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# *Rickettsia africae*: Risks. . . But for Which Travelers?

ABSTRACT & COMMENTARY

***Synopsis:*** *African tick bite fever is an emerging infectious disease affecting travelers to parts of Africa and possibly other areas of the world. The risks of infection and means for prevention should be discussed with travelers and game hunters visiting high-risk areas, especially rural sub-Saharan Africa.*

**Source:** Jensenius M, et al. African tick bite fever in travelers to rural sub-equatorial Africa. *Clin Infect Dis*. 2003;36:1411-1417.

THE NORWEGIAN AFRICAN TICK BITE FEVER STUDY GROUP PROSPECTIVELY assessed travelers to rural sub-equatorial Africa for the incidence, risk factors, and clinical presentations of African tick bite fever (ATBF). The study enrolled travelers at 9 travel clinics in Norway, from Jan. 1, 1999, through Dec. 31, 2000, who were planning to visit rural sub-equatorial Africa. Oral and written information on the disease was distributed to the travelers. Travelers were asked to complete a questionnaire after return to Norway. Only those who completed the questionnaire and had traveled to rural areas were included in the study (n = 940). The study group's infectious disease specialists evaluated travelers who developed flu-like illnesses within 10 days of departure from rural areas. Physical findings, serology, and PCR for rickettsiae were specifically obtained, and suspected ATBF cases were followed up further.

Microbiological diagnosis was established on the basis of a positive "suicide" PCR (a PCR in which the primer is used only once) and the presence of serum antibodies to *R africae* by microimmunofluorescence (MIF), Western blot (WB), and cross-adsorption assay of serum test samples.

Among the 940 travelers in the study, 143 (15.2%) experienced flu-like illnesses, and 83 of the symptomatic travelers presented for medical evaluation. Thirty-eight travelers (4% of the total and 26.6% of those with flu-like symptoms) were diagnosed with ATBF (27 confirmed and 11 probable). An additional 12 travelers were diagnosed as having a nonspecific spotted fever group (SFG) rickettsiosis. Overall incidence of SFG rickettsiosis in the study was 5.3%, or 0.25 cases per person-travel-month.

The incidence of ATBF was highest in the group of hunters (25.3%), when compared to business travelers (2.8%), visitors to friends and relatives (2.6%), leisure travelers (2.1%), and backpackers (1.4%). Clustering of infections was observed in 56% of confirmed cases. Ticks and/or tick bites were noted by 48%

of patients with ATBF. Three risk factors were associated with ATBF: hunting as the reason for travel, travel to southern Africa, and travel during the summer.

Clinical presentation of patients with ATBF included myalgia (87%), headache (83%), fever (81%), eschars (53%, and 21% of all ATBF cases had *multiple* eschars), regional lymphadenitis (50%), maculopapular rash (26%), vesicular rash (16%), and aphthous stomatitis (11%). A total of 39% of the patients received antirickettsial therapy, consisting of either doxycycline or ciprofloxacin.

## COMMENT BY LIN H. CHEN, MD

The causative agent of ATBF is *Rickettsia africae*, a Gram-negative obligate intracellular bacterium that is a member of the SFG rickettsiae. Other species of the SFG rickettsiae that cause human disease include *R rickettsii* (Rocky Mountain spotted fever), *R conorii* (Mediterranean spotted fever or boutonneuse fever), *R australis* (Queensland tick typhus fever), *R sibirica* (Siberian tick typhus fever), *R japonica* (Japanese tick typhus), *R honei* (Flinders Island spotted fever), *R akari* (rickettsialpox; see *TMA Update* 2002;12[4]:30-32 for a recent review), *R felis* (California flea rickettsiosis), and *R mongolotimonae*.[1,2] Rickettsiae of the SFG are transmitted to humans by insect vectors. While *R akari* is mite-borne, most other SFG rickettsiae are tick-borne. Amblyomma ticks, in particular *A hebraeum*, are the vectors of *R africae*.[1] Although the name implies epidemiologic association with Africa, *R africae* infection has also been identified in Guadaloupe.[3] A survey using a PCR assay for SFG rickettsiae in Amblyomma variegatum from St. Kitts and Nevis found that 41% of the ticks tested positive, and results were consistent with *R africae*.[4]

