

INFORMATION PAPER

DHA-IHB
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SUBJECT: Yellow Fever Infection and Yellow Fever Vaccine

1. Purpose. To describe Yellow Fever 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. Its vector borne transmission occurs via the bite of an infected mosquito from one host to another. Primary reservoirs of the virus are humans and non-human primates however, anthroponotic (human-to-vector- to-human) transmission does also occur. There are 3 transmission cycles for yellow fever: sylvatic (jungle), intermediate (savannah), and urban. It is antigenically related to the West Nile virus, St. Louis encephalitis and Japanese Encephalitis virus.
 - b. Disease. Humans infected with YFV have highest levels of viremia and can transmit the virus to mosquitoes before onset of fever and for first 3-6 days of illness. Clinical presentation of the disease can vary widely from a mild febrile illness to a severe infection. The incubation period is typically 3-6 days with asymptomatic infection thought to occur in most individuals infected with YFV. The initial disease symptoms present as a nonspecific influenza like syndrome with sudden onset of fever, chills, headache, backache, myalgia, prostration, nausea, and vomiting. Most individuals improve after the initial presentation; however approximately 15% individuals after a brief remission of hours to a day, progress to a more serious or toxic form of the disease characterized by jaundice, hemorrhagic symptoms, shock, and multisystem organ failure. The case-fatality ratio for severe cases with hepatorenal dysfunction is 20%– 50%. There are no specific medications to treat YFV infections; treatment is directed at symptomatic relief or life-saving interventions. Rest, fluids, and use of analgesics and antipyretics may relieve symptoms of fever and aching. Avoid use of aspirin or NSAIDS due to risk of increased bleeding.
 - c. Epidemiology. Yellow Fever predominantly occurs in sub-Saharan Africa and tropical South America, where it is endemic and intermittently epidemic. Humans and other primates are the main reservoirs. Risks for infection is determined by various factors such as immunization status, location of travel, season traveling, duration of exposure, activities while traveling, and local rate of virus transmission at time of travel. Most yellow fever disease in humans is due to sylvatic or intermediate transmission

cycles. However, urban yellow fever occurs periodically in Africa and sporadically in the Americas. In Africa, natural immunity accumulates with age, and thus, infants and children are at highest risk for disease. In South America, yellow fever occurs most frequently in unimmunized young men who are exposed to mosquito vectors through their work in forested areas. Although some countries are free of the virus, they harbor mosquitoes that could transmit YF if infected. Accordingly, these countries are known to take precautions at their borders to prevent introduction of the virus.

- d. Vaccine. YF-VAX® manufactured by Sanofi Pasteur is a live attenuated 17D-204 strain of yellow-fever virus licensed for use in individuals 9 months of age and older. YF-VAX® is prepared by culturing the 17D-204 strain of yellow fever virus in chicken embryos. The lyophilized vaccine contains gelatin as a stabilizer and no preservatives. The stopper in vials of YFV contains dry natural latex rubber. The vaccine powder must be reconstituted before use with diluent supplied (Sodium Chloride Injection USP); once reconstituted the vaccine will have a slight pink-brown suspension. It should be maintained at 2°C-8°C (35°-46°F) – DO NOT FREEZE and should be used or discarded within 1 hour.

- e. Immunization. Administer reconstituted YF-VAX® vaccine as a single 0.5-mL dose subcutaneously to individuals 9 months of age and older. Immunity develops for 80-100% individuals by the tenth day after vaccination and 99% immunity within 30 days. In February 2015 CDC/ACIP voted that a single dose of yellow fever vaccine provides long-lasting protection and was adequate for most travelers, and recommended at-risk laboratory personnel and certain travelers to continue receiving booster. On 11 July 2016, the amended International Health Regulation (IHR) Annex 7, which stipulates that the period of protection afforded by yellow fever vaccination and the term of validity of the certificate will change from 10 years to the duration of the life of the person vaccinated, entered into force and is legally binding upon all IHR States Parties. Thus, from July 2016 the certificate of vaccination against yellow fever is valid for the life of the person vaccinated. Although booster doses of yellow fever vaccine are not recommended for most travelers, and despite the recent changes to the IHR, clinicians and travelers should review the entry requirements for destination countries and by Area of Responsibility (AOR); at this time, it is uncertain when and if all countries with yellow fever vaccination requirements will adopt and fully implement this change that is stipulated by the IHR. ACIP guidelines specify that additional doses of yellow fever vaccine are recommended for the following groups of travelers: women who were pregnant when they received their initial dose of vaccine: they should receive 1 additional dose of yellow fever vaccine before their next travel that puts them at risk for yellow fever; people who received a hematopoietic stem cell transplant after receiving a dose of

yellow fever vaccine: they should be revaccinated before their next travel that puts them at risk for yellow fever as long as they are sufficiently immunocompetent to be safely vaccinated; and people who were infected with HIV when they received their last dose of yellow fever vaccine: they should receive a dose every 10 years if they continue to be at risk for yellow fever virus infection.

