AHFS Category: 80:12

Yellow Fever Vaccine

**DESCRIPTION**

YF-VAX®. Yellow Fever Vaccine, for subcutaneous use, is prepared by culturing the 17D-204 strain of yellow fever virus in living avian leukosis virus-free (ALV-free) chicken embryos. The vaccine contains sorbitol and gelatin as a stabilizer, is lyophilized, and is hermetically sealed under nitrogen. No preservative is added. Each vial of vaccine is supplied with a separate vial of sterile diluent, which contains Sodium Chloride Injection USP—without a preservative. YF-VAX is formulated to contain not less than 4.74 log10 plaque forming units (PFU) per 0.5 mL dose throughout the life of the product. Before reconstitution, YF-VAX is a pinkish color. After reconstitution, YF-VAX is a slight pink-brown suspension.

The vial stoppers for YF-VAX and diluent are not made with natural rubber latex.

**CLINICAL PHARMACOLOGY**

Yellow fever is an acute viral illness caused by a mosquito-borne flavivirus. Most yellow fever virus infections are asymptomatic. In those individuals who develop disease, the clinical spectrum ranges from a nonspecific flu-like illness with fever, malaise, prostration, headache, photophobia, generalized arthralgia and myalgia, nausea, and vomiting to potentially lethal pansystemic disease, most prominently involving the liver, kidneys, GI tract, and brain, with shock. (1) The case-fatality rate of yellow fever varies widely in different studies but is typically 20% or higher. Jaundice or other gross evidence of severe liver disease is associated with higher mortality rates.

Two live, attenuated yellow fever vaccines, strains 17D-204 and 17DD, were derived in parallel by 17D vaccines. YF-VAX is contraindicated in anyone with a history of acute hypersensitivity reaction to any component of the vaccine. (See DESCRIPTION section.) Because the yellow fever virus used in the production of this vaccine is propagated in chicken embryos, do not administer YF-VAX to anyone with a history of acute hypersensitivity to eggs or egg products due to a risk of anaphylaxis. Less severe or localized manifestations of allergy to eggs or to feathers are not contraindications to vaccine administration and do not usually warrant vaccine skin testing (see WARNINGS section). Generally, persons who are able to eat eggs or egg products may receive the vaccine. (14) (15)

**ADVERSE REACTIONS**

**CONTRAINDICATIONS**

**Hypersensitivity**

YF-VAX is contraindicated in anyone with a history of acute hypersensitivity reaction to any component of the vaccine. (See DESCRIPTION section.) Because the yellow fever virus used in the production of this vaccine is propagated in chicken embryos, do not administer YF-VAX to anyone with a history of acute hypersensitivity to eggs or egg products due to a risk of anaphylaxis. Less severe or localized manifestations of allergy to eggs or to feathers are not contraindications to vaccine administration and do not usually warrant vaccine skin testing (see WARNINGS section). Generally, persons who are able to eat eggs or egg products may receive the vaccine. (14) (15)

**Individually Less Than 9 Months of Age**

Vaccination with YF-VAX is contraindicated in infants less than 9 months of age due to an increased risk of encephalitis.

Vaccination with YF-VAX is also contraindicated in lactating women who are providing breast milk to infants less than 6 months of age due to the potential for transmission of vaccine virus in breast milk. (See WARNINGS section, Nursing Mothers subsection.)

**Immunosuppressed Individuals**

Vaccination with YF-VAX, a live virus vaccine, is contraindicated in individuals with severe immunosuppression, including for example, those with acquired immunodeficiency syndrome, leukemia, lymphoma, thymoma, and patients who are undergoing drug therapy (e.g., systemic corticosteroids, alkylating drugs, antimetabolites or other immunomodulatory drugs) or radiation therapy. Thymic disorders associated with abnormal immune cell function (e.g., myasthenia gravis, thymoma) may be an independent risk factor for the development of yellow fever vaccine-associated viscerotropic disease. (see WARNINGS section). (16)

Do not administer YF-VAX to individuals with severe immunosuppression.