SFG rickettsiae attach to and enter endothelial cells, causing cell injury followed by vascular damage and immunologic responses.[1] Symptoms develop after an incubation period of 4-7 days.[5-8] Clinical manifestations can involve multiple organ systems and may include rash, abdominal pain, nausea, vomiting, cough, pulmonary edema, renal failure, headache, confusion, seizures, and arrhythmias.[1] Nonspecific symptoms such as fever, headache, or myalgias are very common. Skin rash is frequently associated with infections caused by *R conorii*, *R rickettsii*, and *R australis*. However, *R africae* infections are associated with skin manifestations in only 50% of documented cases.[5,9] Recent studies in travelers diagnosed with ATBF have typically found eschars or *taches noire* (single or multiple), regional adenopathy, and sometimes a maculopapular or vesicular rash.[5-9] ATBF can be associated with abnormal laboratory findings such as thrombocytopenia or renal insufficiency.[1]

Diagnosis of ATBF can be established by microimmunofluorescent antibody determinations, serum cross-adsorption, Western blotting, rickettsial cultures, or PCR assay.[9] Specific testing for *R africae* is only available in specialized laboratories (Unite des Rickettsias, Faculte de Medecine, Universite de la Mediterranee, Marseilles, France). However, serologic tests of *R conorii* and *R rickettsii* cross-react with *R africae*, and the diagnosis of ATBF can be established on the basis of positive rickettsial serologies given the right clinical and epidemiologic background. Treatment of ATBF is similar in other SFG rickettsioses: tetracycline, chloramphenicol, or ciprofloxacin are effective.[1] Doxycycline 100 mg b.i.d. for 7-14 days is a convenient and frequently prescribed course; however, chloramphenicol has been the drug of choice for treatment of pregnant women.[1] Ciprofloxacin has shown *in vitro* activity against SFG rickettsiae.[10]

ATBF has emerged as an important vector-borne disease that affects travelers to southern Africa, yet many travelers are not aware of their risk of ATBF. The incidences of ATBF and SFG rickettsial infection in the Jensenius study, 4.0% and 5.3%, respectively, suggests that ATBF is a significant imported tropical infection in travelers. The highest risk appears to be participants in game hunting and travel during the summer (November to April). Because the disease can affect short-term safari visitors, travel medicine specialists should discuss the risk of ATBF if the itinerary includes visits to endemic areas, especially South Africa, Swaziland, Lesotho, Namibia, and Botswana. Prevention is accomplished by wearing long sleeves and long pants, applying repellents containing DEET (N, N- diethyl-m-toluamide) to skin, and/or treating clothing with the insecticide, permethrin. Finally, only about 50% of affected patients presented with skin manifestations. Therefore, ATBF should be considered in the differential diagnosis of febrile returning travelers with possible exposure history, even in the absence of skin lesions. ■

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# Malaria in the United States

COMMENTARY

*By Philip R. Fischer, MD, DTM&H*

**Source:** Filler S, et al. Malaria surveillance—United States, 2001. *MMWR Morb Mortal Wkly Rep*. 2003;52(SS05):1-14.

EVEN THOUGH MALARIA INFECTIONS STILL KILL MORE than a million people each year, the disease itself appears to occur uncommonly among travelers. In this surveillance summary, the US Centers for Disease Control and Prevention (CDC) provide a vivid reminder that malaria still is a real problem for many travelers. A review of the CDC data stimulates discussion of several points that are useful reminders for travel medicine practitioners and their traveling patients. Interestingly, the CDC report contains similar data to that obtained in the United Kingdom, where approximately 2000 individuals are diagnosed with malaria each year.[1]

