Flavivirus (causing yellow fever) (Infection with)

AETIOLOGY

Classification of the causative agent

Yellow fever virus (YFV) is an arboviral flavivirus (enveloped, positive-sense single-stranded RNA), and is considered the "prototype" flavivirus. There is one serotype of YFV divided into three genotypes: I, IIA, and IIB. YFV is maintained in non-human primate reservoirs and is transmitted by mosquitoes via urban and sylvatic cycles. YFV is zoonotic and has been recognised in Central and South America as a significant cause of disease in humans since the 1600s. This technical card focuses on disease in nonhuman primates unless specifically stated.

Resistance to physical and chemical action

Temperature:	Inactivated at 50-60°C for a minimum of 30 minutes; infectivity is preserved when frozen
pH:	Susceptible to acidic pH

Chemicals/Disinfectants: Inactivated by organic solvents such as 3-8% formaldehyde and 2% glutaraldehyde; 2-3% hydrogen peroxide, 500-5,000 ppm available chlorine, alcohol, 1% iodine, and phenol iodophors are also effective

Survival:	Inactivated by ultraviolet light and gamma radiation

EPIDEMIOLOGY

Hosts

- Humans (*Homo sapiens*)
- Neotropical mammals
    - Anteaters (*Tamandua tetradactyla, Cyclopes didactylus*)
    - Epauletted fruit bat (*Epomophorus* spp.), but role in disease ecology unknown
    - Kinkajous (*Potos flavus*)
    - Rodents
        - Fat mice (*Steatomys opimus*)
- Non-human primates
    - Baboons (*Papio* spp.)
    - Bush babies (*Galago senegalensis, G. crassicaudatus*)
    - Capuchin monkeys (*Cebus* spp.)
    - Chimpanzees (*Pan* spp.)
    - Colobus monkeys (*Colobus* spp., *Procolobus* spp.)
    - Guenons, grivets, and green monkeys (*Chlorocebus* spp., *Cercopithecus* spp.)
    - Howler monkeys (*Alouatta* spp.)
    - Mangabeys (*Cercocebus albigena*)
    - Night monkeys (*Aotus trivirgatus*)
    - Patas/red monkeys (*Erythrocebus* spp.)
    - Spider monkeys (*Ateles* spp.)
    - Squirrel monkeys (*Saimiri sciureus*)
    - Tamarins (Family *Callitrichidae*)

Vectors

- *Aedes* mosquito species
    - *Ae. aegypti*
    - *Ae. africanus*
    - *Ae. bromeliae*
    - *Ae. (Ochlerotatus) fulvus*
    - *Ae. furcifertaylori*
    - *Ae. luteocephalus*
- *Sabethes chloropterus*
- *Haemagogus* spp., especially *Hg. janthinomys* and *Hg. equinus*
- *Diceromyia* spp.
- *Amblyomma variegatum* has been shown to transmit YFV in a laboratory setting, but the role of these ticks in natural transmission events is uncertain

Transmission

- Haematophagous mosquitoes (vector-borne)
- Some mosquito species are capable of transovarial transmission

Sources

- Infected hosts (with sufficient circulating viral titres for transmission)
- Infected mosquitoes

Occurrence

YFV is primarily found in Africa and Central and South America. There is concern regarding potential establishment of YFV in Asia and North America due to the presence of presumed competent vector species.

In the Americas, many monkey populations are not large enough to sustain YFV at endemic levels. The virus is referred to as a “wandering epidemic” because it slowly moves through large populations and returns to an area once there are sufficient numbers of susceptible individuals. There have been several epizootics in Brazil. In the Amazon, epizootics occur in a cyclical fashion in both humans and nonhuman primates approximately every 7-14 years.

In Africa, YFV is maintained in primate populations in forest canopies, forest galleries, and savannahs. Many *Aedes* species in Africa readily feed upon both humans and non-human primates.

DIAGNOSIS

Clinical disease in neotropical monkeys is generally more severe than in African primates. There is a 3-6 day incubation period.

