Yellow Fever Vaccine Process for VA Facilities
Frequently Asked Questions (FAQ)
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

Background and Regulations

Yellow fever vaccine is recommended for travelers traveling to or living in areas at risk for yellow fever (YF) transmission in South America and Africa and may be required for entry into certain countries. Yellow fever vaccine administration is regulated by International Health Regulations 2005 (IHR 2005), an international set of laws that are binding in 169 countries, including the United States. IHR 2005 states that yellow fever Vaccine can only be administered at facilities designated by the member state (in this case the United States) to ensure safety and quality of the procedures and materials involved.

In the United States, designation of yellow fever vaccines is covered under The Code of Federal Regulations, Title 42: Public Health, Subpart A, 71.3. In these regulations the Director of the CDC is authorized to issue certificates of vaccination or delegate that to a Director of State or Territorial health departments. Designation may be made upon application and presentation of evidence satisfactory to a State or territorial health department that the applicant has adequate facilities and professionally trained personnel for the handling, storage, and administration of a safe, potent, and pure yellow fever vaccine. **Note, medical facilities of Federal agencies are authorized to obtain yellow fever vaccine without being designated a yellow fever vaccination center by the Director**.

Guidance on yellow fever vaccine in the United States comes from the Centers for Disease Control and Prevention, and includes a Yellow Fever Vaccine Course for health care providers. Many state health departments require providers to take the course prior to applying for validation stamps.

International Certificates of Vaccination against cholera and yellow fever issued for vaccinations performed in the United States must be validated by: (1) The Seal of the Public Health Service; or (2) The Seal of the Department of State; or (3) The stamp of the Department of Defense; or (4) The stamp issued to the National Aeronautics and Space Administration; or (5) The stamp issued by a State or territorial health department; or (6) An official stamp of a design and size approved by the Director for such purpose. The CDC has approved a VHA specific stamp for YF vaccination.

In VHA, the facility interested in becoming a provider of yellow fever vaccine, should ensure all of the requirements above are met prior to initiation of the process. The provider should consider presenting the information to the local facility Pharmacy and Therapeutics (P&T) Committee for approval to proceed and recordkeeping purposes.

What are the steps for a facility interested in becoming a provider of Yellow Fever vaccine?

1. The facility should ensure they can meet all the requirements above for administering yellow fever vaccine, including professionally trained personnel, and adequate facilities for the handling, storage and administration of yellow fever vaccine.
2. A local policy or procedure should be developed, including the following elements
    a. A designated yellow fever vaccine provider(s) will be identified and will be responsible for maintaining records related to patient information, administration and adverse events. Note, designation is not transferable so if a provider leaves and a new provider will need to be designated officially by the facility. The designated provider(s) who will be supervising the ordering, monitoring or administration of yellow fever vaccine should complete the CDC Yellow Fever Vaccine Course prior to initiation of YF vaccine administration.
    b. Resource to determine whether YF vaccine is recommended or required based on travel plans.
    c. What is required for documentation on the YF international vaccination certificates (ICVP), including the traveler's full name as it appears on their passport, the stamp and signature of the clinician supervising administration of YF vaccine and when and how to document medical waivers.
    d. A system should be in place for tracking the following information:
        i. Local site procedure for on-site operations and documentation that all requirements for yellow fever administration have been met
        ii. Names of patients vaccinated against yellow fever, with associated dates and vaccine lot numbers
            1. Best practice also includes documenting travel destinations to support YF vaccination.
        iii. Name of the person administering the vaccine
        iv. Listing of all validated international certificates of vaccination provided
        v. Documented adverse events (should be reported to VA ADERS as a MedWatch report)
3. Once approved through the local P&T committee, the Veterans Health Administration Yellow Fever Vaccine Stamp can

