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Yellow Fever Vaccine

Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002

INSIDE: Continuing Education Examination

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On the Cover: Photo of *Aedes aegypti* mosquito ©1995 Leonard E. Munstermann, Yale School of Medicine. Reproduced with permission.

Urban yellow fever is transmitted from person to person through the bite of an infected *Aedes aegypti* mosquito. In recent years, reinfestations of *Ae. aegypti* have occurred in countries throughout the world, contributing to the threat of epidemic yellow fever reemergence in new locations and highlighting the importance of vaccination programs for prevention.

CONTENTS

Yellow Fever Vaccine

Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002

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Summary

This report updates CDC's recommendations for using yellow fever vaccine (CDC. Yellow Fever Vaccine: Recommendations of the Advisory Committee on Immunizations Practices: MMWR 1990;39[No. RR-6]1–6). *The 2002 recommendations include new or updated information regarding 1) reports of yellow fever vaccine-associated viscerotropic disease (previously reported as febrile multiple organ system failure); 2) use of yellow fever vaccine for pregnant women and persons infected with human immunodeficiency virus (HIV); and 3) concurrent use of yellow fever vaccine with other vaccines. A link to this report and other information related to yellow fever can be accessed at the website for Travelers' Health, Division of Global Migration and Quarantine, National Center for Infectious Diseases, CDC, at http://www.cdc.gov/travel/index.htm, and through the website for the Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, CDC, at http://www.cdc.gov/ncidod/dvbid/yellowfever/index.htm.*

Introduction

Yellow fever occurs only in Africa and South America. The World Health Organization (WHO) estimates that a total of 200,000 cases of yellow fever occur each year (*1*). The clinical spectrum of yellow fever ranges from subclinical infection to overwhelming pansystemic disease (*2*). Yellow fever has an abrupt onset after an incubation period of 3–6 days, and usually includes fever, prostration, headache, photophobia, lumbosacral pain, extremity pain (including the knee joints), epigastric pain, anorexia, and vomiting. The illness might progress to liver and renal failure, and hemorrhagic symptoms and signs caused by thrombocytopenia and abnormal clotting and coagulation can occur. The fatality rate of severe yellow fever is approximately 20%.

Definitive diagnosis is made by viral culture of blood or tissue specimens or by identification of yellow fever virus antigen or nucleic acid in tissues (including liver) using immunohistochemistry (IHC), enzyme-linked immunosorbent assay (ELISA) antigen capture, or polymerase chain reaction tests (*3*). Although antibodies are not always present during the first week of illness, detection of yellow fever-specific immunoglobulin M (IgM) antibody by capture ELISA with confirmation of ≥4-fold rise in neutralizing antibody titers between acute- and convalescent-phase serum samples is also diagnostic.

Treatment for yellow fever consists of providing general supportive care and varies, depending on which organ systems are involved. No effective specific antiviral therapy for yellow fever has been identified.

Two forms of yellow fever, urban and jungle, are epidemiologically distinguishable. Clinically and etiologically they are identical (*4,5*). Urban yellow fever is an epidemic viral disease of humans transmitted from infected to susceptible persons by *Aedes aegypti* mosquitoes, which breed in domestic and peridomestic containers (e.g., water jars, barrels, drums, tires, or tin cans) and thus in close association with humans. In areas where *Ae. aegypti* has been eliminated or suppressed, urban yellow fever has disappeared. In the mid-1900s, eradication of *Ae. aegypti* in multiple countries, notably Panama, Brazil, Ecuador, Peru, Bolivia, Paraguay, Uruguay, and Argentina, led to the disappearance of urban yellow fever. The last documented *Ae. aegypti*-borne yellow fever epidemic in the western hemisphere occurred in Trinidad in 1954. However, in recent years, reinfestation of countries that had previously eradicated *Ae. aegypti* has occurred (*5*). *Ae. aegypti* mosquitoes are strongly suspected as having played a role in transmission in outbreaks occurring in Bolivia in 1989, 1990, and 1998

The material in this report originated in the National Center for Infectious Diseases, James M. Hughes, M.D., Director, and the Division of Global Migration and Quarantine, Tony D. Perez, Director.

(*6,7*). Other countries remain infested, including areas of Venezuela and the Guianas, which include enzootic areas for jungle yellow fever. In Africa, yellow fever epidemics caused by transmission by *Ae. aegypti* continue to occur and involve human populations both in towns and in rural villages (*8,9*).

Jungle yellow fever is primarily an enzootic viral disease transmitted among nonhuman primate hosts by different mosquito vectors, but endemic and epidemic jungle yellow fever can occur. It is observed only in forest-savannah zones of tropical Africa and in forested areas of South America but, in the past, occasionally extended into parts of Central America; it is enzootic in the jungles on the island of Trinidad. In South America, approximately 500 human cases are reported annually, primarily among men with occupational exposures in forested areas; however, the disease is believed to be substantially underreported (*10*). In Africa, epidemics involving tree-hole–breeding mosquito vectors affect thousands of persons at intermittent intervals, but only a limited number of cases are officially reported. Sometimes the disease is not detected in an area for years but then will reappear. Delineation of affected areas depends on surveillance for animal reservoirs and vectors, accurate diagnosis, and prompt reporting of all human cases. The jungle yellow fever cycle might be active but unrecognized in forested areas of countries within the yellow fever-endemic zone (Figure).

Urban yellow fever can be prevented by vaccinating human populations at risk for infection or by suppressing populations of *Ae. aegypti* mosquitoes so that they no longer perpetuate infection. Jungle yellow fever can most effectively be prevented by vaccination of human populations at risk for exposure.

