

1 AHFS Category: 80:12

Rx only

2

3 **YELLOW FEVER VACCINE**

4 **YF-VAX®**

5

6 **DESCRIPTION**

7 YF-VAX®, Yellow Fever Vaccine, for subcutaneous use, is prepared by culturing the 17D-204
8 strain of yellow fever virus in living avian leukosis virus-free (ALV-free) chicken embryos. The
9 vaccine contains sorbitol and gelatin as a stabilizer, is lyophilized, and is hermetically sealed
10 under nitrogen. No preservative is added. The vaccine must be reconstituted immediately before
11 use with the sterile diluent provided (Sodium Chloride Injection USP – contains no preservative).
12 YF-VAX vaccine is formulated to contain not less than 4.74 log₁₀ plaque forming units (PFU) per
13 0.5 mL dose throughout the life of the product. YF-VAX vaccine is a slight pink-brown
14 suspension after reconstitution.

15

16 **CLINICAL PHARMACOLOGY**

17 Yellow fever is an acute viral illness caused by a mosquito-borne flavivirus. The clinical spectrum
18 of yellow fever is highly variable, from subclinical infection to overwhelming pansystemic
19 disease. Yellow fever has an abrupt onset after an incubation period of 3 to 6 days, and usually
20 includes fever, prostration, headache, photophobia, lumbosacral pain, extremity pain (especially
21 the knee joints), epigastric pain, anorexia, and vomiting. The illness may progress to liver and

1 renal failure, and hemorrhagic symptoms and signs caused by thrombocytopenia and abnormal
2 clotting and coagulation may occur. The case-fatality rate of yellow fever varies widely in
3 different studies and may be different for Africa compared to South America, but is typically 20%
4 or higher. Jaundice or other gross evidence of severe liver disease is associated with higher
5 mortality rates. (1)

6

7 Two live, attenuated yellow fever vaccines, strains 17D-204 and 17DD, were derived in parallel
8 in the 1930s. Historical data suggest that these “17D vaccines” have identical safety and
9 immunogenicity profiles. Despite a marked reduction in the world-wide incidence of yellow fever
10 in the last five decades due to the extensive use of 17D vaccines and mosquito eradication
11 programs, at least seven tropical South American countries (Bolivia, Brazil, Colombia, Ecuador,
12 French Guiana, Peru, and Venezuela) and much of sub-Saharan Africa (2) currently experience
13 yellow fever epidemics. However, the actual areas of yellow fever virus activity far exceed the
14 infected zones officially reported for epidemics. Approximately 200,000 yellow fever cases
15 have been reported to occur world-wide each year. Six fatalities from yellow fever were reported
16 between 1996 and July 2002, among unimmunized American and European travelers who visited
17 rural areas within the yellow fever endemic zone. (3) (4) (5) (6) (7) (8)

18

19 Vaccination with 17D strain viruses is predicted to elicit an immune response identical in quality
20 to that induced by wild-type infection. This response is presumed to result from initial infection of

1 cells in the dermis or other subcutaneous tissues near the injection site, with subsequent
2 replication and limited spread of virus leading to the processing and presentation of viral
3 antigens to the immune system, as would occur during infection with wild-type yellow fever
4 virus. The humoral immune response to the viral structural proteins, as opposed to a cell-mediated
5 response, is most important in the protective effect induced by 17D vaccines. Yellow fever
6 antibodies with specificities that prevent or abort infection of cells are detected as neutralizing
7 antibodies in assays that measure the ability of serum to reduce plaque formation in tissue culture
8 cells. The titer of virus neutralizing antibodies in sera of vaccinees is a surrogate for efficacy. A
9 \log_{10} neutralization index (LNI, measured by a plaque reduction assay) of 0.7 or greater was
10 shown to protect 90% of monkeys from lethal intracerebral challenge. (9) This is the definition of
11 seroconversion adopted for clinical trials of yellow fever vaccine. The standard has also been
12 adopted by the World Health Organization (WHO) for efficacy of yellow fever vaccines in
13 humans. (10)

14

15 The neutralizing antibody response to 17D vaccines has been evaluated in several uncontrolled
16 studies since the late 1930s. In 24 studies conducted world-wide between 1962 and 1997 using
17 17D vaccines involving a total of 2,529 adults and 991 infants and children, the seroconversion
18 rate was greater than 91% in all but two studies and never lower than 81%. There were no
19 significant age-related differences in immunogenicity. (1)

