Yellow Fever and Dengue Viruses

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Yellow Fever: Historical background

• **1648**: First recognized outbreak of YF occurring in the New World. YF virus most likely introduced by slave-trading vessels from West Africa infested with *Aedes aegypti* (mosquito), with outbreaks also occurring in port cities in the New World and Europe.

• **1778**: Saint Louis, Senegal: First YF outbreak reported in Africa.

• **1900**: Cuba: Walter Reed's decisive investigations proved viral transmission by *Aedes aegypti*.

• **By 1927**, YF virus had been isolated for the first time by inoculating monkeys from patients in West Africa.

• **By 1935**, vaccines were developed and Fred Soper discovered the jungle cycle of YF (no *A. aegypti* involved) and established the first relationship between the disease in monkeys and in humans (1932).
Yellow fever endemic regions (outlined in red)
Range of number of cases reported to WHO for period 1990-1999.

Yellow Fever: Symptoms

- **incubation period**: 3-6 days (travelers may be viremic before demonstrating symptoms).

- **Clinical symptoms** manifest in 1 in 20 partially immune patients and 1 in 5 immunologically naïve patients.

- **Initial symptoms** (viremic phase), followed by a transient (up to 24 h) remission:
  - Fever and chills
  - Severe headache
  - Back pain,
  - Myalgia
  - Nausea
  - Prostration
Yellow Fever: Symptoms

- **Toxic phase** develops as the fever returns. Symptoms include high fever, headache, lumbosacral back pain, nausea, vomiting, abdominal pain, and somnolence.
- **Hepatic-induced coagulopathy** produces hemorrhagic manifestations: the characteristic black vomit (hematemesis), epistaxis, gum bleeding, petechial and purpuric hemorrhages.
- **Systemic manifestations** include deepening jaundice and albuminuria.

- **In the late stages of disease** hypotension, shock, metabolic acidosis, acute tubular necrosis, myocardial dysfunction, and arrhythmia dominate the picture.
- Confusion, seizure, and coma in the late CNS manifestations of the disease. Death within 7-10 days of onset.

- **Secondary bacterial infections** are frequent complications

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Yellow fever patient during period of infection. Patient is febrile, acutely ill, with prominent conjunctival congestion

Pathogenesis of Yellow Fever

Histopathological features of yellow fever infection of the liver

Eosinophilic degeneration of hepatocytes (Councilman bodies)

Yellow Fever: Epidemiology

Frequency:
• **In the US:** Last YF epidemic in North America occurred in New Orleans in 1905 (>3,000 cases, 452 deaths). Because *Aedes aegypti* now has re-infested the southeastern United States, autochthonous transmission in the United States is possible.
• **Internationally:** YF transmission predominately occurs in areas of sub-Saharan Africa and South America 15° North and 10° South of the Equator. Never documented in Asia.

  **Africa:** Yellow fever epidemics were dominant in Africa from 1986-1991, with close to 20,000 cases and 6,000 deaths. These epidemics commonly include 30-1000 cases with fatality ratios of 20-50%. In West Africa, large epidemic may occur

  **In South America,** an annual mean of 100 cases has been reported for the last 25 years. These cases predominate from January to March among males aged 15-45 years who work outdoors in agriculture and forestry. The last outbreak in the western hemisphere occurred in 1954 in Trinidad.
Two types of yellow fever exist, the jungle & the urban types.

In jungle yellow fever, *Haemagogus* mosquitoes in South America and *Aedes africanus* in Africa acquire the disease from monkeys, which serve as hosts for the virus. Mosquitoes then bite and infect humans, usually young men engaged in forestry or agricultural activities, resulting in sporadic outbreaks in South America and Africa.

In urban yellow fever, humans serve as viremic hosts and the disease is spread between humans by the domestic mosquito vector, *Aedes aegypti*. Because of widespread control of this vector in the 1930s, urban yellow fever has become uncommon. However, these mosquitoes recently reinvaded South America; thus, the potential for transmission exists.
### Yellow Fever: Epidemiology (Americas)

<table>
<thead>
<tr>
<th>Cycle</th>
<th>NHP</th>
<th>Mosquitoes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enzootic forest cycle</strong></td>
<td><em>Alouatta</em></td>
<td><em>Haemagogus janthinomys</em></td>
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<tr>
<td></td>
<td><em>Aotus</em></td>
<td><em>H. spegazzini</em></td>
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<td></td>
<td><em>Cebus</em></td>
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<td></td>
<td><em>Ateles</em></td>
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<td></td>
<td><em>Callithrix</em></td>
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<td></td>
<td><em>Saimiri</em></td>
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<tr>
<td><strong>Jungle Yellow fever</strong></td>
<td>As above</td>
<td><em>H. janthinomys</em></td>
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<tr>
<td></td>
<td></td>
<td><em>Aedes leucocaelenus</em></td>
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<tr>
<td></td>
<td></td>
<td><em>Sabethes chloropterus</em></td>
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<tr>
<td><strong>Urban YF</strong></td>
<td>None</td>
<td><em>Aedes aegypti</em></td>
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<td>(before 1942)</td>
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### Yellow Fever: Epidemiology (Africa)