## Malaria Still Happens

Some travelers think that malaria is "just for other people," such as the "poor" who reside in developing countries. People can become complacent when they haven't actually experienced malaria themselves or had some personal acquaintance with the disease. The CDC report provides a stark reminder to the contrary. There were 1383 reported individuals who became ill with malaria in the United States during 2001. In addition, others became ill while overseas. Even though the exact number of Americans traveling abroad is unknown and only a small percent of them became ill with malaria, the incidence of malaria in the United States reminds us that this is not an uncommon problem. Cases occurred in Guam, Puerto Rico, the Virgin Islands, the District of Columbia, and 49 states; only South Dakota was spared.

## Malaria Still Kills

Sadly, 11 individuals died of malaria in the United States during 2001. The fatal cases occurred in individuals aged 12-79 years and included 7 males and 4 females. Most had been to Africa and had been previously well. Ten of the 11 had *P falciparum* infections, and several had high-level (> 10%) parasitemia. Some died within hours of reaching medical care, but others died within days following their first medical contact. Despite attempts at good medical care and, and in some cases even with initially improving clinical and parasitologic courses, patients died. Malaria still kills, and it can kill seemingly healthy American travelers.

## African Travel Accounts for Most US Malaria Cases

Two-thirds of malaria cases imported to the United States were in travelers returning from Africa. Two-thirds of African cases were from West Africa, as Nigeria (254 cases) and Ghana (179 cases) were the most commonly represented destination countries. This likely reflects, at least in part, the travel patterns of Americans. Most of the Asian cases were from the Indian subcontinent. Even "safer" areas, however, were not completely safe; fatal cases occurred after travel to Haiti and China.

## Compliance with Chemoprophylaxis Might Have Prevented Most Cases

Among civilians with malaria, 60% had used no prophylaxis, and an additional 15% had used a chemoprophylactic regimen that was not recommended by the CDC. Half of the nonrecommended regimens included chloroquine for travel to areas where chloroquine resistance is already well known.

Two hundred cases of malaria occurred after recommended prophylaxis use. Of these, 37% were due to *P vivax* and 7% were due to *P ovale*. In at least a fourth of these cases, adherence to recommended prophylaxis dosing was incomplete, and about a third of these cases became symptomatic more than 45 days after arrival in the United States (suggesting relapsing infection rather than primary failure of prophylaxis). There was no evidence for new areas of chloroquine-resistant *P vivax* among these patients reported in 2001. For the cases of *P falciparum* following use of a recommended chemoprophylactic agent, there was clearly documented noncompliance in about one third of cases; the level of compliance was unknown for the other patients.

### VFR Malaria was Common

Of 678 civilian travelers with malaria and a known purpose for travel, nearly half (333) were traveling to visit friends and/or relatives. Tourism accounted for 94 cases, and 82 cases occurred in missionaries and their dependents. There were 50 business travelers, and, interestingly, no cases among aircrew members or sailors. It is clear that potentially effective efforts to decrease the incidence of malaria in the United States should focus on preventive care for individuals traveling overseas to visit friends and relatives.

### Pay Attention to Pregnant Women

Twenty-two cases of malaria were reported among pregnant women. This accounted for 5% of cases among women. Only 4 (18%) of the pregnant women reported taking prophylaxis even though 31% of nonpregnant women reportedly used prophylaxis. Realizing that the consequences of malaria can be more severe during pregnancy, efforts to provide prophylaxis should be emphasized rather than decreased during pregnancy.

There was also one case of congenital malaria[2] reported in 2001. The mother, a native of Pakistan, previously had malaria that had resolved on chloroquine more than a year prior to delivery. She became symptomatic with malaria 10 days after delivery, and her newborn became febrile with *P vivax* parasitemia at 2 months of age. Both mother and baby recovered with standard chloroquine and primaquine therapy.