- f. Precautions. YF vaccine is contraindicated for infants aged <9 months due to high risk of encephalitis. Yellow Fever vaccine is also contraindicated in individuals with a history of hypersensitivity to vaccine components, eggs, egg products, chicken proteins and gelatin. If vaccination of an individual with a questionable history of vaccine hypersensitivity is considered essential because of a high risk for acquiring yellow fever, skin testing as described in the vaccine package insert should be performed under close medical supervision and with allergy specialty consultation. Further YFV is contraindicated in individuals with moderate to severe illness, thymus disorders, and in persons who are immune compromised due to disease, treatment, or medication. If an asymptomatic HIV-infected individual has no evidence of immune suppression based on CD4 counts (CD4 T-lymphocyte values $\geq 500/\text{mm}^3$ or $\geq 25\%$ of total lymphocytes for children aged <6 years), yellow fever vaccine can be administered if recommended. However, a vaccinated, HIV-infected individual should have neutralizing antibody response measured after vaccination to assure an adequate response. It is not known whether YF vaccine can cause harm to a fetus when administered to a pregnant woman; consequently, pregnant women should be vaccinated with YFV only if clearly needed. There is a theoretical risk of transmission of vaccine components to infants from breast-feeding; lactation constitutes a contraindication, particularly if infant <9 months of age. Vaccination of individuals >60 years of age is a precaution, particularly if this is the first dose as research indicates increased risk of serious adverse events (see Adverse Events).
- g. Adverse Events. Adverse reaction to YF-Vax® are generally mild with 10-30% vaccinees reporting mild headaches, myalgia, low-grade fevers, local site reactions (pain, swelling, redness), or other minor symptoms that may begin within days after vaccination lasting up to 5-10 days. Immediate hypersensitivity reactions characterized by rash, urticarial, asthma, or combination of, are uncommon and occur principally among individuals with histories of egg allergies. While rare, anaphylactic reactions have been reported to YF vaccine and in individuals with no history of reactions to vaccine components. 1% vaccinees reported temporary alterations to activities of daily living. All individuals should be observed for 15 minutes after vaccinations for adverse reactions. All individuals should be advised of signs and symptoms of an allergic reaction (provide Vaccine Information Sheet-VIS). Two extremely rare, but serious, adverse events

are yellow fever vaccine associated viscerotropic disease and yellow fever vaccine associated neurotropic disease (also known as post-vaccinal encephalitis). Yellow fever vaccine-associated neurotropic disease (YEL-AND) represents a conglomerate of clinical syndromes, including meningoencephalitis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, and rarely, cranial nerve palsies. Historically, YEL-AND was seen primarily among infants as encephalitis, but more recent reports have been among people of all ages. YEL-AND is rarely fatal. Among all cases of YEL-AND reported globally, almost all occurred in first-time vaccine recipients. The onset of illness for documented cases in the United States is 2–56 days after vaccination. The incidence of YEL-AND in the United States is 0.8 per 100,000 doses administered. The rate is higher in people aged ≥ 60 years, with a rate of 2.2 per 100,000 doses. Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) is a severe illness similar to wild-type disease, with vaccine virus proliferating in multiple organs and often leading to multiple organ dysfunction syndrome or multiorgan failure and death. Since the initial cases of YEL-AVD were published in 2001, >100 confirmed and suspected cases have been reported throughout the world. YEL-AVD has been reported to occur only after the first dose of yellow fever vaccine; worldwide, there have been no laboratory-confirmed reports of YEL-AVD following booster doses. For YEL-AVD cases reported in the United States, the median time from yellow fever vaccination until symptom onset is 4 days (range, 1–18 days). The case-fatality ratio for all reported YEL-AVD cases in the United States is approximately 46%. The incidence of YEL-AVD in the United States is 0.3 cases per 100,000 doses of vaccine administered. The rate is higher for people aged ≥ 60 years, with a rate of 1.2 per 100,000 doses. The rate is even higher for people aged ≥ 70 years.

- h. DoD Policy. YF vaccination is required for military and civilian/DOD personnel deploying or traveling to YF-endemic areas. Refer to service-specific policies for Service Members not on deployment or travel orders at <https://health.mil/Military-Health-Topics/Health-Readiness/Immunization-Healthcare/Vaccine-Recommendations/Vaccine-Recommendations-by-AOR>. Military requirements fluctuate at any given time; therefore civilian and military personnel should be advised to contact the nearest military medical facility to determine deployment requirement for designated areas.
- i. Special Considerations. Some countries in Africa require evidence of yellow fever vaccination from all travelers entering and passing through their borders. As proof of vaccination individuals must possess and International Certificate of Vaccination or Prophylaxis (ICVP), Form CDC 731, that validates with the provider's signature and an official YF vaccination stamp. An ICVP will become valid 10 days after vaccination

for a period of 10 years. Travelers who arrive in a country that has a yellow fever vaccination entry requirement without proof of yellow fever vaccination or a medical waiver may be quarantined for up to 6 days, refused entry, or vaccinated on site. International Health Regulations stipulate that a medical provider may issue a waiver of YF vaccination to a traveler if the provider judges the vaccination to be medically contraindicated. To be granted a waiver the following is required: completion of the “medical Contraindications of Vaccinations” section of the ICVP, a letter that clearly states the contraindication and that bears the official YF vaccine stamp. In addition, the letter must be typed on official letterhead stationary; and must be signed and dated by the traveler’s provider. Individuals that are unable to be vaccinated should be advised of the risk for travel and instructed in methods to avoid vector mosquitos. Reasons other than medical contraindications are not acceptable for exemption from vaccination. The traveler should be advised that issuance of a waiver does not guarantee its acceptance by the destination country. To improve the likelihood that the waiver will be accepted at the destination country, clinicians can suggest that the traveler take the following additional measures before beginning travel: Obtain specific and authoritative advice from the embassy or consulate of the destination country or countries. Request documentation of requirements for waivers from embassies or consulates and retain these, along with the completed Medical Contraindication to Vaccination section of the ICVP.

3. References.

- a. Centers for Disease Control and Prevention. Yellow Fever Vaccines Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2010;59 (RR#7):[1-26]
- b. Centers for Disease Control and Prevention. CDC Health Information for International Travel 2014 (Yellow Book). Atlanta: U.S. Department of Health and Human Services, Public Health Service, 2018.
- c. Multiple resources (e.g., product insert, Vaccine Information Statements) assembled by the Immunization Healthcare Branch:
<http://www.health.mil/YellowFever>.

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