# Yellow fever

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## 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 ≥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.

LAST UPDATED BY ADMIN ON JUNE 15TH, 2022