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Arboviruses

Summary

- Arboviruses: Arthropod-borne viruses are viruses that can be transmitted to man by arthropod vectors (mosquitoes, ticks, flies)
- Over 500 virus species can be transmitted by arthropods, approximately 150 of those cause human disease
- Arboviruses belong to 5 different Families (Togaviridae, Flaviviridae, Bunyaviridae, Rhabdoviridae and Reoviridae)
- The main clinical syndromes are skin rash, arthralgia, neurological and/or hemorrhagic manifestations.
- Clinical distinction between arboviral infections is difficult, because symptoms are often non-specific. Clinical presentation is also similar to many non-arboviral infections.
- Geographical distribution of arboviral infections varies and is often related to outbreaks; knowledge of possible exposure is important for recognition of clinical cases and for choosing diagnostic tests.
- Laboratory diagnosis is required for confirmation of arboviral infections; the timeline of infection (date of exposure, date of symptom onset) is required to choose the appropriate diagnostic assays.
- Treatment is mainly supportive
- Preventive measures include personal protective measures like the use of protective clothing and insect repellents. Vaccination for selected arboviral infections is available.

General

Transmission

The WHO definition of arthropod-borne viruses (arboviruses) is as follows: “Viruses that are maintained in nature principally, or to an important extent, through biological transmission between susceptible vertebrate hosts by hematophagous arthropods or through trans-ovarian and possibly venereal transmission in arthropods.” Over 500 virus species can be transmitted by arthropods, and approximately 150 of those cause human disease. The viruses multiply in the vector, migrate towards the salivary glands and are transmitted via the saliva to the vertebrate host during a blood meal. There is therefore no simple mechanical transmission (e.g. the mosquito as a flying injection needle). Different arthropod species often have different vector competence for a particular (strain of) arbovirus. Transovarial transmission in the vector has epidemiological significance, because it allows the arthropod to act both as a vector and as a reservoir.
Aetiologic agents of arboviral diseases are primarily zoonotic pathogens. Spillover from the enzootic cycle to humans occurs when humans enter areas of zoonotic transmission or when enzootic transmission is increased near humans. Examples include Eastern (EEEV) and Western equine encephalitis viruses (WEEV), as well as West Nile (WNV), St. Louis encephalitis (SLEV) and Yellow fever viruses. Spillover may involve direct transmission to humans by primary enzootic vectors (e.g. WNV, SLEV and WEEV) or by bridge vectors, i.e. vectors that take bloodmeals across species, including humans (e.g. EEEV). Some viruses, such as Rift Valley fever, Japanese encephalitis and Venezuelan equine encephalitis viruses (VEEV) infect livestock animals, resulting in increased risk of infection in persons living in rural communities. Two of the most important human arboviral pathogens, Yellow fever and dengue viruses (DENV) have adapted to replication in humans only, allowing for urban transmission.
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Urban epidemic cycle

Enzootic cycle

Rural epizootic cycle

*Aedes aegypti*

Enzootic vectors and/or bridge vectors

*Ochlerotatus* and *Psorophora* spp. (VEEV), *Culex tritaeniorhynchus*, *Culex* spp. (JEV)

Human amplification (for example, urban dengue virus, YFV, chikungunya)

Spillover from enzootic cycle (for example, WNV, sylvatic dengue virus, YFV, VEEV)

Amplification in domestic animals (for example, epizootic VEEV, JEV)
Arboviruses

Figure: Typical mechanisms of arboviral emergence (Weaver et al, Nat Rev Microbiol. 2004)

**Virology**

Thus, the acronym ‘arbovirus’ does not refer to a virological classification, but rather to the main mode of transmission. Taxonomy divides Arboviruses into 4 different classes, that all have a single stranded RNA genome:

1. Togaviridae (genus Alphavirus, not Rubivirus); examples Chikungunya virus (CHIKV), Eastern/Western/ Venezuelan equine encephalitis viruses (E,W,VEEV), Ross river virus (RRV), Mayaro virus
2. Flaviviridae (genera Flavivirus and Pestivirus and not Hepacivirus); examples Dengue virus (DENV), Japanese encephalitis (JEV), West Nile virus (WNV), Yellow fever virus (YFV), Zika virus (ZIKV), Tick-borne encephalitis (TBEV), Kyasanur forest disease virus
3. Bunyaviridae (genera Bunyavirus, Phlebovirus, and Nairovirus but not Hantavirus); examples Crimean-Congo hemorrhagic fever (CCHKV), Toscana virus (TOSV), Sandfly fever virus (SFV), Rift Valley fever virus (RVFV)
4. Rhabdoviridae; example Indiana vesiculovirus
5. Reoviridae; example Colorado tick fever virus

This Chapter will focus on the arboviral families most important in human medicine: Togaviridae, Flaviviridae and Bunyaviridae.

**Vectors**

Aedes mosquitoes are the most important vector species of arbovirus infections in Africa, America and Asia.

Aedes aegypti prefers peridomestic settings, where water containers are a typical example of preferred breeding sites. It also enters houses to feed. Aedes mosquitoes bite during the day, mainly in the late afternoon (unlike Anopheles). The adult mosquitoes buzz a little but do not keep people awake in their siesta (unlike night biting Culex mosquitoes).

**Mosquito biology**

Traditionally it was thought that Aedes aegypti had limited flying ability (100 m). This was called
into question by more recent data. Studies with labelled mosquitoes revealed an area of ± 840 meters in diameter in which eggs were laid. In order to study the density of vectors in an area, entomological surveys are used. A frequently used index is the number of positive water containers per 100 houses (“Breteau index”). Dumps of old car tyres are favourite breeding sites.

Aedes albopictus is another dengue vector. The mosquito is recognisable because unlike A. aegypti, it has one longitudinal white stripe down its back. This vector breeds in all kinds of water reservoirs, from lucky bamboo stems to septic tanks, which is important for control purposes. This mosquito also called Asian Tiger mosquito, has been recognized among the world’s most invasive species. Its territorial expansion has already been associated with dengue and other arboviral outbreaks in non-tropical countries, like France and Croatia in 2010 and on the Madeira islands of Portugal 2012 (over 2000 cases).

Culex species are the vector of Japanese Encephalitis and West Nile virus.

Vector control

If only the adult mosquitoes are to be controlled, for example with so-called “adulticides”, very rapid reduction in the number of adult mosquitoes can be achieved. This reduction will however only be for a short time. The insecticides soon lose their effect, after which mosquitoes that have hatched occupy the ecological niche that has been vacated. It is therefore strongly advised that the breeding sites are controlled also using larvicides. Slow-release formulations of methoprene (Altocid®) can be used here for this purpose.

Aedes aegypti is a peridomestic mosquito and this means that the population can be controlled. The elimination of small water reservoirs (=breeding sites) near housing (cans, car tyres, vases, bottles, buckets, snail shells, coconut shells, bamboo stubble, hollows in plants, waste gullies, etc.) by clearing away rubbish and by having a “dry” day systematically once a week is important in controlling Aedes aegypti. On “dry days”, all small water containers (buckets, vases) are emptied to interrupt the cycle of the mosquitoes. The larvae and pupae of the insects are destroyed before adult mosquitoes can emerge. Large reservoirs – drinking water for example – cannot of course be emptied quite so simply. Because large water containers have such a great epidemiological importance in some areas (Thailand for example) covering these with a fine-mesh net is effective in considerably reducing the population of Aedes mosquitoes (much better than a normal cover). Temephos pellets (Abate®, a larvicide) can be placed in water containers and is non-toxic for humans.

If Aedes albopictus plays an important role, appropriate measures are necessary for this (for example
by expandable polystyrene beads that float on the water of septic tanks).

In epidemics the vector can also be controlled by using insecticides such as Bacillus thuringiensis H-14 or organophosphate larvicides (eg. Temephos pellets= Abate®).

Vector control for Culex mosquitoes consists of reducing contact with the vector by use of personal protective measures, such as protective clothing, mosquito repellents and impregnated mosquito nets.

Insecticide can also be sprayed indoors. In the case of large epidemics, outdoor vector control is also important (larvicides and adulticides). Today, several biological control methods can be used to diminish mosquito populations: the sterile insect technique (SIT) is a form of insect birth control where male mosquitoes are sterilized through irradiation. They are then released to mate with wild females that will lay non-viable eggs. RIDL (Release of Insects carrying Dominant Lethals) is a new tool to control Aedes aegypti. Genetically engineered mosquitoes carry a lethal gene that is inherited by all offspring of RIDL mosquitoes. The lethal gene, which has an on and of switch, is switched on when the insects are released in the environment. The RIDL genes will then kill the larvae and pupae. Incompatible Insect Technique (IIT) makes use of the Wolbachia gram-negative bacteria that competes with viruses like dengue, zika, chikungunya and yellow fever in Aedes aegypti. Wolbachia-carrying mosquitoes are bread and then released into areas affected by mosquito-borne diseases.

Ixodes ticks are the vector of Tick-borne Encephalitis viruses. The main prevention is vaccination. Vector control measures are not very effective. They include the use of tick repellents in combination with the wearing of appropriate clothing (for example, long trousers) and avoidance of the tick habitat if possible, although a recent study has shown that tick repellents are only moderately effective.

Hyalomma ticks are involved in the transmission of Crimean-Congo Haemorrhagic Fever (CCHF) virus, although sometimes other up to 31 tick species are involved (e.g. Rhipicephalus, Haemaphysalis, Amblyomma and Dermacentor sp). The virus can survive in a tick population because it is transmitted both by the transovarial and the transstadial route.

**Geographical Distribution**

Geographical distribution of arboviral infections varies and is often related to outbreaks; knowledge of possible exposure is important for recognition of clinical cases and for choosing diagnostic tests. When the distribution of arthropod vectors for pathogens overlaps, the distribution of the arboviruses can be similar (see also Figure). Co-infections (eg. two different serotypes of DENV, two different
Arboviruses and co-infections of malaria with arboviral infections do occur. Online resources should be used to obtain up-to-date information concerning ongoing epidemics (e.g. www.cdc.gov, www.who.int, http://ecdc.europa.eu/, http://www.promedmail.org/).

Figure: Overlapping distribution of selected arboviruses (Cleton et al, PLoS Negl Trop Dis)

Arbovirus include different families of viruses, as presented in this figure with colours. The Flaviviridea family, which is coloured in red, includes DENV, ZIKV and other species. The blue coloured viruses belong to the Togaviridea family, which include CHIKV among other species. The viruses belonging to the Bunyaviridea family are coloured in green and the viruses belonging to the Reoviridea family are coloured in black.

Clinical aspects

The clinical presentation of arbovirus infection varies from asymptomatic to critical illness with organ failure and death. It is not possible to distinguish between arboviral infections clinically, because symptoms are often non-specific. The clinical presentation is also similar to that of many non-arboviral infections.

However, a number of clinical syndromes may be distinguished. These are:

- Fever
- Skin rash
- Arthralgia
- Neurological manifestations
- Haemorrhagic manifestations

**Skin rash**

A non-pruritic skin rash tends to occur frequently. It can be maculopapular or morbilliform. Skin desquamation is uncommon. Skin vesicles can form in Sindbis virus infection.

**Arboviral-induced arthritis**

Arthralgia is a frequent finding in mosquito-borne arboviral disease, but some of them play a more prominent role than others. The six main mosquito-borne viruses associated with arthritis in humans belong to the Family of Togoviridae, genus Alphavirus. They are: Chikungunya, Sindbis, O’nyong-nyong, Mayaro, Ross River and Barmah Forest virus.

All these viruses are transmitted via culicine mosquitoes, such as Aedes or Culex spp, except O’nyong-nyong virus, which is transmitted via anopheline spp. Incubation is usually 2 to 10 days. The illness begins suddenly. The most common symptoms are fever, arthralgia and rash. Fever is usually low grade in O’nyong-nyong, Sindbis and Ross River virus infections, but high in Mayaro and Chikungunya infections.

Headache, photophobia, retro-orbital pain, myalgia and backache occur frequently. Anorexia, nausea and vomiting are also part of the clinical spectrum. Weakness can persist for several weeks, sometimes even months.

The severity of arthralgia can vary from vague stiffness to excruciating pain. Patients with Alphavirus infections (Chikungunya, Ross River virus) often have swollen tender joints; this does not occur in dengue or West Nile fever. Fingers, wrists, elbows, toes, ankles and knees are the most common affected. In most cases, the symptoms persist for several days and complete recovery follows. However, arthralgias may persist for several months and even for years. This results in prolonged disability. Intermittent attacks of joint pain and swelling can occur.

Incidence of arthralgia after Chikungunya virus infection varies greatly with factors such as genetic susceptibility of populations, cultural perceptions, and quality of study. In some cohorts, over 50% of patients develop chronic arthralgias and clinically detectable joint swelling at 3 years after their acute
infection, so called post-Chikungunya rheumatic disorder. A 6-year retrospective study in La Réunion looked at patients referred to a rheumatologist due to rheumatic symptoms lasting more than 4 months following CHIKV infection. Out of 159 cases, they found that 59% met the criteria for de novo chronic inflammatory rheumatism (CIR) like rheumatoid arthritis, spondylarthropathy, and undifferentiated polyarthritis, and 31% had pre-existing rheumatic musculoskeletal disorders. Amongst those with de novo rheumatoid arthritis, 80% developed joint damage within 3–4 years. They found that some patients remained symptomatic for 6–8 years.

