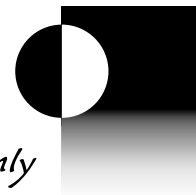


A.H.F.S. Category 80:12

Yellow Fever Vaccine

YF-VAX[®]


 Rx only


Caution: Federal (USA) law prohibits dispensing without prescription.

DESCRIPTION

YF-VAX[®], Yellow Fever Vaccine, for subcutaneous use, is prepared by culturing the 17D strain of yellow fever virus in living avian leukosis virus-free (ALV-free) chicken embryos. The vaccine, containing sorbitol and gelatin as a stabilizer, is lyophilized, and hermetically sealed under nitrogen. No preservative is added. The vaccine must be reconstituted immediately before use with the sterile diluent provided (Sodium Chloride Injection USP – contains no preservative). YF-VAX[®] is formulated to contain not less than 5.04 Log₁₀ Plaque Forming Units (PFU) per 0.5 mL dose. The vaccine appears slightly opalescent and light orange in color after reconstitution.

YF-VAX[®] complies with official potency tests and other requirements of the US Food and Drug Administration (FDA) and the World Health Organization (WHO).

CLINICAL PHARMACOLOGY

A clinical study to evaluate the serological responses and adverse reactions of Aventis' YF-VAX[®] was performed on healthy young adults. One group of six received yellow fever vaccine non-ALV-free (manufactured by Aventis Pasteur Inc.) and another group of 18 received an immunization with YF-VAX[®].¹

Immunologic protection was measured utilizing a serum neutralizing antibody assay. No neutralizing antibody was detected prior to immunization. Both groups demonstrated a 100% conversion in the post-immunization sera. The incidence and severity of adverse reactions in each group were comparable.¹

In a study involving 101 Nigerian women in various stages of pregnancy, it was concluded that vaccinating pregnant women with the 17D vaccines was not associated with adverse effects on the fetus or with risk of fetal infection. However, the percentage of pregnant women without neutralizing antibodies, who sero-converted, was significantly less than a non-pregnant control group (38.6% vs. 81.5%).² Following a mass immunization campaign in Trinidad, congenital infection based on the observation of virus specific IgM in the blood of one infant exposed through maternal immunization with the 17D strain has been reported.³ This infant appeared normal at delivery.

One case of fatal vaccine-associated encephalitis occurred after 17D yellow fever vaccine was administered to an apparently healthy 39-month-old girl.⁴

INDICATIONS AND USAGE

YF-VAX[®] is recommended for active immunization of all persons \geq 9 months of age traveling to or living in areas of South America and Africa where yellow fever infection is officially reported or to countries which require a certificate of vaccination against yellow fever.^{5,6}

Vaccination is also recommended for travel outside the urban areas of countries that do not officially report the disease but that lie in the yellow fever endemic zone. In recent years, fatal cases of yellow fever have occurred among unvaccinated tourists visiting rural areas within the yellow fever endemic zone.⁵

Laboratory personnel who might be exposed to virulent yellow fever virus by direct or indirect contact or by aerosols also should be vaccinated.⁵

For simultaneous administration of other vaccines see **DOSAGE AND ADMINISTRATION** section.

Infants < 9 months of age and pregnant women should be considered for vaccination if traveling to areas experiencing ongoing epidemic yellow fever when travel cannot be postponed and a high level of prevention against mosquito exposure is not feasible. *However, in no instance should infants < 4 months of age receive yellow fever vaccine because of the risk of encephalitis.*⁵ (See **CONTRAINDICATIONS**, **WARNINGS** and **PRECAUTIONS** sections.)

United States vaccination certificates are valid for a period of 10 years commencing 10 days after initial vaccination or revaccination.⁶ (See **DOSAGE AND ADMINISTRATION** section.)

As with any vaccine, vaccination with YF-VAX[®] may not protect 100% of susceptible individuals.

