YF-VAX®

Yellow Fever Vaccine

DESCRIPTION
YF-VAX® (Yellow Fever Vaccine) is prepared by culturing the 17D strain of yellow fever virus in living avian leukosis virus-free (ALV) chicken embryos. The vaccine, which contains sorbitol and gelatin as stabilizers, is lyophilized and hermetically sealed under nitrogen in glass vials. YF-VAX® is formulated to contain not less than 5.04 log_{10} Plaque Forming Units (PFU) per 0.5 mL dose. The vaccine must be reconstituted immediately before use with the proper diluent, Sodium Chloride Injection (provided). The product appears slightly opalescent and light orange in colour after reconstitution.

Neither the vaccine nor the diluent contain a preservative.

YF-VAX® complies with the standards of the World Health Organization (WHO).

INDICATIONS
YF-VAX® (Yellow Fever Vaccine) is recommended for all persons ≥9 months of age travelling to or living in areas where yellow fever infection is reported or yellow fever vaccination is required. Infants 4 to 9 months of age and pregnant women should be considered for immunization only if they are travelling to high-risk areas, travel cannot be postponed and a high level of prevention against mosquito exposure is unfeasible. In no circumstances should infants <4 months of age be given yellow fever vaccine because of the risk of encephalitis after vaccination which may occur in as many as 1% of infants <3 months of age. (See CONTRAINDICATIONS and WARNINGS.)

The vaccine is recommended for all travellers passing through or living in countries in Africa, Central America and South America where yellow fever infection is officially reported. It is also recommended for travel outside the urban area of countries that do not officially report yellow fever but lie in the yellow fever “endemic zones.”

Yellow fever vaccination is required by law upon entry to certain countries irrespective of the traveller’s country of origin, and in other countries when travellers are coming from endemic areas. In some cases, vaccination against yellow fever is recommended, although not required by law, e.g., if yellow fever has been reported in the country of destination. In some Asian and other tropical countries where yellow fever does not exist but the transmitting mosquito is found, vaccination is required for arrivals from an endemic country to prevent importation of the disease. Current information on the countries for which an International Certificate of Vaccination is required can be obtained from local health departments.

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

For simultaneous administration of other vaccines see PRECAUTIONS.

Under the International Health Regulations the validity period of the certificate of vaccination or revaccination is 10 years beginning 10 days after vaccination.
CONTRAINDICATIONS

General
Immunization with YF-VAX® (Yellow Fever Vaccine) should be deferred in the presence of any acute illness, including febrile illness to avoid superimposing adverse effects from the vaccine on the underlying illness or mistakenly identifying a manifestation of the underlying illness as a complication of vaccine use. A minor afebrile illness such as mild upper respiratory infection is not usually reason to defer immunization.¹

Absolute Contraindications
Allergy to any component of YF-VAX® (Yellow Fever Vaccine) (see components listed in DESCRIPTION) an anaphylactic or other allergic reaction to a previous dose of Yellow Fever Vaccine are contraindications to vaccination. Infants <4 months of age should not be given YF-VAX® because of the risk of encephalitis.

Because yellow fever virus is propagated in chick embryos, it should not be administered to persons with hypersensitivity to the ingestion of eggs or chicken protein, manifested as hives, swelling of the mouth and throat, difficult breathing, hypotension and shock. If vaccination of a person with a questionable history of egg hypersensitivity is considered essential because of a high risk of exposure, an intradermal test dose may be administered under close medical supervision.¹ Specific directions for skin testing are found in PRECAUTIONS section.

Generally, persons who are able to eat eggs or egg products may receive the vaccine.² (See PRECAUTIONS section for sensitivity testing.)

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 mosquitos, and supplied with vaccination waiver letters by their physicians.²⁴ Infection with yellow fever 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 mosquitos, and supplied with vaccination waiver letters by their physicians.²⁴

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 considered 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. Vaccinées should be monitored for possible adverse effects. The vaccination of such persons may be less effective than that for non-HIV-infected persons. Family members of immunosuppressed persons, who themselves have no contraindication, may receive yellow fever vaccine.²

WARNINGS
Infants 4 to 9 months of age and pregnant women should be considered for immunization only if they are travelling to high-risk areas, travel cannot be postponed and a high level of prevention against mosquito exposure is unfeasible.

Anaphylaxis may occur following the use of YF-VAX® (Yellow Fever Vaccine) even in persons with no prior history of hypersensitivity to the vaccine components.

The stopper of the vial for this product contains dry natural latex rubber.

As with any vaccine, immunization with YF-VAX® may not protect 100% of susceptible persons.

The health status of individuals 65 years of age and older travelling to areas experiencing ongoing epidemic yellow fever should be evaluated prior to vaccination and these individuals should be carefully monitored for adverse events for 10 days post-vaccination. (See ADVERSE REACTIONS section.)
US Centers for Disease Control and Prevention have raised a concern about a possible increased risk of a serious adverse event to YF vaccine in elderly persons, i.e. ≥65 years. Health Canada recommends that elderly persons who travel to yellow fever endemic areas should be informed of the possible risk of serious adverse reactions to the vaccine (approximately 8.3 per 100,000 doses, CDC data). However, the possible risk associated with the vaccine must be balanced by the risk of exposure to yellow fever and the potentially serious illness that could result in death. Thus, in general, Health Canada continues to recommend that all persons travelling to yellow fever endemic areas be vaccinated against yellow fever.  