In those with persistent symptoms, there is little evidence on effective therapies. Several disease modifying drugs (DMARDs) have been studied with varying success. Chloroquine has some antiviral effect but has not been found to be more effective than other anti-inflammatories like meloxicam in acute and chronic CHIKV arthralgia. Methotrexate has been widely used, particularly in patients who present with a systemic polyarthritis. Up to 75% of patients may have a positive clinical response to this. Sulfasalazine has been shown to have good clinical efficacy, particularly when combined with methotrexate.

There are no vaccines against Togaviridae. Vector control and personal protection are the only effective preventive measures.

**O’nyong-nyong virus**

Poorly understood epidemiology. It was first isolated in East Africa in 1961. In this period, there was a massive epidemic involving millions of people. The virus is transmitted via anopheline mosquitoes, which is very unusual for an arbovirus.

**Mayaro virus**

This virus has been reported from Brazil, Colombia, Bolivia, Trinidad and Surinam. Most infections seem to occur in the forest. Forest-dwelling mosquitoes of the genus Haemagogus are believed to be the principal vector. Rodents or monkeys probably serve as reservoir.

**Ross River virus**

Human infection has been documented from Australia, New Guinea, the Solomon Islands, Fiji, Samoa and a number of South Pacific Islands. New Zealand seems to be spared. In Australia,
infection with this virus is known as epidemic polyarthritis. The first recorded outbreak was described in 1928. A major epidemic occurred in 1979-80 on a number of South Pacific Islands. The disease occurs in both an endemic and epidemic form. In Australia, the virus seems to be maintained in a wild vertebrate-mosquito cycle, with Culex annulirostris and Aedes vigilax serving as the principal vectors. In the Pacific the virus can be transmitted via Aedes polynesiensis.

**Barmah Forest virus**

This virus is so far only found in Australia. Barmah Forest virus was first isolated in 1974 from Culex annulirostris mosquitoes collected in the Barmah Forest of northern Victoria. It has also been isolated from numerous other mosquitoes including the coastal species Ochlerotatus vigilax and O. camptorhynchus, which have a salt marsh habitat, and from the midge Culicoides marksi in the Northern Territory. The virus was found to be pathogenic for man since 1988. Infections with this virus are less common than infections with Ross River virus. Wallabies and kangaroos are thought to form the reservoir.

**Sindbis virus**

Sindbis is the most widely geographically distributed of the six alphaviruses causing arthritis. It has been recovered from Europe, Africa, Asia, Australia and the Philippines. It has a broad host range. The basic life cycle involves Culex mosquitoes and wild birds. Because the vectors are mainly ornithophilic (“bird-loving”), human infection is uncommon.

**Neurological symptoms**

Although neurological symptoms may occur with many arboviral infections, the most important causes of neurological symptoms belong to the genus Flavivirus, of the family Flaviviridae. Important Flavivirus species which frequently cause neurological symptoms belong to the Japanese Encephalitis serogroup (Japanese encephalitis virus (JEV), West Nile virus (WNV), St Louis encephalitis virus (SLEV), Murray Valley encephalitis virus (MVEV)) and Tick-borne encephalitis virus (TBEV). Zika virus also has marked neurotropism.

Because of the clinical importance and vast distribution, these viruses are discussed in separate sections.
Laboratory diagnosis of arboviral infections

Laboratory diagnosis is required for confirmation of arboviral infections. As explained below, information regarding the timeline of infection (date of exposure, date of symptom onset) is required to choose the appropriate diagnostic assays. This is illustrated for dengue virus in Figure 3.

Figure 1 Typical timeline of arboviral infection (Dengue) (Guzman et al, Nat Rev Microbiol)
Direct tests

After the incubation period, the arbovirus is viraemic (i.e. it circulates in human blood). In the acute phase of infection, the virus can be detected in serum or whole blood by molecular detection assays that target virus-specific sequences, such as real-time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR). The viraemic phase is usually short-lived (up to 7 days after symptom onset, depending on the arbovirus). RT-PCR may be used for detection of the arbovirus in other body fluids, thus possibly extending the diagnostic window. In addition, antigen detection tests have been developed. In the case of dengue virus infection, a rapid test targeting NS1, a glycoprotein that is essential for viral replication and viability has been introduced; this test can be used within 7 days after onset of dengue virus infection. Virus isolation from body fluids or tissues in cell lines is another means of confirming infection, but due to high costs and sophisticated technical requirements, its use is restricted to research settings.
**Indirect tests**

Antibody detection assays such as Enzyme Linked Immuno Sorbent Assay (ELISA) or Immune Fluorescence Assays (IFA) are available for detection of arbovirus-specific antibodies. Only after developing a humoral immune response to an arbovirus, these tests can be used for detection of that virus. This generally limits their use in the acute phase of arboviral illness. Apart from limited sensitivity in the early course of the disease, serological assays that detect immunoglobulins present challenges to interpretation; specificity is frequently affected by cross-reactivity (particularly with other flavivirus infections or previous flavivirus vaccinations). It may also be difficult to discriminate subsequent infections because of persistence of IgG-class antibodies (see Figure 4).

A single indirect test can rarely confirm the diagnosis. To confirm a case by antibody detection assays, demonstration of seroconversion is required. Both seroconversion from negative to positive IgM antibody detection as well as a demonstration of a fourfold or greater increase in IgG antibody titres in paired sample analysis can be used to this end. Consecutive samples should ideally be taken at least 14 days apart.

To confirm the specificity of an antibody reaction to an arbovirus, Virus Neutralization Tests (VNT) can be used. Neutralization of a virus is defined as the loss of infectivity by binding to virus-specific antibody. Virus and serum are mixed and then inoculated into cell culture. Sera that contain antibodies that neutralise the virus will then prevent infection of the cells in culture. When little or no neutralizing antibody to the virus is present, the virus remains infectious. This can be observed microscopically by demonstrating a CytoPathogenic Effect (CPE) in the cell line, or by detecting higher viral loads using RT-PCR.

**Table 1 Advantages and limitations of arboviral diagnostics tests (Peeling et al, Nat Rev Microbiol)**

* virus neutralisation test is not included in this comparison

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<th>Advantages</th>
<th>Limitations</th>
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<td>Virus isolation and identification</td>
<td>Confirmed infection</td>
<td>Requires acute sample</td>
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<tr>
<td></td>
<td>Specific</td>
<td>Requires expertise and appropriate facilities</td>
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<tr>
<td></td>
<td>Identifies serotypes</td>
<td>Does not differentiate between primary and secondary infection</td>
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<td></td>
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<td>Expensive</td>
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## Viral RNA detection
- **Confirmed infection**
- Sensitive and specific
- Identifies serotype and genotype
- Results within hours
- Potential false-positives owing to contamination
- Requires acute sample
- Doesn’t differentiate between primary and secondary infection
- Expensive

## Antigen detection
- **Confirmed infection**
- Easy to perform
- Less expensive
- Not as sensitive as virus isolation or RNA detection

## Serological tests
- **IgM or IgG seroconversion (paired samples)**
  - Confirmed infection
  - Least expensive
  - Easy to perform
  - Can differentiate between primary and secondary infection
  - IgM levels can be low in secondary infections
  - Confirmation requires two or more serum samples

- **IgM detection (single sample)**
  - Identifies probable cases
  - Useful for surveillance, tracking outbreaks and monitoring effectiveness of interventions
  - IgM levels can be low in secondary infections

## Medically Important Arboviruses

### Table 2: Medically Important Arboviruses

<table>
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<th>Virus</th>
<th>Vector</th>
<th>Host</th>
<th>Transmission cycle</th>
<th>Incubation period</th>
<th>Clinical syndrome</th>
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<td>Tick</td>
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<td>R; H2H</td>
<td>1–3 (1–9)</td>
<td>FD, HS, (NS)</td>
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<td>FD, AR, (NS)</td>
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<td>Family Genus</td>
<td>Virus</td>
<td>Vector</td>
<td>Host</td>
<td>Transmission cycle</td>
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<td>West Nile virus</td>
<td>Mosquito</td>
<td>Birds</td>
<td>R, U; H2H</td>
<td>3-5 (2-14)</td>
<td>FD, NS, (AR)</td>
<td></td>
</tr>
<tr>
<td>St. Louis encephalitis virus</td>
<td>Mosquito</td>
<td>Birds</td>
<td>R, U</td>
<td>2-21</td>
<td>FD, NS</td>
<td></td>
</tr>
<tr>
<td>Family Genus</td>
<td>Virus</td>
<td>Vector</td>
<td>Host</td>
<td>Transmission cycle</td>
<td>Incubation period</td>
<td>Clinical syndrome</td>
</tr>
<tr>
<td>--------------</td>
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<tr>
<td>Murray Valley virus</td>
<td>Mosquito</td>
<td>Ardeid birds</td>
<td>R</td>
<td>1-28</td>
<td>FD, NS</td>
<td></td>
</tr>
<tr>
<td>Kyasanur Forest disease virus</td>
<td>Tick</td>
<td>Small mammals, humans</td>
<td>R</td>
<td>3-8</td>
<td>FD, HS, conjunctivitis, pneumonia</td>
<td></td>
</tr>
<tr>
<td>Alkhurma hemorrhagic fever virus</td>
<td>Tick</td>
<td>Small mammals</td>
<td>R</td>
<td>3-12</td>
<td>FD, HS</td>
<td></td>
</tr>
<tr>
<td>Tick-borne encephalitis virus</td>
<td>Tick</td>
<td>Small mammals, birds</td>
<td>R; H2H</td>
<td>7-14</td>
<td>FD, NS, (HS)</td>
<td></td>
</tr>
<tr>
<td>Ilheus virus</td>
<td>Mosquito</td>
<td>Birds</td>
<td>R</td>
<td>Unknown</td>
<td>FD, NS</td>
<td></td>
</tr>
<tr>
<td>Yellow fever virus</td>
<td>Mosquito</td>
<td>Primates, humans</td>
<td>R, U; H2H</td>
<td>3-6</td>
<td>FD, HS, hepatitis</td>
<td></td>
</tr>
<tr>
<td>Zika virus</td>
<td>Mosquito</td>
<td>Primates, humans</td>
<td>R, U; H2H</td>
<td>3-12</td>
<td>FD, AR, NR, conjunctivitis, congenital syndrome</td>
<td></td>
</tr>
</tbody>
</table>

Reoviridea

Coltivirus | Colorado tick fever virus | Tick | Small mammals | R; H2H | 3-5 (0-20) | FD, NS, AR, HS |
Seadronivirus | Banna virus | Mosquito | Unknown | R | Unknown | FD, AR, NS |

Togaviridea

Alphaviruses | Barmah Forest virus | Mosquito | Birds, marsupials | R, U | 7-9 (5-2) | FD, AR |
<p>| Eastern equine encephalitis virus | Mosquito | Birds, small mammals, marsupials | R | 3-10 | FD, NS |
| Chikungunya virus | Mosquito | Primates, humans | R, U | 3-7 (1-12) | FD, AR, HS, NS, Conjunctivitis |</p>
<table>
<thead>
<tr>
<th>Family Genus</th>
<th>Virus</th>
<th>Vector</th>
<th>Host</th>
<th>Transmission cycle</th>
<th>Incubation period</th>
<th>Clinical syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mayaro virus</td>
<td>Mosquito</td>
<td>Primates</td>
<td>R, U</td>
<td>6–12 (3–12)</td>
<td>FD, AR, HS</td>
</tr>
<tr>
<td></td>
<td>O’Nyong Nyong virus</td>
<td>Mosquito</td>
<td>Primates, humans</td>
<td>R, U</td>
<td>&gt;8</td>
<td>FD, AR</td>
</tr>
<tr>
<td></td>
<td>Ross river virus</td>
<td>Mosquito</td>
<td>Marsupials, mammals</td>
<td>R, U</td>
<td>7–9 (3–21)</td>
<td>FD, AR, HS</td>
</tr>
<tr>
<td></td>
<td>Sindbis virus</td>
<td>Mosquito</td>
<td>Birds</td>
<td>R</td>
<td>1–7</td>
<td>FD, AR</td>
</tr>
<tr>
<td></td>
<td>Western equine encephalitis virus</td>
<td>Mosquito</td>
<td>Birds, small mammals</td>
<td>R</td>
<td>2–10</td>
<td>FD, NS</td>
</tr>
<tr>
<td></td>
<td>Venezuelan equine encephalitis virus</td>
<td>Mosquito</td>
<td>Small mammals</td>
<td>R</td>
<td>&lt;1–5</td>
<td>FD, NS</td>
</tr>
</tbody>
</table>

A. Clinical syndromes: FD = febrile disease; AR = atralgia/ rash; HS = haemorrhagic syndrome; NS = neurological syndrome; () = less frequent.