### Avert Tragedy with Appropriate Diagnosis

Any case of malaria in the United States represents a failure of our preventive measures, and travel medicine practitioners have work to do in reaching and helping the traveling population. Deaths due to malaria, however, are particularly tragic—especially when they are associated with delayed diagnosis.

While games of "what if?" are not always productive, it is useful to consider the pediatric death reported by the CDC. It should serve as a reminder to all physicians to provide appropriate prophylaxis to travelers, to consider the travel history when caring for febrile patients, and to seek a diagnosis of malaria in a febrile-returned traveler. Helpful reviews of the prevention[3] diagnosis, and treatment[4] of malaria in children are being published in 2003.

The first fatal US case of malaria in 2001 was a 12-year-old boy who had lived in the United States for 10 years. In December 2000, he visited Nigeria for 3 weeks; chloroquine prophylaxis had been prescribed. On Jan. 11, 2001, he presented to a clinic with a 2-day history of fever with chills, fatigue, cough, and a single episode of vomiting. He was diagnosed to have an "upper respiratory infection complicated by nausea and vomiting" and was prescribed a cephalosporin antibiotic. Three days later, he collapsed, was transported to an emergency room, and died. Retrospectively, blood taken on Jan. 11 had 0.8% of red cells infected with *P falciparum*; by the day of death, he had a 14% parasitemia.

The CDC report provides a reminder about both the frequency and the seriousness of malaria in the United States. Travel medicine practitioners can use this report to upgrade their efforts to reach international travelers, to provide appropriate malaria prevention guidance and intervention, and to carefully diagnose illness in returned travelers. ■

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## Monkeypox 2003: Tracing the Path of Exotic Pets

ABSTRACT & COMMENTARY


***Synopsis:*** *The recent monkeypox outbreak in 6 midwestern states has been associated with exposure to sick pet prairie dogs that were infected through contact with imported Gambian giant rats and dormice at an Illinois animal facility.*



**Source:** CDC Update: Multistate outbreak of monkeypox—Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. *MMWR Morb Mortal Wkly Rep*. 2003;52(27):642-646.


As of July 8, 2003, a total of 71 cases of monkeypox were reported to the CDC of which 35 cases (49%) were laboratory confirmed. One additional case has been added from Illinois bringing the final count to 72 cases. Some cases reported in earlier CDC updates were later excluded when they met the exclusion criteria of the updated monkeypox case definition.

On April 9, 2003, a Texas animal distributor received a shipment of approximately 800 small mammals from Ghana. That shipment contained 762 African rodents including rope squirrels, tree squirrels, Gambian giant rats, brushtail porcupines, dormice, and striped mice.

The CDC has since confirmed the presence of monkeypox by PCR or virus isolation in 1 Gambian rat, 3 dormice, and 2 rope squirrels from that shipment. From Texas, some of the Gambian giant rats and dormice were sent to an animal distributor in Iowa, who in turn sold them to another animal distributor in Illinois. At the Illinois facility, approximately 200 prairie dogs overlapped with the arrival of the African rodents and hence were exposed to monkeypox. The exposed prairie dogs were then sent out to 5 other states causing a wave of monkeypox illness in persons exposed to these prairie dogs.

Wisconsin reported 39 human monkeypox cases of which 17 were confirmed (CF) and 22 probable (P). Indiana reported 16 cases (7 CF, 9 P), Illinois reported 13 cases (9 CF, 4 P), and Missouri reported 2 cases (CF). Ohio had 1 probable case and Kansas had 1 confirmed case. Only 93 of the original 200 infected or potentially infected prairie dogs were able to be traced. The others may have either died or were sold at "swap meets" (gatherings of animal traders, exhibitors and buyers); therefore, further tracing could not be done.

