

Yellow Fever Virus and Yellow Fever Vaccine

Disease Agent:

- Yellow fever virus (YFV)

Disease Agent Characteristics:

- Family: *Flaviviridae*; genus *Flavivirus*
- Morphology: Enveloped, spherical, particles 50 nm in diameter with icosahedral nucleocapsid symmetry and surface projections; virions contain three structural proteins, C, E (the major envelope protein) and either prM in immature virions or M in mature virions and seven non-structural proteins. There are seven genotypes.
- Nucleic acid: Linear, positive-sense, single-stranded RNA, ~11 kb long
- Physicochemical properties: Virions are stable at slightly alkaline pH 8.0 and low temperatures (particularly at -60°C and below), readily inactivated at acidic pH (<4.0), temperatures equal to or above 56°C for 30 min, in organic solvents, detergents, ultraviolet light, gamma irradiation, and various disinfectants.

Disease Name:

- Yellow fever (YF)

Priority Level:

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical, although transfusion transmission presumably occurs due to viremia in infected, asymptomatic individuals
- Public perception and/or regulatory concern regarding blood safety: Absent in nonendemic areas including the US and Canada
- Public concern regarding disease agent: Absent in non-endemic areas; high in endemic areas and during epidemics

Background:

- YF recognized, clinically described and named in 1750, but YFV was not isolated until 1900.
- Natural distribution of YF is throughout the tropical Americas and sub-Saharan Africa. Epidemics, outbreaks and clusters of cases occurred in *Aedes aegypti* (mosquito)-infested areas of Central and North America, islands of the Caribbean and southern Europe through the early 1900s. These areas may still be at risk, should the virus be reintroduced.
- The last epidemic of yellow fever in North America occurred in New Orleans in 1905.

Common Human Exposure Routes:

- Vector-borne; transmission occurs through a mosquito-human or other vertebrate host (principally other primates)-mosquito cycle.

Likelihood of Secondary Transmission:

- Unlikely if mosquito access to infected individuals is prevented.
- Transmission of YF 17D vaccine virus from recently immunized donors to recipients and through breast milk has been reported.

At-Risk Populations:

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

Vectors and Reservoir Involved:

- An urban cycle of YFV is accomplished via *Aedes aegypti* 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*. YFV is maintained in natural cycles in rural, forested areas by mosquito transmission between various nonhuman primates of many species. The "savannah" 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. 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.

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 to YFV are produced 7-10 days after infection, resulting in the reduction of viremia.

Survival/Persistence in Blood Products:

- Unknown
- In one documented event of YF vaccine-associated transfusion transmission, YFV IgM seroconversion occurred 33 days following receipt of a single unit of Platelets, at 36 days following receipt of a single unit of irradiated Platelets and 26 days following transfusion of a Fresh Frozen Plasma (FFP) unit. No transmission occurred in a premature infant who received irradiated red blood cells at 37 days posttransfusion.
- Work published in 1929-1930 to determine the persistence of YFV through passage in Rhesus monkeys demonstrated that citrated or clotted blood was infectious for 35 days and for 60 days if preserved with glycerol.

Transmission by Blood Transfusion:

- In a single report, blood products collected from 89 US active duty military trainees, who had received YF vaccine 4

days prior to donation, were investigated. Despite recalling components, six blood products (3 Platelets, 2 FFP and 1 packed Red Blood Cell unit) were transfused into five recipients. No clinical or laboratory abnormalities attributable to YF vaccine occurred in four. The fifth died of his underlying disease. Among the four surviving patients, three developed IgM antibody to YFV 26-36 days posttransfusion, suggesting transfusion transmission of vaccine virus. Two of the three recipients (Platelets, FFP) had received the YF vaccine at least 20 years earlier.

- Only 15-25% of naturally infected humans develop classic YF. Blood donations from the asymptomatic group may be infectious. Based on the live, attenuated vaccine virus results, it should be assumed that wild-type YFV can be transmitted by blood transfusion if the donor blood was to be collected in the several days to weeks after infection.

Cases/Frequency in Population:

- Based on adjustments for underreporting, WHO estimated the annual number of YF cases worldwide is 200,000, with a resultant 30,000 deaths. Unless imported, YF is limited to areas of Africa and Central and South America.
 - 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 area. Reported 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 account for these differences.
- YF is a very rare cause of illness in US travelers.
- Over 400 million doses of YF 17D vaccine have been distributed worldwide with 400,000 to 600,000 doses of this vaccine distributed annually in the US (personal communication, Sanofi Pasteur US, February 22, 2011).
- In the US, YF 17D-associated disease has an incidence of 0.4 cases per 100,000 vaccinees, with the highest incidences in those >60 years (1.6 per 100,000) and infants <6 months of age (50-400 per 100,000).

Incubation Period:

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

Likelihood of Clinical Disease:

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

Primary Disease Symptoms:

- Ranges from nonspecific flu-like illness to classic YF, the latter being potentially lethal. Classic YF is said to 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 hours, when the patient becomes severely ill. At this time, although virus is not detected in the 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, i.e., "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. The patient might die or remain in this condition for 3-4 days to 2 weeks, after which illness will persist for many months followed by recovery without significant organ damage or death in about 50%, probably due to cardiac failure.

Severity of Clinical Disease:

- The mildest and the most severe cases of YF are similar in Africa and in the Americas.
- Approximately 15-25% of infected, symptomatic persons develop severe disease.

Mortality:

- The overall case-fatality rate reported between 1985 and 2004 in Africa was approximately 24% and in South America was 58%.

Chronic Carriage:

- None

Treatment Available/Efficacious:

- Supportive treatment only

Agent-Specific Screening Question(s):

- 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 vaccination or other shots?" An affirmative answer for YF vaccine requires 2 week deferral.

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 is also 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 antibody peaks within a month after infection and declines thereafter, whereas neutralizing antibodies continue to increase in titer for weeks to months or years after onset. Serodiagnosis can most rapidly and specifically be done with IgM-capture ELISA, 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 use of highly specific neutralization assays (e.g. plaque-reduction neutralization testing).

Currently Recommended Donor Deferral Period:

- No FDA Guidance or AABB Standard exists.
- A prospective donor with a history of YF or YF vaccine must have recovered, be afebrile and asymptomatic on the day of donation.
- 2 weeks after live virus immunization with the YF 17D vaccine.

Impact on Blood Availability:

- Agent-specific screening question(s); Not applicable
- Laboratory test(s) available: Negligible except in settings where mass YF vaccination may occur (e.g., among military recruits).

Impact on Blood Safety:

- Agent-specific screening question(s); Not applicable
- Laboratory test(s) available: Not applicable

Leukoreduction Efficacy:

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

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.

Other Prevention Measures:

- Vaccination with YFV; vaccine available since the 1940s produced in embryonated eggs.
 - In the US, recommended for travelers and active duty military members visiting endemic areas of sub-Saharan Africa and Central/South America.
 - About half of vaccinees develop low-grade viremia that can be detected 3-7 days following vaccination; protec-

tion neutralizing antibody levels are produced in 99% of vaccinees by day 30 following vaccination.

- Serious 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.
- Elimination/reduction in mosquito breeding sites.

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 to 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 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 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.

Suggested Reading:

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