20

1 Five of these 24 studies were conducted in the US between 1962 and 1993 and included 208
2 adults who received YF-VAX vaccine. The seroconversion rate was 81% in one study involving
3 32 subjects and 97% to 100% in the other four studies. (11) (12) (13) (14) (15)

4

5 In 2001, YF-VAX vaccine was used as a control in a double-blind, randomized comparison trial
6 with another 17D-204 vaccine, conducted at nine centers in the US. YF-VAX vaccine was
7 administered to 725 adults ≥ 18 years old with a mean age of 38 years. Three hundred twelve of
8 these subjects who received YF-VAX vaccine were evaluated serologically, and 99.3% of them
9 seroconverted with a mean LNI of 2.21. The LNI was slightly higher among males compared to
10 females and slightly lower among Hispanic and African-American subjects compared to others,
11 but these differences were not significant with respect to the protective effect of the vaccine.
12 There was no difference in mean LNI for subjects < 40 years old compared to subjects ≥ 40
13 years old. Due to the small number of subjects (1.7%) with prior flavivirus immunity, it was not
14 possible to draw conclusions about the role of this factor in the immune response. (16)

15

16 Results of one clinical trial involving 33 HIV-positive adults residing in the US indicate that the
17 seroconversion rate to 17D-204 vaccine may be reduced in these patients. (17)

18

19 In pregnancy or in immunosuppressed individuals the seroconversion rate after administration of
20 yellow fever vaccine may be significantly reduced. (18)

21

1 Existing data suggest that the small percentage of immunologically normal subjects who fail to
2 develop an immune response to an initial vaccination may do so upon re-vaccination. (19)

3

4 In two separate clinical trials of 17D-204 vaccines, 90% of subjects seroconverted within 10 days
5 after vaccination, (20) and 100% of subjects seroconverted within 14 days. (11) Thus,

6 International Health regulations stipulate that the vaccination certificate for yellow fever is valid
7 10 days after administration of YF-VAX vaccine. (21)

8

9 **INDICATIONS AND USAGE**

10 YF-VAX vaccine is recommended for active immunization of persons 9 months of age and older
11 in the following categories:

12

13 **Persons Living in or Traveling to Endemic Areas**

14 While the actual risk for contracting yellow fever during travel is probably low, variability of
15 itineraries and behaviors and the seasonal incidence of disease make it difficult to predict the
16 actual risk for a given individual traveling to a known endemic or epidemic area. Persons greater
17 than or equal to 9 months of age traveling to or living in areas of South America and Africa
18 where yellow fever infection is officially reported at the time of travel should be vaccinated.
19 Vaccination is also recommended for travel outside the urban areas of countries that do not
20 officially report the disease but that lie in a yellow fever endemic zone.

21

1 **International Travel**

2 Yellow fever vaccination may be required for international travel. Some countries in Africa
3 require evidence of vaccination from all entering travelers and some countries may waive the
4 requirements for travelers staying less than 2 weeks that are coming from areas where there is no
5 current evidence of significant risk for contracting yellow fever. Some countries require an
6 individual, even if only in transit, to have a valid International Certificate of Vaccination if the
7 individual has been in countries either known or thought to harbor yellow fever virus. The
8 certificate becomes valid 10 days after vaccination with YF-VAX vaccine. (2) (21)

9
10 **In no instance should infants less than 9 months of age receive yellow fever vaccine, because**
11 **of the risk of encephalitis (see [CONTRAINDICATIONS](#) and [ADVERSE REACTIONS](#)**
12 **sections).**

13 14 **Laboratory Personnel**

15 Those laboratory personnel who might be exposed to virulent yellow fever virus or to
16 concentrated preparations of the yellow fever vaccine strain by direct or indirect contact or by
17 aerosols should be vaccinated. (2)

18
19 As with any vaccine, vaccination with YF-VAX vaccine may not protect 100% of individuals (see
20 [CLINICAL PHARMACOLOGY](#) section).

21

1 For concomitant administration with other vaccines see **PRECAUTIONS** section, **Drug**
2 **Interactions** subsection.

