ALEX R. KEMPER, MD, MPH, MS
MATTHEW M. DAVIS, MD, MAPP
GARY L. FREED, MD, MPH
Child Health Evaluation and Research (CHEAR) Unit
Division of General Pediatrics
Division of General Internal Medicine
University of Michigan
Ann Arbor, Mich

Eff Clin Pract. 2002;5:84–90.

Expected Adverse Events in a Mass Smallpox Vaccination Campaign

CONTEXT. Recent anthrax attacks in the United States have raised concern about the nation's vulnerability to a smallpox attack. Many strategies have been suggested to minimize the impact of such an attack, ranging from quarantine and vaccination of case contacts to resumption of routine vaccination. Before the latter strategy is adopted, an understanding of the likely consequences of mass vaccination is essential.

COUNT. Number of adverse events resulting from two vaccination campaigns: vaccinating persons 1 to 29 years of age and vaccinating those 1 to 65 years of age.

CALCULATION. Number of adverse events = incidence rate of adverse events × number vaccinated. We assumed 75% vaccine uptake in the target group (i.e., we estimated that about 25% of potential vaccine recipients would be excluded because they are, or have close contact with, individuals who have eczema or are immunocompromised).

DATA SOURCE. Historical data on the incidence of adverse events from smallpox vaccination were identified by a literature search. Number vaccinated was drawn from the January 2000 U.S. Census estimate.

RESULTS. Fever (<1 case per 5 vaccine recipients) and rash (<1 case per 100 vaccine recipients) would be the most common adverse events. Serious adverse events, including encephalitis (<3 cases per million) and death (<2 cases per million), although rare, would be more common than with other currently recommended vaccines. After excluding high-risk individuals and their contacts, we estimate that a vaccination strategy directed at people aged 1 to 29 years would result in approximately 1600 serious adverse events and 190 deaths. Vaccinating people aged 1 to 65 years would result in approximately 4600 serious adverse events and 285 deaths.

LIMITATIONS. While advances in health care over the past three decades could mitigate vaccine complications, the increased number of unimmunized high-risk individuals (e.g., those with eczema or immune suppression) could increase complication rates.

CONCLUSIONS. The decision to resume smallpox vaccination depends on weighing the likelihood of a smallpox attack and its anticipated mortality against expected harm from a mass immunization program. Smallpox vaccine has a higher complication rate than any other vaccine currently being used. Careful prevaccination exclusion of high-risk individuals and their close contacts would be essential to minimize complications of a mass vaccination campaign, although such exclusions necessarily mean that some proportion of the population will remain susceptible to smallpox.

Edited by James Sargent, MD

See related editorial on pages 98–99.

The events of September 11, 2001, and the subsequent anthrax attacks have raised concern about the possibility of a bioterrorist smallpox attack. In the United States, routine smallpox vaccination was stopped in 1972—8 years before global eradication of smallpox was declared.[1] Routine vaccination was discontinued when it was judged that the risk for serious adverse events from vaccination, including

This paper is available at ecp.acponline.org.

encephalitis and death, outweighed the low risk for infection in a well-vaccinated population with minimal potential exposure to smallpox.[2] This decision was bolstered by effective smallpox eradication efforts, including "ring vaccination," where cases are quarantined and persons with possible exposure are vaccinated.[1]

Vaccination against smallpox (variola) is achieved through inoculation with the live cowpox (vaccinia) virus. The effectiveness of cowpox to protect against smallpox has been widely recognized since the 18th century, when Edward Jenner published his work establishing smallpox as the first disease preventable through immunization.[1] Before 1972, children in the United States were routinely vaccinated after 1 year of age to minimize the higher risk for vaccine-associated encephalitis in infants.[3]