B. Transmission cycle: R = rural, U = urban; H2H = human transmission reported

(adapted from Cleton¹⁰)

LAST UPDATED BY ADMIN ON AUGUST 16TH, 2023

Dengue

Summary

- Up to 390 million infections annually, 500 thousand cases of severe dengue, with an estimated 36,000 deaths
- Vector: mosquitoes, Aedes species
- Flavivirus, 4 main serotypes (DEN 1-4)
- Infection with one serotype produces lifelong immunity against this serotype, but only short-lasting cross-protection against other serotypes.
- Main clinical presentations: fever, arthralgia-rash, hemorrhagic syndrome (FD, AR, HS)
- Plasma leakage is the hallmark of severe dengue
- WHO 2009 classification: Dengue and Severe Dengue (D/SD); Warning signs (WS) help clinicians identify cases in need of closer surveillance (dengue with warning signs [D +/- WS])
- No antiviral treatment is available at present, but mortality is greatly reduced by appropriate supportive treatment
- 2 Dengue vaccines are licensed: CYD-TDV (Dengvaxia®) should only be administrated to seronegative people, TAK-003 (Qdenga®) may be used in seropositive and seronegative individuals. Future efficacy and safety monitoring is warranted

**Virus**

Dengue viruses belong to the family of Flaviviridae (yellow viruses), genus *Flavivirus*. The virus has a positive sense single-stranded RNA genome. It is translated into a large precursor protein, which is then cleaved by host-cell and viral proteases into three structural and seven non-structural proteins (See Figure 5).
Dengue virus has 4 main serotypes. Infection with one serotype results in lifelong immunity to subsequent infection with that particular serotype (homologous immunity). There is no lasting cross-protection between the serotypes (heterologous immunity).

In 2013, a 5th serotype (DEN-5) was described, of which the clinical significance is not yet understood. Contrary to DEN 1-4, it has a sylvatic transmission cycle, which may hamper current dengue control efforts.

**Epidemiology and transmission**

Dengue prevalence increased over 15-fold over the last two decades, attributable to three principal drivers: urbanization, globalization and lack of effective mosquito control. Dengue viruses have fully adapted to a human-*Aedes aegypti*-human transmission cycle in large, crowded urban centers in the tropics. In rapidly developing suburbs, running tap water is often lacking, and people depend on fetching water in small reservoirs. Sewage systems are often open and are ideal breeding sites for mosquitoes. Increased mobilization with more car tires, together with a surge in the use of plastics, contributes to mosquito propagation since water containing mosquito larvae is co-transported.
International travel can transport the virus to new regions with little mosquito control. Transported rubber car tires and lucky bamboo plants have been shown to carry *Aedes spp.* larvae.

Dengue virus infects an estimated 300-530 million cases annually, of which almost 100 million manifest clinically. The estimated annual death rate of 36,000 deaths due to dengue virus is relatively low, but high numbers of less sick dengue patients can overburden health structures. Dengue occurs in 129 countries and 70 percent of the burden is in Asia. As with other arboviruses, the geographic distribution of dengue is determined by the distribution of its vectors (See Figure 6). The main reservoir of the dengue serotypes 1-4 is probably man.

Figure 6: Probability of dengue occurrence (Bhatt et al, Nature)

The bite of infected female *Aedes* mosquitoes transmits dengue. The virus develops a life-long non-cytocidal infection in the mosquito. It may infect the mosquito ovaries and offspring (transovarial transmission). *Aedes* eggs can withstand dehydration for several months, and eggs of some *Aedes* species survive for several years. This cycle can be repeated for multiple generations and drive new outbreaks. It takes at least one week from the egg’s hatching to the mosquito’s adult stage. This is essential information for understanding the “dry day” principle (see below). Infection of humans occurs when dengue virus is introduced into the skin via the insect’s saliva during a bite of female mosquitoes. *Aedes albopictus* is a less competent vector for dengue virus but survives in a more temperate climate. Global warming might therefore increase the population at risk for dengue.

Dengue transmission follows two patterns that are not mutually exclusive. “Epidemic” dengue occurs
when a single virus strain is introduced into a new region. Adults and children are affected, but dengue hemorrhagic fever is rare. In “hyperendemic” dengue, there is continuous circulation of multiple dengue serotypes. Seasonal variation is common and urban areas are particularly affected. Children are more at risk than adults, with a higher risk of dengue hemorrhagic fever.

**Clinical aspects**

Three-quarters of the estimated 390 million dengue virus (DENV) infections annually are clinically unapparent. These asymptomatic cases have the potential to contribute significantly more to virus transmission to mosquitoes than previously recognized, as high levels of viremia have been detected in infected people who do not have an interruption of their daily routine and who continue to have exposure to the virus’ vectors.

Symptomatic dengue infection begins with a sudden onset of a flu-like syndrome. The febrile phase lasts 2-7 days, and the fever is biphasic (saddleback fever) in 5 percent of cases. Skin rash, headache, myalgia and arthralgia are frequent symptoms. The rash may have a dengue-specific appearance of “white isles in a red sea” (Figure), but this finding has low sensitivity (up to 20%).
There may be marked muscle pain (breakbone fever), especially in the back and in the extraocular eye muscles (pain around and behind the eyes when looking sideways).

According to the 2009 WHO guidelines for diagnosis, treatment, prevention and control of dengue, a positive tourniquet test (aka. Rumpel-Leede or capillary fragility test) increases the probability of dengue in acute febrile illness. The sphygmomanometer is inflated around the upper arm to mid-systolic blood pressure. After the cuff is left in place for 5 minutes, more than 20 petechiae in a 3 cm diameter circle in the crease of the elbow indicate a positive test. Recent literature suggests that the tourniquet test is more effective in detecting true negative than true positive cases, and the test should not be used for diagnosing dengue.
Severe dengue

Severe dengue may be rapidly fatal and usually results from a second dengue infection more than 18 months after a resolved first infection. An estimated 500,000 people with severe dengue require hospitalization each year, a large proportion of whom are children.

Complications may develop after 3 to 5 days when the first fever subsides (defervescence), and endothelial dysfunction may lead to hemoconcentration. Patients may develop hemorrhage, ranging from petechiae, ecchymosis and purpura to overt bleeding from mucosal surfaces (epistaxis, melena), injection sites and cerebrovascular accidents. They may develop shock with plasma leakage; pleural or pericardial effusion or ascites can be observed by ultrasonography. Detection of an oedematous gallbladder wall by serial ultrasonography identifies patients at risk for developing severe dengue.

Prediction of severe dengue remains challenging, mainly because the determinants of a complicated course of dengue virus infection are poorly understood. Severe dengue was observed to occur more frequently in secondary dengue infections. In 1977, this led to the development of the concept of ‘Antibody-Dependent Enhancement (ADE). Secondary dengue infections were found to be correlated with higher levels of viremia. A molecular model to support the ADE hypothesis was described by Dejnirattisai et al. Briefly: Dengue infection leads to the development of homologous neutralizing and protective antibodies. Upon subsequent infection with a different serotype, these antibodies may enhance the replication of even immature virus particles. This results in higher levels of viremia (replication of both mature and immature virions), thereby increasing the release of pro-inflammatory cytokines and, thus, the severity of the disease.

The prevailing dengue serotype may be a determinant of severe dengue. This should probably also be evaluated against existing population immunity to previous dengue serotypes. In a recent meta-analysis, Soo et al. compared the percentage of severe cases of both primary and secondary infections with different serotypes of dengue virus. They found that the presence of certain serotypes, including primary infection with DENV-3 from the SEA region and secondary infection with DENV-2, DENV-3, and DENV-4 also from the SEA region, as well as DENV-2 and DENV-3 from non-SEA regions, increased the risk of severe dengue infections.

Apart from the fever, rash, arthralgia, hemorrhage and symptoms related to the plasma leakage syndrome, additional manifestations of dengue infection are described:

- Liver failure, which is caused by hypoperfusion or hypoxia rather than direct viral liver damage
- Neurological symptoms such as encephalopathy and seizures
Cardiac manifestations, including myocarditis, arrhythmias and heart failure
Secondary hemophagocytic lymphohistiocytosis

There is no specific treatment for dengue or severe dengue, but early detection and access to proper medical care lowers fatality rates below 1%. To facilitate the clinical management of patients with dengue virus infections, a new classification system was introduced by the WHO in 2009.

**WHO dengue classification**

Recognizing severe dengue remains a challenge for the clinician. In 2009, WHO adopted a new classification of symptomatic dengue infections i.e., dengue with or without warning signs (WS +/-). While the performance of the triage based on the presence of warning signs (WS) need further validation across different clinical settings, this practical classification helps clinicians identify those patients in need of closer surveillance and/or hospitalization. Dengue warning signs include spontaneous or provoked bleeding, severe abdominal pain, persistent vomiting, painful hepatomegaly, dyspnoea, lethargy and effusions (see Figure 8). Severe dengue is defined by the occurrence of plasma leakage and or fluid accumulation leading to shock or respiratory distress, and/or severe bleeding, and/or severe organ impairment.

The former WHO classification (1975, revised in 1997) was derived from a pediatric population. It
identified Dengue fever, dengue hemorrhagic fever and dengue shock syndrome (DF/ DHF/ DSS). It was used to classify disease severity for surveillance purposes. The main criticisms are summarized below:

1. poorly related to disease severity
2. misdirecting clinicians in identifying severe disease
3. difficult to use (tests required are often not available/difficult to apply)
4. does not help for triage in outbreaks
5. leads to different reporting globally due to the difficulties in using the classification for reporting clinicians.

Further comparison of the usefulness of the 1997 and 2009 WHO Dengue Case Classifications can be found in recent publications.

**Diagnosis**

(see also the section: Laboratory diagnosis of arboviral infections).

Common hematological abnormalities include leukopenia and thrombocytopenia. Both are poor predictors of disease severity. Increased hematocrit (≥20% increase) indicates severe disease since it can point towards plasma leakage syndrome and evolution to shock syndrome.

Biochemical abnormalities correlate with disease severity and organ failure. Increased transaminase levels and hypoproteinemia are observed in severe dengue. Proteinuria, where proteins as large as albumin are lost, occurs and is consistent with disruption in the function of the endothelial glycocalyx layer. Hyperferritinemia in dengue-infected patients is associated with immune activation and coagulation disturbances and may reflect macrophage activation.

Patients with dengue or other febrile illness usually seek medical attention within several days of fever onset. Documenting the day of symptom onset (day 0) is essential to choose a single specimen diagnostic approach. DENV viremia occurs 3–5 days before fever onset and continues for approximately 5 days into the febrile illness. Viremia can be detected by molecular assays targeting DENV RNA (such as RT-PCR) or by immunoassays targeting DENV nonstructural protein 1 (NS1) antigen. An anti-DENV IgM response becomes detectable by IgM-capture immunoassays (Enzyme-Linked Immuno Sorbent Assay (ELISA) or Immune Fluorescence Assays (IFA)) 3–5 days after onset of fever. IgM levels peak 6-10 days after fever onset and may persist for up to 90 days. IgG antibodies can be detected from day 7 onwards and may persist for life. Anti-dengue IgG-antibodies may
increase sooner in the event of secondary dengue infection. In view of these kinetics, laboratory diagnostic tests in a patient with suspected dengue infection should consider the day of symptom onset (Figure 9).

Flaviviruses share antigenic epitopes, which elicit cross-reacting antibodies. This cross-reactivity may result in false positive test results. To identify false positive test results or confirm true positives, virus neutralization tests can be performed. Because of the costs and technical expertise required, the use of these tests is mainly restricted to reference laboratories.
**Treatment**

No antiviral compounds are available for the treatment of dengue virus infections. Corticosteroids are not effective.

Most cases can be treated on an outpatient basis. Symptomatic treatment should avoid aspirin and NSAIDs (risk of bleeding), but paracetamol can be used. The patient or the parents of the sick child should be counseled on dengue complications. In-patient care is required if warning signs appear as these may predict severe dengue to occur on days 4-7 after symptom onset.

In the case of warning signs, isotonic crystalloid fluids such as Ringer’s lactate should be used to restore circulating blood volume. Fluid resuscitation requires observation in intensive care units. When the endothelial function recovers, fluid overload may cause iatrogenic complications. In patients with severe dengue infection, adjuvant therapy, including vasopressor and inotropic therapies, renal-replacement therapy and further treatment of organ impairment may be necessary.

Blood transfusion and fresh frozen plasma are sometimes required to treat severe bleeding. In case of massive bleeding, platelet transfusion may be needed in addition to packet cell transfusion. Platelet transfusion is warranted in patients with a platelet count <10.000/µl and active bleeding, but there is no benefit in prophylactic platelet transfusion without active bleeding.

**Prevention**

**Personal protection**

Contact with *Aedes* mosquitoes can be reduced using insect repellents. Sleeping at night under a bed net does not give any protection against *Aedes* sp. that bite during the day but can be useful for e. g., children sleeping during the day.

**Vaccination**

Immunity to dengue virus infections is complex, as is the development of dengue vaccines. As discussed under the section ‘Severe dengue’, dengue infection with one serotype leads to the development of lasting homologous neutralizing and protective antibodies, but it induces only short-term immunity against other (heterologous) serotypes. Because of antibody-dependent enhancement (ADE), infection with a second serotype may lead to more severe illness. Hence there is concern over increasing the risk of severe dengue by vaccination. After infection with 2 different serotypes, broad
immunity is observed.

