

48 | YELLOW FEVER VIRUS AND YELLOW FEVER VACCINE

48.1 | Disease agent

- Yellow fever virus (YFV)

48.2 | Disease agent characteristics

- Family: *Flaviviridae*; genus *Flavivirus*.
- Morphology: Enveloped, spherical, particles 40-60 nm in diameter with icosahedral nucleocapsid symmetry and surface projections; virions contain three structural proteins: C (capsid), E (the major envelope protein) and M (membrane) and produce seven nonstructural proteins. The M protein is a small proteolytic fragment of the precursor (pr)M protein produced during viral maturation. There is one serotype of YFV associated with seven genotypes.
- Nucleic acid: Linear, positive-sense, single-stranded RNA, ~11 kb long
- Physicochemical properties: Inactivated by heating for 10 min at >56°C; half-life of 7 h at 37°C; sensitive to treatment with lipid solvents, detergents, ether, trypsin, chloroform, formaldehyde, and β -propiolactone; infectivity reduced after exposure to irradiation and inactivated at pH 1–3.

48.3 | Disease name

- Yellow fever (YF)

48.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical, although transfusion transmission might potentially occur due to viremia in infected, asymptomatic individuals.
- Public perception and/or regulatory concern regarding blood safety: Absent in nonendemic areas including the United States and Canada.
- Public concern regarding disease agent: Absent in nonendemic areas; high in endemic areas and elsewhere during epidemics.

48.5 | Background

- YF was brought to the Western hemisphere by the slave trade with the first epidemic reported in the Yucatan in

1648. Walter Reed and colleagues confirmed that the infection was arthropod-borne and that mosquitoes were the putative vector. YFV was not isolated until 1927, the first human virus to be identified. In 1937, the live-attenuated 17D vaccine was obtained by passaging virus recovered from a Ghanaian patient (the Asibi strain) 176 times through a variety of hosts. Following extensive efforts by PAHO, YFV was eradicated in 20 Latin American countries including Brazil, but viral resistance, concern about the effects of DDT, lack of funding and other causes led to its reemergence.

- Natural distribution of YF is throughout the tropical Americas and sub-Saharan Africa. Through the early 1900s epidemics, outbreaks and clusters of cases occurred in areas of Central and North America, islands of the Caribbean and southern Europe infested with *Aedes* species. Where competent vectors and susceptible hosts are present, these areas are at risk should the virus be reintroduced.
- The last epidemic of YF in North America occurred in New Orleans in 1905. The largest outbreak of YF in the Americas in the last 50 years took place in Brazil between 2016 and 2018 with 2154 human cases and 745 deaths. This was likely the result of the virus expanding from the Amazon region, where it is endemic, to other areas in Brazil where the boundaries between the jungle and urban areas have become blurred.
- More than 130 arboviruses are known to cause human disease; most of public health importance belong to the genera: *Flavivirus*, *Alphavirus* and *Orthobunyavirus*. Many are nationally notifiable via state reporting to the US CDC (ArboNet); for example, dengue virus, Zika virus, California serogroup viruses, chikungunya virus, eastern equine encephalitis virus, Powassan virus, St Louis encephalitis virus, West Nile virus, western equine encephalitis virus and YFV.

48.6 | Common human exposure routes

- Mosquito-borne; transmission occurs through an infected mosquito to susceptible human or nonhuman vertebrate host (principally other primates).

48.7 | Likelihood of secondary transmission

- Unlikely if mosquito access to infected and susceptible individuals is prevented.
- Transmission of YF17D vaccine virus from recently immunized donors to recipients and through breast milk has been reported.

48.8 | At-risk populations

- Unvaccinated and other nonimmune individuals in endemic and epidemic areas. These might include forestry workers, oilfield workers and agricultural workers in forests where YFV may be found, military personnel, travelers, and people in urban settings where YFV has been introduced.