Yellow Fever Vaccine

Yellow fever vaccine is a live, attenuated virus preparation made from the 17D yellow fever virus strain (*11*). Historically, the 17D vaccine has been considered to be one of the safest and most effective live virus vaccines ever developed (*2,12*). The virus is grown in chick embryos inoculated with a seed virus of a fixed passage level. The 17D yellow fever vaccine virus family is the foundation for both the 17D-204 lineage and 17DD lineage. Vaccine type 17D-204 is used in both the United States and Australia, whereas vaccine type 17DD is used in Brazil. The two vaccine types share 99.9% sequence homology (*13*).

The 17D-204 strain YF-VAX® (manufactured by Aventis, Swiftwater, Pennsylvania) vaccine is a freeze-dried supernatant of centrifuged embryo homogenate, packaged in 1-dose and 5-dose vials for domestic use. The vaccine should be stored at temperatures of 2°C–8°C (35°F–46°F) until it is reconstituted by the addition of diluent (sterile, physiologic saline) supplied by the manufacturer. Multidose vials of reconstituted vaccine should be held at 2°C–8°C (35°F–46°F); unused vaccine should be discarded within 1 hour after reconstitution.

Vaccine Use

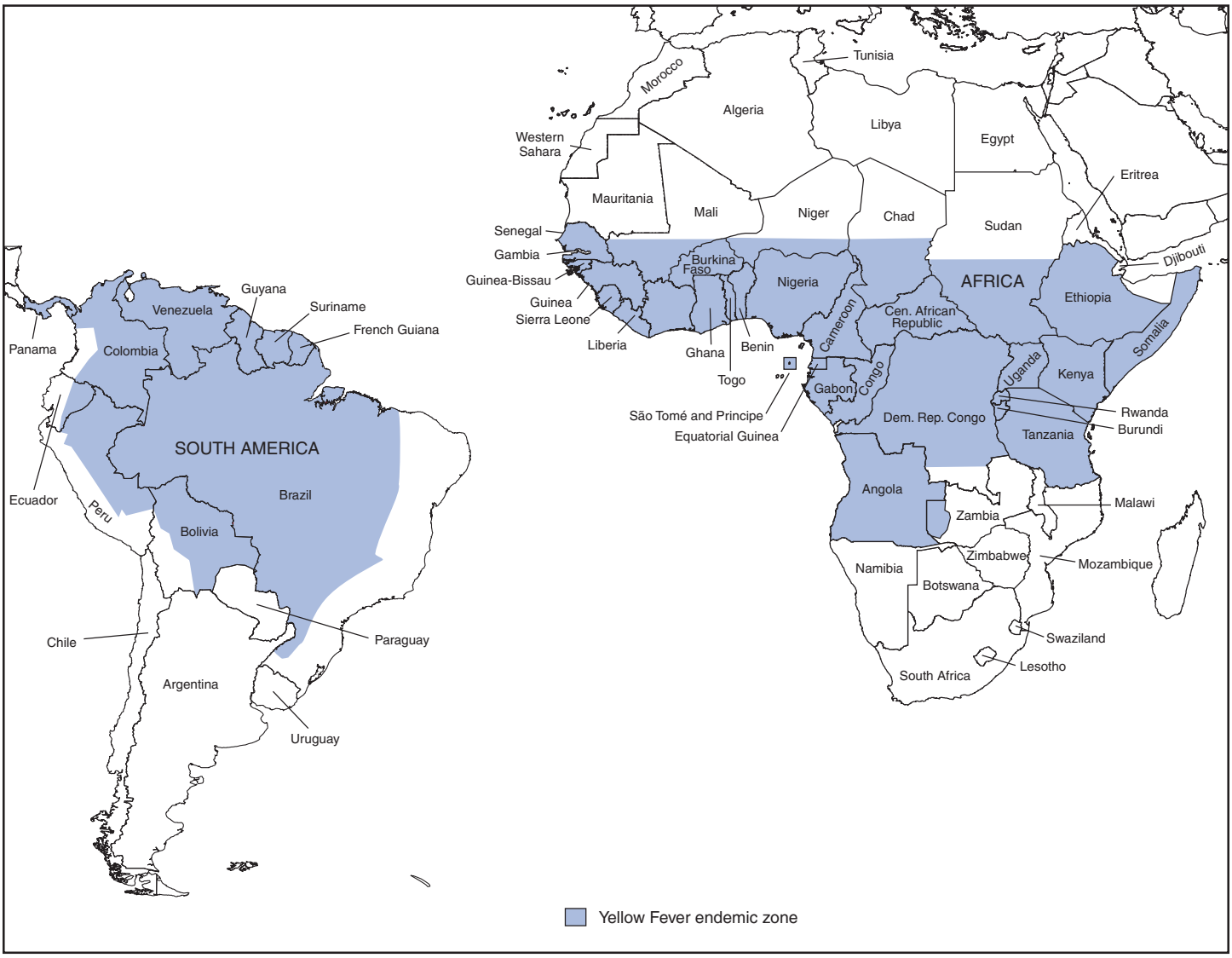
Persons Living or Traveling in Endemic Areas

Persons aged ≥9 months who are traveling to or living in areas of South America and Africa where yellow fever infection is officially reported should be vaccinated. These areas are listed in the "Bi-Weekly Summary of Countries with Areas Infected with Quarantinable Diseases," available at state and local health departments. Information concerning known or probable infected areas is also available from WHO (http://www.who.int), the Pan American Health Organization, the Division of Vector-Borne Infectious Diseases (telephone: 970-221-6400) or the Division of Global Migration and Quarantine (telephone: 404-498-1600) at CDC, or at http://www.cdc.gov/travel.

Vaccination is also recommended for travel to countries that do not officially report the disease but that lie in the yellow fever-endemic zone (see shaded areas in the figure). In recent years, fatal cases of yellow fever have occurred among unvaccinated tourists from the United States and Europe who visited rural areas within the yellow fever-endemic zone (*3,14–18*). Because of incomplete surveillance, the actual areas of yellow fever virus activity might exceed the infected zones officially reported by individual ministries of health.