Chimeric Yellow Fever-Dengue-Tetravalent Dengue Vaccine or CYD-TDV (Denvaxia®) is a tetravalent, live attenuated, chimeric vaccine and combines four chimeric yellow fever 17D-dengue vaccine viruses, where the premembrane and envelope proteins from each of the four DENV types replace the same proteins in a yellow fever 17D backbone virus. Three doses at months 0, 6 and 12 are administered. CYD-TDV is now used in about 20 countries in Latin America and Southeast Asia as part of their dengue control program after a study had shown an 80.3% efficacy against hospitalization and a 56.5 – 60.8% efficacy in contracting dengue disease in children. An additional analysis with retrospective determination of serostatus at the time of vaccination showed that children that were seronegative at the time of the first vaccination had a higher risk of developing severe dengue. Vaccination is therefore limited to people living in endemic areas ranging from 9-45 years of age who have had at least 1 documented dengue virus infection previously. This pre-vaccination screening for past dengue disease complicates the rollout of this vaccine in many low-resource settings.

TAK-003 (Qdenga®) is a tetravalent live attenuated DENV-2 virus with chimeras replacing the premembrane- and envelop genes of the DENV-2 with those from wild-type DENV-1, DENV-3 and DENV-4 strains. Two doses at months 0 and 3 are administered. The overall vaccine efficacy in children and adolescents 4 to 16 years of age was 80.9 % and 73.3 % at 12 and 18 months of follow-up, respectively. There was a 90.4 % efficacy against hospitalization for dengue. The vaccine efficacy was slightly higher among the baseline seropositive than baseline seronegative, without increased risk of severe dengue. Since DENV-2 was the backbone of TAK-003, efficacy was highest against DENV-2. There was no efficacy against DENV-3, and data were insufficient to evaluate efficacy against DENV-4.

Vector control

See general section.

LAST UPDATED BY ADMIN ON OCTOBER 6TH, 2023

Chikungunya
Summary

- Togavirus family, genus alphavirus
- Vector: mosquito, Aedes species
- Main clinical presentation: arthralgia/ rash, febrile disease (AR, FD), frequently post-Chikungunya rheumatic syndrome

Virus

Chikungunya virus (CHIKV) is a single-strand RNA virus of positive polarity; its genome encodes 4 non-structural (nsP1-4) and three structural proteins (C, E1, E2). Phylogenetically, there are 3 distinct genotypes: the West African, the Asian and the Eastern-Central-South African genotype.

Figure: Structure of Chikungunya virus (Weaver et al, NEJM)
Transmission

Chikungunya virus was isolated during an epidemic in Tanzania in 1952 from both patients and mosquitoes. It has since been isolated frequently from humans and mosquitoes in tropical Africa, India and Southeast Asia, where large epidemics occur from time to time. Non-human reservoir species have not been identified unequivocally. Both Aedes aegypti and A. albopictus are vectors.

In 2004, there was an outbreak of Chikungunya fever in Kenya. The next year it reached the Comores. In 2005-6, outbreaks followed in Reunion (with 265,000 clinical cases out of a population of 770,000), Mauritius, Madagascar and other islands in the Indian Ocean. In Reunion, mortality was 237 deaths, about 1 per 1000 clinical cases. A single mutation (A236V) was identified in chikungunya virus strains in the 2005-2006 Reunion Island outbreak, that facilitated transmission by the Asian tiger mosquito (A. albopictus). CHIKV was capable of spreading via travellers, as was witnessed in July 2007, when about 160 people in Ravenna province, Italy fell ill. This was the first example of Chikungunya transmission via exotic mosquitoes (Aedes albopictus) outside the tropics.
Contrary to expectations and reports of introduction of so-called Indian Ocean Lineage of the ECSA genotype by travellers into the Americas, it was an Asian-lineage Chikungunya virus strain that caused a major epidemic in the Americas. The strain was introduced into the island of St. Martin in October 2013.

**Clinical aspects**

The clinical picture resembles that of classic dengue fever with which chikungunya fever is often confused. After a brief incubation period of 2 to 5 days, there is sudden onset of fever followed by crippling joint pains that may temporarily incapacitate the patient. In the Makonde language, “chikungunya” means “doubled up; that which bends up”, referring to this important arthralgia. Conjunctivitis and skin rash are common. Arthralgias occur in around 70 percent of cases and can persist for weeks to months. If no complications ensue, recovery takes 5 to 7 days. New severe clinical forms were reported in Reunion, including cases caused by peripartum mother-to-infant transmission. Rare complications include meningoencephalitis (also in newborns) and probably hepatic failure (possible role of high doses of acetaminophen). Common hematologic abnormalities in the acute phase include lymphopenia and thrombocytopenia that may lead to bleeding. Hepatic enzymes are commonly increased.

Chronic joint pains can be persistent or relapsing. These arthralgias are located mostly in the distal joints and may be associated with arthritis and may mimic rheumatoid arthritis (chronic inflammatory, erosive, and rarely deforming polyarthritis) in up to 50% of patients.

**Diagnosis**

Diagnosis in endemic areas is clinical, although it is very difficult to discriminate from co-circulating arboviral infections. A definitive diagnosis relies on virus detection through reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing during the viraemic phase (the first week). RT-PCR can be designed in a multiplex format to simultaneously detect several other arboviruses, such as dengue virus, which can be very useful for triage of patients. Chikungunya virus culture in a variety of cells permits further virologic characterization but has no added value over RT-PCR in clinical practice and is not performed routinely.

Sero-diagnosis is facilitated by the limited antigenic diversity of chikungunya virus and extensive cross-reactivity of the antibodies induced by different strains. Serum IgM is detectable from day 5 (and even earlier) to several months after the onset of illness and is also considered diagnostic. Seroconversion can also be detected as a fourfold increase in IgG between acute-phase and
convalescent-phase serum samples.

Figure: Chikungunya diagnostics in relation to kinetics of viremia and antibody response (Johnson et al, J Infect Dis)

**Treatment**

Treatment is symptomatic. Post-chikungunya rheumatism may require long-term treatment with nonsteroidal anti-inflammatory drugs or Disease Modifying Anti Rheumatic Drugs (DMARDs) such as methotrexate, although their safety and efficacy also have yet to be demonstrated in clinical trials.

LAST UPDATED BY ADMIN ON JULY 14TH, 2022

**Zika virus**
Summary

- Flavivirus, belongs to Spondweni serogroup
- Vector: mosquito, Aedes species; human to human transmission occurs (sexually)
- Main clinical presentation: Artralgia/ rash, Febrile disease, neurological syndrome (AR, FD, NS), conjunctivitis, congenital syndrome
- WHO declared the Zika virus epidemic in the Americas a Public Health Emergency of International Concern (PHEIC), because of its association with microcephaly and other neurodevelopmental disorders

Virus

Zika virus (ZIKV) is a member of the virus family Flaviviridae, genus Flavivirus. It is a 40-nm virus and has icosahedral symmetry. ZIKV has a non-segmented, single-stranded, positive sense RNA genome.

Transmission

Prior to the 2007 outbreak in the Yap islands (Micronesia), no outbreaks and only 14 cases of human ZIKV disease had been recorded, although sero-surveillance studies in Africa had already indicated anti-ZIKV antibody presence of ca. 6% in some populations. The Yap outbreak indicated that the virus could now spread in human communities and establish a so-called urban transmission cycle. The biggest epidemic occurred in 2015-2017 in the Americas with spread to several countries in Asia. In 2016 the incidence peaked in the Americas and declined substantially throughout 2017 and 2018 probably due to herd immunity. In 2020, a total of 87 countries have had evidence of autochthonous transmission of Zika virus.

The reservoir of ZIKV are primates, both human and non-human. The virus is primarily transmitted by mosquitoes from the genus Aedes, most commonly Aedes aegypti. However sexual transmission of the virus (male to female, male to male, female to male) from symptomatic or asymptomatic persons is now well established. Uncertainty remains over the duration of infectivity of one person.

Table 4 A brief history of Zika virus infections

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1947</td>
<td>ZIKV was first detected from rhesus monkey in Uganda.</td>
</tr>
<tr>
<td>1952</td>
<td>First human case has been identified in Uganda.</td>
</tr>
<tr>
<td>1968</td>
<td>ZIKV has been reported from Nigeria.</td>
</tr>
<tr>
<td>Year</td>
<td>Event</td>
</tr>
<tr>
<td>----------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>1951-1981</td>
<td>Incidences of this virus have been reported from various countries of Asia and Africa.</td>
</tr>
<tr>
<td>2007</td>
<td>The first outbreak was reported in Yap Islands, part of the Federated States of Micronesia. Prior to this event, no outbreaks and only 14 cases of human Zika virus disease had been documented worldwide. Zika virus infection is estimated to be asymptomatic in 80% of cases.</td>
</tr>
<tr>
<td>2012-2014</td>
<td>Cases have been reported from Thailand.</td>
</tr>
<tr>
<td>2013</td>
<td>The virus spread to French Polynesia with an estimated 28,000 cases. ZIKV rapidly spreads to the Cook Islands and Easter Island. An association of Zika virus with Guillain Barré Syndrome is observed.</td>
</tr>
<tr>
<td>2015</td>
<td>Zika virus infection was first diagnosed in Brazil. It was found to be associated with microcephaly in the infants of mothers with suspected ZIKV infection.</td>
</tr>
<tr>
<td>February 2016</td>
<td>WHO declares the Zika virus epidemic in the Americas a Public Health Emergency of International Concern (PHEIC) because of its association with microcephaly and other neurodevelopmental disorders.</td>
</tr>
<tr>
<td>2015-2017</td>
<td>Epidemic in the Americas with 500,000 symptomatic cases reported at the peak of the pandemic in 2016</td>
</tr>
</tbody>
</table>
Figure: Important transmission routes of Zika virus (Blázquez A-B et al, World J Virol)
Clinical aspects

Symptomatic ZIKV infections

After a mosquito bite, the incubation period is 3-12 days, with a mean of 5.9 days (95% credible interval, CrI: 4.4–7.6), and 95% of people who developed symptoms doing so within 11.2 days (95% CrI: 7.6–18.0) after infection. Approximately 20% of patients are symptomatic. They can present with acute onset of low-grade fever with maculopapular rash, arthralgia or non-purulent conjunctivitis. These symptoms feature in the (E)CDC case definition. Other commonly reported clinical manifestations are lymphadenopathy and ulcers on the mucous membrane are less common. Thrombocytopenia, palatal petechiae, and uveitis have been reported. In adults, ZIKV infection generally produces very mild disease. Infants and young children may present with irritability, walking with a limp, difficulty moving an extremity. There may be pain on palpation, or pain with active or passive movement of the affected joint.
Guillain Barré syndrome

Guillain-Barré Syndrome (GBS) is a post-infectious peripheral autoimmune neuropathy, characterized by progressive weakness of the limbs and absent or depressed deep tendon reflexes and cytoalbuminologic dissociation in cerebrospinal fluid (CSF) examination. Several electro-myographic (EMG) types exist. Up to 25% of those affected may require mechanical ventilation. Mortality is estimated at 3-5%. Global incidence of GBS varies from 0.8-1.9/ 100,000.

The incidence of ZIKV-associated GBS is estimated to be 2 tot 3 cases per 10,000 ZIKV infections. The median time before onset of neurological symptoms was 6 days.

Neurodevelopmental disorders

The most disconcerting finding is the association of ZIKV infection with neurodevelopmental disorders. Health care personnel and authorities in Brazil observed a sharp increase in the number of neonates born with congenital microcephaly and found an epidemiological association with the ZIKV epidemic which hit Brazil early in 2015.

![Graph showing the number of cases of different diseases over time](source: Data published by the Pernambuco State Secretary of Health, Brazil.)
Microcephaly is defined as Head Circumference (HC) at birth less than the 3rd percentile for gestational age and sex.

Maternal-fetal ZIKV transmission can occur in all trimesters of pregnancy. There is no suggestion that pregnant women are more susceptible to ZIKV infection and there is no evidence of greater severity of this infection during pregnancy.

20-30% of foetuses and neonates will become infected when mothers are infected during pregnancy. This will lead to foetal loss in 14%, to congenital Zika syndrome in 21% with microcephaly in about half the cases. 80-90% of all foetuses exposed to Zika (not necessarily vertically infected) will be asymptomatic during the first weeks of life. Follow-up is needed to know whether longer term sequelae (learning difficulties, ...) in this last group will occur. Not just the brain that is affected in the congenital zika syndrome: infants from ZIKV infected mothers frequently show retinal defects, such as chorioretinal atrophy surrounded by a hyperpigmented halo and hyperpigmented mottling. Hence, the
neurodevelopmental disorders observed in neonates and children after ZIKV infection of the mother can be referred to as Zika virus congenital syndrome.