3

4 **CONTRAINDICATIONS**

5 **Hypersensitivity**

6 YF-VAX vaccine is contraindicated in anyone with a history of acute hypersensitivity reaction to
7 any components (including gelatin). (22) Because the yellow fever virus used in the production of
8 this vaccine is propagated in chicken embryos, YF-VAX vaccine should not be administered to
9 anyone with a history of acute hypersensitivity to eggs or egg products; anaphylaxis may
10 occur. *Less severe or localized manifestations of allergy to eggs or to feathers are not*
11 *contraindications to vaccine administration and do not usually warrant vaccine skin testing (see*
12 **PRECAUTIONS** *section,* **Hypersensitivity Reactions** *subsection). Generally,*
13 *persons who are able to eat eggs or egg products may receive the vaccine.*(2) (23)

14

15 **Acute or Febrile Disease**

16 Vaccination should be postponed in case of an acute or febrile disease; a disease with low-grade
17 fever is usually not a reason to postpone vaccination.

18

19 **Infants**

20 Vaccination of infants less than 9 months of age IS CONTRAINDICATED because of the risk of
21 encephalitis, and travel of such persons to rural areas in yellow fever endemic zones or to
22 countries experiencing an epidemic should be postponed or avoided, whenever possible.

1

2 Immunosuppressed Patients

3 Exposure to yellow fever vaccine, which is a live virus vaccine, poses a risk of encephalitis or
4 other serious adverse events to patients with illnesses that commonly result in immunosuppression
5 (eg, acquired immunodeficiency syndrome or other manifestations of human immunodeficiency
6 virus (HIV) infection, leukemia, lymphoma, thymic disease, generalized malignancy), or patients
7 whose immunologic responses are suppressed by drug therapy (eg, corticosteroids, alkylating
8 drugs, or antimetabolites) or radiation. There is evidence suggesting that thymic dysfunction is an
9 independent risk factor for the development of yellow fever vaccine-associated viscerotropic
10 disease, and health care providers should be careful to ask about a history of thymus disorder,
11 including myasthenia gravis, thymoma or prior thymectomy. (24)

12

13 Immunosuppressed subjects should not be immunized, and travel to yellow fever endemic areas
14 should be postponed or avoided. If travel to a yellow fever-infected zone is unavoidable,
15 immunosuppressed patients should be advised of the risk, instructed in methods for avoiding
16 vector mosquitoes, and supplied with vaccination waiver letters by their physicians (see
17 **ADVERSE REACTIONS** section). Family members of immunosuppressed persons, who
18 themselves have no contraindications, may receive yellow fever vaccine. (2) (25)

19

20 Lactation

21 Lactation: (See **PRECAUTIONS** section, **Nursing Mothers** subsection.)

1

2 WARNINGS

3 The stopper of the vial contains dry natural latex rubber that may cause allergic reactions.

4

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

7

8 **EPINEPHRINE INJECTION (1:1000) SHOULD ALWAYS BE IMMEDIATELY**
9 **AVAILABLE IN CASE OF AN UNEXPECTED ANAPHYLACTIC OR OTHER SERIOUS**
10 **ALLERGIC REACTION.**

11

12 Yellow fever vaccines must be considered as a possible, but rare, cause of vaccine-associated
13 viscerotropic disease (2) (previously described as multiple organ system failure), (2) (26) that is
14 similar to fulminant yellow fever caused by wild-type yellow fever virus. Available evidence
15 suggests that the occurrence of this syndrome may depend upon the presence of undefined host
16 factors, rather than intrinsic virulence of the yellow fever strain 17D vaccine viruses isolated from
17 subjects with vaccine-associated viscerotropic disease. (26) (27) (28) (29) (See **ADVERSE**
18 **REACTIONS** section.)

19

20 Vaccine-associated neurotropic disease (2), previously described as post-vaccinal encephalitis (1),
21 is a known rare adverse event associated with yellow fever vaccination. Age less than 9 months

1 and immunosuppression are known risk factors for this adverse event. (See
2 **CONTRAINDICATIONS** and **ADVERSE REACTIONS** sections.)

3

4 **PRECAUTIONS**

5 **General**

6 Prior to an injection of any vaccine, all known precautions should be taken to prevent adverse
7 events. The patient's previous immunization history, current health status, and medical history
8 should be reviewed for previous hypersensitivity reactions and other adverse events related to this
9 vaccine or similar vaccines and for possible sensitivity to dry natural latex rubber. **The stopper of**
10 **the vial contains dry natural latex rubber that may cause allergic reactions.** In some
11 instances where symptoms appear soon after a vaccine is administered, differentiation between
12 allergic reaction to the vaccine and reaction to an environmental allergen may not be possible.