PRECAUTIONS  

General  
The possibility of allergic reactions in persons sensitive to components of the vaccine should be evaluated. Epinephrine Hydrochloride Solution (1:1000) and other appropriate agents should be available for immediate use in case an anaphylactic or acute hypersensitivity reaction occurs. Health-care providers should be familiar with current recommendations for the initial management of anaphylaxis in non-hospital settings, including proper airway management.  

A separate sterile needle and syringe, or a sterile disposable unit, must be used for each individual patient to prevent the transmission of infectious agents.  

There have been case reports of transmission of HIV and hepatitis by failure to scrupulously observe sterile technique. In particular, the same needle and/or syringe must never be used to re-enter a multi-dose vial to withdraw vaccine even when it is to be used for inoculation of the same patient. This may lead to contamination of the vial contents and infection of patients who subsequently receive vaccine from the vial.  

Before administration of any vaccine, all appropriate precautions should be taken to prevent adverse reactions. This includes a review of the patient’s history with respect to possible hypersensitivity to the vaccine or similar vaccine, to dry natural latex rubber, determination of previous immunization history, and the presence of any contraindications to immunization, current health status, and a current knowledge of the literature concerning the use of the vaccine under consideration.  

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. (See CONTRAINDICATIONS section.)  

Hypersensitivity Reactions  
Since the yellow fever virus is propagated in chicken embryos, it should not be administered to any person 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.  

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.  

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

• **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.
• **Intradermal test.** A dose of 0.02 mL of a 1:100 dilution of the vaccine in physiologic saline is injected intradermally; 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.**

If the result of the test is positive, the vaccine should not be given (or should only be given after desensitization) (see below).

**Desensitization**

If the person 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. A suggested protocol is subcutaneous administration of the following successive doses of vaccine at 15 to 20 minute intervals as follows:

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

Scratch, prick, or puncture tests with other allergens have resulted in fatalities in highly allergic persons. Although such untoward effects have not been reported for vaccine testing, all skin tests and desensitization procedures should be performed by trained personnel experienced in the management of anaphylaxis. Necessary medications and equipment should be readily available.

**Administration with Other Vaccines**

The serologic response to yellow fever vaccine is not inhibited by concurrent administration of other live vaccines, including live oral cholera and live oral typhoid vaccines. If live vaccines are not given concurrently, they should be spaced at least 4 weeks apart. Inactivated vaccines, except inactivated cholera vaccine, may be given concurrently or at any interval after yellow fever vaccine. Inactivated parenteral cholera vaccine and yellow fever vaccine should be given 3 or more weeks apart to avoid interference with antibody responses. The simultaneous administration of the most widely used live and inactivated vaccines has not resulted in impaired antibody responses or increased rates of adverse reactions. Thus, if time is a critical factor for required vaccinations, the clinical judgment of the responsible physician should prevail.

The administration of immune globulin and yellow fever vaccine either simultaneously or within a short span of time, does not alter the immunologic response, because immune globulin is unlikely to contain antibody to yellow fever virus.

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; typhoid, meningococcal and yellow fever vaccines have been administered concurrently with full efficacy of each of the components.

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.
Pregnancy

Animal reproduction studies have not been conducted with YF-VAX® (Yellow Fever Vaccine). 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.

A small study showed that yellow fever vaccine virus given in pregnancy can infect the developing fetus, but the potential risk of adverse events associated with congenital infection is unknown. Therefore, it is prudent to avoid vaccinating pregnant women and for non-immunized pregnant women to postpone travel to epidemic areas until after delivery. If the travel itinerary of a pregnant woman does not present a substantial risk of exposure and immunization is contemplated solely to comply with an international travel requirement, then efforts should be made to obtain a waiver letter from the traveller’s physician. Pregnant women who must travel to areas with active ongoing transmission should be vaccinated. It is believed that under these circumstances, the small theoretical risk for mother and fetus from vaccination is far outweighed by the risk of yellow fever infection.4

The decision to immunize pregnant women should be based upon estimates of the risk of exposure.2,11,12 (See WARNINGS, above.)

Nursing Mothers

Yellow fever virus is not excreted in breast milk following vaccination and there is no contraindication to vaccinating breast-feeding mothers with yellow fever vaccine.11

ADVERSE REACTIONS

Local reactions including edema, hypersensitivity, pain or mass at the injection site have been reported following yellow fever vaccine administration.13

Reactions to 17D yellow fever vaccines are generally mild. Two percent to 5% of vaccinees have mild headaches, myalgia, low-grade fevers, or other minor symptoms 5 to 10 days after vaccination. 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.4

Two cases of encephalitis temporally associated with vaccinations have been reported in the US; in one fatal case, 17D virus was isolated from the brain.2,14

Three deaths have been reported following vaccination with the onset of the illness occurring within seven days after vaccination. In addition, a 76-year-old male, who subsequently recovered, developed an illness with an onset of three days following vaccination characterized by liver dysfunction, renal insufficiency, hypotension and shock. However, no cause and effect relationship has been established between vaccination and subsequent illness.13 (See WARNINGS section.)