48.9 | Vectors and reservoir involved

- An urban cycle of YFV infection occurs primarily via *Aedes aegypti* or *Ae. albopictus* mosquitoes. The extrinsic incubation period in the urban vector is ~10 days (range, 2–37 days). The sylvatic (rural or jungle) cycle depends on the presence of other *Aedes* spp. and other mosquito species, such as *Haemagogus* spp. and *Sabethes* spp. YFV is maintained in natural cycles in rural, forested areas by mosquito transmission between nonhuman primates of many species. The sylvatic or “savanna” cycle (aedine mosquitoes to humans and nonhuman primates and vice versa) in Africa occurs in areas characterized by the juxtaposition of rain forests and grasslands. Infected mosquitoes remain infected throughout their life and pass the virus transovarially through infected eggs. Ticks have been shown to be persistently infected with YFV and transovarial transmission of YFV has been demonstrated in mosquitoes, probably accounting for virus persistence in the absence of enzootic transmission.
- *Aedes aegypti* and/or *Ae. albopictus* are present in a number of areas of the continental United States and Hawaii and in Puerto Rico.

48.10 | Blood Phase

- High-titer viremia is detectable 3–6 days after infection at the time when the patient becomes markedly ill; uninfected mosquitoes can become infected by feeding on the patient at this time. Antibodies are produced 7–10 days after infection, resulting in the reduction of viremia.

48.11 | Survival/persistence in blood products

- Unknown.
- Work published in 1929–1930 to determine the persistence of YFV during passage in *Rhesus* monkeys demonstrated that citrated or clotted blood was infectious for 35 days and for 60 days if preserved with glycerol.

48.12 | Transmission by blood transfusion

- A 2009 report describes the outcomes of transfusing blood products collected from 89 US active-duty military trainees who had received YF vaccine 4 days before donation. Despite recalling components, six blood products (3 platelets, 2 FFP and 1 packed RBC unit) were transfused into five recipients. No clinical or laboratory abnormalities attributable to YF vaccine occurred in four, including a premature infant exposed to RBCs. The fifth patient died of his underlying disease. Among the four surviving patients, three developed IgM anti-YFV 26–37 days posttransfusion, suggesting transfusion transmission of vaccine virus. Two of the three IgM-positive recipients (platelets, FFP) had received a YF vaccine at least 20 years earlier.
- A second report describes transfusion transmission of the attenuated YFV vaccine in 2021 from a deceased organ donor (from traumatic brain injury) who was transfused with one of two apheresis RBCs 3 days before organ procurement (and 24 days after donation), collected from a blood donor who had received YF vaccine 6 days prior to blood donation.
 - The blood donor failed to provide deferring information related to recent YF vaccination to the blood collection facility during the donor history despite the required direct query regarding recent vaccination.
 - Four patients received a heart, liver and 2 kidneys from the organ donor. Metagenomic next-generation sequencing (mNGS) of CSF from one of 4 organ recipients (kidney) identified a single 106 base-pair read of YFV at subthreshold reporting levels.
 - All 4 developed fever, and neurologic signs and symptoms. Three progressed to severe encephalitis. Two died from complications of their illness. Neither YFV antigen nor nucleic acid was detected in archived organ donor serum, nor in recipient sera or CSF. Postmortem brain from the heart recipient was positive for YF RNA by RT-PCR. Sequencing was consistent with the vaccine virus. All four recipients were YF-IgM positive in CSF and/or serum.
 - Three recipients seroconverted with both IgM and neutralizing antibodies after transplant.
 - The second apheresis RBC from the blood donation was transfused to a different recipient who subsequently died of cancer. No adverse events attributable to the vaccine virus were identified on medical record review.

- Based on the live, attenuated vaccine virus results, it may be assumed that wild-type YFV can be transmitted by blood transfusion if the donor blood was collected early after infection prior to the occurrence of symptomatic disease. Because only 15%–25% of naturally infected humans develop classic YF, blood donations from those who are infected but asymptomatic represent a transmission risk.