13 (23)

14

15 **EPINEPHRINE INJECTION (1:1000) SHOULD ALWAYS BE IMMEDIATELY**
16 **AVAILABLE IN CASE OF AN UNEXPECTED ANAPHYLACTIC OR OTHER SERIOUS**
17 **ALLERGIC REACTION.**

18

19 A separate, sterile syringe and needle or a sterile disposable unit should be used for each patient to
20 prevent transmission of blood borne infectious agents. Needles should not be recapped and should
21 be disposed of according to biohazard waste guidelines.

1

2 **Hypersensitivity Reactions**

3 YF-VAX vaccine should not be administered to an individual with a history of hypersensitivity to
4 egg or chicken protein (see **CONTRAINDICATIONS** section). However, if a subject is suspect
5 as being an egg-sensitive individual, the following test can be performed before the vaccine is
6 administered: (23)

7

8 **1. Scratch, prick, or puncture test:** Place a drop of a 1:10 dilution of the vaccine in physiologic
9 saline on a superficial scratch, prick, or puncture on the volar surface of the forearm. Positive
10 (histamine) and negative (physiologic saline) controls should also be used. The test is read after
11 15 to 20 minutes. A positive test is a wheal 3 mm larger than that of the saline control, usually
12 with surrounding erythema. The histamine control must be positive for valid interpretation. If the
13 result of this test is negative, an intradermal (ID) test should be performed.

14

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

18

19 If vaccination is considered essential, despite a positive skin test, then desensitization can be
20 considered (see **DOSAGE AND ADMINISTRATION** section, **Desensitization** subsection).

21

1 **Information for Patients**

2 Prior to administration of YF-VAX vaccine, potential vaccinees or their parents or guardians
3 should be asked about their recent health status. All potential vaccinees or their parents or
4 guardians should be fully informed of the benefits and risks of immunization and potential for
5 adverse events that have been temporally associated with YF-VAX vaccine administration.
6 Vaccinees or their parents or guardians should be instructed to report all serious adverse events
7 that occur up to 30 days post-vaccination to their health-care provider.

8

9 All travelers should seek information regarding vaccination requirements by consulting local
10 health departments, the Centers for Disease Control and Prevention (CDC), and WHO. Travel
11 agencies, international airlines, and/or shipping lines may also have up-to-date information. Such
12 requirements may be strictly enforced, particularly for persons traveling from Africa or South
13 America to Asia. Travelers should consult the latest published version of Health Information for
14 International Travel to determine requirements and regulations for vaccination. (25)

15

16 An International Certificate of Vaccination should be completed, signed, and validated with the
17 center's stamp where the vaccine is administered and provided to all vaccinees. The immunization
18 record should contain the date, lot number and manufacturer of the vaccine administered. (30)

19 (31) (32) Subjects should be told that US vaccination certificates are valid for a period of 10 years
20 commencing 10 days after initial vaccination or revaccination.

21

1 **Drug Interactions**

2 Data are limited in regard to the interaction of YF-VAX vaccine with other vaccines.

3

4 • Measles (Schwartz strain) vaccine, diphtheria and tetanus toxoids and pertussis vaccine
5 adsorbed (DTP), (33) Hepatitis A and Hepatitis B vaccines, (2) (12) (34) (35) meningococcal
6 vaccine, Menomune® – A/C/Y/W-135, and typhoid vaccine, Typhim Vi®, (2) (12) (34) have
7 been administered with yellow fever vaccine at separate injection sites.

8

9 • No data exist on possible interference between yellow fever and rabies or Japanese
10 encephalitis vaccines. (2)

11

12 • In a prospective study, persons given 5 cc of commercially available immune globulin did not
13 experience alterations in immunologic responses to the yellow fever vaccine. (2) (36)

14

15 • The anti-malarial drug chloroquine has been administered with yellow fever vaccine. (2) (37)

16

17 **Patients on Corticosteroid Therapy**

18 Oral Prednisone or other systemic corticosteroid therapy may have an immunosuppressive effect
19 on recipients of yellow fever vaccine that potentially decreases immunogenicity and increases the
20 risk of adverse events (see **CONTRAINDICATIONS** section). Intra-articular, bursal, or tendon
21 injections with Prednisone or other corticosteroids should not constitute an increased hazard to

1 recipients of yellow fever vaccine.

2

3 **Patients with Asymptomatic HIV Infection**

4 Subjects with asymptomatic HIV infection who have had recent laboratory verification of

5 adequate immune system function and who cannot avoid potential exposure to yellow fever virus

6 should be offered the choice of vaccination. Vaccinees should be monitored for possible adverse

7 effects. The seroconversion rate to 17D vaccines is likely to be reduced in these patients. (17)

8 Therefore, documentation of a protective antibody response is recommended before travel. (See

9 **CLINICAL PHARMACOLOGY** section.) For discussion of this subject and for documentation

10 of the immune response to vaccine where it is deemed essential, the CDC may be contacted 1-

11 970-221-6400.

