# Notice to Readers: Fever, Jaundice, and Multiple Organ System Failure Associated With 17D-Derived Yellow Fever Vaccination, 1996--2001

*Weekly*

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At the June 2001 meeting of the Advisory Committee for Immunization Practices (ACIP), seven cases of multiple organ system failure (MOSF) in recipients of 17D-derived yellow fever (YF) vaccine were presented (*1--3*). In response, an ACIP working group was formed to review the cases, assess the risk for serious adverse events following YF vaccination, and consider revision of the 1990 YF vaccination recommendations (*4*). This notice summarizes these cases and describes an enhanced surveillance program designed to refine risk estimates and improve histopathologic documentation of MOSF potentially associated with YF vaccination.

Derived from the original 17D YF vaccine strain, the live, attenuated 17D-204 and 17DD YF strains are the most commonly used YF vaccines (*5*). In 1999 and 2000, two Brazilian residents aged 5 and 22 years became ill after receiving 17DD YF vaccine administered during a campaign initiated in response to a local YF epidemic. During 1996--2001, five persons aged 56--79 years, including four U.S. residents and one Australian resident (two countries where YF is not endemic) became ill after receiving 17D-204 YF vaccine administered in anticipation of international travel. Two of the five persons were planning to travel to countries where local YF transmission had never been reported.

All seven persons became ill within 2--5 days of vaccination and required intensive care; six died. None had documented immunodeficiency, and all were in their usual state of health before vaccination. Illness was characterized by fever, lymphocytopenia, thrombocytopenia, mild-to-moderate elevation of hepatocellular enzymes, hypotension with poor tissue perfusion, and respiratory failure. Most patients also had headache, vomiting, myalgias, hyperbilirubinemia, and renal failure requiring hemodialysis.

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 YF. Using immunohistochemistry (IHC), YF viral antigen was identified in areas of midzonal necrosis in liver specimens from the two 17DD recipients. In a liver specimen from the third patient (a 17D-204 recipient), electron microscopy showed flavivirus-like particles in the areas of midzonal necrosis. Vaccine-type YF virus was isolated from blood and autopsy material (i.e., brain, liver, kidney, spleen, lung, skeletal muscle, or skin) of these three persons, who died 8--11 days after vaccination. Vaccine-type YF virus was isolated from the blood of two of the four U.S. patients (17D-204 recipients) 7--8 days after vaccination. Viremia after vaccination with YF may occur in healthy persons. Virus also was isolated from the cerebrospinal fluid (CSF) of one of these two patients, although the presence of red blood cells and absence of white blood cells in CSF may suggest that blood contaminating the CSF was the possible source of virus. No hepatocellular necrosis was observed in a liver specimen from the only U.S. case-patient who underwent biopsy; however, IHC revealed rare YF virus

antigen within Kupffer cells.

The 17D-204 and 17DD YF vaccines are among the safest and most effective viral vaccines (*5*). Since 1965, approximately eight million doses of 17D-derived YF vaccine have been administered to U.S. travelers and approximately 300 million doses have been administered to persons in areas where YF is endemic. Although 2%--5% of persons who receive vaccine report headaches, myalgia, and low-grade fever 5--10 days after vaccination, <1% report having to curtail their usual activities. The frequency of anaphylaxis attributed to YF vaccine is approximately one in 130,000 vaccinees (*4,6*). Reports of other severe illnesses attributed to YF vaccination (including encephalitis, primarily in infants) are rare. Since 1965, post-YF vaccination encephalitis has been reported in one U.S. resident aged >9 months (estimated incidence: one in eight million) (*5*). MOSF associated with 17D-derived YF vaccination was not reported before 1996. The frequency of febrile MOSF cases reported to the Vaccine Adverse Event Reporting System (VAERS) after vaccination with 17D-204 YF vaccine in the United States during 1990--1998 is approximately one in 400,000 distributed doses (*7*).

An estimated 200,000 cases of YF occur each year in South America and Africa (*5*). As a result, YF is an important vaccine-preventable disease among travelers to areas where YF occurs on these continents. In 1996 and 1999, two U.S. and two European unvaccinated travelers to areas where YF is endemic died of YF viral infection (*1,8*). The risk for YF in unvaccinated travelers probably is increasing because potential YF transmission zones are expanding to include urban areas with large populations of susceptible humans and abundant competent mosquito vectors. Vaccination is the most effective preventive measure against YF, a disease that has no specific treatment and may cause death in 20% of patients (*5*). Despite a rare, possibly causal relation between YF vaccination and MOSF, YF vaccination of persons traveling in areas where YF transmission occurs should continue as currently recommended, at least until more definitive and complete data are available and analyzed by the ACIP working group. However, health-care providers should provide YF vaccine only to persons planning to travel to areas reporting YF activity or areas in the YF endemic zone. More information on YF activity and appropriate indications for YF vaccine is available at <http://www.cdc.gov/travel/yfever.htm>.

A causal association between MOSF and 17DD YF vaccination is supported by histopathologic studies for two cases. Because of a lack of tissue specimens from most U.S. cases (recipients of 17D-204 YF vaccine), no definitive histopathologic support for a causal relationship exists. However, the temporal association with recent receipt of YF vaccine and the similarity of the clinical presentations in all four U.S. cases suggest the possibility of a causal association. The 17DD and 17D-204 YF vaccine strain genomes are >99% homologous; however, the strains differ in the amino acid sequence of some of the structural proteins (*9*). The pathophysiologic mechanisms causing MOSF may differ among recipients of 17DD and 17D-204 YF vaccine. To clearly define a causal association between 17D-204 and MOSF, more tissue histopathology and molecular virologic studies of specimens from 17D-204 YF vaccinees with MOSF are needed.

To refine estimates of the risk for MOSF following YF vaccination, enhanced surveillance is essential. Through VAERS, the Food and Drug Administration and CDC receive reports of adverse effects potentially related to YF vaccine and other vaccines. VAERS report forms can be obtained by telephone,( 800) 822-7967, or at <http://www.vaers.org>. Completed reports can be submitted by fax ([877] 721-0366), mail (P.O. Box 1100, Rockville, Md 20849-1100), or e-mail (info@vaers.org). Reporters may be asked to provide supplemental clinical information about patients with fever of 101.3 F (38.5 C) lasting ≥24 hours and illness within 10 days of YF vaccination and information about the availability of previously collected clinical or autopsy specimens.

CDC will conduct virologic and immunohistochemical studies of these specimens to clarify the role of the 17D-204 YF vaccine strain in the patient's illness. Additional information about this enhanced surveillance is available at <http://www.cdc.gov/ncidod/dvbid/yellowfever/index.htm>.

## References*


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*All *MMWR* references are available on the Internet at <http://www.cdc.gov/mmwr>. Use the search function to find specific articles.



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