The manufacturer and the Food and Drug Administration (FDA) recommend that vaccination of infants aged <9 months be avoided because of the risk for encephalitis, and that travel of such persons to countries in yellow fever-endemic zones or to countries experiencing an epidemic be postponed or avoided, whenever possible. Using yellow fever vaccine among infants aged <9 months has not been formally evaluated. Since 1945, among the reported cases of vaccine-associated encephalitis, only two cases have been reported of children aged 6 and 7 months developing encephalitis after yellow fever vaccination. In comparison, 14 such cases have occurred among children aged ≤4 months and seven cases among persons aged ≥3 years (including two fatal cases in persons aged 3 and 53 years). Because recent experience in use of the vaccine among children aged <6 months is limited and because age-specific vaccine administration records are not available, calculation of age-specific rates of yellow fever vaccine-associated encephalitis is impossible. In unusual circumstances, physicians considering vaccinating infants aged <9 months or pregnant women should contact the Division of Vector-Borne

FIGURE 1. Yellow Fever endemic zones



Infectious Diseases (telephone: 970-221-6400) or the Division of Global Migration and Quarantine (telephone: 404-498-1600) at CDC for advice (see Precautions and Contraindications).

Despite the lack of such information, ACIP and WHO recognize that situations occur in which vaccination of an infant aged <9 months might be considered. One such situation is the unavoidable exposure of children aged 6–8 months to an environment where an increased likelihood of becoming infected with the yellow fever virus exists (e.g., a setting of endemic or epidemic yellow fever) (*1*). Because of the risk for encephalitis, in no instance should infants aged <6 months receive yellow fever vaccine.

Because the seroconversion rate after vaccination of pregnant women might be markedly reduced compared with that of other healthy women, serologic tests to determine if a specific yellow fever immune response exists should be considered. To discuss the need for serologic testing, the appropriate state health department or the Division of Vector-Borne Infectious Diseases (telephone: 970-221-6400) or the Division of Global Migration and Quarantine (telephone: 404-498-1600) at CDC should be contacted (see Precautions and Contraindications).

Laboratory Personnel

Laboratory personnel who might be exposed to virulent yellow fever virus or to concentrated preparations of the 17D vaccine strain by direct or indirect contact or by aerosols should also be vaccinated.

Requirements for Vaccination Before International Travel

For purposes of international travel, yellow fever vaccines produced by different manufacturers worldwide must be approved by WHO and administered at an approved yellow fever vaccination center. In addition to CDC's Division of Global Migration and Quarantine, state and territorial health departments have the authority to designate nonfederal vaccination centers; these centers can be identified by contacting state or local health departments. Vaccinees should receive an International Certificate of Vaccination that has been completed, signed, and validated with the center's stamp when the vaccine is administered. Vaccination for international travel might be required under circumstances other than those specified in this report. Certain countries in Africa require evidence of vaccination from all entering travelers. Other countries might waive the requirements for travelers coming from areas where no evidence exists of substantial risk for yellow fever and who are staying <2 weeks. Because requirements might change, all travelers should seek up-to-date information from health departments, CDC, and WHO. Travel agencies, international airlines, or shipping lines also should have up-to-date information. Certain countries require persons, even if only in transit, to have valid International Certificates of Vaccination if they have been in countries either known or thought to have yellow fever virus. Such requirements might be enforced strictly, including for persons traveling from Africa or South America to Asia. Travelers should consult CDC's travel information website at http://www.cdc.gov/travel (*19*) to determine requirements and regulations for vaccination.

Primary Vaccination

For persons of all ages for whom vaccination is indicated, a single subcutaneous injection of 0.5 mL of reconstituted vaccine is used.

Booster Doses

The International Health Regulations require revaccination at intervals of 10 years. Revaccination can boost antibody titer; however, evidence from multiple studies (*20–23*) demonstrates that yellow fever vaccine immunity persists for 30–35 years and probably for life.

Safety

General Events

Reactions to 17D yellow fever vaccine are typically mild. After vaccination, vaccinees have reported mild headaches, myalgia, low-grade fevers, or other minor symptoms for 5–10 days. In clinical trials, where symptoms are actively elicited, incidence of mild adverse events has been ≤25% (*24,25*). Approximately 1% of vaccinees curtail regular activities.

Immediate hypersensitivity reactions, characterized by rash, urticaria, or asthma, are uncommon (i.e., an estimated incidence of 1/130,000–250,000) and occur principally among persons with histories of allergies to egg or other substances (*26*). Gelatin is used as a stabilizer in different vaccines, including yellow fever vaccine. Gelatin has been implicated as a cause of allergic reaction related to other vaccines and, therefore, might also do the same regarding yellow fever vaccine (*27–29*). Vaccine strain viremia after primary vaccination with yellow fever vaccine frequently occurs among healthy persons, but is usually waning or absent after the first week (*2,30*).

Yellow Fever Vaccine-Associated Neurotropic Disease

Historically, yellow fever vaccine-associated neurotropic disease (formerly known as postvaccinal encephalitis) among children has been the most common serious adverse event associated with yellow fever vaccines. Worldwide, only 23 cases of encephalitis temporally associated with or confirmed to be caused by 17D vaccine have been reported in the scientific literature since the introduction of the 17D seed lot system in 1945 (*2,31–33*); of these, 16 have occurred among children aged <9 months. The other seven cases occurred among persons aged 3–76 years. Only three of these cases of encephalitis were associated with vaccinations in the United States; one occurred in 1959 (in a person aged 10 weeks); the second in 1965 (in a person aged 3 years); and one in 1998 (in a person aged 76 years). One of the three cases was fatal, and 17D virus was isolated from the brain of this patient (*33*). Since 1965, only one case of yellow fever vaccine-associated encephalitis in the United States has been reported in the scientific literature. The case occurred in a male aged 76 years who suffered both yellow fever vaccine-associated neurotropic disease and yellow fever vaccine-associated viscerotropic disease (*31*). The most recent case of possible yellow fever vaccine-associated neurotropic disease was reported in 2002 from Thailand and involved a man aged 53 years who had unrecognized human immunodeficiency virus (HIV) infection (*32*). Recently, four reports have been made to the Vaccine Adverse Event Reporting System (VAERS) of encephalitis among adult recipients of yellow fever vaccine (persons aged 16, 36, 41, and 71 years) with onset of illness 4–23 days after vaccination. The occurrence of vaccine-associated neurotropic disease does not appear to be confined to infants but does appear to be limited. The risk for vaccine-associated neurotropic disease has been estimated as <1/8,000,000 persons (*2*).