Family members of immunosuppressed individuals who themselves have no contraindications, may receive YF-VAX. (14) (17)

**WARNINGS**

**Severe Allergic Reactions**

Severe allergic reactions (e.g., anaphylaxis) may occur following the use of YF-VAX, even in individuals with no prior history of hypersensitivity to the vaccine components. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

**Yellow fever virus-associated viscerotropic disease**

Age greater than 60 years is a risk factor for yellow fever vaccine-associated viscerotropic disease (YEL-AVD) (14) which may present as non-specific multi-organ system failure or can be similar to fulminant yellow fever caused by wild-type yellow fever virus, with liver failure and internal bleeding, leading to death. (See ADVERSE REACTIONS section.) Available evidence suggests that the occurrence of this syndrome may depend upon undefined host factors, rather than intrinsic virulence of the yellow fever strain 17D vaccine, based on characterization of vaccine viruses isolated from individuals with YEL-AVD. YEL-AVD has been reported to occur only after the first dose of yellow fever vaccine; there have been no reports of YEL-AVD following booster dose. (17) The decision to variocinate individuals 60 years of age and older needs to weigh the risks and benefits of vaccination and the risk for exposure to yellow fever virus. (18) (19) (20) (21)

**Yellow fever vaccine-associated neurotropic disease**

Age greater than 60 years and immunosuppression are risk factors for post-vaccinal encephalitis, also known as yellow fever vaccine-associated neurotropic disease (YEL-AND). (See ADVERSE REACTIONS section.) Almost all cases of YEL-AND have been in first-time vaccine recipients. (17) The decision to variocinate individuals 60 years of age and older and immunosuppressed individuals needs to weigh the risks and benefits of vaccination and the risk for exposure to yellow fever virus.
PRECAUTIONS

General
Vaccination with YF-VAX may not protect 100% of individuals. Do not administer YF-VAX by intravenous, intramuscular, or intradermal routes. Use a separate, sterile syringe and needle for each patient to prevent transmission of bloodborne infectious agents. Do not recap needles. Dispose of needles and syringes according to biohazard waste guidelines.

Testing for Hypersensitivity Reactions
Do not administer YF-VAX to an individual with a history of hypersensitivity to egg or chicken protein (see CONTRAINDICATIONS section). However, if an individual is suspected of being egg-sensitive, the following test can be performed before the vaccine is administered:

1. Scratch, prick, or puncture test: Place a drop of a 1:10 dilution of the vaccine in physiologic saline on a superficial scratch, prick, or puncture on the solar surface of the forearm. Positive (histamine) and negative (physiologic saline) controls should also be used. The test is read after 15 to 20 minutes. A positive test is a wheal (superficial bump) 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 should be performed.

2. Intradermal test: Inject a dose of 0.02 mL of a 1:100 dilution of the vaccine in physiologic saline. Positive and negative control skin tests should be performed concurrently. A wheal 5 mm or larger than the negative control with surrounding erythema is considered a positive reaction.

If vaccination is considered essential despite a positive skin test, consider desensitization (see DOSAGE AND ADMINISTRATION section, Desensitization subsection).

Information for Patients
Prior to administration of YF-VAX, ask potential vaccinees or their parents or guardians about their recent health status and history of yellow fever vaccination. Inform potential vaccinees or their parents or guardians about the benefits and risks of immunization and potential for adverse reactions to YF-VAX administration. Instruct vaccinees or their parents or guardians to report to their health-care providers all serious adverse events that occur up to 30 days post-vaccination.

All travelers should seek information regarding vaccination requirements by consulting with their travel agencies, international airlines, and/or shipping lines. The vaccination certificate should contain the date, lot number, and manufacturer of the vaccine administered. Inform vaccinees that vaccination certificates are valid commencing 10 days after vaccination. (14)

Drug Interactions
Data are limited in regard to the interaction of YF-VAX with other vaccines. Measles (Schwartz strain) vaccine, diphtheria and tetanus toxoids and whole cell pertussis vaccine (DTP), Hepatitis A and Hepatitis B vaccines, meningococcal vaccine, Menomune®ACY/W-135, and typhoid vaccine, Typhim Y®, have been administered with yellow fever vaccine at separate injection sites.