In a susceptible community such as the United States today, as few as 10 cases of smallpox would rapidly lead to a major epidemic if no control measures were implemented.[4] Such an epidemic would be devastating given the smallpox case-fatality rate of 30%.[4] In this light, it is not surprising that a recent poll found that half of U.S. adults would seek vaccination against smallpox if the vaccine were available.[5] Although current supplies of smallpox vaccine are insufficient to allow resumed universal vaccination, the government recently awarded a contract to build the stockpile of smallpox vaccine to more than 200 million doses by the end of 2002.[6] This new vaccine will be produced by using cell culture techniques instead of producing the virus in animal (cow) hosts.[7]

In the event of a smallpox attack, current plans call for ring vaccination.[7] However, as more vaccine doses become available, the debate over whether to resume routine vaccination will grow. The decision to pursue universal smallpox vaccination will depend on several factors, including the probability of smallpox attack, the effectiveness of universal immunization compared with ring vaccination, and the expected harm of vaccination.

To estimate the potential harm of vaccination, we calculated the number of expected adverse events in a mass vaccination campaign. We considered two possible vaccination campaigns: 1) vaccinating individuals 1 to 29 years of age (i.e., those born after 1972 when routine vaccination was stopped) and 2) vaccinating all individuals 1 to 65 years of age (because there is doubt that immunity lasts 30 years after vaccination).

Methods

Adverse Events

We focused on eight adverse events associated with smallpox vaccination (**Table 1**). Of these, postvaccinial encephalitis, progressive vaccinia, fetal vaccinia, and eczema vaccinatum are the most serious. Other possible adverse events, including rash, fever, generalized vaccinia, and accidental inoculation, are usually, but not always, self-limited (e.g., accidental inoculation of the eyes may lead to blindness).

TABLE 1
Adverse Events Associated with Smallpox Vaccination*

ADVERSE EVENT	DESCRIPTION
Most serious	
Postvaccinial encephalitis	Similar to other postinfectious encephalitides. May be fatal. Survivors may be left with residual paralysis or other central nervous system symptoms. No known risk factors other than young age.
Progressive vaccinia	Progressive growth of vaccination lesion without healing. Often fatal. Occurs in immunocompromised individuals.
Fetal vaccinia	Passage of vaccinia to fetus may lead to stillbirth.
Eczema vaccinatum	Development of vaccinial lesions over sites where there is or has been eczema. May be fatal.
Less serious	
Generalized vaccinia	Generalized rash caused by hematogenous spread of vaccinia. No known risk factors. Usually resolves with supportive care.
Accidental inoculation	Vesicles develop distant to the vaccination site as a result of direct contact with vaccinia. Often occurs on the genitalia or around the eye; latter exposure can lead to blindness.
Fever	Common side effect.
Rash	Nonspecific rashes, urticaria, and erythema multiforme can occur after vaccination.

* *Information from Goldstein et al.[9] and Henderson et al.[15]*

Among individuals at risk for complications from smallpox vaccination, even those who are not immunized, adverse events may develop upon exposure to someone who was recently vaccinated. For example, eczema vaccinatum is more severe among unvaccinated individuals exposed to a vaccine recipient than among recent vaccine recipients.[8] We consider these adverse events to be indirect, in contrast to the direct adverse events experienced by vaccine recipients themselves.

Mass Vaccination Campaigns

For both vaccination campaigns, we assumed that children younger than 1 year of age would not be vaccinat-

ed because of the greater incidence of adverse events in infants.[9] We chose 65 years of age as the upper age limit to balance the goal of vaccinating the entire public with the desire to minimize potential side effects of administering a live vaccine in the elderly (complications of viral infections, such as shingles, increase with age).[10]

Excluding High-Risk Populations and Their Potential Contacts

We assumed that individuals would be screened before vaccination for risk factors, such as eczema, immunodeficiency, or pregnancy, in themselves or in their close contacts. The prevalence of eczema and the number of immunocompromised individuals have increased over the past three decades. High-risk populations would be excluded from vaccination, as would their potential contacts, since recent vaccine recipients are "infectious" and can transmit the virus (vaccinia).