CONTRAINDICATIONS

Since the yellow fever virus is propagated in chicken embryos, it should not be administered to an individual with a history of hypersensitivity to egg, chicken protein, or to any other component of the vaccine. Generally, persons who are able to eat eggs or egg products may receive the vaccine. (See **PRECAUTIONS** section for sensitivity testing.)⁵

Infection with yellow fever vaccine virus poses a theoretical risk of encephalitis to patients with immunosuppression in association with acquired immunodeficiency syndrome (AIDS) or other manifestations of human immunodeficiency virus (HIV) infection, leukemia, lymphoma, generalized malignancy, or to those whose immunologic responses are suppressed by corticosteroids, alkylating drugs, antimetabolites, or radiation. Such patients should not be vaccinated. If travel to a yellow fever-infected zone is necessary, patients should be advised of the risk, instructed in methods for avoiding vector mosquitoes, and supplied with vaccination waiver letters by their physicians.^{5,6}

Low-dose (10 mg prednisone or equivalent) or short-term (< 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive and constitute no increased hazard to recipients of yellow fever vaccine. Persons who have had previously diagnosed asymptomatic HIV infections and who cannot avoid potential exposure to yellow fever virus should be offered the choice of vaccination. Vaccinees should be monitored for possible adverse effects. Since the vaccination of such persons may be less effective than that for non-HIV-infected persons, their neutralizing antibody response to vaccination may be desired before travel. For such determinations, the appropriate state health department or Centers for Disease Control and Prevention (CDC) (303-221-6400) may be contacted. Family members of immunosuppressed persons, who themselves have no contraindications, may receive yellow fever vaccine.⁵

Infants < 4 months of age should not be immunized because they are more susceptible to encephalitis temporally associated with yellow fever vaccination than older children.^{5,6,7} (See **INDICATIONS AND USAGE** and **WARNINGS** sections.)

WARNINGS

This product contains dry natural latex rubber as follows: The stopper to the vial contains dry natural latex rubber.

Infants < 9 months of age and pregnant women should not be vaccinated. *The decision to immunize infants between 4 and 9 months of age and pregnant women should be based upon estimates of the risk of exposure.*^{5,6,7}

Anaphylaxis may occur following the use of YF-VAX[®], even in individuals with no prior history of hypersensitivity to the vaccine components.

The clinical judgment of the responsible physician should prevail.

PRECAUTIONS

GENERAL

Care is to be taken by the health-care provider for the safe and effective use of YF-VAX[®].

EPINEPHRINE INJECTION (1:1000) ALWAYS MUST BE IMMEDIATELY AVAILABLE TO COMBAT UNEXPECTED ANAPHYLACTIC OR OTHER ALLERGIC REACTIONS.

Prior to an injection of any vaccine, all known precautions should be taken to prevent side reactions. This includes a review of the patient's history with respect to possible sensitivity to the vaccine or similar vaccines and to possible sensitivity to dry natural latex rubber.

Health-care providers should obtain the previous immunization history of the vaccinee, and inquire about the current health status of the vaccinee.

Administration of YF-VAX[®] is not contraindicated in individuals infected with HIV.⁷

A separate, sterile syringe and needle should be used for each patient to prevent transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped and should be properly disposed (e.g., sterilized or disposed in red hazardous waste containers).

INFORMATION FOR PATIENTS

Patients, parents or guardians should be fully informed of the benefits and risks of immunization with YF-VAX[®].

Prior to administration of YF-VAX[®], patients, parents or guardians should be asked about the recent health status of the patient to be immunized.

The health-care provider, at an approved yellow fever vaccination center, should inform the patients, parents or guardians about the significant adverse reactions that have been temporally associated with YF-VAX[®] administration and obtain informed consent. Patients, parents or guardians should be instructed to report any serious adverse reactions to their health-care provider.

As part of the patient's immunization record, the date, lot number and manufacturer of the vaccine administered should be recorded.^{8,9,10}

Vaccinees should receive an International Certificate of Vaccination completed, signed, and validated with the center's stamp where the vaccine was given.