Yellow Fever Vaccine-Associated Viscerotropic Disease

Recently, a new serious adverse reaction syndrome has been described among recipients of different yellow fever vaccines. This syndrome was previously reported as febrile multiple organ system failure, and is now called yellow fever vaccine-associated viscerotropic disease. In July 2001, the first seven case reports of this syndrome appeared in the scientific literature. These cases occurred during 1996–2001 and described patients with severe multiple organ system failure; 6 of the 7 patients died (*31,34–36*). Subsequently, retrospective and prospective case finding has identified three additional suspected cases (*37–39*). These additional cases demonstrate that this serious adverse reaction probably occurs as a clinical spectrum of disease severity, from moderate illness with focal organ dysfunction to severe disease with overt multiple organ system failure and death. These 10 cases demonstrate the viscerotropic potential of 17D vaccine virus among certain persons.

A phase III nonplacebo controlled clinical trial was recently completed that compared safety and reactogenicity among 1,440 healthy volunteers randomized to receive either one of two 17D-204 vaccines, ARILVAX™ (manufactured by Evans Vaccines Speke, Liverpool, United Kingdom) or YF-VAX® (Aventis Pasteur Inc., Swiftwater, Pennsylvania) (*24*). Adverse events were actively monitored for 30 days. Although no placebo group was included, which limits the interpretation of results, 3%–4% of vaccine recipients in both arms of the study experienced mild elevation of hepatic transaminases within the first 10 days after vaccination; all enzyme elevations returned to normal by day 30 postvaccination. Finally, mounting evidence exists that persons are most at risk for yellow fever vaccine-associated viscerotropic disease after their first vaccination. All cases reported thus far have occurred among such persons. In addition, clinical studies have demonstrated that mild adverse events after yellow fever vaccination are less common among previously immunized persons (*24*) and that vaccine viremia is not detectable among those receiving booster doses (*30*).

Vaccine-Associated Viscerotropic Disease Among U.S. Citizens. During 1996–1998, four U.S. citizens (aged 63, 67, 76, and 79 years) became ill 2–5 days after receiving YF-VAX (17D-204 vaccine) (*31*). All four persons required intensive care after they experienced fever, hypotension, respiratory failure, elevated hepatocellular enzymes, hyperbilirubinemia, lymphocytopenia, and thrombocytopenia; three of the four also experienced renal failure, which required hemodialysis. Three of the four died.

Blood was available for viral isolation from two of the four patients. Vaccine-type yellow fever virus was isolated from the blood of both of these patients 7–8 days after vaccination. Cerebrospinal fluid was also available from one of the two patients. Virus was isolated from this specimen, which was obtained when the patient experienced encephalitis (*31*). Minimal periportal inflammation without hepatocellular necrosis was observed in the liver specimen from the only U.S. patient who underwent a liver biopsy 28 days after illness onset; IHC revealed limited numbers of Kupffer cells containing yellow fever virus antigen.

In the United States, safety-monitoring data were available for an estimated 1.55 million vaccine doses of YF-VAX (17D-204) vaccine distributed to civilian vaccination centers in the United States during 1990–1998 (*40*). During this period, four cases of yellow fever vaccine-associated viscerotropic disease were reported to VAERS, providing an estimated reported incidence of 2.5/1,000,000 (or 1/400,000) doses distributed. YF-VAX was also administered to approximately 9 million military personnel during the same period of observation (1990–1998). This estimated incidence based on VAERS might be low because of limitations (e.g., underreporting of cases and imprecise information regarding the number of doses actually administered, including to nonimmune primary vaccinees who appear to be the major, if not only, risk group) (*41*).

Vaccine-Associated Viscerotropic Disease Among Persons Outside the United States. In addition to the cases reported in the United States, in 2001, one Australian citizen (aged 56 years) became ill after receiving a 17D-204 yellow fever vaccination (*34*), and in 1999 and 2000, two Brazilian citizens (aged 5 and 22 years) became ill 3–4 days after receiving 17DD vaccine (*35*). Strain 17DD is different from strain 17D-204, which is used in both the United States and Australia, but the two viruses are derived from a common ancestor (17D virus) and are closely related (*13*). In the Brazilian and Australian cases, histopathologic changes in the liver included midzonal necrosis, microvesicular fatty change, and Councilman bodies, which are characteristic of wild-type yellow fever. Yellow fever antigen was identified by IHC in areas of midzonal necrosis in liver specimens from the two 17DD recipients, and flavivirus-like particles consistent with yellow fever virus were identified by electron microscopy in areas of midzonal necrosis in a liver specimen from the 17D-204 recipient. Yellow fever vaccine virus (17DD or 17D-204) was isolated from blood and autopsy material (i.e., brain, liver, kidney, spleen, lung, skeletal muscle, or skin) from each of these three persons, all of whom died 8–11 days after vaccination.