Individuals with eczema are at high risk for developing eczema vaccinatum. The prevalence of eczema is at least 10%, or more than 28 million people in the United States.[11] Immunocompromised persons are at high risk for progressive vaccinia. We know of no overall estimate for the number of immunocompromised individuals in the United States. This number would include recipients of organ transplants (184,000 solid-organ transplants in the 1990s), individuals with diagnosed and undiagnosed HIV infection or AIDS (850,000), and patients with cancer (approximately 8.5 million).[12–14] We estimate, therefore, that in the entire U.S. population as many as 10 million individuals (3.6%) may be at increased risk for developing progressive vaccinia.

Therefore, approximately 15% of the population may have increased risk for a direct adverse event after smallpox vaccination. In addition to exclusion of these individuals from vaccination, persons in close contact with them should not be vaccinated to avoid inadvertent transmission and subsequent indirect adverse events. Close contacts would include, at minimum, household members. Insufficient data are available to precisely estimate the number of close contacts who would be excluded from a vaccination campaign. We estimate that another 10% of the population would be excluded. On the basis of the foregoing, we estimate that 25% of the population would be excluded from vaccination because of high risk or the possibility of coming in contact with a high-risk individual.

Treating Complications with Immune Globulin

We also assumed that people who developed certain complications would be treated with vaccinia immune globulin (and that sufficient immune globulin would be available in this hypothetical vaccination campaign). Vaccinia immune globulin is recommended for progressive vaccinia, eczema vaccinia, generalized vaccinia (if this reaction appears to be toxic or if serious underlying disease is present), or for accidental inoculation (if the reaction appears to be toxic or in persons with periocular implantation).[9, 15]

Back-of-the-Envelope Calculation: Estimation of Direct Adverse Events

We reviewed the literature to identify data on the incidence of adverse events in primary vaccine recipients. To minimize ascertainment bias, we searched for studies that included strategies for case finding that did not depend only on physician survey. We also searched for data that stratified the incidence of adverse events by age.

We calculated the number of expected adverse events by multiplying age-specific incidence rates by the number of people in specific age categories (**Figure 1**). To calculate direct risks, we assumed 75% uptake of the vaccine on the basis of our estimate of the number of individuals excluded because of high-risk for an adverse event or because they have close contact with another high-risk individual. We assume that persons receiving the vaccination for a second time would react as if it were their first vaccination because of the long interval between vaccinations (at least 30 years). Population data were drawn from U.S. Census estimates for January 2000.[16]

Results

Historical Data on Adverse Events

Few population-based studies are available on the incidence of adverse events from smallpox vaccination. The

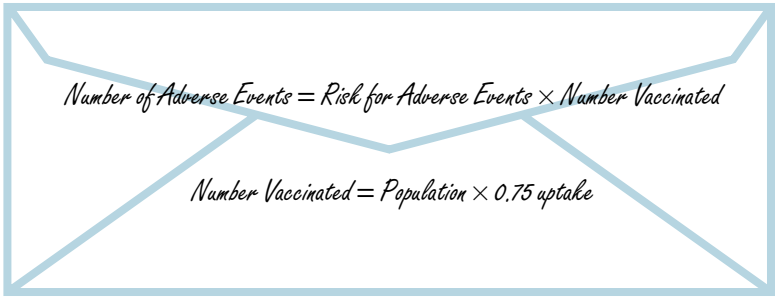

FIGURE 1. Back-of-the-envelope calculation of the number of direct adverse events after smallpox vaccination.

earliest identifiable report that met our criteria was from a 1947 mass vaccination campaign in New York.[17] The incidence of fatal postvaccinial encephalitis was estimated to be 1 case per 1 million persons. However, the data presented are of limited value because of differences in disease classification and inconsistency in case-finding efforts.