Clinical information was available for 69 of the human monkeypox patients. Eighteen patients (26%) were hospitalized, some for isolation precautions only. No deaths occurred, but 2 children had serious clinical illness. One child with severe monkeypox-associated encephalitis was hospitalized for 14 days but recovered. Another child had diffuse pox lesions and profound cervical and tonsillar adenopathy. Despite difficulty breathing, the child did not require mechanical ventilation. Affected patients were either exposed to prairie dogs, exposed while in premises where prairie dogs were kept, or exposed to persons with monkeypox. No cases of monkeypox that could be attributed exclusively to person-to-person contact have been confirmed.

## COMMENT BY MARY-LOUISE SCULLY, MD

The recent monkeypox outbreak appears to have ended with no new cases reported since mid June. The last issue of *TMA Update* reported the initial early data on the outbreak, as well as historical background and clinical features of monkeypox.[1] Highlights to recall are that the rash of monkeypox may not be distinguishable from smallpox often, but not always, showing synchronous progression through vesicular, pustular, umbilicated, and crusted stages. This could differ from the rash of *chickenpox* where lesions are often found at different stages of development. In contrast to smallpox, monkeypox patients often develop either localized or, more often, generalized lymphadenopathy. The nodes can be firm and often tender, appearing shortly after the prodromal fever, rarely 1-2 days after the onset of the rash. The rate of person-to-person transmission of monkeypox is much lower than smallpox, with secondary attack rates of about 10% in unvaccinated persons.[2] This lower rate of transmission, coupled with much lower reported case fatality rates (2-10%), make monkeypox a less likely candidate than smallpox for biological terrorism.

On June 11, 2003, the CDC and Food and Drug Administration (FDA) jointly issued an order prohibiting the further importation of African rodents to the United States and also banned the sale, transport between states, or release into the environment of prairie dogs or any of the 6 genera of rodents in the original April 9 shipment from Ghana. Important information and guidelines can be accessed on the CDC monkeypox web site including advice for health care and community exposures, exposures of veterinarians and pet owners, and quarantine and euthanasia of exposed or infected animals (www.cdc.gov/ncidod/monkeypox/index/htm). These guidelines remind pet owners not to release their sick or exposed prairie dogs or African rodents out into local environments. Also, any remains of infected deceased or exposed animals should be incinerated and not simply buried in the environment to prevent monkeypox from becoming established and maintained in native wildlife.

Smallpox vaccination has been shown to reduce the risk of monkeypox if given pre-exposure (> 85% effective), and it is believed that it may prevent or ameliorate disease if given postexposure as well. Since June 13, 2003, smallpox vaccine has been administered to 30 persons in 6 states to prevent monkeypox. The vaccine was given pre-exposure to 7 persons and post-exposure to 23 persons. One of the 30 persons given smallpox vaccine developed a rash that was confirmed as monkeypox. No serious adverse events have been reported in those receiving smallpox vaccinations to prevent monkeypox.

Rapid response, detailed epidemiologic tracing, and vigorous quarantine and euthanasia of infected animals appear to have halted this outbreak of monkeypox. The outbreak has heightened awareness of the need for more stringent rules governing importation of exotic wildlife for private ownership. Currently, both state and federal legislation oversee the importation of wild animals. The federal responsibility is divided between the Customs and Border Protection Service (part of the Department of Homeland Security), the CDC, the Department of Agriculture, and the Fish and Wildlife Service. A permit is required from the Fish and Wildlife Service to import wildlife, and imported animals must then enter through a designated port. A recent editorial in the *Lancet Infectious Disease* notes that since 800,000 iguanas are imported to the United States for pet trade every year, it seems unlikely that these permits are difficult to obtain.[3] New regulations and restrictions in exotic pet trade are needed and will no doubt be forthcoming, to better pro-

tect against diseases from zoonotic pathogens. ■


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## *Special Feature*

# Adverse Reactions to the Smallpox Vaccine

*By John R. Lonks, MD, and Maria D. Mileno, MD*


***Synopsis:*** *Infectious disease experts and their colleagues in government continue to struggle to determine just who should receive smallpox vaccine in approaching the bioterrorism threat. While the vaccine is not available for use in travel clinics, the risks and benefits surrounding the process of smallpox vaccination should be known and are described here, based upon the most recent published experience.*