In Brazil, an estimated 23 million vaccine doses were distributed in vaccination campaigns during the 15-month period in which the two reported cases occurred 6 months apart (*42*). Thus, a crude estimate of occurrence for this

serious adverse event in Brazil might be 0.09/1,000,000 doses distributed. However, certain limitations to this estimate exist. First, the number of doses administered during a vaccination campaign substantially overestimates the true number of persons vaccinated since certain persons receive multiple vaccinations. Second, experience in Brazil indicates that approximately half of vaccinees are already immune to yellow fever and thus, theoretically, would not be at risk for this adverse event. And finally, the numerator is only derived from published case studies, not from formal surveillance systems and therefore probably underestimates the true number of cases of this adverse event.

Because mutational changes associated with a reversion to virulence were not detected in the genomes of 17DD vaccine viruses recovered from patients and because these viruses had a vaccine-type phenotype among experimental animals, Brazilian authorities assume that the occurrences are caused by undefined host factors (*43*).

Additional Case Reports. Three additional cases of severe adverse events after yellow fever vaccination have been reported in the scientific literature (*37–39*). These cases occurred among persons aged 45, 50, and 71 years, and the patients required hospitalization for illness, which was characterized by fever and elevated liver enzymes (*37–39*) and renal abnormalities (*37,38*). All three persons recovered from their illness. Yellow fever virus was isolated from the blood of the one person tested (*38*). Vaccine strain viremia after primary vaccination with yellow fever vaccine frequently occurs among healthy persons, but is usually waning or absent after the first week (*2,30*). Two persons were tested for antibodies to yellow fever virus; one of these patients had unusually high levels of yellow fever antibodies (*39*), and the antibody levels of the other person were described as having increased during the 3 days after administration (*38*).

Summary of Case Reports. In the cases from Brazil and Australia, a causal association between yellow fever vaccine-associated viscerotropic disease and vaccination with 17DD or 17D-204 yellow fever vaccine is supported by histopathologic studies, isolation of genetically stable vaccine-type virus from multiple tissues other than blood, and the temporal relationship between vaccination and illness onset. Thus, both the 17DD and 17D-204 yellow fever vaccines must be considered as a possible, but rare, cause of yellow fever vaccine-associated viscerotropic disease that is similar to fulminant yellow fever caused by wild-type yellow fever virus. Accurately measuring the incidence of this rare vaccine-associated viscerotropic disease is impossible because adequate prospective data are unavailable; however, crude estimates of the reported frequency range from 0.09 (in Brazil) to 2.5 (in the United States) per 1,000,000 doses distributed. The real incidence might be higher (*41*).

Because of a lack of tissue specimens from the majority of the U.S. cases of yellow fever vaccine-associated viscerotropic disease, no definitive laboratory support for a causal relationship exists for these cases. However, the recent receipt of yellow fever vaccination and the similarity of the clinical symptoms among all four U.S. cases indicate that yellow fever vaccine is a probable cause of the disease in these cases. Whether and in what way underlying host factors (genetic or acquired) or preexisting clinical conditions might have contributed to the course or outcome of yellow fever vaccine-associated viscerotropic disease is unknown.

Because of recent reports of yellow fever deaths among unvaccinated travelers to areas endemic for yellow fever and of these reports of vaccine-associated viscerotropic disease, physicians should be careful to administer yellow fever vaccine only to persons truly at risk for exposure to yellow fever. Additional surveillance to better monitor and quantify yellow fever vaccine-specific adverse outcomes should also be established. Studies are being conducted to clarify the cause and risk factors for these rare adverse events associated with the 17D yellow fever vaccines.

Precautions and Contraindications

Age

Infants aged <6 months are likely to be more susceptible to the serious adverse reaction of yellow fever vaccine-associated neurotropic disease (also known as postvaccinal encephalitis) than older children, and vaccination of infants aged <6 months is contraindicated. The risk for this complication appears age-related. The manufacturer and FDA recommend that vaccination of infants aged <9 months be avoided because of the risk for encephalitis, and that travel of such persons to countries in yellow fever-endemic zones or to countries experiencing an epidemic should be postponed or avoided, whenever possible. In unusual circumstances, physicians considering vaccinating infants aged <9 months who are traveling to endemic areas should contact the Division of Vector-Borne Infectious Diseases (telephone: 970-221-6400) or the Division of Global Migration and Quarantine (telephone: 404-498-1600) at CDC for advice.

A recent analysis of adverse events passively reported to VAERS during 1990–1998 indicates that persons aged ≥65 years might be at increased risk for systemic adverse events after vaccination, compared with younger persons (*40*). Travelers aged ≥65 years should discuss with their physicians the

risks and benefits of vaccination in the context of their destination-specific risk for exposure to yellow fever virus. Nevertheless, yellow fever remains a key cause of illness and death in South America and sub-Saharan Africa where potential yellow fever transmission zones have expanded to urban areas with substantial populations of susceptible humans and the *Ae. aegypti* vector mosquito. In addition, unvaccinated U.S. travelers to South America have contracted fatal yellow fever (*3,14–18*). Consequently, despite these rare adverse events, yellow fever vaccination of travelers to high-risk areas should be encouraged as a key prevention strategy.