In 1968, researchers attempted to identify all U.S. cases of serious adverse events after smallpox vaccination.[18] Cases were identified through multiple sources, including local epidemiologists and tracking use of vaccinia immune globulin. Incidence rates were calculated by comparing the number of reported adverse events to estimates of the number vaccinated from the National Immunization Survey. This study provides the highest-quality evidence for serious adverse events after smallpox vaccination, and it has become the principal reference for smallpox experts and national public health authorities.[7,15] Because of the high rates of previous smallpox vaccination in the 1960s among adults, only 288,000 adults 20 years of age and older were vaccinated in 1968. No fatal outcomes were reported for this group. For our calculations, we assume that the mortality rate for persons 20 years of age and older would be 1 case per million, the overall mortality rate for those vaccinated in 1968. Because the risk for postvaccinial encephalitis decreases with age, we assumed that the mortality would result principally from progressive vaccinia. Rare adverse events may be underestimated because of the relatively low number of adult primary vaccine recipients.

The 1968 study does not provide data on the incidence of fever, nonspecific rash, blindness due to accidental inoculation, or fetal vaccinia. We know of no population-based data on the incidence of fever in a smallpox vaccination campaign. For our calculations, we used the incidence of fever in a study comparing four different smallpox vaccines.[19] Because only children were included in this study, we have no separate estimate of the incidence of fever in adults. For our calculations, we assumed that the fever rate in adults would be the same as for children. Data on rashes resulting from smallpox vaccination were gathered during a 1962 campaign in Wales, in which 900,000 people were vaccinated.[20] As with the study of fever, data are insufficient to stratify the risk for rash by age, so we assumed a uniform age distribution.

We could not estimate the incidence of blindness due to accidental inoculation because of insufficient data. Similarly, we were unable to calculate the incidence of fetal vaccinia. Fewer than 50 cases of fetal vaccinia have ever been reported.[8,9]

Back-of-the-Envelope Estimates

Table 2 lists the expected number of direct adverse events for each vaccination campaign. For each campaign, minor complications would generally number in

TABLE 2
Expected Direct Adverse Events Associated with Smallpox Vaccination

VARIABLE	CAMPAIGN 1: MASS VACCINATION OF PEOPLE 1–29 YEARS OF AGE	CAMPAIGN 2: MASS VACCINATION OF PEOPLE 1–65 YEARS OF AGE
Number vaccinated, *n*	82.5 million	178.5 million
Number with adverse events, *n*		
Most serious		
Postvaccinial encephalitis		
Survived	165	495
Died	10	10
Progressive vaccinia		
Survived	240	570
Died	180	275
Eczema vaccinatum	1200	3525
Less serious		
Generalized vaccinia	2100	6450
Accidental inoculation	2475	3825
Fever	14.9 million	32.1 million
Rash	8175	17,625

the thousands, and rare (but more severe) complications would number in the hundreds. If we assume that the population was similar to that in earlier studies, vaccinating people 1 to 29 years of age would result in approximately 1600 serious adverse events and 190 deaths. Vaccinating people age 1 to 65 years would result in 4600 serious adverse events and 285 deaths.

Table 3 compares the rate of adverse events to two other recommended vaccines—the measles, mumps, and rubella (MMR) vaccine and varicella vaccine—that have similar rates of fever and rash but are not associated with death.[21]

Discussion

The risk for fatal and life-threatening adverse events is greater with smallpox vaccination than with other recommended and widely accepted vaccines. The most important implication is that serious adverse outcomes, including death, would be expected from a mass vaccination campaign.

Findings from this analysis may help in planning for the first phase of a mass vaccination campaign. For example, at least 1600 doses of vaccinia immune globulin would be necessary to treat progressive vaccinia and eczema vaccinatum, which would directly develop in a campaign targeted to 1- to 29-year-olds, and at least 4300 doses would be required for similar purposes in a larger campaign targeted to those between 1 and 65 years of age.

Our analysis has limitations that may cause us to overestimate or underestimate the number of direct adverse events. Reasons for overestimation include improvements in health care over the past 30 years, which might improve survival for persons with progressive vaccinia or encephalitis, and improvements in the manufacture of smallpox vaccine. Smallpox vaccine will now be grown in cell culture,[6] which may lead to fewer cases of fever or nonspecific rash. However, production in cell culture is unlikely to decrease the number of serious complications.