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<tbody>
<tr>
<td><strong>Enzootic forest cycle</strong></td>
<td><em>Cercopithecus</em></td>
<td><em>Aedes africanus</em></td>
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<tr>
<td></td>
<td><em>Colobus</em> (East Afr.)</td>
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<tr>
<td><strong>Jungle Yellow fever</strong></td>
<td></td>
<td><em>Aedes africanus</em></td>
</tr>
<tr>
<td>(forest/savanna,<em>Cercopithecus</em></td>
<td></td>
<td><em>A. simpsoni</em> (East Afr.)</td>
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<tr>
<td>humid savanna)</td>
<td></td>
<td><em>A. opok</em> (West Afr.)</td>
</tr>
<tr>
<td>(semi-humid/dry savanna)</td>
<td><em>Cercopithecus</em></td>
<td><em>A. fusciger</em></td>
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<tr>
<td></td>
<td><em>Erythrocebus</em></td>
<td><em>A. taylori</em></td>
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<td></td>
<td><em>Papio</em></td>
<td><em>A. luteocephalus</em></td>
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<td></td>
<td><em>Galago</em></td>
<td><em>A. vittatus</em></td>
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<td><em>A. metallicus</em></td>
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<td>None</td>
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Yellow Fever: Diagnostic

- **Specific diagnosis** made using serologic tests such as ELISA or detection of the virus or viral antigen in blood during the pre-icteric phase.

- Laboratory diagnosis of yellow fever depends principally on **serological testing of serum immunoglobulins**. Immunoglobulin M (IgM) testing by ELISA is the preferred method of testing. This assay is 95% sensitive when serum specimens are collected 7-10 days after the onset of illness. Paired acute and convalescent sera indicate the diagnosis.

- Detection of antigen with monoclonal ELISA. Polymerase chain reaction can be used to identify viral ribonucleic acid (RNA) during acute infection. Virus isolated by intracerebral inoculation of suckling mice, intrathoracic inoculation of mosquitoes or inoculation of cell cultures (mosquito or mammalian).

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**Role of Yellow Fever proteins in provoking the infected host’s immune response and as targets for immunity.**

Dengue Virus

• Causes dengue and dengue hemorrhagic fever
• Is an arbovirus
• Transmitted by mosquitoes
• Composed of single-stranded RNA
• Has 4 serotypes (DEN-1, 2, 3, 4)

Source: CDC

Dengue Viruses

• Each serotype provides specific lifetime immunity, and short-term cross-immunity
• All serotypes can cause severe and fatal disease
• Genetic variation within serotypes
• Some genetic variants within each serotype appear to be more virulent or have greater epidemic potential
Clinical Characteristics of Dengue Fever

**Incubation:** 5-8 days

**Symptoms:**
- Fever
- Headache
- Muscle and joint pain
- Nausea/vomiting
- Rash
- Hemorrhagic manifestations
Signs and Symptoms of Encephalitis/Encephalopathy Associated with Acute Dengue Infection

- Decreased level of consciousness: lethargy, confusion, coma
- Seizures
- Nuchal rigidity
- Paresis

American countries with laboratory-confirmed hemorrhagic fever, prior to 1981 and from 1981 to 1997
Hemorrhagic Manifestations of Dengue

• Skin hemorrhages: petechiae, purpura, ecchymoses
• Gingival bleeding
• Nasal bleeding
• Gastro-intestinal bleeding: hematemesis, melena, hematochezia
• Hematuria
• Increased menstrual flow
Replication and Transmission of Dengue Virus (Part 1)

1. Virus transmitted to human in mosquito saliva
2. Virus replicates in target organs
3. Virus infects white blood cells and lymphatic tissues
4. Virus released and circulates in blood

Replication and Transmission of Dengue Virus (Part 2)

5. Second mosquito ingests virus with blood
6. Virus replicates in mosquito midgut and other organs, infects salivary glands
7. Virus replicates in salivary glands
Aedes aegypti Mosquito

- Dengue transmitted by infected female mosquito
- Primarily a daytime feeder
- Lives around human habitation
- Lays eggs and produces larvae preferentially in artificial containers
Dengue Fever: Epidemiology

Dengue, a rapidly expanding disease in most tropical and subtropical areas of the world, has become the most important arboviral disease of humans.

More than 2.5 billion persons now live in areas at risk of infection, and an estimated 50 million–100 million cases of dengue fever occur each year, 200,000–500,000 of which are DHF. The case-fatality rate for DHF averages 5%.

Epidemics caused by all four virus serotypes have become progressively more frequent and larger in the past 20 years.

Three types of dengue fever cycle sylvatic, rural and urban.

- **Sylvatic dengue**: primitive, silent cycle NHP-mosquito-NHP. Very rare human infection. May be lower pathogenicity of sylvatic strains for humans?

- **Rural dengue**: monkey-mosquito-man?? In areas subjacent to dense forests or plantations. Aedes albopictus mosquito active at ground level simiophile and anthropophile. Role in dengue maintenance between epidemics?

- **Urban cycle**: At beginning of XXth Century, A. aegypti replaced A. albopictus in urban areas. Virulence enhanced through passages in new vector? Could have led to DHF. Preeminent and almost exclusive cycle now.