Pregnancy

The safety of yellow fever vaccination during pregnancy has not been established, and the vaccine should be administered only if travel to an endemic area is unavoidable and if an increased risk for exposure exists. On the basis of clinical evaluation of a total of 81 infants in two different studies who were born to mothers vaccinated during pregnancy, infection of the fetus with YF17D apparently occurs at a low rate (i.e., 1 of 81) and has not been associated with congenital anomalies (*2,44,45*). In a recent case-control study of women vaccinated with YF 17D during early pregnancy, the relative risk for spontaneous abortion was 2.3, but the difference was not statistically significant (95% confidence interval = 0.65–8.03) (*46*). Information from limited clinical trials in Africa and Europe indicates that the risk from vaccination for pregnant women who cannot avoid mosquito exposure in yellow fever-endemic areas is outweighed by the risk for yellow fever infection (*44*). If international travel requirements are the only reason to vaccinate a pregnant woman, rather than an increased risk for infection, efforts should be made to obtain a waiver letter from the traveler's physician (Appendix). Pregnant women who must travel to areas where the risk for yellow fever infection is high should be vaccinated and, despite the apparent safety of this vaccine, infants born to these women should be monitored closely for evidence of congenital infection and other possible adverse effects resulting from yellow fever vaccination. If vaccination of a pregnant woman is deemed necessary, serologic testing to document an immune response to the vaccine can be considered, because the seroconversion rate for pregnant women in a developing nation has been reported to be substantially lower than that observed for other healthy adults and children (*45*). To discuss the need for serologic testing, the appropriate state health department or the Division of Vector-Borne Infectious Diseases (telephone: 970-221-6400) or the Division of Global Migration and Quarantine (telephone: 404-498-1600) at CDC should be contacted.

Nursing Mothers

Whether this vaccine is excreted in human milk is unknown. No reports exist of adverse events or transmission of the 17D vaccine viruses from nursing mother to infant. However, as a precautionary measure, vaccination of nursing mothers should be avoided because of the theoretical risk for the transmission of 17D virus to the breast-fed infant. When travel of nursing mothers to high-risk yellow fever-endemic areas cannot be avoided or postponed, such persons can be vaccinated.

Altered Immune Status

Infection with yellow fever vaccine virus poses a theoretical risk for encephalitis to 1) patients with acquired immunodeficiency syndrome (AIDS); 2) patients who are infected with HIV and have other manifestations of HIV infection (*32*); 3) patients with leukemia, lymphoma, generalized malignancy; or 4) 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 risks posed by such travel, instructed in methods for avoiding vector mosquitoes, and supplied with vaccination waiver letters by their physicians (Appendix). Low-dose (i.e., 20-mg prednisone or equivalent/day), short-term (i.e., <2 weeks) systemic corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be sufficiently immunosuppressive to constitute an increased hazard to recipients of yellow fever vaccine.

Persons who are HIV-infected but do not have AIDS or other symptomatic manifestations of HIV infection, who have established laboratory verification of adequate immune system function, and who cannot avoid potential exposure to yellow fever virus should be offered the choice of vaccination. Despite the theoretical risk for neuroinvasion and encephalitis, clinical or epidemiologic studies to evaluate the risk for yellow fever vaccination among such recipients have not been reported. If international travel requirements are the only reason to vaccinate an asymptomatic HIV-infected person, rather than an increased risk for infection, efforts should be made to obtain a waiver letter from the traveler's physician (Appendix). Asymptomatic HIV-infected persons who must travel to areas where the risk for yellow fever infection is high should be offered the choice of vaccination and monitored closely for possible adverse effects.

Data regarding seroconversion rates after yellow fever vaccination among asymptomatic HIV-infected persons are limited, but they do indicate that the seroconversion rates among such persons is reduced. One month after receiving a 17D

yellow fever vaccination, only 70% of 33 HIV-infected adults with $CD4^+$ T lymphocyte cell counts >200/mm^3 developed neutralizing antibody (*47*). Yellow fever vaccine typically induces seroconversion among >90% of healthy adults. Among HIV-infected infants simultaneously vaccinated with a 17D yellow fever and measles vaccines, only 3 of 18 developed neutralizing antibody, compared with 74% of 57 HIV-seronegative infants who simultaneously received the two vaccines (*48*). Because vaccination of asymptomatic HIV-infected persons might be less effective than that for persons not infected with HIV, measurement of their neutralizing antibody response to vaccination should be considered before travel. To discuss the need for serologic testing, the appropriate state health department or the Division of Vector-Borne Infectious Diseases (telephone: 970-221-6400) or the Division of Global Migration and Quarantine (telephone: 404-498-1600) at CDC should be contacted. Family members of immunosuppressed or HIV-infected persons, who themselves have no contraindications, can receive yellow fever vaccine.

Hypersensitivity

Yellow fever vaccine is produced in chick embryos and should not be administered to persons hypersensitive to eggs; typically, persons who are able to eat eggs or egg products can receive the vaccine. If international travel regulations are the only reason to vaccinate a patient hypersensitive to eggs, efforts should be made to obtain a waiver (Appendix). If vaccination of a person with a questionable history of egg hypersensitivity is considered essential because of a high risk for exposure, an intradermal test dose can be administered under close medical supervision. Specific directions for skin testing are located in the package insert (*49*).

Simultaneous Administration of Other Vaccines

Determination of whether to administer yellow fever vaccine and other immunobiologics simultaneously should be made on the basis of convenience to the traveler in completing the desired vaccinations before travel and on information regarding possible interference. The following discussion should help guide these decisions.

Limited clinical studies have demonstrated that the serologic response to yellow fever vaccine is not inhibited by the administration of certain other vaccines concurrently or at intervals of a 1 day–1 month (*50*). Measles, smallpox, and yellow fever vaccines have been administered in combination (*51,52*); Bacillus Calmette-Guérin (BCG) and yellow fever vaccines have been administered simultaneously without interference.

Yellow fever vaccine can be administered concurrently with hepatitis A or hepatitis B vaccines (*53, 54*). In addition, yellow fever vaccine has been administered concurrently with the typhoid fever vaccine, Typhim Vi® (manufactured by Aventis Pasteur, Inc., Swiftwater, Pennsylvania) and the meningococcal vaccine, Menomune® (Aventis Pasteur, Inc., Swiftwater, Pennsylvania), with no reported evidence of an effect on the immune response to any of the three vaccines individually and no unusual safety problems (*55*). No data exist regarding possible interference between yellow fever and rabies or Japanese encephalitis vaccines.