48.13 | Cases/frequency in population

- Based on adjustments for underreporting, WHO estimates that the annual number of YF cases worldwide is 200,000 with 30,000 deaths. Unless imported, YF is limited to areas of sub-Saharan Africa and Central and South America.
 - Sub-Saharan Africa, particularly West Africa, reports the most cases (about 90% of cases reported annually worldwide). In South America, YF occurs mostly in the Amazon River basin and adjacent areas. Annual incidence rates probably reflect highly variable reporting.
 - The South American genotypes may be more virulent than the African genotypes but confounding factors (underreporting, reporting only severe cases, vaccine application, immunity due to cross-reacting flaviviruses, fluctuating epizootic activity, and transmission by vectors of differing competence, etc.) may explain these differences.
- YF is a very rare cause of illness in US travelers, possibly mitigated by vaccination.
- Over 400 million doses of YF 17D vaccine have been distributed worldwide. Sanofi Pasteur currently manufactures the only YF vaccine approved for use in the United States. After a period of shortage due to manufacturing problems that required use of an alternative Sanofi product (Stamaril) under an expanded access IND, the availability of YF vaccine was restored in April 2021.
- In the United States, YF 17D-associated vaccine disease has an incidence of 0.4 cases per 100,000 vaccinees, with the highest incidence in those >60 years of age (1.6 per 100,000) and infants <6 months of age (50–400 per 100,000).

48.14 | Incubation period

- 3–6 days after infection but can be as long as 14 days.

48.15 | Likelihood of clinical disease

- 15–25% of infected humans develop classic YF. Mild YF cannot be distinguished from many other causes of febrile illness.

48.16 | Primary disease symptoms

- This ranges from nonspecific flu-like illness to classic YF, the latter being potentially lethal. Classic YF can have three stages: infection, remission and intoxication, which are not clearly demarcated. The first or “acute” phase, is characterized by headache, fever, chills, muscle and joint pain, loss of appetite, vomiting and jaundice. The “yellow” in the name reflects the development of jaundice. In the second stage, which may occur 3–4 days after onset, the patient may go into temporary remission and symptoms subside. Most patients who recover do so at this time. However, if a third stage is to occur (in about 15%–25% of patients), it does so within 24 h, when the patient becomes severely ill. Although viruses are not detected in blood, neutralizing antibodies are present. Fever rises, pulse slows, moderate jaundice may be observed, abdominal pain is present, vomiting is persistent, and the vomitus and feces contain blood blackened by gastric juices, that is, “black vomit.” Albuminuria is almost always present, and the patient becomes oliguric and “toxic” due to multi-organ dysfunction or failure. It is at this stage when heart, liver, and kidneys fail, bleeding (hemorrhaging) from the mouth, nose, eyes, or stomach may be seen, and brain abnormalities become apparent. Death may occur within 7–10 days, or the patient might remain in this condition for 3–4 days to 2 weeks, after which the illness will either persist for many months followed by recovery without significant organ damage or lead to death in about 50%, mostly attributable to cardiac failure.

48.17 | Severity of clinical disease

- The frequency of severe disease or classic YF (15%–25% of infected, symptomatic persons) is similar in Africa and in the Americas. Data from the Brazil YFV outbreak in 2018 and 2019 included two cases of late-relapsing hepatitis in returning travelers, and in another study 26 of 71 cases had a relapse of their hepatitis suggesting that for some patients the virus may remain in the liver for a longer period of time after acute infection than previously recognized. Relapsing

hepatitis was defined as a new elevation in aminotransferase levels within 6 months after an improvement in or normalization of liver function.

48.18 | Mortality

- The overall case-fatality rate reported between 1985 and 2004 in Africa was approximately 24% and in South America was 58%; current range commonly reported for all regions is 20%–60%.

48.19 | Chronic carriage

- None

48.20 | Treatment available/efficacious

- Supportive treatment only

48.21 | Agent-specific screening question(s)

- Travel-related questions designed to prevent transfusion-transmitted malaria theoretically will interdict YF acquired where the two infections coexist.
- The Donor History Questionnaire, when appropriately applied and responded to, should prevent transmission of the 17D vaccine virus: “In the past 8 weeks, have you had any vaccinations or other shots?” AABB 33rd edition of Standards requires a 2-week blood donation deferral after receipt of a YF vaccine.