Clinical diagnosis

Clinical signs in non-human primates include a sudden onset of fever, depression, vomiting, lumbosacral pain, myalgia, and haemorrhage; however, many individuals can remain asymptomatic. After 3-4 days, there may be subsequent resolution of clinical signs or development of biphasic, so-called “toxic” disease, characterised by recurrent fever, bradycardia, conjunctival congestion, gingival haemorrhage, epistaxis, haematemesis, epigastric pain, dehydration, and prostration. Gastrointestinal and uterine haemorrhage, marked icterus, hepatic and renal failure, shock, convulsions, and death can occur in severe cases.

Lesions

- Blood-filled gastrointestinal tract
- Hepatic enlargement with a decreased lobular pattern
    - Degeneration and lytic necrosis of midzonal regions, hepatocyte apoptosis
        - Sparing of cells adjacent to central veins and portal triads
    - Hyaline intracytoplasmic bodies (Councilman bodies) and intranuclear eosinophilic granular inclusions
    - Centrilobular fatty change
    - No disruption of reticular architecture
- Renal tubular epithelial degeneration and necrosis
- Lymphoid depletion of the spleen and lymph nodes
- Classic histopathological features are present only during acute and subacute stages of disease
- Histopathological features may vary somewhat in their severity and presentation between species

Differential diagnoses

- Dengue haemorrhagic fever
- Simian haemorrhagic fever
- Marburg haemorrhagic fever
- Viral hepatitis

Laboratory diagnosis

Samples

For isolation of agent

- Peripheral blood
- Liver
    - Fresh tissue is more reliable for nucleic acid detection but formalin-fixed tissues may be used if necessary
- There are data to support the use of semen and urine as diagnostic fluids in humans but has not been proven in primates.

Serological tests

- Serum
- Whole blood

Procedures

Identification of the agent

- Histopathology is preferred when antemortem serum or blood is unavailable, when samples are not suitable for genome detection or virus isolation, or when there is severe haemolysis or autolysis
- Virus isolation
- Reverse-transcriptase polymerase chain reaction (RT-PCR)
    - Avoid the use of assays specifically targeted towards vaccine strains
    - Choose assays targeted towards American and African strains as appropriate
- Antigen-capture enzyme linked immunosorbent assay (ELISA)
- Immunohistochemistry (IHC)
    - Kupffer cells, renal tubular epithelial cells, and myocardial fibers are particularly useful

Serological tests

- Antibody-capture ELISA
    - The presence of IgM in the absence of prior vaccination is strongly suggestive of infection, but other flaviviruses must be ruled out
    - Serology is prone to cross-reactivity with other flaviviruses
- Paired acute and convalescent IgG titres
- Immunoperoxidase monolayer assay
- Indirect immunofluorescence
- Multiplex microsphere immunoassay (MIA)
- Plaque reduction neutralization assay (PRNT) or virus neutralization test (VNT)
    - Current gold standard assays
    - Requires multiple days to perform and may therefore not be well-suited to inform outbreak responses

PREVENTION AND CONTROL

Sanitary prophylaxis

- Do not allow accumulation of standing water as these conditions are favorable for mosquito reproduction

Medical prophylaxis

- There is an effective attenuated vaccine available for human use
    - Rare cases of yellow fever vaccine-associated viscerotropic or neurotropic diseases have occurred and can be fatal
- Mosquito control in populated areas
    - Control is costly and often not continuously performed due to other financial demands or limitations within a community
    - Elimination of the sylvatic cycle is not feasible

POTENTIAL IMPACTS OF DISEASE AGENT BEYOND CLINICAL ILLNESS

Risks to public health

- YFV is a zoonotic disease that is capable of causing severe illness in humans.
- In the tropics, outbreaks of sylvatic cycles of YFV in humans are often called “woodcutter’s disease”; felling of trees in the forest causes mosquitoes to come to ground level and creates an opportunity for human (and other animal species) exposure. At this point, individuals working in the forest are frequently bitten by the mosquitoes, and some mosquitoes will travel to clearer tracts of land (ex: agricultural fields). Infected forest workers then return to more densely populated areas and become a source of virus for other mosquitoes. This then begins the urban transmission cycle.
- Reduce the likelihood of being bitten by a mosquito by wearing long-sleeved, loose-fitting clothing (preferably treated with permethrins), using insect repellant, and using mosquito netting and screens.