be ordered by emailing orders@spectrastamps.com

4. Yellow Fever international vaccine certificates can be ordered from the U.S. Government Bookstore (GPO).
5. Vaccine can be ordered from Sanofi Pasteur: contact number 1-800-VACCINE (1-800-822-2463)
6. Documentation in the patient medical record should include the date of vaccination, product name, lot number, expiration date, injection site and name of person administering the vaccine. Providers should also document if any precautions or contraindications exist, and travel destinations planned, if known.
7. When issuing an international certificate of vaccination proof (ICVP), it must contain:
    a. The name of the patient **as it appears on their passport**
    b. The signature of the clinician supervising the administration of the vaccine
    c. The official stamp of the facility administering the vaccine
    d. For a patient with a medical contraindication, the provider may issue a waiver by completing the medical contraindication to vaccination section of the ICVP

What is Yellow Fever, who is at risk and how does it present?

- **What is yellow fever?**
    - Yellow fever virus (YFV) is a mosquito-borne flavivirus transmitted primarily by daytime biting mosquitos.
- **How does yellow fever present clinically?**
    - Clinical disease due to yellow fever (YF) varies from a mild, undifferentiated febrile illness to severe disease with jaundice and hemorrhagic manifestations.
    - After an incubation period of 3-6 days, symptomatic yellow fever (YF) infections typically manifest with an abrupt onset of fever and headache.
    - As the illness progresses, other symptoms might occur, including, myalgia, arthralgia, epigastric pain, anorexia, vomiting, and jaundice.
    - At this point, most patients improve, but 5-26% will go on to develop severe YF, often after a short period of improvement. This can present as renal or liver failure, relative bradycardia, and hemorrhagic complications.
        - Case fatality rates in this group can range from 30-60%, with death typically within 7-10 days of illness onset. Elderly patients are among the highest case fatality rates.
    - **Because no specific antiviral treatment exists for YF, prevention is critical to lower disease risk and mortality.**
- **Where does YFV transmission occur?**
    - YFV is found in sub-Saharan Africa, especially in West Africa, and tropical South America and is endemic but also periodically causes large epidemics, including in Angola in 2015.
    - In South America, the highest risk is in persons entering heavily forested areas.
    - Specific information on countries with risk of YFV transmission can be found on the CDC travel site. Some countries require proof of yellow fever vaccination prior to entry (see below)

What is the Yellow Fever Vaccine, how is it administered?

- **Yellow fever vaccine is a freeze-dried, lyophilized, live-attenuated yellow fever virus strain (17D), manufactured by Sanofi Pasteur under the brand name YF-VAX.**
    - Previously supply of the YF vaccine was controlled by the CDC, due to ongoing vaccine shortage. Now YF-vaccine is available directly from the manufacturer to designated Yellow Fever Vaccine providers and Federal facilities.
    - YF-VAX is available as a single-dose or 5 dose multi-dose vial.
    - It should be stored at 2-8° C (35-46°F) and should not be frozen.
- **How is yellow fever vaccine administered?**
    - **YF-VAX must be reconstituted with the supplied sodium chloride diluent,** which then should be allowed to sit for 1-2 minutes before swirling the mixture carefully until a uniform mixture is achieved. Using aseptic technique and using a separate needle and syringe, 0.5 mL should be withdrawn from the vial.
    - YF-VAX is given as a 0.5 mL subcutaneous injection of reconstituted vaccine to the upper-outer triceps.
    - YF-VAX must be given within 60 minutes of reconstituting the vial.
- **How long does it take for protection to develop against YF?**
    - Protective antibodies take 7-10 days to develop. Yellow fever international certificates of vaccination are considered valid beginning 10 days after the date of vaccination.
- **How long does protection last, and are booster doses necessary?**
    - Yellow fever vaccination produces long lasting protection against yellow-fever
    - Booster doses were previously recommended every 10 years. However, in 2014, the WHO adopted the recommendation to remove the requirement for a booster dose, and all countries are expected to follow the 2014

policy (although travelers are encouraged to check entry requirements to the specific area they will be visiting).