**Sources:** Grabenstein JD, Winkenwerder W. US military smallpox vaccination program experience. *JAMA*. 2003; 289(24):3278-3282; Halsell JS, et al. Myopericarditis following smallpox vaccination among vaccinia-naïve US military personnel. *JAMA*. 2003;289(24):3283-3289; Frey SE, et al. Clinical responses to undiluted and diluted smallpox vaccine. *N Engl J Med*. 2002;346(17):1265-1274.

Smallpox vaccine (vaccinia virus) consists of a live virus vaccine that replicates locally within the skin. Successful vaccination provides protection against infection with smallpox. Some vaccine recipients (27-77%) develop local symptoms such as pain at the vaccination site. Systemic symptoms may also occur. High rates of successful vaccination, which include full skin reactions as defined by WHO response rates, were reported recently from the US military immunization program clinics. Four sites conducted the vaccinations: Walter Reed Army Medical Center, Washington, DC; Aberdeen Proving Ground, Maryland; Wilford Hall Air Force Medical Center, Lackland Air Force Base, San Antonio, Tex; and the National Naval Medical Center, Bethesda, Md. Nine hundred seventy-one of 1017 (95.5%) **primary** vaccinees were successfully vaccinated with a single vaccination. Nine hundred thirty-four of 975 (95.8%) **previously** vaccinated individuals also achieved successful responses.

A study reported in the *New England Journal of Medicine* in 2002 indicated that adults showed adverse reactions between days 7 and 9 following vaccination, 8.9% had fever ‡100°F, 3.0% had fever ‡101°F, and 0.8% had fever ‡102°F. From days 0 to 14 after vaccination, 16-44% of vaccine recipients had headache, 17-53% had fatigue, 9-50% had muscle aches, 2-18% had chills, and 4-16% had nausea. The majority of patients categorized these symptoms as mild or moderate, while the minority (3% or less) were severe.

Data obtained in 1963 provide us with some insight and perspective regarding a number of additional serious adverse reactions and their rates of occurrence in primary vaccinees. Note that all of these adverse events were much less common after revaccination than after primary vaccination. **Inadvertent inoculation** occurred in 14 per 1 million; generalized vaccinia in 21 per 1 million; eczema vaccinatum in 9 per 1 million; progressive vaccinia in 1 per 1 million; and postvaccinial encephalopathy/postvaccinial encephalitis in 2 per 1 million. **Inadvertent inoculation** (accidental implantation) refers to the transfer of vaccinia, usually via the hands, from the vaccination site to other parts of the body such as the face, eyelid, genitalia, and rectum where the virus reproduces and a lesion develops. Historically, accidental implantation was the most common adverse event. **Vaccinia keratitis** is the result of accidental implantation of vaccinia into the cornea and could result in blindness. Generalized vaccinia occurs when vesicular or pustular lesions occur beyond the vaccination site. It is self-limited when it occurs in those who are not immunocompromised. **Eczema vaccinatum** refers to localized or systemic spread beyond the vaccination site of vaccinia virus to areas of the skin affected by eczema or atopic dermatitis. This includes areas of skin with inactive or active eczema/atopic dermatitis. However, it may also occur in those with chronic exfoliative skin lesions such as moderate or severe psoriasis, severe acne, epidermolysis bullosa, pemphigus vulgaris; or acute self-limited disorders that disrupt the epidermis such as impetigo, varicella, varicella zoster, acute burns, acute contact dermatitis and pityriasis rosea; or a history of Darier's disease (keratosis follicularis). The severity of eczema vaccinatum ranges from a mild self-limited reaction to a severe and sometimes fatal illness.