In a prospective study of persons administered yellow fever vaccine and an intramuscular dose of commercially available immune globulin, no alteration of the immunologic response to yellow fever vaccine was detected when compared with controls (*56*). Although chloroquine inhibits replication of yellow fever virus in vitro, it does not adversely affect antibody responses to yellow fever vaccine among humans receiving antimalaria prophylaxis (*57*).

Surveillance and Research Priorities

Yellow fever vaccine has been considered to be one of the safest vaccines. The frequency of the adverse events reported in these recommendations is low enough that, given the relatively limited numbers of yellow fever vaccine doses administered in the United States, sporadic cases of severe adverse events that occurred earlier might not have been appreciated or investigated. Unfortunately, yellow fever vaccine has been used most widely during outbreaks and in areas where surveillance for vaccine-associated adverse events has been difficult and might have been masked by wild-type yellow fever infections. The YF17D-associated adverse event reports, combined with the growing momentum for mass vaccination in the wake of increased yellow fever activity, underscore the importance of further investigations to define and quantify YF17D vaccine risks and to characterize their pathogenesis. Accordingly, the following activities are recommended:

- Enhanced surveillance for systemic adverse events after yellow fever vaccination should be introduced at U.S.-certified yellow fever vaccination centers and in settings where yellow fever vaccine is administered in other countries. The majority of yellow fever vaccine administered in the United States is done through the vaccination of U.S. military personnel and their dependents. The vaccine safety profile among U.S. military personnel might not be representative of the U.S. population at large; however, this population might still serve as an excellent source

of additional information in quantifying the risk for adverse events through both retrospective and prospective studies. Accordingly, the U.S. military should be encouraged to share information regarding its yellow fever vaccination program, including annual number of doses administered and substantial adverse events that might be related to yellow fever vaccine.

- Although neurovirulence assays among primates were required to qualify yellow fever vaccine in different production stages, certain patients described in a recent report exhibited viscerotropic (e.g., hepatic, renal, or cardiac) abnormalities that might not have been detected earlier. Viscerotropic safety tests consist of assays to measure viremia on days 2, 4, and 6 (*2*). Additional tests to monitor hepatic, renal, and cardiac function and injury should be considered.
- A protocol for the appropriate clinical, epidemiologic, and laboratory evaluation of cases of viscerotropic or neurotropic disease after yellow fever vaccine should be created. This protocol should highlight the challenges in establishing causality and emphasize the importance of histopathology, viral isolation, molecular analysis, and virulence testing of samples from patient specimens and vaccine lots.
- Additional research is needed to identify host, as well as vaccine-specific, risk factors associated with neurotropic or viscerotropic disease after yellow fever vaccination.
- Additional research is also needed to better identify the reasons why certain travelers to yellow fever-endemic areas do not get yellow fever vaccinations. Related research is needed to develop interventions to decrease the percentage of travelers who are not properly vaccinated.

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Appendix

Waiver Letters from Physicians

A physician's letter stating the contraindication to vaccination has been acceptable to certain governments outside the United States. Ideally, the letter should be written on letterhead stationary and bear the stamp used by health department and official vaccination centers to validate the International Certificate of Vaccination. When planning to use a waiver letter, the traveler should also obtain specific and authoritative advice from the embassy or consulate of the country or countries she or he plans to visit. Waivers of requirements obtained from embassies or consulates should be documented by appropriate letters and retained for presentation with the International Health Certificate.

MMWR™

Morbidity and Mortality Weekly Report

Recommendations and Reports November 8, 2002 / Vol. 51 / No. RR-17

Yellow Fever Vaccine
Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002

EXPIRATION — November 8, 2005

You must complete and return the response form electronically or by mail by **November 8, 2005**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 1.2 hours Continuing Medical Education (CME) credit; 0.1 Continuing Education Units (CEUs); or 1.3 contact hours Continuing Nursing Education (CNE) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

INSTRUCTIONS

By Internet

1. Read this *MMWR* (Vol. 51, RR-17), which contains the correct answers to the questions beginning on the next page.
2. Go to the *MMWR* Continuing Education Internet site at <http://www.cdc.gov/mmwr/cme/conted.html>.
3. Select which exam you want to take and select whether you want to register for CME, CEU, or CNE credit.
4. Fill out and submit the registration form.
5. Select exam questions. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
6. Submit your answers no later than **November 8, 2005**.
7. Immediately print your Certificate of Completion for your records.

By Mail or Fax

1. Read this *MMWR* (Vol. 50, RR-17), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for CME, CEU, or CNE credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
5. Sign and date the response form or a photocopy of the form and send no later than **November 8, 2005**, to
   Fax: 404-639-4198 Mail: MMWR CE Credit
   Office of Scientific and Health Communications
   Epidemiology Program Office, MS C-08
   Centers for Disease Control and Prevention
   1600 Clifton Rd, N.E.
   Atlanta, GA 30333
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Continuing Nursing Education (CNE). This activity for 1.3 contact hours is provided by CDC, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

Goal and Objectives

This *MMWR* provides recommendations regarding use of yellow fever vaccine. These recommendations were developed by CDC staff members and the Yellow Fever Working Group of the Advisory Committee on Immunization Practices (ACIP). The goal of this report is to provide health-care professionals guidance regarding administration of yellow fever vaccine. Upon completion of this educational activity, the reader should be able to 1) describe the epidemiology of yellow fever; 2) describe the components, handling, usage, and documentation requirements of the licensed yellow fever vaccine; 3) list primary target groups for yellow fever vaccination; and 4) recognize the known adverse reactions after administration of yellow fever vaccine.

To receive continuing education credit, please answer all of the following questions.

