from day 2–3 post onset and with a shorter duration. An increase of dengue IgG titre has to be measured.
- Serological cross-reactions between dengue viruses and closely related flaviviruses are reported.

CASE MANAGEMENT AND TREATMENT

- Supportive therapy is the only option, with strict avoidance of aspirin and other anticoagulants.

EPIDEMIOLOGY

- Dengue is endemic in more than 100 countries in Africa, the Americas, South East Asia, the Western Pacific and the eastern Mediterranean.
- Dengue viruses are highly mobile, transported by infected travellers to all four serotypes now co-circulate in many cities around the world. The number of dengue cases has been increasing dramatically in the past few decades and large outbreaks have been reported.
- Imported cases of dengue fever are frequently reported by travelers returning to the EU from endemic areas and may generate a local transmission in areas where the vector is present. In August 2010, several autochthonous cases (mild cases) were reported in Croatia and France in areas infested by *Aedes albopictus*. Cases in France were detected through enhanced surveillance.
- The last dengue epidemics in the European continent started from 1989-1991 in Greece, with high mortality and *Aedes* aegypti mosquitoes vectored. Through entomological surveillance, distribution maps of potential dengue vectors in Europe are regularly updated (see the VBDNET maps). The presence of *Aedes albopictus* and *Aedes japonicus* in the Mediterranean is a concern. The presence of *Aedes albopictus* in the Mediterranean is a concern. The presence of *Aedes albopictus* in the Mediterranean is a concern.
Dengue in Madera is a major concern.

- The risk of transmission of dengue through blood donations is under investigation.
- Dengue illness in the Americas was estimated to cost $2.1 billion US dollars (1.55 billions Euros) per year on average from 2000 to 2007 (in 2010 US$). The cost did not include the vector control activities.
- Enhanced surveillance of dengue in areas where potential vectors are present during the mosquito season is crucial for an early detection and appropriate vector and disease control measures.
- Early detection of infectious dengue patients is important to prevent local transmission in areas where the vector is present and active. As dengue is a "viral hemorrhagic fever", it is a notifiable disease in the EU and information is collected through the TESSy system.
- There is no specific case definition for dengue. The EU case definition for "viral hemorrhagic fevers" (VHF) - Commission decision of 28 April 2008 - is used:
  - **Clinical Criteria:** Any person with at least one of the following two:
    - Fever
    - Haemorrhagic manifestations in various forms that may lead to multi-organ failure
  - **Laboratory Criteria:** At least one of the following two:
    - Isolation of specific virus from a clinical specimen
    - Detection of specific virus nucleocapsid in a clinical specimen and genotyping
  - **Epidemiological Criteria:** At least one of the following:
    - Travel in the last 21 days to a area where VHF cases are known or believed to have occurred
    - Exposure within the last 21 days to a probable or confirmed case of VHF whose onset of illness was within the last 6 months
- **Case classification**
  A. Possible case
  B. Probable case: Any person meeting the clinical criteria and with an epidemiological link
  C. Confirmed case: Any person meeting the clinical and laboratory criteria

**PUBLIC HEALTH CONTROL MEASURES**

- The vector mosquitoes mainly colonise water collections, such as the saucers underneath flower pots, water containers that are not tightly covered, wells and water storage tanks, tree holes and rock pools. Therefore, the removal of these breeding sites by emptying stagnant water in and around the houses on a weekly basis is the most efficient way to avoid mosquito proliferation.
- The World Health Organization has recommended this 'community-based source reduction' for several decades, but there is no evidence that this has been successful anywhere in the world.
- The technique of insecticidal aerosols delivered from hand-held machines, road vehicles or aircraft is expensive and ineffective. Moreover, even if a high kill rate was attainable, the impact on adult populations would probably be too short for effective impact on transmission.

**PERSONAL PROTECTION AND PREVENTION**

- There are no particular risk groups; anyone exposed to the infected vector may become infected with the virus. However more severe cases are reported in children in endemic countries.
- Prevention of dengue is currently based on individual protection against mosquito bites. Many authorities recommend personal protection (long-sleeved shirts, trousers tucked into socks, insect repellent, etc.) but the approach is hardly practical in warm climates, particularly as the vectors bite in mid-afternoon.
- There is no dengue vaccine, but this is an active field of research and a few candidate vaccines are currently on clinical trial.

**ADVICE TO TRAVELLERS**

- Dengue is one of the most common vector-borne diseases contracted by travelers in tropical and sub-tropical countries.
- The use of repellents is recommended as well as the use of bed nets during slumber (these mosquitoes bite during the day).
- No specific risk for pregnant women.

**REFERENCES**