Recently the US Centers for Disease Control and Prevention (CDC) reviewed 110 YF adverse event reports received by the US Vaccine Adverse Event Reporting System (VAERS) during the 1990-98 period. Of these 110 reports, 35% were categorized as “serious” (defined in the report as neurologic or systemic reactions persisting for >48 hours), 39% as non-serious, and 25% as not related to YF vaccine. A total of 14 patients were hospitalized and there were 3 deaths in elderly patients aged 63, 67 and 79.5

Health Canada’s Laboratory Centre for Disease Control (LCDC) has reviewed Canadian data on YF adverse events reported to the Canadian Vaccine Associated Adverse Events Surveillance System (VAESS). From 1987 through October 1999, there were 117 reports associated with YF vaccine. Of these 117 reports, 6.7% of persons were hospitalized. No deaths were reported. A total of 5 reports were received involving persons ≥65 years of age. None were hospitalized.5
Anaphylaxis may occur following the use of YF-VAX (Yellow Fever Vaccine) even in persons with no prior history of hypersensitivity to the vaccine components.

Physicians, nurses, and pharmacists should report any adverse occurrences temporally related to the administration of the product in accordance with local requirements and to the Medical Director, Aventis Pasteur Limited, 1755 Steeles Avenue West, Toronto, ON, Canada M2R 3T4, 1-888-621-1146 (phone) or 416-667-2939 (fax).

**ADMINISTRATION**

Parenteral biological products should be inspected visually for extraneous particulate matter and/or discoloration before administration. If these conditions exist, the product should not be administered.

Needles should not be recapped and should be disposed of properly.

Before administration of YF-VAX®, health-care personnel should inform the parent or guardian or the patient to be immunized of the benefits and risks of immunization, inquire about the recent health status of the patient and comply with any local requirements with respect to information to be provided to the patient before immunization.

**Reconstitution of Freeze-Dried Product and Withdrawal from Stoppered Vial**

**DO NOT REMOVE THE STOPPER FROM THE VIAL.**

Reconstitute the vaccine using only the diluent supplied (Sodium Chloride Injection). Draw the volume of the diluent, shown on the diluent label, into a suitable size syringe. Slowly inject the diluent into the vial containing the vaccine, let stand for one or 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.

SWIRL THE PRODUCT VIAL WELL before withdrawing each dose.

Withdraw the required dose (0.5 mL) of the reconstituted vaccine into a syringe. Aseptic technique must be used for withdrawal of each dose. (See PRECAUTIONS.)

Use vaccine within 60 minutes following reconstitution. *All reconstituted vaccine and containers which remain unused after one hour must be disposed of properly (e.g., sterilized or disposed in hazardous waste containers).*

Before injection, the skin over the site to be injected should be cleansed with a suitable germicide.

A single immunizing dose of 0.5 mL should be administered **subcutaneously.**

**DO NOT INJECT INTRAVENOUSLY OR INTRAMUSCULARLY.**

If immunization is imperative to a person with a history of severe egg sensitivity and a positive skin test to the vaccine is imperative, see PRECAUTIONS, Hypersensitivity Reactions and Desensitization section.

**DOSAGE**

**Primary vaccination.** For persons of all ages, a single subcutaneous injection of 0.5 mL of reconstituted vaccine is administered. Immunity develops by the 10th day after primary vaccination.

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

Each person who is immunized should be given a permanent personal immunization record. In addition, it is essential that the physician or nurse record the immunization history in the permanent medical record of each patient. This permanent office record should contain the name of the vaccine, date given, dose, manufacturer and lot number.
STORAGE
YF-VAX® (Yellow Fever Vaccine) must be maintained continuously at temperatures between 5°C and -30°C (41°F and -22°F) until reconstituted for use.

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

The vial of diluent should not be allowed to freeze.

The reconstituted vaccine must be kept refrigerated and used within sixty minutes following reconstitution.

All reconstituted vaccine and containers which remain unused after one hour must be disposed of properly (e.g., sterilized or disposed in hazardous waste containers).8

Do not use vaccine after expiration date.

HOW SUPPLIED
Package of 1 x 5 dose vial of vaccine and package of 1 x 3 mL vial of diluent.

Package of 5 x 1 dose vials of vaccine and package of 5 x 0.6 mL vials of diluent.

REFERENCES


Manufactured by:
Aventis Pasteur Inc.
Swiftwater, PA 18370 USA

Distributed by:
Aventis Pasteur Limited
Toronto, Ontario, Canada

Full Product Monograph available call:
Vaccine Information Service 1-888-621-1146 or (416) 667-2779.