Limitations that may lead to an underestimate of the number of direct adverse events include insufficient data to calculate the expected number of cases of fetal vaccinia and blindness due to accidental inoculation and the paucity of historical data on adverse events in adult primary vaccine recipients.

To minimize direct and indirect adverse events among high-risk individuals, we assumed that 25% of potential vaccine recipients would be excluded. The expected effectiveness of prevaccination screening of these individuals is unknown. The development of eczema vaccinatum and progressive vaccinia indicates that in 1968, the effectiveness of risk factor screening was less than 100%, but without a denominator it is not possible to ascertain the effectiveness precisely. The extent to which potential contacts of high-risk individuals should be excluded from mass immunization efforts is unknown. The time from initial vaccination to full

TABLE 3

Number of Direct Adverse Events per Million Vaccine Recipients: Immunization against Smallpox; Measles, Mumps, and Rubella (MMR); and Varicella

ADVERSE EVENTS	ADVERSE EVENTS PER MILLION POPULATION		
		BENCHMARKS	
	SMALLPOX	MMR	VARICELLA
Fever	< 200,000	≤ 167,500	≤ 100,000
Rash	< 10,000	≤ 50,000	≤ 50,000
Febrile seizure	Not associated	≤ 350	≤ 1000
Thrombocytopenia	Not associated	33	Not associated
Pneumonia	Not associated	Not associated	Extremely rare
Encephalitis*	< 3	Extremely rare or not associated	Extremely rare or not associated
Death	< 2	Not associated	Not associated

**While most cases are not fatal, some have residual neurologic deficits.*

resolution of the resulting pustule is between 2 and 3 weeks.[15] However, the risk this poses to a high-risk individual is unclear.

One way to exclude close contacts would be to refrain from vaccinating household members who live with a high-risk individual. However, these high-risk individuals may have close contacts outside the home, as in the case of a child in daycare who has eczema. More restrictive exclusion criteria would eliminate more of the potential contacts of high-risk individuals and thus decrease the probability of an indirect adverse event. **Figure 2** illustrates that a more restrictive exclusion strategy reduces the risk for adverse events at the cost of reducing overall vaccination uptake, which would leave more of the U.S. population susceptible to death from a smallpox attack.

Determining the expected rate of indirect adverse events is challenging. More than 15% of the population is at high risk for an indirect adverse event. For these individuals, this risk depends on the probability of exposure and the probability that exposure leads to an adverse outcome. In 1968, 3% of the U.S. population received primary smallpox vaccination.[18, 22] In a mass immunization campaign with a target coverage of 75%, 25-fold more of the population would be vaccinated; this would increase the risk for exposure among high-risk unvaccinated individuals. Although the 1968 study reports cases of indirect adverse events, including 61 patients with eczema vaccinatum, of whom 1 died, no appropriate denominator is available to allow us to determine the risk for an indirect adverse event.[18] We are unaware of any data that would permit us to predict the risk for developing an indirect adverse event after exposure. However, without careful screening to minimize close contact with recent vaccine recipients, all individuals who have eczema or who are immunocompromised may be at risk for indirect adverse events. This highlights the importance of careful prevaccination screening efforts in a mass vaccination campaign.

Our calculations evaluate only one-time vaccination. However, if the threat of smallpox bioterrorism continues, the expected adverse events of periodic booster vaccination to maintain immunity and of vaccinating young children as they reach their first birthday, will need to be considered.

Ultimately, the decision to resume mass vaccination must weigh these potential harms—the direct adverse events in vaccine recipients and the indirect adverse events in high-risk contacts of recent vaccines—against the effectiveness of ring vaccination and the substantial morbidity and mortality from a smallpox attack.