12

13 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

14 YF-VAX vaccine has not been evaluated for its carcinogenic or mutagenic potential or its effect

15 on fertility.

16

17 **Pregnancy Category C**

18 Animal reproduction studies have not been conducted with YF-VAX vaccine. It is also not known

19 whether YF-VAX vaccine can cause fetal harm when administered to a pregnant woman or can

20 affect reproductive capacity. YF-VAX vaccine should be given to a pregnant woman only if

21 clearly needed. The seroconversion rate to 17D vaccines is markedly reduced in pregnant women.

1 (See **CLINICAL PHARMACOLOGY** section.) (18) For discussion of this subject and for
2 documentation of a protective immune response to vaccine where it is deemed essential, the
3 CDC may be contacted at 1-970-221-6400.

4

5 **Nursing Mothers**

6 As there is a theoretical risk of transmission of vaccine components to the infants from breast-
7 feeding mothers, lactation constitutes a contraindication, particularly when infants are below 9
8 months of age because of the risk of encephalitis. (See **CONTRAINDICATIONS** section.) The
9 risks and benefit should therefore be assessed before making the decision as to whether to
10 immunize a nursing woman. (2)

11

12 **Pediatric Use**

13 **Vaccination of infants less than 9 months of age IS CONTRAINDICATED because of the**
14 **risk of encephalitis. (See **CONTRAINDICATIONS** and **ADVERSE REACTIONS** sections.)**

15

16 **Geriatric Use**

17 Vaccination of subjects greater than 65 years of age should be limited to individuals who are
18 traveling to or reside in known yellow fever endemic or epidemic areas, because of the increased
19 risk for systemic adverse events in this age group. When vaccination is deemed necessary, the
20 health status of such individuals should be evaluated prior to vaccination. Additionally, if
21 vaccinated, elderly subjects should be carefully monitored for adverse events for 10 days post-
22 vaccination (see **ADVERSE REACTIONS** section). (24) (38)

1

2 **ADVERSE REACTIONS**

3 Adverse reactions to 17D yellow fever vaccine include mild headaches, myalgia, low-grade

4 fevers, or other minor symptoms for 5 to 10 days. Local reactions including edema,

5 hypersensitivity, pain or mass at the injection site have also been reported following yellow fever

6 vaccine administration. Immediate hypersensitivity reactions, characterized by rash, urticaria,

7 and/or asthma, are uncommon and occur principally among persons with histories of egg allergy.

8 (1) (2) (24)

9

10 No placebo-controlled trials to assess the safety of yellow fever 17D vaccines have been

11 performed. However, between 1953 and 1994, reactogenicity of 17D-204 vaccine was monitored

12 in 10 uncontrolled clinical trials. The trials included a total of 3,933 adults and 264 infants greater

13 than 4 months old residing in Europe or in yellow fever endemic areas. Self-limited and mild local

14 reactions consisting of erythema and pain at the injection site and systemic reactions consisting of

15 headache and/or fever occurred in a minority of subjects (typically less than 5%) 5 to 7 days after

16 immunization. In one study involving 115 infants age 4 to 24 months the incidence of fever was

17 as high as 21%. Also in this study, reactogenicity of the vaccine was markedly reduced among a

18 subset of subjects who had serological evidence of previous exposure to yellow fever virus. Only

19 two of the ten studies provided diary cards for daily reporting; this method resulted in a slightly

20 higher incidence of local and systemic complaints. (1)

21

1 In 2001, YF-VAX vaccine was used as a control in a double-blind, randomized comparative trial
2 with another 17D-204 vaccine, conducted at nine centers in the US. YF-VAX vaccine was
3 administered to 725 adults ≥ 18 years old with a mean age of 38 years. Safety data were collected
4 by diary card for days 1 through 10 after vaccination and by interview on days 5, 11, and 31.
5 Among subjects who received YF-VAX vaccine, there were no serious adverse events, and 71.9%
6 experienced non-serious adverse events judged to have been related to vaccination. Most of these
7 were injection site reactions of mild to moderate severity. Four such local reactions were
8 considered severe. Rash occurred in 3.2% and urticaria in two subjects. Systemic reactions
9 (headache, myalgia, malaise, and asthenia) were usually mild and occurred in 10% to 30% of
10 subjects during the first few days after vaccination. The incidence of non-serious adverse
11 reactions, including headache, malaise, injection site edema, and pain, was significantly lower in
12 subjects >60 years compared to younger subjects. Adverse events were less frequent in the 1.7%
13 of vaccinated subjects who had pre-existing immunity to yellow fever virus, compared to those
14 who had not been previously exposed. (16)