**Progressive vaccinia (vaccinia necrosum)** is characterized by continuing and progressive necrosis at the vaccination site. Lesions may develop at other body sites. It is both a severe and potentially fatal adverse event. Progressive vaccinia usually occurs in persons with some

form of immunodeficiency. Other rare adverse events affecting the skin include generalized rashes (erythematous, urticarial, nonspecific), erythema multiforme (Stevens-Johnson syndrome) and secondary bacterial infections at the site of vaccination.

Neurological complications include **postvaccinial encephalopathy and postvaccinial encephalitis;** the distinction between these 2 entities is based on pathologic findings. Postvaccinial encephalopathy usually occurs in children younger than 2 years, resulting in fevers and convulsions beginning 6-10 days after vaccination. Postvaccinial encephalitis usually affects those older than 2 years and begins 11-15 days after vaccination. Both postvaccinial encephalopathy and postvaccinial encephalitis can be fatal, and those who survive may have permanent sequelae. Some studies have referred to both processes as postvaccinial encephalitis. Death has occurred in 1 or 2 persons per million vaccinated and was most often due to postvaccinial encephalitis or progressive vaccinia.

Smallpox vaccine has not caused congenital malformations. Rare reports describe fetal infection in pregnant women who experienced stillbirths or infant deaths shortly after delivery. These events usually occurred after primary vaccination. Women of childbearing potential should be instructed not to become pregnant for at least 4 weeks after vaccination.

Vaccinia, because it is a live virus, can be spread to unvaccinated contacts such as those living in the same household (contact vaccinia) or sexual partners. Besides developing lesions at the accidental implantation site, the individual is at risk for developing other complications. Historically, accidental implantation (inadvertent inoculation) and eczema vaccinatum were the 2 most common complications of contact vaccinia. In 1963, there were 22 cases of inadvertent inoculation, mostly children age 1-4 years old, and 54 reported cases of eczema vaccinatum in contacts. During the same year, 6.239 million individuals received primary vaccination and 7.775 million received revaccination.

Of the 35,903 civilians who received the smallpox vaccine from Jan. 24 to May 2, 2003, there were no cases of eczema vaccinatum, progressive vaccinia, postvaccinial encephalitis or postvaccinial encephalomyelitis, fetal vaccinia, or erythema multiforme major. There were 12 suspected and 3 confirmed cases of inadvertent inoculations that did not involve the eye, 2 confirmed cases of ocular vaccinia and 2 suspected and 1 confirmed case of generalized vaccinia. There were no cases of transmission from vaccinees to others in the health care setting or other settings while there were 9 cases spread from military vaccinees to civilian contacts. More than 430,000 individuals in the military received the vaccine since December 2002. There were 36 cases of generalized vaccinia all of which were mild, 48 cases of autoinoculation, 19 cases of transmission to others, and no cases of eczema vaccinatum or progressive vaccinia. According to the National Smallpox Vaccine in Pregnancy Registry, 6 women in the civilian population and 85 in the military were inadvertently exposed to the smallpox vaccine during pregnancy.

In the past, **myocarditis** was reported as an adverse vaccine event in a European cohort only. In the United States, where a different vaccine strain was used, myocarditis had not been a well-recognized complication. During the recent vaccination program, there have been 14 suspected, 1 probable, and no confirmed cases of myocarditis/pericarditis among 35,903 civilian vaccinees as a result of the smallpox vaccine. In the military study, there were 26 probable and 1 confirmed case of myocarditis and/or pericarditis among more than 430,000 vaccinees. There were 18 primary vaccinees among the US military personnel with probable myocardial disease. All cases survived and all returned to duty or are on short-term leave. The mechanistic relationship between vaccination and myocarditis/pericarditis is still not clear and is under investigation. Angina and myocardial infarctions have been reported following receipt of the smallpox vaccine. It is not known whether the vaccine actually caused these problems.