The potential for interference between yellow fever vaccine and rabies or Japanese encephalitis vaccine has not been established. (14) In a prospective study, persons given 5 cc of commercially available immune globulin did not experience alterations in immunologic responses to the yellow fever vaccine. (14) Although chloroquine inhibits replication of yellow fever vaccine in vitro, it does not appear to adversely affect antibody responses to yellow fever vaccine among persons receiving chloroquine. (14) (27)

Patients on Corticosteroid Therapy
Oral Prednisone or other systemic corticosteroid therapy, depending on dose and duration of exposure, may have an immunosuppressive effect on recipients of yellow fever vaccine that potentially decreases immunogenicity and increases the risk of adverse events. Intra-articular, bursal, or tendon injections with corticosteroids should not constitute an increased hazard to recipients of yellow fever vaccine.

Patients with Asymptomatic Human Immunodeficiency Virus (HIV) Infection
The rate of seroconversion following YF-VAX is reduced in individuals with asymptomatic HIV infection and appears to depend on HIV viral load and CD4+ T-cell count. (14) Therefore, documentation of a protective antibody response is recommended before travel. (See CLINICAL PHARMACOLOGY section.) For discussion of this subject and for documentation of the immune response to vaccine where it is deemed essential, contact the CDC at 1-970-221-6400.

Carcinogenesis, Mutagenesis, Impairment of Fertility
YF-VAX has not been evaluated for its carcinogenic or mutagenic potential or its effect on fertility.

Pregnancy
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 it clearly needed.

YF-VAX has not been evaluated in pregnant women. However, based on experience of other yellow fever vaccines, the following findings have been determined for safety and effectiveness. A case-control study of Brazilian women found no significant difference in the odds ratio of spontaneous abortion among vaccinated women compared to a similar unvaccinated group. (28) In a separate study in Trinidad, 100 to 200 pregnant females were immunized with yellow fever vaccine. No adverse events related to pregnancy were reported. In addition, 41 cord blood samples were obtained from infants born to mothers immunized during the first trimester. One of these infants tested positive for IgM antibodies in cord blood. The infant appeared normal at delivery and no subsequent adverse sequelae of infection were reported. However, this result suggests that transplacental infection with 17D vaccine viruses can occur. (29) In another study involving 101 Nigerian women, the majority of whom (88%) were in the third trimester of pregnancy, none of the 40 infants who were delivered in a hospital tested positive for IgM antibodies as a criterion for transplacental infection with vaccine virus. However, the percentage of pregnant women who seroconverted was reduced compared to a non-pregnant control group (38.6% vs. 81.5%). (30)

For further discussion of vaccination with YF-VAX during pregnancy and for documentation of a protective immune response to vaccine where it is deemed essential, contact the CDC at 1-970-221-6400.

Nursing Mothers
Because of the potential for serious adverse reactions in nursing infants from YF-VAX, a decision should be made whether to discontinue nursing or not to administer the vaccine, taking into account the importance of the vaccine to the mother. As of July 2015, three vaccine-associated neurotropic disease cases have been reported worldwide in exclusively breastfed infants whose mothers were vaccinated with yellow fever vaccines, including one case reported after vaccination with YF-VAX. All three infants were diagnosed with encephalitis and were less than one month of age at the time of exposure. (17) Because age less than 9 months is a risk factor for yellow fever vaccine-associated neurotropic disease, YF-VAX is contraindicated in lactating women who are providing breastmilk to infants younger than 9 months of age. (see CONTRAINDICATIONS section.) Discuss the risks and benefits of vaccination with lactating women who are providing breastmilk to infants 9 months of age and older. (14)

Pediatric Use
Vaccination of infants less than 9 months of age is contraindicated because of the risk of yellow fever vaccine-associated neurotropic disease. (See CONTRAINDICATIONS and ADVERSE REACTIONS sections.)

Geriatric Use
There is an increased risk of severe systemic adverse reactions to YF-VAX in infants of 6 years of age and older. Monitor elderly individuals for signs and symptoms of yellow fever vaccine-associated viscerotropic disease, which typically occurs within 10 days post-vaccination. (See WARNINGS and ADVERSE REACTIONS sections.)