**Significance of asymptomatic ZIKV infections and sexual transmission**

At present, approximately 80% of ZIKV infected patients are thought to have no clinical manifestations of infection. In areas where suitable mosquito vectors are present, these patients will add to the reservoir and fuel the epidemic. It is estimated that 1% of ZIKV infections reported in Europe and the United States were acquired through sexual transmission. ZIKV RNA is detected up to 3±0 days after onset of symptoms, but shedding of infective virus is unlikely to occur after 30 days from the onset of illness.

**Diagnosis**

Laboratory diagnosis is needed to confirm the diagnosis of ZIKV infection.

Specific laboratory diagnosis is based on detection of viral RNA from clinical specimens by RT-PCR. The window of detection in blood samples is a period of 1–5 days after the start of symptoms. However, the sensitivity of RT-PCR is estimated to be 40%. Because of the longer persistence of the virus in urine, RT-PCR on urine can be attempted up to the 15th day after the start of symptoms. Seroconversion (detection of anti-ZIKV IgM antibodies) is thought to occur from the 4th day after infection and IgG a little later. Seroconversion occurs on average at 9 days and 95% by 14 days.
As with other serological tests for flavivirus infections, cross-reactivity of ZIKV antibody detection assays can yield false positive results; in endemic areas this may be a significant problem, because of possible simultaneous or previous circulation of other flaviviruses. Virus neutralization tests can be used to increase specificity.

### Treatment

#### General

There is no specific antiviral treatment for treating ZIKV. Antipyretics or analgesics can be used for symptom relief. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should not be used until dengue has been ruled out. NSAIDs should not be used in pregnant women beyond the 32nd week of gestation because of the risk of early closure of the arterial duct.

#### Management of pregnant women

Current CDC recommendations for the management of pregnant women with ZIKV infection include:
• Use of serial ultrasound examinations.
• In case of a confirmed diagnosis of fetal microcephaly, amniocentesis should be considered from the 15th week of pregnancy onwards.

Management of microcephaly/ ZIKV congenital syndrome

There is no specific treatment for microcephaly. Microcephaly may be accompanied by epilepsy, cerebral palsy, delayed cognitive, motor and speech development and hearing and eyesight problems. Since each child develops complications of different type and severity (eg. respiratory, neurological and motor problems), follow-up by specialists in different fields is warranted.

Guillain Barré Syndrome

Treatment of GBS in the acute phase consists of immunotherapy, such as plasmapheresis or application of human immunoglobulin (IVIG, dose: 400 mg/ kg of body weight per day, for a period of 5 days). IVIG is relatively simple to administer, however expensive and can be difficult to obtain. The best results of IVIG or plasmapheresis are obtained when it is started within the first 2 weeks after the onset of neurological symptoms. Use of corticosteroids as a stand-alone treatment does not accelerate the recovery or alter the long-term result.

Prevention

A vaccine is not yet available.

LAST UPDATED BY ADMIN ON JULY 14TH, 2022

Yellow fever

Summary

• Flavivirus, prototype
• Zoonosis
• Endemic and epidemics in Africa, South America.
• Vector: mosquito, Aedes species
• Main clinical presentations: Fever, haemorrhagic syndrome (FD, HS), hepatitis
Effective vaccine available

**Virus**

The Yellow Fever virus (YFV) is the prototype virus of the family Flaviviridae, a group that also includes the epidemic arthropod-borne viruses causing dengue, Japanese encephalitis (JE), and Zika. It is an enveloped positive-sense, single-stranded RNA virus. The genome presents a single open reading frame encoding a polyprotein. Host proteases cut this polyprotein into 3 structural (C, prM, E) and 7 nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5).

**Transmission**

Yellow fever is a zoonosis, caused by infection with Yellow Fever Virus (YFV). Yellow fever causes 200,000 infections and 30,000 deaths every year with nearly 90% of these occurring in Africa. It is endemic to large parts of Africa and South America. Its vectors are mosquitoes belonging to the Aedes genus. YFV maintains a sylvatic cycle mosquito-monkey-mosquito. In monkeys, viraemia lasts 2-9 days. African monkeys do not die from the infection. Once infected African monkeys develop a lifelong immunity. In South American monkeys, the infection is often fatal. Sometimes large numbers of animals die.

Humans can be infected when they enter this biotope during the day, resulting in sporadic cases of yellow fever (sylvatic or ‘jungle’ transmission). Upon returning in their communities, infected persons may infect peridomestically living Aedes mosquitoes (notably Aedes aegypti). Subsequent transmission by peridomestic mosquitoes can take on epidemic proportions (epidemic or urban yellow fever).

Large outbreaks occurred Ethiopia (1960-62, 30,000 to 100,000 deaths), Senegal (1965, 2000 to 20,000 cases), Nigeria (1969, 1986 and 1988-1990), Uganda (2010), and Sudan (2003, 2005, 2012-2013) and Ethiopia (2012–2013). In 2016, Angola suffered an outbreak of yellow fever. Authorities have reported at least 3,867 suspected and confirmed cases nationally, including 369 deaths. There are frequently small outbreaks. The southern part and the east coast of Africa are relatively free of the disease. In South America, recent outbreaks affected southern Brazil, Paraguay and Argentina (2007-2009).

Early 2016, sporadic yellow fever cases were introduced into China from Angola, where a large Chinese workforce is present. Since suitable vector species are also widespread in Asia, the prospect of sustained introduction of viraemic travellers raises the possibility of a yellow fever epidemic in Asia.
Urban yellow fever transmission in an unimmunized population is a major public health concern.

In order to prevent yellow fever from being imported, many countries where yellow fever does not occur require proof of vaccination following a recent visit to an endemic country.

**Clinical features**

Yellow fever begins after an incubation period of 3–6 days. It presents as a flu-like syndrome, with fever, chills, headache, backache, muscle aches, fatigue and vomiting. This phase lasts 3-4 days. A second febrile episode develops in 15% of infected persons (biphasic fever), characterised by mild jaundice (yellow or toxic phase). Liver (transaminases up to 15,000-40,000 IU/l) and kidney failure occurs. There is no splenomegaly. The patient’s general condition then deteriorates dramatically, with haemorrhaging (skin, mucosa, uterus, intestines), hypotension and shock. Gastric bleeding (“Vomito Negro”) is an indication of an extremely poor prognosis. There is considerable kidney involvement (proteinuria, oliguria). There is no real encephalitis but neurological signs such as convulsions can occur due to cerebral bleeding as well as hepatic encephalopathy.

Death occurs mainly between 7-10 days. If the patient survives after 12 days, complete recovery can be expected. Surviving the infection results in lifelong immunity and normally there is no permanent organ damage.

The toxic phase is fatal in 20 – 50 % of cases, resulting in an overall fatality rate for yellow fever of 3.0 to 7.5 %. Case fatality appears lower in Africa (20%) than in South America (40–60%); this suggests that genetic factors determine lethality of the infection.

The differential diagnosis of any case of fulminating hepatitis in an endemic area should include yellow fever, particularly if there is haemorrhaging and kidney involvement. If confirmed, the authorities must be made aware of it and the WHO notified.

**Diagnosis**

A presumptive diagnosis of yellow fever is often based on the patient’s clinical features, places and dates of travel (if the patient is from a non-endemic country or area), activities, and epidemiologic history of the location where the presumed infection occurred.

Laboratory diagnosis of YFV faces several challenges, such as a lack of commercial test kits, a lack of biosafety level 3 (BSL3) laboratories for virus isolation and the presence of serological cross-reactivity
with other flavivirus infections. Current WHO recommendations for laboratory confirmation of YFV entail testing for specific IgM antibodies and/or a \( \geq 4 \)-fold increase in the specific serum IgG level when other flaviviruses are ruled out.

Antibody detection assays (IgM antibody capture by enzyme-linked immunosorbent assay (MAC-ELISA), hemagglutination inhibition (HI), complement fixation (CF) and virus neutralization tests (VNT)) can be used for the diagnosis of YFV. However, anti-YFV IgM is detectable only from 5 days after the onset of symptoms, when the severity increases. There is cross-reactivity with other flaviviruses.

Yellow fever may be diagnosed on samples obtained during acute illness by the isolation of the virus in mosquito cell lines or by genome detection through PCR-based methods. A negative test result does not rule out infection.

Antigen detection: Antigen detection is only positive in serum during the first 3 days of illness. Monoclonal antibody-based antigen detection by ELISA are being developed, but they are currently not commercially available. Immunohistochemical detection of YFV antigen is performed on tissues in reference laboratories for post-hoc diagnosis.

**Treatment**

No anti-viral treatment is available for the treatment of YFV infection. Ribavirin reduced mortality and hepatocellular dysfunction in a hamster model, but was not effective in non-human primates.

Supportive treatment reduces mortality. This requires hospitalization and close monitoring of vital functions and fluid balance. Hypotension, hypoxaemia and hypoglycaemia must be prevented or corrected.

Kidney failure often has a combined aetiology here. Pre-renal failure can be corrected by giving fluid. Renal replacement therapy might be indicated for patients with acute tubular necrosis.

**Prevention**

There are 3 main strategies for preventing Yellow Fever virus infections.

1. Vaccination
2. Isolation of patients
3. Vector control

**Vaccination**

There is a very efficient vaccine. This consists of a live attenuated virus (17D strain). It is cultured on embryonated chicken eggs and is stored in freeze-dried form. After adding solvent the reconstituted vaccine is administered subcutaneously. A single vaccination offers lifelong protection in immunocompetent persons from 10 days after the injection. In rare cases post-vaccination encephalitis has been reported in babies (younger than 4 months) and the vaccine is therefore not recommended for children under 9 months of age. Other contra-indications to vaccination are pregnancy (except during a yellow fever outbreak); severe allergies to egg protein; and people with severe immunodeficiency.

Routine vaccination is part of the Extended Programme of Immunisation (EPI) of in number of endemic African countries. In the event of an epidemic vector control and a mass vaccination campaign is essential. The WHO keeps a special stock of yellow fever vaccine available to combat epidemics. During an big Yellow Fever outbreak in 2016, millions of people were vaccinated and there was a threat for an international stock rupture. WHO authorized the us of fractional dose (one-fifth the usual dose) during the outbreak. A follow-up study showed that 98% of people had developed sufficient antibodies.

**Isolation**

During outbreaks; patients should be isolated in mosquito-free rooms. Medical staff should take personal protective measures: blood and body fluids of patients are infectious during the first few days. Staff and family members must be vaccinated. Suspected cases should be held in quarantine for the duration of the maximum incubation period, which is 6 days.

**Vector control**

Vector control efforts should target both peridomestic and sylvatic vectors: improving basic sanitation, improving the water supply and destroying breeding grounds. Sylvatic vectors have to be combated with appropriate agents.
Japanese encephalitis

Summary

- Flavivirus, belongs to JEV serogroup
- Vector: mosquito, Culex species
- Main clinical presentation: Febrile disease, neurological syndrome (FD, NS)
- Vaccine available.

Virus

JEV is the prototype virus of the JE serogroup Flaviviruses, which also includes several medically important etiological agents of encephalitis (see below). Taxonomically, JEV is closely related to other clinically important flaviviruses, including yellow fever virus (YFV), dengue virus, and tick-borne encephalitis virus. Like all flaviviruses, JEV is a small enveloped virus, with a single-stranded positive-sense RNA genome. The genome encodes a single long open reading frame (ORF) flanked by 2 short non-coding regions (NCRs) at the 5’ and 3’ ends.

The Japanese encephalitis serological group of flaviviruses counts 8 virus species and 2 subtype viruses with an extensive geographic distribution (Figure 11):

- Japanese encephalitis virus (JEV) in South-east Asia, Papua New Guinea and the Torres Strait of northern Australia.

- West Nile virus (WNV) in Africa, southern and central Europe, India, the Middle East and North America.

- Kunjin virus (a subtype of WNV) in Australia and Papua New Guinea.

- Murray Valley encephalitis virus (MVEV) in Australia, Papua New Guinea and the western Indonesian archipelago.

- St. Louis encephalitis virus (SLEV) in North and South America.

Other minor members of the group are Usutu (USUV), Koutango and Yaounde viruses in Africa; Cacipacore virus in South America; and Alfuy, a subtype of MVEV, in Australia. Most members have
Avian vertebrate hosts and are vectored primarily by Culex spp. mosquitoes.