Treatment with Vaccinia Immune globulin (VIG) is available from the CDC for some of the complications of the smallpox vaccine. It is indicated for treatment of the following complications: progressive vaccinia, eczema vaccinatum, severe or recurrent cases of generalized vaccinia, and extensive accidental implantation. VIG is not indicated for mild cases of accidental implantation, mild cases of generalized vaccinia, erythema multiforme, postvaccinial encephalitis, and vaccinia keratitis. Patients with vaccinia keratitis should be treated with topical antiviral agents by a knowledgeable ophthalmologist.

**Postscript**

Hundreds of millions of people have died of smallpox throughout history. Soldiers and sailors were often targets of this disease. Civilian outbreaks also occurred and vaccinated service members spread vaccinia to several civilians as recently as the 1980s. The disease begins with fever, aches, and nausea and later develops into a blistering rash. Death is due to overwhelming viremia and hypotension. To prepare against biological attacks using this agent, the United States Department of Defense implemented the US military smallpox vaccination program in December 2002. The experience described here suggests that a broad smallpox vaccination program may be implemented safely, with expected temporary symptoms. *However, some individuals who*

*set out to be first responders should avoid vaccination*. Practitioners should identify those individuals who have susceptibilities known or thought to predispose to adverse events for themselves (the vaccinees) or their close contacts. These include pregnancy or breast-feeding; extensive skin eruptions present at the time of vaccination; atopic dermatitis (active or history of atopic dermatitis or "eczema"); presence or probability of T-cell immune defects or disease, congenital, or acquired; immunosuppressive therapy; inflammatory or disruptive diseases of the cornea or surrounding structures; and age < 1 year. Antibody deficiency generally has not led to adverse events, except in very few instances, usually in association with temporary loss of T-cell function. Nevertheless, such individuals should not be vaccinated in situations in which no risk of contact with smallpox is present.

Myopericarditis should be considered an expected adverse event associated with smallpox vaccination. Clinicians should consider myopericarditis in the differential diagnosis of patients presenting with chest pain 4 to 30 days following smallpox vaccination. Echocardiography to document decreased ventricular function and an elevated serum troponin level suggest significant myocyte injury and may indicate the need for diagnostic endomyocardial biopsy. Such specimens should be tested for the presence of vaccinia virus. Persons with known cardiac disease or serious potential risk factors for cardiac disease should also be considered exempt from vaccination. ■

### Suggested Reading


1. Neff JM, et al. Complications of smallpox vaccination. I. National survey in the United States, 1963. *N Engl J Med*. 1967;276(3):125-132.
2. Update: Adverse events following civilian smallpox vaccination—United States, 2003. *MMWR Morb Mortal Wkly Rep*. 2003;52(19):444-446.
3. Fulginiti VA, et al. Smallpox vaccination: A review, part II. Adverse events. *Clin Infect Dis*. 2003;37: 251-271.


## CME Questions

**11. Indications for the use of vaccinia immune globulin (VIG) include treatment for all of the following complications of smallpox vaccination *except*:**

a. progressive vaccinia.
b. eczema vaccinatum.
c. severe and recurrent cases of generalized vaccinia.
d. extensive accidental implantation.
e. myopericarditis.

**12. Which one of the following statements regarding African tick bite fever is *incorrect*?**

a. African tick bite fever has been acquired in Guadaloupe as well as sub-Saharan Africa.
b. The vector of *Rickettsia africae*, the causative agent of African tick bite fever, is an Amblyomma tick.
c. Usual symptoms of ATBF include fever, myalgia, headache, regional adenopathy, maculopapular, or vesicular rash.
d. Doxycycline, fluoroquinolones, and chloramphenicol are effective in treating ATBF.
e. Eschars are rarely associated with ATBF.

**Answers:** 11.(e); 12.(e)