- There are situations where the Advisory Committee on Immunization Practices (ACIP) recommends an additional dose or doses. These include:
  - **Women who were pregnant when first vaccinated against YF should receive 1 additional dose**
  - **Hematopoietic stem cell transplant recipients vaccinated prior to transplantation should receive an additional post-transplant dose before their next travel, but must be sufficiently immunocompetent**
  - **HIV + patients should receive a booster every 10 years (provided no contraindications or precautions)**
  - **Providers may consider a booster dose in travelers who received the initial vaccination at least 10 years ago and who would be at higher risk (such as a prolonged region in an endemic area)**

What contraindications, warnings and precautions exist for Yellow Fever Vaccine and what adverse events can be expected?

- **What are contraindications to yellow fever vaccine?**
  - Acute hypersensitivity to a prior dose of YF vaccine or any of its components
  - Severely immunosuppressed individuals
  - Thymic disorders with abnormal immune function (e.g. myasthenia gravis, thymoma)
  - Women who are breastfeeding an infant younger than 9 months of age
  - *Note: for those with a medical contraindication to YF vaccine, the medical waiver section of the international certificate of vaccination can be completed.*
- **What are the warnings and precautions for yellow fever vaccine?**
  - **Warnings:**
    - Severe allergic reactions – patients should be monitored for 15 minutes
    - YF vaccine associated viscerotropic disease (age greater than 60 years is a risk factor)
      - Rate 1.2/100,000 doses if ≥ 60 years vs. 0.3/100,000 if younger
    - YF vaccine associated neurotropic disease (age greater than 60 years and immunosuppression are risk factors)
      - Rate 2.2/100,000 doses if ≥ 60 years vs. 0.8/100,000 if younger
  - **Precautions:**
    - Should not be administered intravascular, intramuscular or intradermal
    - Syncope
    - Testing for hypersensitivity can be considered for those with egg hypersensitivity.
    - Rate of seroconversion is reduced in those with HIV infection, so documentation of protective antibody is recommended before travel.
    - Pregnancy
    - **Lactation: three cases of vaccine-associated neurotropic disease have been seen in infants who were exclusively breastfed where the mother received vaccination against YF. All were less than one month of age.**
    - *Note: YF vaccine is associated with an increased risk of severe adverse events in individuals if ≥ 60 years of age (see above).*
- **What common and severe adverse events are seen with YF vaccine?**
  - Common adverse events include fever, headache, backache, myalgias, injection site inflammation
  - Severe, uncommon adverse events include
    - Hypersensitivity reactions (including anaphylaxis)
    - Yellow fever vaccine associated neurologic disease – can present as meningoencephalitis or Guillain-Barre. See above for risk estimates based on age.
    - Yellow fever vaccine associated viscerotropic disease – this mimics yellow fever and can result in multi-organ failure and death. See above for risk estimates based on age.
- **Are there any drug-drug interactions of importance with yellow fever vaccine?**
  - Other live-attenuated viral vaccines should be given at the same time or at least 30 days apart
  - Note: oral typhoid vaccine (bacteria) and inactivated vaccines can be administered at any time relative to YF vaccine
  - PPD testing should either be before or on the same day as YF vaccine, or 4 or more weeks after
- **Will the VA be monitoring for adverse events with yellow fever vaccine?**

- All serious events and all medication errors are to be reported to VA ADERS as a MedWatch report (a separate FDA MedWatch report is not required when submitted in VA ADERS)
    - Serious adverse events are defined as:
        - Death or life-threatening events
        - Hospitalization or prolongation of an existing hospitalization
        - Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions
        - Congenital anomaly/birth defect
        - Medical or surgical intervention is needed to prevent death, a life-threatening event, hospitalization, disability or a congenital anomaly

Other issues

- **What other things are important to know about the yellow fever vaccine process?**
    - As part of the travel consultation, patients should be counseled on ways to prevent mosquito bites to reduce the risk of YF and other mosquito borne diseases.

References:

1. International Health Regulations (2005), third ed. World Health Organization, 2016, Accessed 7/15/21
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4. Code of Federal Regulation 42, 5/26/21. Accessed 5/27/21
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