ADVERSE REACTIONS
Data from Clinical Studies
Adverse reactions to YF-VAX include mild headaches, myalgia, low-grade fever, or other minor symptoms for 5 to 10 days. Local reactions including edema, hypersensitivity, pain or mass at the injection site have also been reported following yellow fever vaccine administration. Immediate hypersensitivity reactions, characterized by rash, urticaria, and/or asthma, occurred principally among persons with histories of allergy to eggs or other substances contained in the vaccine.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

No placebo-controlled trial has assessed the safety of YF-VAX. However, between 1953 and 1994, reactogenicity of 17D-204 vaccine was monitored in 10 uncontrolled clinical trials. The trials included a total of 3,333 adults and 264 infants greater than 4 months old residing in Europe or in yellow fever endemic areas. Self-limited and mild local reactions consisting of erythema and pain at the injection site and systemic reactions consisting of headache and/or fever occurred in a minority of subjects (typically less than 5%) 5 to 7 days after immunization. In one study involving 115 infants age 4 to 24 months the incidence of fever was as high as 21%. Also in this study, reactogenicity of the vaccine was markedly reduced among a subset of subjects who had serological evidence of previous exposure to yellow fever virus. Only two of the ten studies provided diary cards for daily reporting; this method resulted in a slightly higher incidence of local and systemic complaints. YF-VAX was used as a control in a double-blind, randomized comparative trial with another 17D-204 vaccine, conducted at nine centers in the U.S. YF-VAX was administered to 725 adults ≥18 years old with a mean age of 38 years. Safety data were collected by daily card for days 1 through 10 after vaccination and by interview on days 5, 11, and 31. Among subjects who received YF-VAX, there were no serious adverse events, and 75.9% experienced non-serious adverse events judged to have been related to vaccination. Most of these were injection site reactions of mild to moderate severity. Four such local reactions were considered severe. Rash occurred in 3.2%, including two subjects with urticaria. Systemic reactions (headache, myalgia, malaise, and asthma) were usually mild and occurred in 10% to 30% of subjects during the first few days after vaccination. The incidence of non-serious adverse reactions, including headache, malaise, injection site edema, and pain, was significantly lower in subjects >60 years compared to younger subjects. Adverse events were less frequent in the 1.7% of vaccinated subjects who had pre-existing immunity to yellow fever virus, compared to those without pre-existing immunity. (8)
Data from Post-marketing Experience

The following additional adverse events have been spontaneously reported during the post-marketing use of YF-VAX worldwide. These events are reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency reliably or establish a causal relationship to vaccine exposure. This list includes adverse events based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to YF-VAX.

- **Immune System Disorders** (14)
  - Immediate hypersensitivity reactions or anaphylaxis, characterized by rash and/or urticaria and/or respiratory symptoms (e.g., dyspnea, bronchospasm, or pharyngeal edema) occur principally among persons with histories of allergies to egg or other substances contained in the vaccine.
  - Nervous System Disorders (1) (32) (33) (34)
    - Isolated cases of Yellow Fever Vaccine-Associated Neurotropic Disease (YEL-AND), sometimes fatal, have been reported to occur within 30 days following vaccination with YF-VAX, and other yellow fever vaccines (see WARNINGS section). Yellow fever vaccine-associated neurotropic disease (subsection). Age less than 9 months and congenital or acquired immunodeficiency have been identified as risk factors for this event. (See WARNINGS and CONTRAINDICATIONS sections.) Twenty-one cases of YEL-AND associated with all licensed 17D vaccines have been reported between 1996 and 2004. Eighteen of these cases were in children or adolescents. Fifteen of these cases occurred prior to 1990, thirteen of which occurred in infants 4 months of age and younger, and two of which occurred in infants six and seven months old. The incidence of vaccine-associated neurotropic disease in infants less than 4 months old is estimated to be between 50 and 400 cases per 1,000,000, based on two historical reports where denominators are available. (33) (34) (35) (36) A study in Senegal (34) described two fatal cases of encephalitis possibly associated with 17D-204 vaccination among 67,325 children between the ages of 6 months and 2 years, for an incidence rate of 3 per 100,000. The incidence of YEL-AND in the United States is less than 1:100,000 doses administered. (17)

Other neurological complications have included Guillain-Barre syndrome (GBS), acute disseminated encephalomyelitis (ADEM), and bulbar palsy.

