

SUBJECT: Yellow Fever Disease and Yellow Fever Vaccine

1. Purpose. To describe Yellow Fever disease and the vaccine to prevent it.
2. Facts.
  - a. Microbiology. Yellow Fever virus (YFV) is a single-stranded RNA virus (arbovirus) that belongs to the genus *Flavivirus*. Transmission of YFV occurs via the bite of an infected mosquito. Humans and nonhuman primates are the main reservoirs of the virus, and anthroponotic (human-to-vector-to-human) transmission occurs. YFV has 3 transmission cycles: sylvatic (jungle), intermediate (savannah), and urban. It is related to the Japanese Encephalitis, St. Louis Encephalitis, and West Nile viruses.
  - b. Epidemiology. Yellow Fever disease (YF) occurs in sub-Saharan Africa and tropical South America, where it is endemic and intermittently epidemic. YF risk is determined by immunization status as well as destination-specific (e.g., local rate of virus transmission) and travel-associated (e.g., exposure duration, occupational and recreational activities, season) factors. Most YF in humans is due to sylvatic or intermediate transmission cycles. Urban YF occurs periodically in Africa and sporadically in the Americas. In areas of Africa with persistent circulation of YFV, natural immunity accumulates with age; thus, infants and children are at greatest risk for disease. In South America, YF occurs most frequently in unimmunized young people exposed to mosquitos while working in forested areas. Humans infected with YFV experience the highest levels of viremia (presence of viruses in the blood) shortly before onset of fever and for the first 3–5 days of illness, during which time they can transmit the virus to mosquitoes. Bloodborne transmission can theoretically occur, and one case of fatal perinatal transmission of wild-type YFV has been documented.
  - c. Disease. YF is a nationally notifiable disease. Most people infected with YFV have minimal or no symptoms. For those who develop symptoms, the incubation period is typically 3–6 days. The initial illness is nonspecific: backache, chills, fever, headache, myalgia, nausea, vomiting, and fatigue. Although most improve after initial presentation, approximately 12% of patients progress to a more serious form of the disease after a brief remission of  $\leq 48$  hours. These patients experience hemorrhagic symptoms, jaundice, and eventually shock and multisystem organ failure. The fatality rate for severe cases is 30%–60%.
  - d. Vaccine. Only one YF vaccine (YF-VAX, Sanofi Pasteur) is currently licensed for use in the United States. YF-VAX is a live attenuated vaccine

containing the 17D-204 strain of yellow-fever virus cultured in chicken embryos. The vaccine is preservative-free, lyophilized (freeze dried), and contains sorbitol and gelatin as a stabilizer. Each vial of vaccine is supplied with a separate vial of sterile diluent, which contains preservative-free Sodium Chloride Injection USP. The vaccine and diluent vial stoppers are not made with natural rubber latex. Before reconstitution, YF-VAX is a pinkish color. After reconstitution, it is a slight pink-brown suspension. YF-VAX cannot be frozen: it must be stored at 2°C - 8°C (35° - 46°F) and used or discarded within one hour of reconstitution.

- e. Immunization. The Advisory Committee on Immunization Practices (ACIP) recommends YF vaccine for people aged  $\geq 9$  months who are living in or traveling to areas in Africa or South America with risk for YFV transmission. YF vaccine is administered as a single 0.5 mL dose given subcutaneously. YF vaccine should be given at the same time as other live viral vaccines or separated by  $\geq 30$  days. Inactivated vaccines and oral Ty21a typhoid vaccine (Vivotif, a live bacterial vaccine) can be administered simultaneously or at any interval before or after YF vaccine. Routine booster doses are no longer recommended, as a single dose of YF vaccine provides lifelong protection for most people. ACIP does recommend booster doses for certain individuals who:
- Were pregnant when they received their initial dose of vaccine
    - Give 1 additional dose before next YF risk
  - Received a hematopoietic stem cell transplant after receiving a dose of YF vaccine
    - Give 1 additional dose before next YF risk if they are sufficiently immunocompetent
  - Were infected with HIV when they received their last dose of YF vaccine
    - Give a dose every 10 years if they continue to be at risk for YF

Laboratory workers who routinely handle wild-type YFV should have titers measured at least every 10 years to determine the need for booster doses. Clinicians can also consider administering a booster dose to travelers who received their last dose of YF vaccine  $\geq 10$  years ago if they will be in higher-risk settings, including those planning prolonged stays in endemic areas, traveling to endemic areas, or visiting areas with ongoing outbreaks.

- f. Contraindications and Precautions. YF vaccine is contraindicated for individuals who:
- Are  $< 6$  months of age
  - Are allergic to a vaccine component
    - If vaccination is essential, skin testing as described in the

vaccine package insert should be performed under close medical supervision and with Allergy consultation.

- Have symptomatic HIV infection or CD4 T lymphocyte counts < 200/mL (or < 15% of total lymphocytes in children aged < 6 years)
- Have primary immunodeficiencies
- Are receiving immunosuppressive and immunomodulatory therapies
- Have a history of malignant neoplasms or organ transplantation
- Have a thymus disorder associated with abnormal immune cell function

Precautions to YF vaccine receipt are:

- Age 6–8 months
- Age ≥ 60 years (risk especially high for primary vaccinees)
- Breastfeeding (see Adverse Events)
- Asymptomatic HIV infection with CD4 T lymphocyte counts 200–499/mL (or 15%–24% of total lymphocytes in children aged < 6 years)
- Pregnancy: if travel is unavoidable and the risk for YF virus exposure outweighs vaccination risk, recommending vaccination is appropriate.