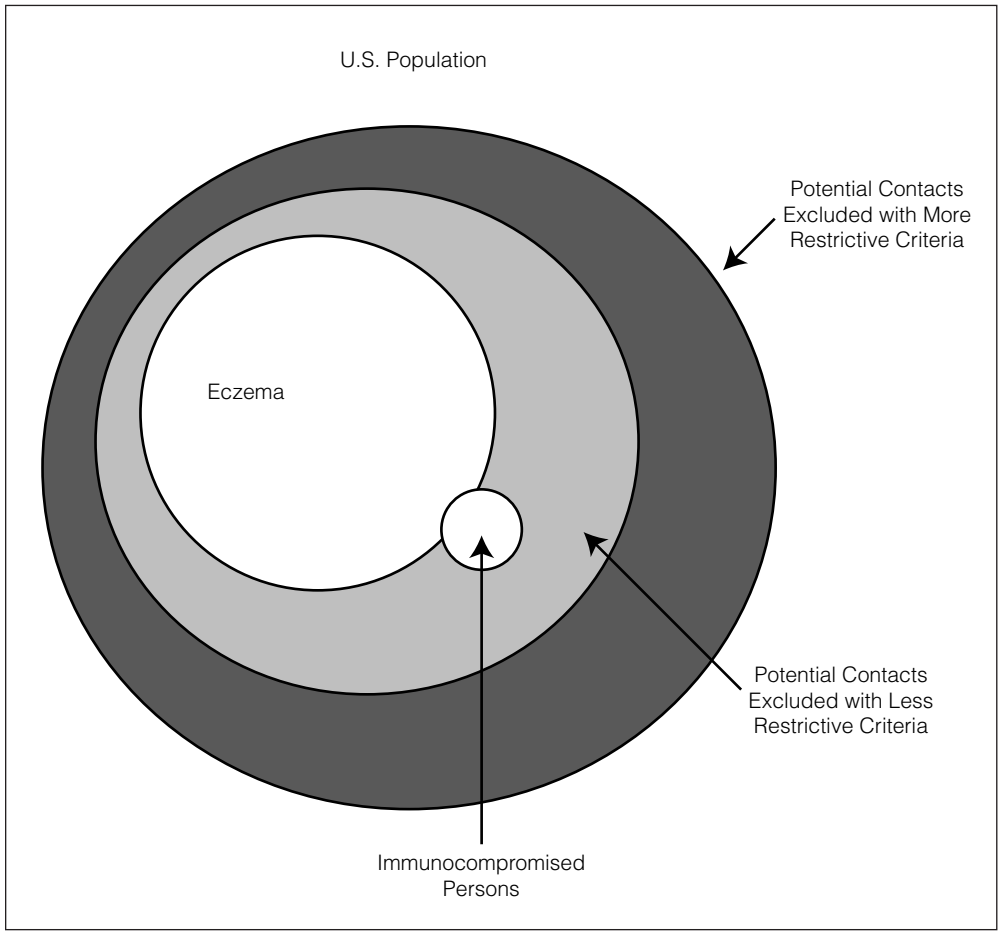

FIGURE 2. Effect of exclusion criteria on overall vaccination uptake. The white circles indicate high-risk individuals with eczema or immunocompromised individuals, who would never be vaccinated. The eccentric circles illustrate the effect of more or less restrictive exclusion criteria of potential contacts of high-risk individuals on the overall number of Americans vaccinated. The remaining area within the square represents the proportion of the U.S. population who could be vaccinated.

Take-Home Points

- **Recent anthrax attacks in the United States have stimulated discussion about the possibility of reinstating a mass smallpox vaccination campaign.**
- **To inform this discussion, we reviewed the available data to estimate the likely number of adverse events resulting from vaccination.**
- **Although serious or life-threatening adverse events with smallpox vaccination are rare (< 3 cases per million for encephalitis and < 2 cases per million for death), they occur more frequently than with other recommended immunizations.**
- **Some deaths would be expected from any smallpox mass vaccination campaign among vaccine recipients and their unimmunized high-risk close contacts.**
- **Excluding potential contacts of high-risk individuals from vaccination would decrease the number of direct and indirect adverse events, but at the cost of decreasing overall vaccine uptake. Better understanding of the transmission rate from recent vaccine recipients to those at high risk for complications (i.e., those who have eczema or are immunocompromised) is needed.**