15

16 A CDC analysis of data submitted to the Vaccine Adverse Events Reporting System (VAERS)
17 between 1990 and 1998 suggests that patients aged 65 or older are at increased risk for systemic
18 adverse events temporally associated with vaccination, compared to the 25- to 44-year-old age
19 group (see **PRECAUTIONS** section, **Geriatric Use** subsection). The rate of systemic adverse
20 events occurring post-vaccination in patients age 65 to 74 was 2.5 times higher than the rate

1 occurring in patients age 25 to 44, based on incidence rates of 6.21 and 2.49 per 100,000 doses of
2 vaccine in the two groups, respectively. (38)

3

4 **Neurotropic Disease**

5 Vaccine-associated neurotropic disease (2), previously described as post-vaccinal encephalitis (1),
6 is a known rare serious adverse event associated with 17D vaccination. Age less than 9 months
7 and immunosuppression are known risk factors. Twenty-one cases of vaccine-associated
8 neurotropic disease associated with all licensed 17D vaccines have been reported between 1952
9 and 2004, 18 in children or adolescents. Fifteen of these cases occurred prior to 1960, thirteen of
10 which occurred in infants 4 months of age or younger, and two of which occurred in infants six
11 and seven months old. Six cases were reported between 1960 and 1996, world-wide. Three
12 occurred in children, including a one-month-old infant, a three-year-old, and a thirteen-year-old.
13 The three-year-old died of encephalitis, and a genetic variant of the vaccine virus was isolated
14 from the brain in this case. (39) This is the only verified fatality due to yellow fever vaccine-
15 associated neurotropic disease. The three remaining cases of vaccine-associated neurotropic
16 disease since 1960 occurred in adults. (1)

17

18 The incidence of vaccine-associated neurotropic disease in infants less than 4 months old is
19 estimated to be between 0.5 and 4 per 1,000, based on two historical reports where denominators
20 are available. (40) (41) No data are available for calculation of an age-specific incidence rate in
21 the 4- to 9-month-age group. A study in Senegal (42) described two fatal cases of encephalitis

1 possibly associated with 17D-204 vaccination among 67,325 children between the ages of 6
2 months and 2 years, for an incidence rate of 3 per 100,000. One study conducted in Kenya in 1993
3 detected four cases of encephalitis temporally associated with vaccination, one in a 2-year-old
4 child and three in adults, for an incidence of 5.3 cases per million vaccinees of all ages. (1)

5

6 Other very rare neurological signs and symptoms have been reported and include Guillain-Barré
7 syndrome, seizures and focal neurological deficits. (43)

8

9 **Viscerotropic Disease**

10 Vaccine-associated viscerotropic disease, previously described as multiple organ system failure
11 (26), is a known rare serious adverse event associated with 17D vaccination. No cause and effect
12 relationship has been established between vaccination and these subsequent illnesses. Physicians
13 should therefore be cautious to administer yellow fever vaccine only to those persons truly at risk
14 of exposure to wild-type yellow fever virus infection. (2)

15

16 Between 1996 and 1998, four patients, ages 63, 67, 76, and 79, became severely ill 2 to 5 days
17 after vaccination with YF-VAX vaccine. Three of these 4 subjects died. The clinical presentations
18 were characterized by a non-specific febrile syndrome with fatigue, myalgia, and headache,
19 rapidly progressing to a severe illness including respiratory failure, elevated hepatocellular
20 enzymes, lymphocytopenia and thrombocytopenia, hyperbilirubinemia, and renal failure requiring
21 hemodialysis. (26) None of these subjects had vaccine-associated neurotropic disease. In two

1 cases where vaccine virus was recovered from serum, limited nucleotide sequence analysis of the
2 viral genome suggested that the isolates had not undergone a mutation associated with an increase
3 in virulence. The incidence rate for these serious adverse events was estimated at 1 per 400,000
4 doses of YF-VAX vaccine, based on the total number of doses administered in the US civilian
5 population during the surveillance period.