1. Where does yellow fever transmission occur in the world?

A. Asia.
B. Africa and South America.
C. Africa and Asia.
D. North America.
E. Throughout the world.

2. Yellow fever has an incubation period of . . .

A. 10–12 days.
B. 6–10 days.
C. 3–6 days.
D. 1–3 days.
E. 12–23 days.

3. Which of the following is not true concerning yellow fever:

A. Two forms of yellow fever, urban and jungle, are clinically and epidemiologically identical.
B. In recent years, reinfestations of the mosquito vector have occurred in certain countries in Central and South America.
C. Jungle yellow fever can most effectively be prevented by vaccination of human populations at risk for exposure.
D. No effective specific antiviral therapy for yellow fever has been identified.
E. The fatality rate of severe yellow fever is approximately 20%.

4. Which of the following best describes the licensed yellow fever vaccine?

A. Live attenuated virus.
B. Inactivated virus.
C. Reassortant.
D. Toxoid.
E. Cloned DNA.

5. Which of the following is not true regarding use of yellow fever vaccine before international travel?

A. The yellow fever vaccine must be administered at an approved yellow fever vaccination center.
B. The manufacturer's produced vaccine must meet World Health Organization standards.
C. The yellow fever vaccine must be administered at a U.S. federal institution.
D. Vaccinees should receive an International Certificate of Vaccination that has been completed, signed, and validated with the official stamp where the vaccine was administered.
E. Certain countries might require proof of vaccination for entry.

6. According to international health regulations, the yellow fever vaccination certificate and stamp are valid for . . .

A. 2 years.
B. 5 years.
C. 10 years.
D. 30 years.
E. the vaccinee's lifetime.

7. All of the following are true regarding yellow fever vaccine-associated neurotropic disease, except:

A. It was previously known as postvaccinal encephalitis.
B. This syndrome was recognized with the early uses of yellow fever vaccine in the 1940s and led to enhanced safety with development of the seed lot system in 1945.
C. This is the most common adverse event associated with the yellow fever vaccine.
D. The majority of these cases have occurred in children aged ≤4 months.
E. These cases can be fatal.

8. Which of the following groups can be vaccinated routinely without special safety considerations?

A. Children aged <9 months.
B. Pregnant women.
C. Persons with compromised immune systems.
D. All of the above.
E. None of the above.

9. Which of the following is not true regarding yellow fever vaccine-associated viscerotropic disease?

A. Since 1996, <50 cases have been reported in the scientific literature.
B. Persons at greatest risk for yellow fever vaccine-associated viscerotropic disease are those who receive booster vaccines.
C. This syndrome was newly recognized in 1996.
D. The clinical spectrum of yellow fever vaccine-associated viscerotropic disease ranges from moderate illness to multiple organ system failure and death.
E. This is a rare form of adverse event associated with yellow fever vaccine; reported frequency of occurrence is 1:400,000, on the basis of review of the Vaccine Adverse Reporting System data of 1990–1998.

10. Which of the following clinical features have been described as part of yellow fever vaccine-associated viscerotropic disease?

A. Hepatic dysfunction.
B. Renal failure.
C. Thrombocytopenia.
D. Respiratory failure.
E. Fever.
F. All of the above.

11. Indicate your work setting.

A. State/local health department.
B. Other public health setting.
C. Hospital clinic/private practice.
D. Managed care organization.
E. Academic institution.
F. Other.

12. Which best describes your professional activities?

A. Patient care — emergency/urgent care department.
B. Patient care — inpatient.
C. Patient care — primary-care clinic or office.
D. Laboratory/pharmacy.
E. Public health.
F. Other.

13. I plan to use these recommendations as the basis for . . . (*Indicate all that apply.*)

A. health education materials.
B. insurance reimbursement policies.
C. local practice guidelines.
D. public policy.
E. other.

14. Each month, to approximately how many patients do you administer yellow fever vaccine?

A. None.
B. 1–5.
C. 6–20.
D. 21–50.
E. 51–100.
F. >100.

15. How much time did you spend reading this report and completing the exam?

A. 1–1.5 hours.
B. More than 1.5 hours but fewer than 2 hours.
C. 2–2.5 hours.
D. More than 2.5 hours.

16. After reading this report, I am confident I can describe the guidance regarding administration of yellow fever vaccine.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can describe the epidemiology of yellow fever.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

18. After reading this report, I am confident I can describe the components, handling, usage, and documentation requirements of the licensed yellow fever vaccine.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

19. After reading this report, I am confident I can list primary target groups for yellow fever vaccination.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

20. After reading this report, I am confident I can recognize the known adverse reactions after administration of yellow fever vaccine.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

Detach or photocopy.

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November 8, 2002/Vol. 51/No. RR-17
Yellow Fever Vaccine
Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002

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Fill in the appropriate blocks to indicate your answers. Remember, you must answer all of the questions to receive continuing education credit!

1.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	14.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F		
2.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	15.	[ ] A	[ ] B	[ ] C	[ ] D				
3.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	16.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E			
4.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	17.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E			
5.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	18.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E			
6.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	19.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E			
7.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	20.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E			
8.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	21.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E			
9.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	22.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E			
10.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F	23.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E		
11.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F	24.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E		
12.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F	25.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E		
13.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E		26.	[ ] A	[ ] B	[ ] C	[ ] D	[ ] E	[ ] F	

Signature *Date I Completed Exam*

21. The objectives are relevant to the goal of this report.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

22. The figure is useful.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

23. Overall, the presentation of the report enhanced my ability to understand the material.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

24. These recommendations will affect my practice.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

25. The availability of continuing education credit influenced my decision to read this report.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

26. How did you learn about this continuing education activity?

A. Internet.
B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
C. Coworker/supervisor.
D. Conference presentation.
E. *MMWR* subscription.
F. Other.

Correct answers for questions 1–10

1. B; 2. C; 3. A; 4. A; 5. C; 6. C; 7. C; 8. E; 9. B; 10. F.

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