The US Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986.^{7,8} The VAERS toll-free number for forms and information is 1-800-822-7967.⁸

HYPERSENSITIVITY REACTIONS

Since the yellow fever virus is propagated in chicken embryos, it should not be administered to an individual with a history of hypersensitivity to egg or chicken protein. In some instances, although symptoms appear soon after a vaccine is administered, differentiation between allergic reaction to the vaccine and reaction to an environmental allergen is impossible.¹¹

Four types of hypersensitivity reactions are:¹¹

1. allergic reactions to egg or egg-related antigens,
2. mercury sensitivity in some recipients of immune globulins or vaccines,
3. antibiotic-induced allergic reactions, and
4. hypersensitivity to some component of the infectious agent or other vaccine components.

Less severe or localized manifestations of allergy to egg or to feathers are not contraindications to vaccine administration and do not usually warrant vaccine skin testing.¹¹

An egg-sensitive individual can be tested with the vaccine before it is used in the following manner:¹¹

1. Scratch, prick, or puncture test: a drop of 1:10 dilution of the vaccine in physiologic saline is applied at the site of a superficial scratch, prick, or puncture on the volar surface of the forearm. Positive (histamine) and negative (physiologic saline) control tests should also be used. The test is read after 15 to 20 minutes. A positive test is a wheal 3 mm larger than that of the saline control, usually with surrounding erythema. The histamine control must be positive for valid interpretation. If the result of this test is negative, an intradermal (ID) test is performed.
2. Intradermal test: a dose of 0.02 mL of a 1:100 dilution of the vaccine in physiologic saline is injected; positive and negative control skin tests are performed concurrently. A wheal 5 mm or larger than the negative control with surrounding erythema is considered a positive reaction.

EPINEPHRINE INJECTION (1:1000) ALWAYS MUST BE IMMEDIATELY AVAILABLE TO COMBAT UNEXPECTED ANAPHYLACTIC OR OTHER ALLERGIC REACTIONS.

DESENSITIZATION¹¹

If the individual has a history of severe egg sensitivity and has a positive skin test to the vaccine, the individual may be given the vaccine using a “desensitization” procedure if immunization is imperative. The following successive doses should be administered subcutaneously at 15- to 20-minute intervals:

1. 0.05 mL of 1:10 dilution
2. 0.05 mL of full strength
3. 0.10 mL of full strength
4. 0.15 mL of full strength
5. 0.20 mL of full strength

This type of skin testing and “desensitization” should be undertaken only if supervised by a physician experienced in the management of anaphylaxis and with necessary emergency equipment immediately available.

DRUG INTERACTIONS

In a prospective study of persons given yellow fever vaccine and 5 cc of commercially available immune globulin, no alteration of the immunologic response to yellow fever vaccine was detected when compared with controls.^{5,11,12}

Studies have shown that the serologic response to yellow fever vaccine is not inhibited by the administration of certain other vaccines concurrently at separate sites or at various intervals of a few days to one month. Measles and yellow fever vaccines have been administered in combination with full efficacy of each of the components; Bacillus Calmette Guérin (BCG) and yellow fever vaccines have been administered simultaneously without interference. Additionally, severity of reactions to vaccination has not been amplified by the concurrent administration of yellow fever and other live virus vaccines. If live virus vaccines are not given concurrently, four weeks should elapse between sequential vaccinations.⁵

Some data have indicated that persons given yellow fever and cholera vaccines simultaneously or 1 to 3 weeks apart had lower than normal antibody responses to both vaccines.⁵ Unless there are time constraints, cholera and yellow fever vaccines should be administered at a minimal interval of 3 weeks. If the vaccines cannot be administered at least 3 weeks apart, the vaccines can be given simultaneously at separate sites or at any time within the 3-week interval.⁵

Hepatitis B and yellow fever vaccine may be given concurrently at separate sites.⁵ No data exist on possible interference between yellow fever and typhoid, paratyphoid, typhus, plague, rabies or Japanese encephalitis vaccines.⁵

Although chloroquine inhibits replication of yellow fever virus in vitro, it does not adversely affect antibody responses to yellow fever vaccine in humans receiving antimalaria prophylaxis.^{5,13} (See **DOSAGE AND ADMINISTRATION** section.)