Figure 11 Global distribution of Japanese Encephalitis serogroup flaviviruses (Mackenzie et al, Nat Med)

**Transmission**

JEV is the most important cause of viral encephalitis SEA, with 30,000–50,000 cases reported annually, although this may be a considerable underestimate because of inadequate surveillance and reporting. JEV is amplified in an enzootic cycle that involves mosquito vectors (mainly Culex species) and vertebrate hosts (primarily pigs and birds) (Figure 12). JEV is occasionally transmitted to dead-end hosts, such as humans and horses.
Clinical features

The incubation period for JEV is 5-15 days. Most infections remain asymptomatic, with estimates of the ratio of symptomatic to asymptomatic infection from 1 in 25 or lower. Sero-surveys in JEV endemic areas have shown that the majority of adults have been exposed to JEV. As with other flaviviruses, the determinants of clinical disease manifestation are ill understood, but are likely to include endemicity, exposure to mosquitoes, pre-existing antibodies to flaviviruses and virus strain differences. Clinical disease often starts with unspecific febrile illness. In neuroinvasive JEV infections, patients usually seek consultation a couple of days after a prodromal syndrome, when meningeal irritation, headache, stupor, coma and convulsions occur. Classical description of Japanese encephalitis includes a Parkinsonian syndrome with a mask-like face, wide unblinking eyes, tremor, generalized hypertonia, cogwheel rigidity and other abnormalities of movement. Along with upper motor neuron signs, cerebellar signs and cranial nerve palsies may occur. Paralysis of the upper extremities is more common than that of the legs. Persistent motor deficits are common (30%), as are severe cognitive and language impairment (20%).
When performing lumbar puncture, CSF opening pressure is increased in about 50% of patients. High pressures (>250 mm) are associated with a poor outcome. Typically, there is a moderate CSF pleocytosis (10–100 cells/mm3), with predominant lymphocytes, mildly increased protein (50–200 mg%) and a normal glucose ratio. However, polymorphonuclear cells may predominate early in the disease, or there may be no CSF pleocytosis.

In about 50% of patients CT shows bilateral non-enhancing low-density areas in one or more of the thalamus, basal ganglia, midbrain, pons and medulla. Magnetic resonance imaging is more sensitive, typically demonstrating more extensive lesions, (typically high signal intensity on T2 weighted images) of the thalamus, cerebral hemispheres, and cerebellum. Thalamic lesions of mixed intensity may also be seen on T1 and T2 weighted scans suggesting haemorrhage.

Encephalitis has a high mortality rate (25-30%). Pregnant women are at risk of intra-uterine infection and death of the foetus during the first two trimesters.

**Diagnosis**

Anti-JEV immunoglobulin M (IgM) is produced soon after infection and is detectable in 90% of cases in cerebrospinal fluid (CSF) by 4 days and in serum by 7-9 days following the development of clinical illness. Anti-JEV IgM is less cross-reactive and therefore more specific than IgG. WHO recommends JEV-specific IgM antibody capture ELISA (MAC ELISA) as the first-line serological assay to diagnose acute JEV infection. However Serology MAC ELISA underestimates recent infection with Japanese encephalitis virus, in comparison to real time reverse transcriptase PCR.

The diagnosis can be made by isolating the virus from the cerebrospinal fluid early in the disease or by serology, but it is not a sensitive method of laboratory diagnosis in clinical specimens because the low-level transient viremia is cleared soon after onset of illness.

**Treatment**

As with other flaviviruses, treatment for Japanese encephalitis is supportive. Convulsions and raised intracranial pressure should be treated when they occur. Randomized controlled trials failed to show benefit for the use of corticosteroids, interferon-alpha-2a or ribavirin. Intravenous Immunoglobulins (IVIG) produced in countries where flaviviruses are endemic contains high titres of specific neutralizing antibody, because most of the population have been exposed to the virus. A recent pilot study (2016) cleared the way for a phase III trial of treatment of JEV with IVIG in Nepal.
**Prevention**

Given its endozootic life cycle JEV cannot be eradicated. In absence of effective antiviral therapy, vaccination is the most important tool to control human JEV infections.

**Vaccination**

Four different vaccines are available, but all induce only short-term immunity. The vaccine IXIARO® (2 injections, on day 1 & 28) is approved in Europe for people aged 18 years and older. Indications for vaccination in travellers include people who travel at least 3-4 weeks in a rural endemic area or who intend to live in these areas for longer periods even in an urban environment. After a 2-dose primary immunization schedule (0-28 days), the seroprotection rate declines from 8% at 1 month to 48% at 24 months but reconversion is complete with a booster after 1 or 2 years. In older people the vaccine can be given safely, but a 3rd dose may be needed at primary immunization.

**Vector control**

In addition to vaccination, Japanese Encephalitis can be prevented by vector control measures, see also general section.

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**West Nile virus**

**Summary**

- Flavivirus, belongs to JEV serogroup
- Vector: mosquito, Culex species
- WNV neuroinvasive disease is an important clinical syndrome with up to 15% mortality and frequently accompanied by long-term sequelae

**Virus**

West Nile Virus (WNV) was originally discovered in 1937 in the West Nile district of the Northern Province of Uganda. It belongs to the Flaviviridae. It belongs to the Japanese Encephalitis group
flaviviruses (see section on Japanese Encephalitis). Kunjin virus is regarded as a variant of West Nile Fever Virus. There is a considerable variation between different strains (isolates).

Transmission

WNV is transmitted by mosquitoes, mainly Culex species. Culex univittatus and C. pipiens are the main vectors in Africa and the Middle East. WNV has also been known to circulate Southern Europe (Romania, southern France, Spain), Israel, Asia, the Ukraine and Southern Russia. The main reservoir is probably formed by viraemic birds and a zoonotic mosquito-bird-mosquito cycle is assumed. Many bird varieties can be infected and can be viraemic for a long time (amplifying host). Since 1999 WNV has become endemic in the USA and Canada, where it demonstrates seasonality: 90% of infections occur in August and September.

One of the reasons why West Nile virus has spread so rapidly in the United States, is due to a hybrid mosquito species (Culex p. s.s. X Culex p. molestus), which bites both birds (ornithophilic) and man (anthropophilic). The infection usually takes a subclinical course in birds, but in an outbreak of West Nile Fever-like virus (afterwards confirmed as being West Nile Fever virus) in Queens in New York in the autumn of 1999 hundreds of birds in this city died from the infection (mainly crows, magpies and a few flamingos in the Bronx zoo). Prior to this the virus was unknown in the New World.

The infection is not transmitted directly from man-to-man, but it can be transmitted by blood transfusion, organ transplantation and breast feeding.

Kunjin virus occurs in Australia, Papua New Guinea (including Saibai island in the Torres Strait) and Borneo.

Geographical distribution

Past epidemics occurred in South Africa in 1974 (with more than 3000 clinical cases), the Camargue (France) and the Ebro delta (Spain). From 1999 through 2010, 3 million WNV infections are thought to have occurred in the USA, resulting in 780 000 clinical illnesses. From 1999-2012 the USA have recorded 16,196 patients with WNV neuroinvasive disease and 1549 deaths.

Clinical aspects

Incubation period varies from 3-15 days. Many infected patients experience a subclinical infection or a mild flu-like syndrome. Symptomatic patients present with headache, generalized weakness, morbilliform or maculopapular rash (often at time of defervescence), fever (often low grade, lasting 5
days on average), myalgia. Less commonly reported symptoms are joint pains, chills, painful eyes, vomiting or diarrhoea and lymphadenopathy.

**Table: Symptoms experienced by WNV viraemic blood donors in 14 days preceding donation**

(Zou et al, J Infect Dis)
Neuroinvasive disease occurs in less than 1% of those infected by a mosquito bite and appears more frequent in elderly persons. The risk may approach 1 in 50 among persons aged at least 65 years, a rate 16 times higher than that for persons aged 16 to 24 years. In addition, a history of cancer,

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. (%) of donors with symptom</th>
</tr>
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<tbody>
<tr>
<td>Headache&lt;sup&gt;a&lt;/sup&gt;</td>
<td>125 (75)</td>
</tr>
<tr>
<td>Generalized weakness&lt;sup&gt;a&lt;/sup&gt;</td>
<td>125 (75)</td>
</tr>
<tr>
<td>New rash&lt;sup&gt;a&lt;/sup&gt;</td>
<td>97 (58)</td>
</tr>
<tr>
<td>Fever&lt;sup&gt;a&lt;/sup&gt;</td>
<td>94 (56)</td>
</tr>
<tr>
<td>Severe muscle pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90 (54)</td>
</tr>
<tr>
<td>Joint pain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>81 (49)</td>
</tr>
<tr>
<td>Chills&lt;sup&gt;a&lt;/sup&gt;</td>
<td>79 (47)</td>
</tr>
<tr>
<td>Painful eyes&lt;sup&gt;a&lt;/sup&gt;</td>
<td>67 (40)</td>
</tr>
<tr>
<td>Vomiting or diarrhea</td>
<td>45 (27)</td>
</tr>
<tr>
<td>Swollen glands</td>
<td>36 (22)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>31 (19)</td>
</tr>
<tr>
<td>New difficulty thinking</td>
<td>29 (17)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>27 (16)</td>
</tr>
<tr>
<td>Tremor</td>
<td>4 (2)</td>
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</tbody>
</table>
diabetes, hypertension, alcohol abuse, or renal disease also increases the risk.

Other host factors associated with an increased risk of neuroinvasive disease are and chemokinereceptor CCR5 deficiency (which diminishes the risk for HIV infection) as well as male sex.

**Figure: Potential mechanisms for neuroinvasion of West Nile virus (Petersen et al, JAMA)**

**Mechanism of neuro invasion**

Neuroinvasive disease occurs in less than 1% of those infected by a mosquito bite and appears more frequent in elderly persons. Potential mechanisms for neuroinvasion of West Nile virus include (1) direct infection of the vascular endothelium and subsequent entry to the central nervous system, (2) viral passage through the vascular endothelium due to disruption of the blood-brain barrier integrity by vasoactive cytokines, (3) a Trojan horse mechanism through which infected monocytes are trafficked into the central nervous system, or (4) retrograde axonal transport to the central nervous system following infection of peripheral neurons.

Reported clinical syndromes of WNV neuro-invasive disease are:
Meningitis, characterized by clinical signs of meningeal inflammation, including nuchal rigidity, Kernig or Brudzinski sign, or photo- or phonophobia.

Encephalitis characterized by depressed or altered level of consciousness, lethargy or personality change lasting more than 24 hours.

Acute flaccid paralysis, characterized by acute onset of limb weakness with marked progression over 48 hours, which is usually asymmetric, areflexic or hyporeflexic, and without sensory abnormalities. 80% of acute flaccid paralysis cases occur in conjunction with encephalitis or meningitis.

Examination of CSF of patients with neuroinvasive disease shows normal glucose, elevated protein (generally <150 mg/dL) and moderate pleocytosis (generally <500 cells/μL) usually with a predominance of lymphocytes; however, neutrophils may predominate in early infection.

Imaging studies are usually normal, but focal lesions in the pons, basal ganglia, thalamus and anterior horns, and enhancement of the leptomeninges, the periventricular areas or both are occasionally seen. These lesions may appear hyperintense on T2-weighted magnetic resonance and fluid attenuated inversion recovery images.

The duration of WNV neuroinvasive disease is weeks to months; long-term functional and cognitive difficulties are common in these patients, but the number of quality studies (with adequate control groups) is low. The mortality rate is 0% in the aspecific flu-like syndrome, 2% in meningitis and up to 15% in the case of encephalitis.

**Diagnosis**

West Nile virus is mostly diagnosed by detection of IgM antibody in serum or cerebrospinal fluid (CSF) by IgM antibody-capture ELISA (MAC-ELISA). Presence of anti-WNV IgM in CSF indicates CNS infection; it is found in 90% of patients with neuro-invasive disease within 8 days of symptom onset. However, anti-WNV IgM may not be detected in serum at clinical presentation. Demonstration of seroconversion in a convalescent sample will provide a definitive diagnosis. Testing for IgG antibodies has no utility in the acute clinical diagnostic setting. Cross-reactivity with other flaviviruses can be distinguished by performing a plaque-reduction neutralization test (PRNT), but the test is only available in reference laboratories.

Nucleic acid amplification testing (eg. RT-PCR) is used in blood donor screening in the United States and Canada has nearly eliminated the risk of West Nile virus transfusion transmission. It also has utility in the diagnosis of WNV in symptomatic patients as an adjunct to MAC-ELISA. In a study of 276
WNV cases, 191 were tested by both serology and NAAT. Of these, 86 (45.0%), 111 (58.1%), and 180 (94.2%) were detected by NAAT, serology, and combined NAAT and serology, respectively. RT-PCR may prove useful to diagnose WNV in immunocompromised patients when antibody development is delayed or absent.

**Treatment**

No antiviral treatment is available. Intravenous immunoglobulin (IVIG), West Nile virus-specific neutralizing monoclonal antibodies, corticosteroids, ribavirin, interferon α-2b, and antisense oligomers were not effective.

**Prevention**

**Vaccination**

In spite of 4 licensed equine vaccines and promising preliminary results from several phase 1 and 2 human vaccine candidates, phase 3 efficacy trials have not been attempted, probably because universal vaccination against WNV disease is unlikely to be cost-effective unless disease incidence increases substantially.

**Surveillance**

Potentially epidemic conditions due to increased virus transmission can be monitored by regularly testing the blood of birds for the presence of the virus or antibodies. So-called “sentinel birds” are used for this. Crows are very sensitive to infection. Analysis of samples of dead crows is useful in the New World.

**Personal protection**

The risk can be limited by reducing contact with mosquitoes. When there is an outbreak it is recommended that covering clothing is worn and that mosquito repellents are used. Insecticide can also be sprayed indoors. In the case of large epidemics, outdoor vector control is also important (larvicides and adulticides).
Rift Valley Fever

Summary

- Main clinical features: fever, haemorrhagic disease and neurological symptoms (FD, HS, NS), hepatitis
- Acute disease mainly of African domesticated ruminants, sometimes humans
- Transmission via mosquitoes and direct contact with infected animals
- Intermittent but severe epidemics

Virus

The virus which causes Rift Valley Fever (RVF) is a Phlebovirus and belongs to the Bunyaviridae family. There are several subtypes with each apparently having their own pathogenic capability. Zinga virus is currently regarded as a variant of the RVF virus. It is possibly identical.