Risks to agriculture

- There is no direct risk to the agricultural industry, however, if working individuals become incapacitated due to YFV infection, they will not be able to perform the duties required of them. This may have negative impacts on farms and livestock ranches.

REFERENCES AND OTHER INFORMATION

- Alberta Health (2018). Yellow fever. *Public Health Management Guidelines* Accessed 2020: https://open.alberta.ca/dataset/adfb8959-5a88-4b7c-a2f0-8cefb7dc6b09/resource/1afe9e80-9200-482b-9e4a-d9af69aceeb0/download/guidelines-yellow-fever-2018-05.pdf

- Carrington, C. V. F., & Auguste, A. J. (2013). Evolutionary and ecological factors underlying the tempo and distribution of yellow fever virus activity. *Infection, Genetics, and Ecolution, 13*, 198-210.
- Centers for Disease Control and Prevention (2019). Yellow fever: prevention. Accessed 2020: https://www.cdc.gov/yellowfever/prevention/index.html
- Domingo, C., Charrel, R. N., Schmidt-Chanasit, J., Zeller, H., & Reusken, C. (2018). Yellow fever in the diagnostics laboratory. *Emerging Microbes and Infections, 7*, 129.
- Fenner, F. J. (2011). Yellow fever virus. In N. J. MacLachlan and E. J. Dubovi (Eds.), *Fenner's Veterinary Virology* (4th ed., p. 474). Elsevier.
- Jácome, R., Carrasco-Hernández, R., Campillo-Balderas, J. A., López-Vidal, Y., Lazcano, A., et al. (2019). A yellow flag on the horizon: the looming threat of yellow fever to North America. *International Journal of Infectious Disease, 87*, 143-150.
- Moreno, E. S., Spinola, R., Tengan, C. H., Brasil, R. A., et al. (2013). Yellow fever epizootics in non-human primates, São Paulo State, Brazil, 2008-2009. *Revista do Instituto de Medicina Tropical de São Paulo, 55*(1), 45-50.
- Public Health Agency of Canada (2010). Pathogen safety data sheets: infectious substances - yellow fever virus. Accessed 2020: https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment/yellow-fever-virus.html
- Valentine, M. J., Murdock, C. C., & Kelly, P. J. (2019). Sylvatic cycles of arboviruses in non-human primates. *Parasites and Vectors, 12*(1), 463.
- Wasserman, S., Tambyah, P., & Lim, P. L. (2016). Yellow fever cases in Asia: primed for an epidemic. *International Journal of Infectious Disease, 48*, 98-103.
- Wermelinger, E. D. & de Carvalho, R. W. (2016). Methods and procedures used in *Aedes aegypti* control in the successful campaign for yellow fever prophylaxis in Rio de Janeiro, Brazil, in 1928 and 1929. *Epidemiologia e Serviços de Saúde, 25*(4), 837-844.
- World Health Organisation (2019). Yellow fever. Accessed 2020: https://www.who.int/news-room/fact-sheets/detail/yellow-fever
- Yuill, T. M. & Seymour, C. (2001). Yellow fever. In E. S. Williams and I. K. Barker (Eds.), *Infectious Diseases of WIld Mammals* (3rd ed., pp. 98-100). Iowa State Press.

*

* *

The OIE will periodically update the OIE Technical Disease Cards. Please send relevant new references and proposed modifications to the OIE Science Department (scientific.dept@oie.int). Last updated 2020. Written by Samantha Gieger and Erin Furmaga with assistance from the USGS National Wildlife Health Center.