- **Infections and infestations**
  - Isolated cases of Yellow Fever Vaccine-Associated Vasculotropic Disease YEL-AVD, formerly described as “Fabry’s Multiple Organ-System-Failure”, sometimes fatal, have been reported following YF-VAX and other yellow fever vaccines (see WARNINGS section). Yellow fever vaccine-associated vasculotropic disease (subsection). In the majority of cases reported, the onset of signs and symptoms was within 10 days after the vaccination. Initial signs and symptoms are non-specific and may include pyrexia, myalgia, fatigue and headache, potentially progressing quickly to fever and muscle cytolysis and possibly to thrombocytopenia, lymphopenia and acute renal failure. (18) The pathophysiological mechanism of such reactions has not been established. In some individuals with YEL-AVD a medical history of thymic disease has been reported. (36) Age older than 60 has also been identified as a risk factor for this event. (9) During surveillance in the U.S. between 1996 and 1998, four individuals (ages 63, 67, 76, and 79) became severely ill 2 to 5 days after vaccination with YF-VAX vaccine. Two of these 4 subjects died. The incidence rate for these serious adverse events was estimated at 1 per 400,000 doses of YF-VAX vaccine, based on the total number of doses administered in the U.S. civilian population during the surveillance period. (21) YEL-AVD has occurred after yellow fever vaccination in fewer than 1:100,000 U.S. vaccinees, (14) most commonly in individuals 60 years of age and older.

In a CDC analysis of data submitted to the Vaccine Adverse Events Reporting System (VAERS) between 1990 and 1998, the rate of systemic adverse events following vaccination was 2.5-fold higher in the 65 years or older age group (6.2 events per 100,000 doses of vaccine) compared to the 25 to 44 year-old age group (2.5 events per 100,000 doses of vaccine). (31)

- **Concomitant Administration with other Vaccines**
  - Reconstitute the vaccine using only the diluent supplied (0.6 mL vial of Sodium Chloride Injection USP for single dose vial of vaccine and 3 mL vial of Sodium Chloride Injection USP for 5 dose vial of vaccine). After removing the “flip-off” caps, cleanse the vaccine and diluent vial stoppers with a suitable germicide. Do not remove the vial stoppers or metal seals holding them in place. Using aseptic technique, use a suitable sterile needle and syringe to withdraw the volume of supplied diluent shown on the diluent label and slowly inject the diluent into the vial containing the vaccine. Allow the reconstituted vaccine to sit 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. Do not dilute reconstituted vaccine. Use aseptic technique and a separate sterile needle and syringe to withdraw each 0.5mL dose from the single dose or multidose vial of reconstituted vaccine.
  - Before reconstitution, YF-VAX is a pinkish color. After reconstitution, YF-VAX is a slight pink-brown suspension. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, do not administer the vaccine.
  - Administer the single dose of 0.5 mL subcutaneously using a suitable sterile needle. Use YF-VAX within 60 minutes of reconstituting the single dose or multi-dose vial. Properly dispose of all reconstituted vaccine and containers that remain unused after one hour according to locally approved guidelines (eg, sterilized or disposed in red hazardous waste containers). (14)

**Desensitization**

If immunization is imperative and the individual has a history of severe egg sensitivity and has a positive skin test to the vaccine, this desensitization procedure may be used to administer the vaccine.

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. 0.1 mL of full strength
4. 0.15 mL of full strength
5. 0.20 mL of full strength

Desensitization should only be performed under the direct supervision of a physician experienced in the management of allergy with necessary emergency equipment immediately available.

**HOW SUPPLIED**

The vial stoppers for YF-VAX vaccine and diluent are not made with natural rubber latex.

1 Dose:
- Vaccine vial, 1 Dose (NDC 49281-915-58) supplied in a package of 5 vials (NDC 49281-915-51).
- Diluent vial, 0.6 mL (NDC 49281-912-59) supplied separately in a package of 5 vials (NDC 49281-912-05).

5 Dose:
- Vaccine vial, 5 Dose (NDC 49281-915-68) supplied in a package of 1 vial (NDC 49281-915-05).
- Diluent vial, 3 mL (NDC 49281-912-69) supplied separately in a package of 1 vial (NDC 49281-912-10).

- **YF-VAX (Yellow Fever Vaccine)** in the US is supplied only to designated Yellow Fever Vaccination Centers authorized to issue 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.

**STORAGE**

Store at 2° to 8°C (35° to 46°F). DO NOT FREEZE.

Do not use vaccine after expiration date. YF-VAX does not contain a preservative.

The following stability information for YF-VAX 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. Half-life is reduced from approximately 14 days at 35° to 3-4.5 days at 45° to 47°C.

REFERENCES


YF-VAX® is a registered trademark of Sanofi Pasteur and its subsidiaries.

Product Information as of June 2016.