Transmission

Between the epidemics it has never been possible to demonstrate a sylvatic vertebrate reservoir, but RVFV has been isolated from over 30 species of mosquitoes in six genera. The virus is passed from generation to generation of mosquito via the transovarial route. Mechanical transmission by arthropods is also documented.

The disease is primarily a zoonosis which affects sheep, goats, cattle and buffalo. Rodents are highly susceptible, although subclinical infections do occur. Birds, reptiles and amphibians are refractory. An epidemic in animals is called an epizootic. In animals the virus causes a severe infection with high mortality, mainly in newborn lambs. Adult pregnant animals often abort. A subclinical infection may occur in dogs, cats and camels (can abort). Horses and pigs are resistant.

The disease was first described in detail by Daubney, in Kenya in 1931 (epidemic in sheep on a farm near Lake Naivasha, one of the lakes in the Rift Valley). Until 1977 it was assumed that the illness only occurred in sub-Saharan Africa and Madagascar, but in 1977-78 there was a great epidemic in Egypt so that the area of distribution was found to be more extensive. Other important epidemics occurred in 1950-51 in South Africa (sheep: an estimated 100,000 dead and 500,000 abortions), in the river basin of the Senegal river in Senegal and southern Mauritania (1987) and in Kenya-Somalia (1997-1998). In 2000 numerous cases were reported from Saudi Arabia and the neighbouring Yemen. More than 200 people died. It was the first time the virus was detected outside Africa.
Rift Valley Fever occurs in intermittent epidemics with intervals of 10 to 15 years, mainly after periods
of exceptionally heavy rainfall. It has been proposed that factors such as rainfall, ocean temperature and climate change all play roles in determining the likelihood of an epidemic.

Transmission of Rift Valley Fever to man can occur either via direct contact with the blood of a viraemic animal (e.g. in slaughterhouses, farmers, butchers, ranchers, veterinary surgeons, herdsman, etc.), possibly via the milk of an infected animal or via a bite from an infected insect. There are numerous types of mosquitoes which can transmit the virus. Aedes sp. are usually the most important but Anopheles, Culex, Eratmopodites, Manson, Mansonoides and Coquillettidiae mosquitoes also play a role. The virus can be transmitted transovarially in Aedes mcintoshi (= Aedes lineatopennis sl.) and can survive for a long time (years) in a mosquito egg. In heavy rainfall, floods etc. numerous infected mosquito eggs will simultaneously hatch due to the rising water level and moistening of the eggs.

Rift Valley Fever virus can also be transmitted by mechanical vectors such as stomoxyds, phlebotomes, simulids and Culicoides sp. Infected insects can be carried over large distances by the prevailing winds such as the north and south trade winds. Transporting infected cattle to a non-epidemic area is an important factor in the epidemiology.

Clinical aspects

The incubation period of Rift Valley fever is 3 to 7 days. Clinically the disease can provoke a non-specific flu-like syndrome, sometimes with biphasic fever. Fever develops together with muscle and joint pain, anorexia, diarrhoea, vomiting, headache and sometimes photophobia and retro-orbital pain. Sometimes there is petechial rash. The acute phase of the disease lasts 4-7 days. Complications occur in fewer than 5% of cases. In case of a haemorrhagic form, diffuse intravascular coagulation, bleeding (epistaxis, melena, haematemesis, seeping of blood at infusion and needle prick sites) and jaundice predominate such that the disease resembles yellow fever. Pneumonitis, shock, hepatic failure and renal failure with proteinuria and shock can occur. Sometimes bilateral vision disturbances occur about a week after the start of the fever. These are the result of vasculitis of the retina with arteriolar thrombosis, retinitis, retinal ischaemia, bleeding and detachment of the retina. The macular and peri-macular areas are affected preferentially. The lesions can result in permanent blindness or slowly improve over the course of the following weeks. Neurological complications also occur (< 1%): meningeal signs, dizziness, confusion, hallucinations, hypersalivation, grinding of teeth, chorea, convulsions and other signs of encephalitis. Coma, with or without decerebration, can occur in the terminal stage. In the complicated forms mortality is high.
Diagnosis

The disease may be suspected if large numbers of young lambs and goats die, with or without epidemic abortion among the animals and when at the same time multiple human cases with fever and haemorrhagic or neurological symptoms occur in an endemic area. In animals there is congestion in the liver, with small haemorrhagic areas and necrotic foci. The bile may be dark, almost black, and may contain blood. Tissue biopsies of animals can be used for anatomopathology, immunoperoxidase techniques for detecting the virus and of course virus isolation. Confirmation of the diagnosis in man is based on serology (IgM antibodies, including in the cerebrospinal fluid) and on virus isolation. Definitive identification is based on neutralisation tests with reference sera. Initially there is leukocytosis, then leukopenia and thrombocytopenia. Schistocytes may be found. With neurological symptoms lymphocytes predominate in the cerebrospinal fluid.

Treatment

There is no specific treatment. Symptomatic therapy is essential and occasionally requires intensive level care. There are insufficient data about the use of ribavirin and/or of convalescent plasma. Ribavirin inhibits virus replication in cell culture. Ribavirin is a ribonucleoside analogue that induces lethal mutagenesis of RNA viral genomes. The possible therapeutic place of interferon is not clear yet. Hepatotoxic medication as well as aspirin and NSAIDs should be avoided during the acute disease.

Prevention

Vaccination

A live attenuated strain (also known as the Smithburn strain) has shown to be potent in inducing protection from viral infection, and it is used as a vaccine for livestock. However, its ability to induce abortions and exhibit pathogenicity in European cattle has limited its use to areas threatened by an imminent outbreak. Studies on new vaccines are ongoing. These candidate vaccines can be classified into four groups: live attenuated, inactivated, viral-recombinant, and DNA vaccines. There is still no commercial vaccine available for humans.

Vector control

The transport of animals should be limited. In epidemics the transporting of cattle should be prohibited, or the animals must be quarantined. Contact with sick or dead animals must be avoided. Cattle can be vaccinated. If the epidemic has already started it is usually too late to employ with
vaccination as a control strategy. Thus in sheep-farming areas it is advised that the animals be vaccinated regularly either with the live Smithburn vaccine (single dose, life-long protection), or vaccination with the formol-inactivated vaccine (boosters needed).

Because of the variety of vectors, it is difficult to control insects breeding sites. Sometimes in epidemics insecticides are used on a large scale. For personal protection covering clothing (long sleeves, long trousers), insect repellents (best with DEET) and impregnated mosquito nets are adequate in normal situations. Barrier-nursing is indicated in the care of patients.

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Crimean Congo Haemorrhagic fever

Summary

- Main clinical presentation: Febrile disease, haemorrhagic symptoms, neurological syndrome (FD, HS (NS))
- Transmission via ticks (esp. Hyalomma marginatum marginatum) and direct contact with infected animals
- Human to human transmission occurs; CAVE nosocomial infection
- High mortality (up to 40%)

Transmission

Crimean-Congo Haemorrhagic Fever (CCHF) occurs throughout Africa, in Asia, in the former USSR and in Eastern Europe, the Balkans (Kosovo, Albania), the Middle East (including Oman and the United Emirates), Pakistan and the Maghreb, including Egypt. The virus was originally isolated in 1944-45 in the Crimean Peninsula in the north of the Black Sea, during an outbreak in Soviet military personnel. In 1956 it was found in Kinshasa, Congo, first in a patient and shortly afterwards in a scientist who acquired a subsequent laboratory infection. In 1967 it was shown by Chumakov and Casals that both viruses were virtually identical, so now it is referred to as Crimean-Congo Haemorrhagic Fever Virus.
Man can be infected by the bite of ticks, especially Hyalomma ticks, although sometimes many other tick species are involved. The virus can survive in a tick population because it is transmitted both by the transovarial and the transstadial route. The larvae and nymphs of the ticks become infected when they suck blood from viremic small mammals and birds. Adult ticks infect themselves through the blood of infected wild or domesticated ruminants. Man can be also infected by direct contact with infected animal tissue or blood (goats, cattle, sheep, hares, ostriches) and during shearing of tick-
infested sheep. In sheep and goats, the viraemia lasts a week. When these animals are slaughtered or die from their babesiosis/anaplasmosis, they can still be viraemic. The people who looks after the animal or deals with the carcass can therefore become infected. Herdsmen, farmers, veterinary surgeons and slaughterhouse workers have an increased risk of infection. Human to human transmission is well documented, and nosocomial transmission also occurs. A classic scenario is a patient with bleeding who requires surgery after which the virus spreads to medical staff and/or members of the family.

**Virus**

CCHF virus that causes Crimean-Congo Haemorrhagic Fever belongs to the family of the Bunyaviridae, genus Nairovirus. Other genera within the family include Orthobunyavirus, Hantavirus, Phlebovirus, and Tospovirus. CCHF is a tripartite, negative-sense, single-stranded RNA genome that comprises Large (L), Medium (M) and Small (S) segments. The three genome segments encode four structural proteins—the RNA-dependent RNA polymerase (L protein) is encoded by the large (L) segment, the glycoproteins (GN and GC) are encoded by the medium (M) segment, and the nucleocapsid protein (N) is encoded by the small (S) segment.

**Clinical aspects**

After an incubation period of 3 days after a tick bite and up to 6 days after contact with infected animal tissues, the disease starts with a sudden onset of fever. Clinical features commonly show a dramatic progression characterised by haemorrhage and myalgia, headache and vomiting. A discrete exanthema/enanthema can be seen, mainly on the palate. On the 4th day petechiae and extensive ecchymoses appear, followed by severe systemic bleeding including melaena, haematemesis, epistaxis and haematuria. There is no direct effect on the central nervous system, although confusion, lethargy and aggressive behaviour can occur.
Haematology results frequently show leukopenia and thrombocytopenia. The levels of liver enzymes, creatinine phosphokinase, and lactate dehydrogenase are raised and coagulation markers are prolonged. Infection of the endothelium has a major pathogenic role. Besides direct infection of the endothelium, indirect damage by viral factors or virus-mediated host-derived soluble factors that cause endothelial activations and dysfunction are thought to occur.

Mortality is high (15-40%), especially during an epidemic but mild cases and spontaneous recovery also occurs.
**Diagnosis**

Early diagnosis is critical both for patient management and for the prevention of human to human transmission. The diagnosis is made by demonstrating the presence of the virus in viraemic phase plasma either by culturing or RT-PCR or by detecting a seroconversion. RT-PCR is highly sensitive and specific.

IgM and IgG antibodies are detectable by ELISA and immunofluorescence assays from about 7 days after the onset of disease. Specific IgM declines to undetectable levels by 4 months post-infection, but IgG remains detectable for at least 5 years.

**Treatment**

General supportive measures and symptomatic therapy. People who are infected should be treated in strict isolation since airborne transmission can occur. Barrier-Nursing should be in place for infection control.

Ribavirin (Virazole®) was used to treat CCHF. There is no evidence from randomised clinical trials for the use of ribavirin to treat human CCHF — its effectiveness has only been described in observational studies. Patients should be treated for 10 days (30 mg/kg as an initial loading dose, then 15 mg/kg every 6 hours for 4 days, and then 7.5 mg/kg every 8 hours for 6 days).

Another study suggested treatment using passive immunotherapy, transferring the plasma of convalescing survivors to infected patients. However, the study had no control groups and was limited to seven patients, therefore conclusions cannot be made.

**Prevention**

**Vector control**

In endemic areas ticks should be eliminated from animals two weeks before they are slaughtered (e.g. with a pyrethroid acaricide). The virus is sensitive to heat and is not resistant to an acid environment. This explains why transmission by eating infected meat is rare.

**Vaccination**

There is no commercial vaccine.
Kyasanur Forest disease

Kyasanur forest disease is caused by Kyasanur forest disease virus, a flavivirus. It occurs principally in the Shimoga and Kanara district of Karnataka (formerly Mysore), India. The geographic distribution of this virus is not restricted to Karnataka, e.g. 22 percent of persons living in the Andaman and Nicobar Islands were found to be seropositive for KFD in 2002. Human infection by closely related viruses is known in Saudi Arabia (Alkhurma virus) and China (Nanjianyin virus).

The virus was identified in 1957 when it was isolated from a sick monkey from the Kyasanur forest in Karnataka state. This happened during a fatal epizootic among wild monkeys. The main hosts of this virus are small rodents, but shrews, bats, and monkeys may also carry the virus. Transmission is via the bite of an infected tick, mainly *Haemaphysalis spinigera*. Apart from tick bite, humans can also get infected by contact with an infected animal, such as a sick or recently dead monkey. Goats, cows, and sheep may become infected with KFD, but they do not have a role in the transmission of the disease. There is no evidence of the disease being transmitted via the unpasteurized milk of any of these animals.