6

7 Vaccine-associated viscerotropic disease temporally associated with yellow fever vaccination has
8 also been reported in Australia and Brazil. One Australian citizen became ill after receiving an
9 immunization with the 17D-204 strain of yellow fever vaccine in his home country, (28) and two
10 Brazilian citizens (age 5 and 22 years) became ill three to four days after receiving 17DD vaccine
11 in Brazil. (29) In the Brazilian and Australian cases, histopathologic changes in the liver included
12 midzonal necrosis, microvesicular fatty change, and Councilman bodies, which are characteristic
13 of wild-type yellow fever. Vaccine-type yellow fever virus was isolated from blood and autopsy
14 material (ie, brain, liver, kidney, spleen, lung, skeletal muscle, or skin) of each of these three
15 persons, all of whom died 8 to 11 days after vaccination. In Brazil, an estimated 23 million
16 vaccine doses were administered during the 15-month period during which the two cases of
17 multiple organ system failure were reported. (29)

18

19 In view of the data cited above, both the 17D-204 and 17DD yellow fever vaccines may be
20 considered as a possible, but rare, cause of vaccine-associated viscerotropic disease (2) that is
21 similar to fulminant yellow fever caused by wild-type yellow fever virus. All available evidence

1 from complete nucleotide sequence analysis and testing in experimental animals of vaccine-type
2 yellow fever viruses isolated from the Brazilian subjects suggests that the occurrences are due to
3 undefined host factors, rather than to intrinsic virulence of the 17DD vaccine viruses. (27)

4

5 Because of a lack of tissue specimens from most of the US cases of vaccine-associated
6 viscerotropic disease and the qualitative differences between the US cases and those identified in
7 Brazil and Australia, no definitive support for a causal relationship exists between receipt of YF-
8 VAX vaccine and vaccine-associated viscerotropic disease. However, the temporal association
9 with recent receipt of yellow fever vaccine and the similarity of the clinical presentations among
10 all four US cases suggest that the vaccine may play a role in pathogenesis of the cases.

11

12 **Pregnancy**

13 Safety of YF-VAX vaccine was evaluated in a study involving 101 Nigerian women, the majority
14 of whom (88%) were in the third trimester of pregnancy. In this study, it appeared that
15 vaccinating pregnant women with the 17D-204 strain of yellow fever vaccine was not associated
16 with adverse events affecting the mother or fetus. There were no adverse events among 40 infants
17 who were carefully followed up for one year after birth, and none of these infants tested positive
18 for IgM antibodies as a criterion for transplacental infection. However, the percentage of pregnant
19 women who seroconverted was significantly reduced compared to a non-pregnant control group
20 (38.6% vs. 81.5%). (18)

21

1 Following a mass immunization campaign in Trinidad, during which 100 to 200 pregnant females
2 were immunized, no adverse events related to pregnancy were reported. In addition, 41 cord blood
3 samples were obtained from infants born to mothers immunized during the first trimester. One of
4 these infants tested positive for IgM antibodies in cord blood. The infant appeared normal at
5 delivery and no subsequent adverse sequelae of infection were reported. However, this result
6 suggests that transplacental infection with 17D vaccine viruses can occur. (44)

7
8 A recent case-control study of spontaneous abortion following vaccination of Brazilian women
9 found no significant difference in the odds ratio among vaccinated women compared to a similar
10 unvaccinated group. (45)

11 12 **Reporting of Adverse Events**

13 The US Department of Health and Human Services has established the Vaccine Adverse Event
14 Reporting System (VAERS) to accept all reports of suspected adverse events after the
15 administration of any vaccine. Reporting of all adverse events occurring after vaccine
16 administration is encouraged from vaccine recipients, parents/guardians and the health care
17 provider. Adverse events following immunization should be reported to VAERS. Reporting forms
18 and information about reporting requirements or completion of the form can be obtained from
19 VAERS through a toll-free number 1-800-822-7967. (30) Reporting forms may also be obtained
20 at the FDA web site at <http://vaers.hhs.gov>.

1 **Health-care providers also should report these events to Sanofi Pasteur Inc., Discovery**
2 **Drive, Swiftwater, PA 18370 or call 1-800-822-2463.**

3

4 **DOSAGE AND ADMINISTRATION**

5 **Primary Vaccination:** For all eligible persons, a single subcutaneous injection of 0.5 mL of
6 reconstituted vaccine (formulated to contain not less than 4.74 log₁₀ PFU throughout the life of
7 the product) should be administered. Immunity develops by the 10th day after primary
8 vaccination. (11) (25) (46)

9

10 **Booster Doses:** Re-immunization with 17D vaccine is recommended every 10 years for those at
11 continuing risk of exposure and is required by International Health Regulations. (23)

12 Revaccination boosts antibody titer, although evidence from several studies suggests that yellow
13 fever vaccine immunity persists for at least 30 to 35 years and probably for life, (47) and
14 epidemiologic data suggest that a single infection with wild-type yellow fever virus provides
15 lifelong immunity against illness due to subsequent exposure.