Usually, YF-VAX[®] should be administered at least one month apart from other live-virus vaccines. However, field observations and clinical data indicate that simultaneous administration of the most widely used live-virus vaccines have not resulted in impaired antibody response or increased adverse reactions.⁷ Thus, if time is a critical factor for required vaccinations, the clinical judgment of the responsible physician should prevail.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

YF-VAX[®] has not been evaluated for its carcinogenic, mutagenic potentials or impairment of fertility.

PREGNANCY

REPRODUCTIVE STUDIES – PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with YF-VAX[®]. It is also not known whether YF-VAX[®] can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. YF-VAX[®] should be given to a pregnant woman only if clearly needed.

NURSING MOTHERS

Yellow fever virus is not excreted in breast milk following vaccination, and there is no contraindication for vaccinating breast-feeding mothers with yellow fever vaccine.⁶

PEDIATRIC USE

Safety and effectiveness of Yellow Fever Vaccine in infants below the age of 9 months have not been established. Therefore, YF-VAX® is *NOT recommended for infants < 9 months of age unless they live in or are traveling to a high-risk area. In NO instance should infants < 4 months of age receive yellow fever vaccine because of the risk of encephalitis.*⁵ (See **INDICATIONS AND USAGE** and **WARNINGS** sections.)

ADVERSE REACTIONS

Adverse reactions to 17D yellow fever vaccine are generally mild. After vaccination, 2% to 5% of vaccinees have mild headaches, myalgia, low-grade fevers, or other minor symptoms for 5 to 10 days. Fewer than 0.2% of the vaccinees curtail regular activities. Immediate hypersensitivity reactions, characterized by rash, urticaria, and/or asthma, are uncommon (incidence <1/1,000,000) and occur principally among persons with histories of egg allergy.⁵

Two cases of encephalitis temporally associated with vaccinations have been reported in the United States; in one fatal case, 17D virus was isolated from the brain.^{4,5}

Anaphylaxis may occur following the use of YF-VAX®, even in individuals with no prior history of hypersensitivity to the vaccine components.

EPINEPHRINE INJECTION (1:1000) ALWAYS MUST BE IMMEDIATELY AVAILABLE TO COMBAT UNEXPECTED ANAPHYLACTIC OR OTHER ALLERGIC REACTIONS.**Reporting of Adverse Events**

Reporting by patients, parents or guardians of all adverse events occurring after vaccine administration should be encouraged. Adverse events following immunization with vaccine should be reported by the health-care provider to the US Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System (VAERS). Reporting forms and information about reporting requirements or completion of the form can be obtained from VAERS through a toll-free number 1-800-822-7967.⁸

Health-care providers also should report these events to the Director of Scientific and Medical Affairs, Aventis Pasteur Inc., Discovery Drive, Swiftwater, PA 18370 or call 1-800-822-2463.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for extraneous particulate matter and/or discoloration prior to administration whenever solution and container permit. If these conditions exist, the vaccine should not be administered.

Reconstitute the vaccine using only the diluent supplied (Sodium Chloride Injection USP). The vaccine appears slightly opalescent and light orange in color after reconstitution. Draw the volume of the diluent, shown on the diluent label, into a suitable size syringe and inject into the vial containing the vaccine. Slowly add diluent to vaccine, let set for one to two minutes and then carefully swirl mixture until a uniform suspension is achieved. Avoid vigorous shaking as this tends to cause foaming of the suspension. Use vaccine within 60 minutes following reconstitution. *All reconstituted vaccine and containers which remain unused after one hour must be properly disposed (e.g., sterilized or disposed in red hazardous waste containers).*⁵ *Do not dilute reconstituted vaccine.*

SWIRL VACCINE WELL before withdrawing each dose. *Administer the single immunizing dose of 0.5 mL subcutaneously at once.*

If immunization is imperative to an individual with a history of severe egg sensitivity and a positive skin test to the vaccine, see **DESENSITIZATION** section.