The incubation period is not well known, some state 3-8 days, others 1-2 weeks. The patient develops sudden onset fever, severe headache, followed by back pain, muscle pain in the extremities, inflammation of the eyes, dehydration, gastrointestinal symptoms with or without gastrointestinal bleeding. Hypotension and pancytopenia can ensue. Some patients develop cough due to bronchopneumonia prior to coma and death. Some patients recover without complications after this first phase. However in most patients, the illness is biphasic, and the patient begins experiencing a 2nd wave of symptoms at the beginning of the 3rd week. These symptoms include fever and signs of encephalitis. The diagnosis is made by virus isolation from blood or by serologic testing using ELISA. There are approximately 400-500 symptomatic cases of KFD per year with a case fatality rate of 3-5 percent.

There was an important outbreak in May and June 2003. Forest workers are particularly at risk. There is a safe, effective formalin-inactivated vaccine available for control of Kyasanur Forest disease since 1990. More than 80,000 people were immunized in trials during 1990 to 1992, with no report of adverse effects. The vaccine is prepared from tissue culture and administered at a dose of 1.0 ml subcutaneously (0.5 ml below age 6), with a booster dose after 4 weeks.
Nipah virus

Nipah virus is at present not considered to be an arbovirus but is included in this chapter because of its close resemblance to Japanese Encephalitis.

From September ‘98 to March ‘99 a new paramyxovirus appeared in Malaysia. It was given the name Nipah virus and is related to Hendra virus which in 1994 caused fatal infections in horses and people in Australia. Nipah virus causes an encephalitis that clinically is indistinguishable from Japanese Encephalitis. An incubation period of 4-18 days is followed by 3-14 days of fever, headache, vomiting, reduced consciousness, meningism, myoclonus, convulsions, areflexia and hypotonia, tachycardia, abnormal pupils, nystagmus. There is often a considerable effect on the brain stem, often resulting in an abnormal oculovestibular reflex (abnormal “doll’s eye reflex”). Sometimes there is a non-productive cough. In man the mortality rate is high. During the first epidemic more adults than children were affected, mainly those who were working as pig-farmers. Pigs can be infected and develop a cough. In animals infection often results in death, unlike with Japanese Encephalitis. Flying foxes (large bats, including Pteropus hypomelanus) are thought to be the reservoir. The virus has been isolated from their urine and saliva.

Bats and zoonoses

There are multiple reasons why several zoonotic diseases originate in bats (rabies, Nipah virus, Hendra virus, SARS-CoV, Marburg, …). About a quarter of all mammal species on the planet are bats. The genetic diversity among the more than 1000 species of bats creates numerous niches for viruses. Bats live from 5 to 50 years, which is much longer than most small mammals. This could be useful for viruses seeking stable reservoirs. Many species roost packed together in large clusters, making it easy for a virus to spread through a colony. Cave-sharing among different species also facilitates infection across species, which in turn increases the chances of viral recombination. Some bats can fly up to 20 km a day, foraging, and some species are migratory. Such animals have the capacity of widely transporting a pathogen over a relatively short period. Some bats seem to be able to carry and shed a virus for a long time without getting sick and without clearing the infection, but more study is required.
Venezuelan Equine Encephalitis

Summary

- New World arboviral infection with mainly neurological symptoms
- Transmission via mosquitoes
- No vaccine available for people

General

The virus only occurs in the New World. It belongs to the Alphaviridae. The virus is normally maintained enzootically in a cycle between small mammals and Culex mosquitoes, mainly those belonging to the subgenus Melanoconion. Rodents form the reservoir. This is an acute viral disease that is transferred from horses to man by various mosquitoes (Aedes and Culex sp.). In a minority of those infected this leads to a serious and sometimes fatal encephalitis. It is the main arbovirus (together with dengue) in (sub)tropical America. The infection occurs in Central America and in a sickle-shaped area in the north of South America. There are regular outbreaks and epidemics, such as in Mexico in ’93 and ’96. In 1995 there was an outbreak in Colombia with ± 75,000 cases (3,000 with neurological complications). Epidemics in man are always preceded by epidemics in horses. Encephalitis occurs in 90% of infected horses, 50% of which die.

Clinical aspects

Asymptomatic infections are rare in man. Usually there is a flu-like syndrome lasting for 3 days. Fever, myalgia, headache, vomiting and diarrhoea are frequent and for this reason the disease is often assumed to be dengue. In a minority of the symptomatic patients (4% in children) this develops into encephalitis with various neurological symptoms. Confusion, stupor and convulsions can follow. There is leukopenia as well as an increased level of proteins and an increased number of lymphocytes in the cerebrospinal fluid. Sequelae are more frequent in children than in adults. Abortion is frequent in infected pregnant women. Diagnosis is clinical, epidemiological and serological.

Prevention

In the case of an epidemic of VEE, horses should be vaccinated, and the vector should be controlled.
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(insecticides). Most horses are not vaccinated because the vaccine is expensive. The vaccine is not in general use or readily available for man. For other encephalitis viruses such as Eastern Equine Encephalitis, Western Equine Encephalitis, St. Louis encephalitis, La Crosse Encephalitis, California Encephalitis, Jamestown Canyon and Cache Valley (now West Nile as well) surveillance is carried out in North America. This involves, among other things, using birds such as chickens or pheasants because the vectors preferably bite birds. Sera are taken from these sentinels every two weeks and tested for antibodies to VEE. Surveillance can also be carried out by catching mosquitoes. After the catch has been sorted, virus culture or PCR is then carried out on the insect collections. If the virus becomes too frequent, insecticides can be sprayed. If a sudden increase in mosquitoes is anticipated, such as after a severe rainstorm or hurricane, surveillance is increased.

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Eastern and Western Equine Encephalitis

Alphaviruses that are related to VEE include the viruses that cause Eastern Equine Encephalitis (EEE) and Western Equine Encephalitis (WEE). EEE is a very serious, but quite rare arbovirosis in the east of the USA, but also occurs sporadically in Central and South America. An incubation period of 7-10 days, fever, meningism, severe encephalitis and a mortality rate that can be as high as 50% characterise the disease. The epidemic potential became evident in 1938. After a severe storm in Boston, Massachusetts there was a major outbreak with a high mortality rate. What was the connection between the storm and the disease? Birds form the reservoir. The virus is transmitted between birds by mosquitoes such as Culiseta melanura. This mosquito lays its eggs in dark underground hollows in an acid soil, such as root hollows in marsh cypresses or red maple trees. It is an unusual habitat for oviposition (egg-laying). The larvae are not in open water and are not easy to find. Such places easily become water-logged after heavy rainfall. In this way huge numbers of mosquitoes can appear simultaneously. Transmission between birds then increases. More than 75 different types of bird can be infected. When mosquitoes that bite both birds and man are infected (such as Aedes vexans, Coquilletidia perturbans), the infection can be transmitted to man. Culex tarsalis is also important in transmission. Horses and donkeys can be infected. In these animals the course of the infection is often dramatic and death among horses can precede an epidemic. Surveillance is carried out with sentinel birds. If there is a threat of an epidemic, insecticides are sprayed, e.g. by ULV (ultra low volume spraying).

In the west of the USA WEE occurs sporadically in man and animals. In other regions of the USA and South America WEE also occurs, but until now apparently only in animals. It is not known whether this
is to do with the different antigenic types in North and South America. Most of the infections in adults are pauci- or asymptomatic. After an incubation period of 5-10 days there is a gradual onset of fever, malaise, headache, neck stiffness and dizziness. In serious cases this develops into stupor, coma, flaccid and spastic paralysis. There is pleocytosis in the cerebrospinal fluid as well as an increase in the protein content. Children often have permanent neurological sequelae. The mortality rate among symptomatic patients is about 10%.

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**Tick-borne encephalitis**

**Summary**

- Flavivirus, 3 subtypes
- Vector: Ticks, Ixodes species
- Main clinical presentation: Febrile disease, neurological syndrome (FD, NS)
- Effective vaccine is available

**Virus**

Tick-borne encephalitis (TBE) is caused by 3 closely related flaviviruses. These as known at present are European, Siberian, and Far Eastern strains.

**Transmission**

Tick-borne encephalitis (TBE) is also called Frühsommer Meningo-Enzephalitis (Early Summer Meningo-Encephalitis). This name is a misnomer, since transmission lasts well into autumn (April till October). TBE refers to both Central European encephalitis (CEE, syn. FSME) and Russian spring-summer encephalitis (RSSE). TBE is transmitted to humans usually by the bite of a tick (either Ixodes persulcatus or Ixodes ricinus). In contrast with Lyme disease, transmission of the TBE virus occurs immediately after the tick bite, hence tick removal will not prevent the disease. Occasionally, cases occur following consumption of infected unpasteurized milk.

All 3 subtypes co-circulate throughout most of the TBEV endemic areas. However, currently the Siberian subtype dominates in many endemic regions from Eastern Europe to Eastern Siberia. The geographical distribution of TBE is from eastern France, over South Germany, Switzerland, Austria,
the previous East Block countries via Russia to northern Japan, and from Scandinavia (Sweden) and the Baltic states to Croatia and northern Italy. In Europe and Asia between 10000 and 15000 TBE cases are reported annually. The number is very likely underestimated because in many countries notification of the disease is not mandatory and only in a subset of the countries TBE case definition is in place. TBE is endemic in 27 European countries, and is a reportable disease in only 16 countries.

Vertical transmission in laboratory animals has been demonstrated to be widespread.

**Accidental hosts**

**Normal cycle of transmission**

Figure: Transmission cycle of TBE (Dumpis et al, Clin Infect Dis)

**Clinical aspects**

The incubation period of TBE ranges from 2 to 28 days (7-14 days). After alimentary TBEV transmission the incubation period is generally 3 to 4 days. Published data suggest that the ratio of asymptomatic infections is between 70% and 98%. However the proportion of asymptomatic cases is hard to ascertain because patients with mild clinical signs and symptoms may remain undiagnosed.
The initial phase correlates with viremia and like in other neurotropic flaviviruses, it presents with aspecific flulike symptoms (moderate fever, headache, body pain (myalgia and arthralgia), fatigue, general malaise, anorexia, nausea).

This phase lasts for 2 to 7 d and is followed by amelioration or even an asymptomatic interval that usually lasts for about 1 wk (1-21 d). Then the second phase appears: in approximately 50% of adult patients it presents as meningitis, in about 40% as meningoencephalitis and in around 10% as meningoencephalomyelitis.

The severity of TBE increases with age; in children and adolescents, meningitis is the predominant form of the disease. The long-term prognosis is unfavourable in about 40% to 50% of patients who sustain sequelae (pareies, ataxia, and other gait disturbances) for months to years, and severity of TBE-related sequelae also seems age-related.

![Classification of sequelae](image)

**Classification of sequelae:**

- **Mild-** without any real impact on quality of life.
- **Moderate-** residual symptoms or signs that affected quality of life but that did not require
adjustments of daily activities.
• Severe symptoms or signs that led to an inability to continue previous activities or that required adjustments of daily activities.

In general the case fatality rate is approximately 1–2% following European subtype infection but can be as high as 20–40% following infection with a far-eastern subtype. Infection with the Siberian subtype produces a mortality rate of 2–3%. However it is possible that the high mortality figures for the far-eastern subtype may be due to the lack of detection of mild cases therefore skewing the mortality data.

**Diagnosis**

As a rule, anti-TBEV- IgM and usually TBEV-IgG antibodies are present in the first serum samples taken when CNS symptoms manifest in the second phase of the disease. In the first phase of illness, the virus can be isolated or detected by RT-PCR from blood, but only rarely is TBEV detected at the beginning of the second phase in CSF and occasionally in cases of progressive disease. Intrathecal IgM and IgG antibody response can be detectable in CSF, but several days later than in serum, and in all cases by day 10.

Enzyme immunoassays are usually used for specific serodiagnosis; these assays could be based on either purified virions or recombinant virus-like particles obtained by expression of prM and E proteins. ELISA for serum and/or CSF IgM antibodies to TBEV has been shown to be the most reliable serological test. Haemagglutination inhibition is also widely used but measures all antibody classes and needs a rise in antibody titre for definitive diagnosis. High cross-reactivity of the antigenic structure in the flavivirus may reduce specificity.

**Treatment**

There is no specific antiviral treatment for TBE. Patients as a rule need hospitalization and supportive care based on the severity of signs/symptoms, and usually encompasses administration of antipyretics, analgesics, antiemetics, maintenance of water and electrolyte balance and if necessary administration of anticonvulsive agents. In patients with neuromuscular paralysis leading to respiratory failure, intubation and ventilatory support are necessary.

**Prevention**
Personal protection

Personal protective measures help in prevention of tick bites (repellents like DEET being less effective than against mosquitoes) and protective clothing.

Vaccination

In Europe two vaccines are licensed: FSME immun® (from Baxter) and Encepur® (from Chiron Behring). 14 days after the second dose of basic vaccination protective antibodies develop in about 85% of the subjects, while after three doses more than 98% of persons with normal immunity are protected.

In some countries, such as Austria, vaccination coverage is very high. Other areas where the cost of vaccination is prohibitive lag behind.

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