16

17 **Concomitant Administration with other Vaccines**

18 Determination of whether to administer yellow fever vaccine and other immunobiologics
19 simultaneously should be made on the basis of convenience to the traveler in completing the
20 desired vaccinations before travel and on information regarding possible interference. Limited
21 data are available related to administration of YF-VAX vaccine with other vaccines. (See

1 **PRECAUTIONS** section, **Drug Interactions** subsection.) In those specific instances where
2 vaccines may be given concurrently, injections should be administered at separate sites. Where
3 there are no data to support administration of YF-VAX vaccine concurrently with other vaccines,
4 4 weeks should elapse between sequential vaccinations. (2)

5

6 **Vaccine Preparation**

- 7 • Reconstitute the vaccine using only the diluent supplied (0.6 mL vial of Sodium Chloride
8 Injection USP for single dose vial of vaccine and 3 mL vial of Sodium Chloride Injection
9 USP for 5 dose vial of vaccine). Draw the volume of the diluent, shown on the diluent label,
10 into a suitable size syringe and slowly inject into the vial containing the vaccine. Allow the
11 reconstituted vaccine to sit for one to two minutes and then carefully swirl mixture until a
12 uniform suspension is achieved. Avoid vigorous shaking as this tends to cause foaming of the
13 suspension. Do not dilute reconstituted vaccine.
- 14
- 15 • YF-VAX vaccine is a slight pink-brown suspension after reconstitution. If the product
16 contains extraneous particulate matter or is discolored, do not administer the vaccine.
- 17
- 18 • **SWIRL VACCINE WELL** before withdrawing each dose. Administer the single immunizing
19 dose of 0.5 mL subcutaneously using a 5/8- to 3/4-inch long needle (23) within 60 minutes of
20 reconstituting the vial.

21

1 Properly dispose of all reconstituted vaccine and containers that remain unused after one hour (eg,
2 sterilized or disposed in red hazardous waste containers). (2)

3

4 **Desensitization**

5 (23)

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

9

10 The following successive doses should be administered subcutaneously at 15- to 20-minute
11 intervals:

12 1. 0.05 mL of 1:10 dilution

13 2. 0.05 mL of full strength

14 3. 0.10 mL of full strength

15 4. 0.15 mL of full strength

16 5. 0.20 mL of full strength

17

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

20

21 **HOW SUPPLIED**

1 1 Dose:

2 Vaccine vial, 1 Dose (NDC 49281-915-58) supplied in a package of 5 vials (NDC 49281-915-01).

3 Diluent vial, 0.6 mL (NDC 49281-912-58) supplied separately in a package of 5 vials (NDC
4 49281-912-01).

5

6 5 Dose:

7 Vaccine vial, 5 Dose (NDC 49281-915-68) supplied in a package of 1 vial (NDC 49281-915-05).

8 Diluent vial, 3 mL (NDC 49281-912-68) supplied separately in a package of 1 vial (NDC 49281-
9 912-03).

10

YF-VAX vaccine (Yellow Fever Vaccine) in the US 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.

11

12 STORAGE

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

14

1 Do not use vaccine after expiration date. YF-VAX vaccine does not contain a preservative;
2 therefore, all reconstituted vaccine and containers, which remain unused after one hour must be
3 properly disposed (eg, sterilized or disposed in red hazardous waste containers). (2)

4

5 The following stability information for YF-VAX vaccine is provided for those countries or areas
6 of the world where an adequate cold chain is a problem and inadvertent exposure to abnormal
7 temperatures has occurred. Half-life is reduced from approximately 14 days at 35° to 37°C to 3-4
8 days at 45° to 47°C.

9

10 YF-VAX vaccine is formulated to satisfy the current US potency requirements of not less than
11 4.74 log₁₀ PFU per 0.5 mL dose throughout the life of the product and meets the minimum
12 requirements of WHO. (10)

13

14

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2 Product Information

3 as of May 2013

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5 Manufactured by:

6 **Sanofi Pasteur Inc.**

7 Swiftwater PA 18370 USA

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