Primary vaccination. For persons of all ages, a single subcutaneous injection of 0.5 mL of reconstituted vaccine (formulated to contain not less than 5.04 Log₁₀ Plaque Forming Units [PFU]) is administered.⁵ Immunity develops by the 10th day after primary vaccination.⁶

Booster doses. The International Health Regulations require revaccination at intervals of 10 years. Revaccination boosts antibody titer; however, evidence from several studies suggests that yellow fever vaccine immunity persists for at least 30 to 35 years and probably for life.⁵

SIMULTANEOUS ADMINISTRATION OF OTHER VACCINES

Studies have shown that the serologic response to yellow fever vaccine is not inhibited by the administration of certain other vaccines concurrently at separate sites or at various intervals of a few days to one month. Measles and yellow fever vaccines have been administered in combination with full efficacy of each of the components; Bacillus Calmette Guérin (BCG) and yellow fever vaccines have been administered simultaneously without interference. Additionally, severity of reactions to vaccination has not been amplified by the concurrent administration of yellow fever and other live virus vaccines. If live virus vaccines are not given concurrently, four weeks should elapse between sequential vaccinations.⁵

Some data have indicated that persons given yellow fever and cholera vaccines simultaneously or 1 to 3 weeks apart had lower than normal antibody responses to both vaccines.⁵ Unless there are time constraints, cholera and yellow fever vaccines should be administered at a minimal interval of 3 weeks. If the vaccines cannot be administered at least 3 weeks apart, the vaccines can be given simultaneously at separate sites or at any time within the 3-week interval.⁵

Hepatitis B and yellow fever vaccine may be given concurrently at separate sites.⁵ No data exist on possible interference between yellow fever and typhoid, paratyphoid, typhus, plague, rabies or Japanese encephalitis vaccines.⁵

HOW SUPPLIED

Vial, 1 Dose (5 per package) with vial of diluent (5 per package) for administration with needle and syringe. Product No. 49281-915-01

Vial, 5-Dose, with vial of diluent, for administration with needle and syringe. Product No. 49281-915-05

Vial, 20-Dose, with vial of diluent, for administration with needle and syringe (NOT to be used with jet injector). Product No. 49281-915-20

YF-VAX® (Yellow Fever Vaccine) in the United States is supplied only to designated Yellow Fever Vaccination Centers authorized to issue valid certificates of Yellow Fever Vaccination. Location of the nearest Yellow Fever Vaccination Centers may be obtained from the Centers for Disease Control and Prevention, Atlanta, GA 30333, state or local health departments, or the USPHS booklet "Immunization Information for International Travel" (obtainable from the Superintendent of Documents, US Government Printing Office, Washington, DC 20402).

STORAGE

Storage Temperature

Freeze-dried vaccine must be maintained continuously at a temperature between 0° – 5°C (32° – 41°F).

YF-VAX® does not contain a preservative, therefore all reconstituted vaccine and containers which remain unused after one hour must be properly disposed (e.g., sterilized or disposed in red hazardous waste containers).⁵

Shipping Temperatures

YF-VAX® is shipped in a container with solid carbon dioxide; use is not recommended unless the shipping case contains some dry ice upon arrival.

STABILITY STUDIES**STABILITY OF YF-VAX® (FREEZE-DRIED) AT ELEVATED TEMPERATURES¹**

The following information is provided for those countries or areas of the world where an adequate cold chain is a problem and inadvertent exposure to abnormal temperatures has occurred.

Temperature °C	Test	Number of Lots Tested	Computed Half-Life (Days)
35° – 37°C	Mouse Assay	3	14.0
35° – 37°C	Vero Cell Assay	3	13.9
45° – 47°C	Mouse Assay	3	3.3
45° – 47°C	Vero Cell Assay	3	4.5

YF-VAX® is formulated to satisfy the current US potency requirements of not less than 5.04 Log₁₀ Plaque Forming Units (PFU) per 0.5 mL dose and meets the minimum requirements of WHO.¹⁴

REFERENCES

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Aventis Pasteur

 **Aventis**