References

1. Radetsky M. Smallpox: a history of its rise and fall. Pediatr Infect Dis J. 1999;18:85-93.
2. Neff JM. The case for abolishing routine childhood smallpox vaccination in the United States. Am J Epidemiol. 1971;93: 245-7.
3. Katz SL. The case for continuing "routine" childhood smallpox vaccination in the United States. Am J Epidemiol. 1971; 93:241-4.
4. Meltzer MI, Damon I, LeDuc JW, Millar JD. Modeling potential responses to smallpox as a bioterrorist weapon. Emerg Infect Dis. 2001;7:959-69.
5. Langer G. Smallpox Vaccine: Side Effects Raise Concern. ABC News.com. Available at http://more.abcnews.go.com/sections/living/dailynews/smallpox011204.html. Accessed December 7, 2001.
6. HHS News. HHS Awards $428 Million Contract to Produce Smallpox Vaccine. Available at www.hhs.gov/news/press/2001pres/20011128.html. Accessed December 7, 2001.
7. Centers for Disease Control and Prevention. Interim Smallpox Response Plan & Guidelines. Available at www.bt.cdc.gov/DocumentsApp/Smallpox/RPG/index.asp. Accessed January 28, 2001.
8. Lane JM, Millar JD. Risks of smallpox vaccination complications in the United States. Am J Epidemiol. 1971;93:238-40.
9. Goldstein JA, Neff JM, Lane JM, Koplan JP. Smallpox vaccination reactions, prophylaxis, and therapy of complications. Pediatrics. 1975;55:342-7.
10. Centers for Disease Control and Prevention. Shingles (Herpes Zoster). Available at www.cdc.gov/nip/diseases/varicella/faqs-gen-shingles.htm. Accessed January 14, 2002.
11. Diepgen TL. Is the prevalence of atopic dermatitis increasing? In: Williams HC, ed. Atopic Dermatitis: The Epidemiology, Causes and Prevention of Atopic Eczema. New York: Cambridge Univ Pr; 2000:96-112.
12. Joint United Nations Programme on HIV/AIDS. Epidemiological Fact Sheets on HIV and Sexually Transmitted Infections: United States. Available at www.unaids.org/fact_sheets/index.html. Accessed January 14, 2002.
13. United Network for Organ Sharing (UNOS). All Recipients: Age at Time of Transplant. Available at www.unos.org/. Accessed January 14, 2002.
14. National Cancer Institute. CanQues. Available at http://srab.cancer.gov/Prevalence/canques.html. Accessed January 3, 2002.
15. Henderson DA, Inglesby TV, Bartlett JG, et al. Smallpox as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. JAMA. 1999;281: 2127-37.
16. U.S. Census Bureau. National Estimates: Monthly Population Estimates, 1990 to 2000. Available at http://www.census.gov. Accessed December 7, 2001.
17. Greenberg M. Complications of vaccination against smallpox. Am J Dis Child. 1948;76:492-502.
18. Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968. N Engl J Med. 1969;281:1201-8.
19. Cherry JD, McIntosh K, Connor JD, et al. Clinical and serologic study of four smallpox vaccines comparing variations of dose and route of administration. Primary percutaneous vaccination. J Infect Dis. 1977;135:145-54.
20. Waddington E, Bray PT, Evans AD, Richards ID. Cutaneous complications of mass vaccination against smallpox in South Wales 1962. Annual Report and Transactions of the London Dermatological Society. 1964;50:22-42.
21. Centers for Disease Control and Prevention. Vaccine Side Effects. Available at www.cdc.gov/nlp/vacsafe/concerns/side-effects.htm. Accessed January 2, 2002.
22. U.S. Census Bureau. Historical National Population Estimates. Available at http://www.census.gov. Accessed January 14, 2002.

Correspondence

Alex R. Kemper, MD, MPH, MS, 6C19 300 North Ingalls Building, Ann Arbor, MI 48109-0456; telephone: 734-615-8153; fax: 734-764-2599; e-mail: kempera@med.umich.edu.