- g. Adverse Events. Reactions to YF vaccine are generally mild; 10%–30% of vaccinees report mild systemic symptoms, including headache, low-grade fever, and myalgia that begin within days after vaccination and last 5–10 days. Immediate hypersensitivity reactions, characterized by bronchospasm, rash, or urticaria, are uncommon. Anaphylaxis after YF vaccine is reported as 1.3 cases per 100,000 doses. All individuals should be observed for ≥ 15 minutes after receipt of any vaccine. Clinicians should be prepared to manage a medical emergency related to the administration of vaccines by having a written emergency medical protocol available, as well as appropriate equipment and medications. All vaccinees should be provided with a copy of the most current federal [Vaccine Information Statement \(VIS\)](#).

Two extremely rare, but serious, adverse events seen after YF vaccine receipt are yellow fever vaccine–associated neurologic disease (YEL-AND) and yellow fever vaccine–associated viscerotropic disease (YEL-AVD). YEL-AND is a collection of clinical syndromes, including acute disseminated encephalomyelitis, Guillain-Barré syndrome, meningoencephalitis, and cranial nerve palsies. Historically, YEL-AND was diagnosed primarily among infants as encephalitis, though more recent reports have been among people of all ages. YEL-AND is rarely

fatal, and almost all cases occur in first-time vaccine recipients. In the US, symptom onset is generally 2–56 days after vaccination, and the incidence rate is 0.8 per 100,000 doses administered but is greater (2.2 per 100,000 doses) in people aged  $\geq 60$  years. At least three YEL-AND

cases have been reported in exclusively breastfed infants whose mothers received YF vaccine. All three infants were  $< 1$  month old at the time of exposure, and all were diagnosed with encephalitis. Vaccination during breastfeeding should be avoided but is recommended when travel to YF-endemic areas cannot be deferred.

YEL-AVD is a severe illness similar to wild-type YF disease, often leading to multiorgan dysfunction or failure. Since 2001, over 100 confirmed and suspected cases of YEL-AVD have been reported worldwide. YEL-AVD has only been reported after the first dose of vaccine; no laboratory-confirmed YEL-AVD has been reported after booster doses. In the US, the median time from vaccination until symptom onset is 4 days (range 1–18 days). The case-fatality ratio is approximately 48% and the incidence is 0.3 cases per 100,000 doses. The incidence of YEL-AVD is greater for people aged  $\geq 60$  years (1.2 per 100,000 doses) and greater still for people aged  $\geq 70$  years. Because of the risk for serious adverse events after YF vaccination, clinicians should only vaccinate people at risk for YFV exposure or who require proof of vaccination to enter a country.

- h. DOD Policy. YF vaccination is required for military and civilian personnel deploying or traveling to YF-endemic areas. Service-specific policies and more information can be found at <https://www.health.mil/CCMDvaccines>. DOD personnel should contact their healthcare team or the nearest military treatment facility (MTF) for questions on current travel requirements.
- i. Special Considerations. Some countries require proof of YF vaccination for entry. The International Certificate of Vaccination or Prophylaxis (ICVP) or CDC 731, also referred to as the “yellow card” or “yellow shot record”, is the official, internationally recognized document for vaccination. Individuals who received YF vaccine after December 15, 2007, must provide proof of vaccination on the ICVP. Those who received the vaccine before that date can still use their original record on the earlier version (International Certificate of Vaccination against Yellow Fever card, or ICV). ICVPs are valid beginning 10 days after the date of primary YF vaccination. The ICVP must bear the clinician's original signature (a signature stamp is unacceptable) and Uniform Stamp of the vaccinating facility. Information on properly completing an ICVP can be found on the [CDC Traveler's Health website](#). Individuals without a valid ICVP may be

denied entry, quarantined, or be revaccinated at the point of entry to a country.

Clinicians can consider providing a waiver when YF vaccination is medically contraindicated. Acceptance of a medical waiver is at the discretion of the destination country. Clinicians must complete and sign the ICVP "Medical Contraindications to Vaccination" section and validate it with a Uniform Stamp. They should also provide the traveler with a signed and dated exemption letter on facility letterhead, clearly stating the contraindications to vaccination (e.g., age, allergic reaction, an immunocompromising condition, etc.). This letter must also bear the facility's Uniform Stamp. Travelers may wish to consult the destination country's embassy or consulate to confirm entry and waiver requirements. When no risk for YF exists in the traveler's itinerary but proof is required, the vaccine risk outweighs the disease; deferring vaccination and providing a medical waiver is reasonable, but shared clinical decision making should be used to determine the appropriate action.

The Centers for Disease Control and Prevention (CDC) publishes the ICVP but does not provide replacements or blank copies. DOD travelers should contact their nearest MTF to request a replacement for a lost or damaged ICV or ICVP. DOD clinics can obtain blank ICVPs from their MTF publications office or the [US Government Bookstore](https://www.gpo.gov/bookstore/). The Uniform Stamp must be procured from a commercial vendor. It must be in black ink, not exceed 5/8 inch by 1 1/4 inch in size, and include the DoD seal encircled by text reading "Military Services Certified Immunization" (see example):



### 3. References.

- a. Nemhauser, J. (Ed.). (2023). *CDC Yellow Book 2024: Health Information for International Travel*. Oxford University Press.  
<https://wwwnc.cdc.gov/travel/page/yellowbook-home>.
- b. Staples, J., Bocchini, J., Rubin, L., & Fischer, M. (2015). Yellow Fever Vaccine Booster Doses: Recommendations of the Advisory Committee on Immunization Practices, 2015. *MMWR Recommendations and*

*Reports*, 64(23), 647-650.

<https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6423a5.htm>.

- c. Staples, J., Gershman, M., & Fischer, M. (2010). Yellow Fever Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recommendations and Reports*, 59(7), 1-27.  
<https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5907a1.htm>.

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