48.22 | Laboratory test(s) available

- Many techniques have been applied to the diagnosis of YF and all are useful. YFV PCR positivity of blood or other tissues is a specific, sensitive, and rapid method; detection of YFV antigens in human and primate tissues also is useful. Virus isolation is the most specific method but requires extended incubation in laboratory animals and cell culture that can delay diagnosis compared to PCR and serology.
- IgM and neutralizing IgG antibodies are detectable within about a week after infection. IgM peaks within a month after infection and declines thereafter, whereas neutralizing antibody levels persist for years after onset. Serodiagnosis can most rapidly and specifically be done with IgM-capture assays, although other methods (neutralization,

hemagglutination-inhibition, complement-fixation, immunofluorescence) have been shown to be useful.

- In areas hyperendemic for multiple flaviviruses, cross-reactive antibodies to other viruses may confound an accurate diagnosis of YF. This is less relevant with highly specific neutralization assays (e.g., plaque-reduction neutralization testing).

48.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists.
- A prospective donor with a history of YF must have recovered, be afebrile and asymptomatic on the day of donation. Malaria deferral should suffice for most situations regarding travel.
- 2-week deferral after live attenuated virus immunization with the YF 17D vaccine.

48.24 | Impact on blood availability

- Agent-specific screening question(s); Not applicable but would be negligible except in settings where mass YF vaccination may occur (e.g., in the 2-week period following vaccination among military recruits).
- Laboratory test(s) available: Not applicable

48.25 | Impact on blood safety

- Agent-specific screening question(s): Not applicable

48.26 | Leukoreduction efficacy

- No data available. Plasma viremia makes a clinically significant impact unlikely.

48.27 | Pathogen reduction efficacy for plasma derivatives

- Multiple pathogen reduction steps used in the fractionation process have been shown to be robust in the removal of enveloped viruses.

48.28 | Other prevention measures

- Vaccination with live-attenuated YFV vaccine; vaccine available since the 1940s produced in embryonated eggs.

- In the United States, recommended for travelers and active-duty military members visiting endemic areas of sub-Saharan Africa and Central/South America and some countries require proof of vaccination if traveling from endemic areas.
- About half of vaccinees develop low-grade viremia that can be detected 3–7 days following vaccination; protective neutralizing antibody levels are produced in 99% of vaccinees by day 30 following vaccination.
- Hypersensitivity, viscerotropic or neurotropic disease occurs only rarely, and then 7–21 days after vaccination, with generally good recovery.
- Avoidance of mosquitoes in endemic or epidemic areas; mosquito control.
- Multiple inactivation procedures involving a chemical treatment with visible light or UVA, or UVC alone have demonstrated the ability to inactivate YFV in plasma and platelet concentrates, respectively.
- Flaviviruses are inactivated by multiple pathogen reduction processes that are available or in development for labile components.

48.29 | Other comments

- Due to the increased risk of vaccine-associated encephalitis, breast-feeding mothers should avoid vaccination, and vaccination should be avoided for infants prior to 6 months of age and limited at less than 9 months of age except in situations where possible YFV exposure cannot be avoided or postponed.
 - In a study to determine whether YF vaccine administered in pregnancy causes fetal infection, women who were vaccinated during unrecognized pregnancy in a mass campaign in Trinidad were studied retrospectively. One of 41 infants had IgM anti-YFV antibody and elevated neutralizing antibodies to YFV, indicating congenital infection. The infant, the first reported case of YFV infection after immunization in pregnancy, was delivered after an uncomplicated full-term pregnancy and appeared normal.
 - One confirmed and one probable case of YFV transmission through breast feeding; both infants developed meningoencephalitis and recovered completely.
 - A mother received YF vaccine and 5 days later developed headache, malaise and low-grade fever; her infant was exclusively breast-fed and hospitalized at 23 days of age with symptom onset at 8 days following vaccine receipt. YFV RNA of identical nucleotide sequence to the 17D YFV RNA was detected by RT-PCR in the infant's cerebrospinal fluid (CSF) with IgM present in serum and CSF.
 - A 5-week-old infant who had been breast-feeding developed YF following his mother's receipt of YF vaccine when the infant was 10 days of age. At presentation, a serum sample from the infant was IgM positive with a plaque-reduction neutralization titer of 1:5120 and YF hemagglutination inhibition titer of 1:160; CSF was also IgM positive; RT-PCR of CSF was negative.

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