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Contact Vaccinia—Transmission of Vaccinia From Smallpox Vaccination

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CONCERN THAT SMALLPOX VIRUS MIGHT BE USED AS a biological weapon has led to proposals that smallpox vaccination be offered to at least some of the US population.¹⁻⁴ In June 2002, the US Department of Health and Human Services' Advisory Committee on Immunization Practice recommended that vaccination be offered to limited numbers of health care personnel who may be investigating possible cases of smallpox and to those who might be caring for patients in selected hospitals.⁵ On September 23, 2002, the Centers for Disease Control and Prevention (CDC) distributed detailed operational and logistic guidelines for implementing a large-scale volunteer smallpox vaccination program in response to introduction of smallpox as an act of terrorism.⁶ These events raise concern about the frequency of serious adverse events, including death, that may occur from vaccination. These have been well documented.⁷⁻¹³ Such severe reactions are far more frequent following smallpox vaccination than following any other vaccine. Most complications occur in the vaccinees themselves, but vaccinia virus can be transmitted inadvertently from vaccinees to others, sometimes causing serious and even fatal adverse reactions.

This article reviews the data regarding the transmission of vaccinia (contact vaccinia), assesses the potential risks of such transmission, and suggests preventive measures. The clinical definitions of conditions that could result from contact with a vaccinated person or from vaccination were used in the surveillance activities of the CDC during the 1960s and 1970s as follows: (1) *vaccinia necrosum* (progressive vaccinia): spreading necrosis at the site of vaccination, with or without metastatic necrotic lesions occurring elsewhere on the body; (2) *eczema vaccinatum* (EV): vaccinia lesions either generalized or as individual lesions elsewhere than at the vaccination site in a person who has eczema or a history of eczema; and (3) *accidental infection* (AI): vaccinia lesions resulting from unintentional implantation of vaccinia virus in the eye or mouth or in other parts of the body in the absence of eczema or other preexisting skin lesions.⁸ The diagnosis of eczema

was determined by the physician reporting the case and did not distinguish atopic dermatitis from other eczematous-like skin conditions.

Reports Before the 1960s

Transmission of vaccinia virus to close contacts has long been recognized. The unusual susceptibility of patients with what was called eczema was first described in the late 19th century.¹⁴ Reports by Weinstein¹⁵ and by Greenberg¹⁶ on the outbreak of smallpox in New York City in 1947 described the adverse events following the vaccination campaign during which approximately 5 million to 6 million New Yorkers were vaccinated. Of 45 cases that were reported as generalized vaccinia (a generalized spread of vaccinia lesions), 38 had preexisting eczema and 7 had no active skin lesions at the time of exposure.¹⁶ Twenty-eight of these cases acquired vaccinia by close contact with someone recently vaccinated rather than by vaccination. "Most contacts were in the home, but a few" patients apparently acquired vaccinia from a recently vaccinated nurse in the hospital.¹⁶ There were 2 deaths in infants 4 and 6 months old who acquired their infection as a result of contact.¹⁶

In a review of all dermal and central nervous system adverse events reported following 544 350 primary vaccinations from 1950 to 1954 in Sweden, Lundstrom¹⁷ documented 330 cases of nonencephalitic adverse events, including 2 patients, a 9-month-old and a 1-year-old, who died of EV. Both acquired vaccinia from vaccinated siblings.

Communitywide Studies in the 1960s

Six communitywide studies conducted during the 1960s, 2 in the United Kingdom and 4 in the United States, provide information regarding the risk of adverse events following vaccination of large numbers of persons. In an assessment of the risk of dermal adverse events following 3.8 million primary vaccinations and 1.2 million revaccinations for smallpox in Great Britain from 1951 to 1960,

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Table. Summary of 1960s Data on Risk of Transmission of Vaccinia by Contacts*

Source	No. of Primary Vaccinations	Cases (Deaths)				Cases per Million Primary Vaccinations			
		Eczema Vaccinatum		Accidental Infection		Eczema Vaccinatum		Accidental Infection	
		Vaccinated	Contact	Vaccinated	Contact	Vaccinated	Contact	Vaccinated	Contact
National Surveys									
England and Wales, ¹⁹ 1962	3 250 000	48 (4)†	89 (7)†	14.8	27.4
United States, ⁹ 1963	6 239 000	54 (0)	54 (2)	85	22	8.7	8.7	13.6	3.5
United States, ¹⁰ 1968	5 594 000	58 (0)	60 (1)	142	44	10.4	10.7	25.4	7.9
State Surveys									
United States, ⁹ 1963	298 000	24	5	80.5	16.8
United States, ¹¹ 1968	650 000	25	13	344	29	38.5	20.0	529.2‡	44.6

*Ellipses indicate data not reported.

†Based on 137 cases with full information on age, sex, and source of infection.

‡The rate of accidental infection in a pediatric clinic was found to be equal to 1 case per 170 primary vaccinations.²¹

Conybear¹⁸ noted that 16 cases of EV were reported, including 4 deaths, all in primary vaccinees; all 4 deaths were in children younger than 1 year.

Copeman and Wallace¹⁹ published a retrospective study of all cases of EV reported following a mass vaccination program in England and Wales in 1962 to contain an epidemic of importation smallpox. At least 3.2 million individuals were vaccinated within a few months. Following vaccination, 185 cases of EV were reported, including 11 deaths. All reported cases had a history of or active skin disease, including 148 with atopic dermatitis, 8 with seborrheic eczema, and 29 with unclassified dermatitis. The authors reported that “two thirds” of these cases did not have active and obvious eczema at the time of vaccination. Of 137 patients with full details regarding age, sex, and source of infection, 89 cases were the result of contact: 74 had exposure to a family member, 7 had contact with close friends or schoolmates, and 3 patients were receiving treatment for eczema in a hospital with infection acquired from a newly vaccinated patient; for an additional 5 cases, the infection could not be traced. Nineteen cases were younger than 1 year, 29 were aged 1 to 4 years, 19 were between 5 and 9 years, 5 were between 10 and 19 years, and 17 were older than 20 years. Four patients older than 20 years acquired the disease from recently vaccinated infants. In addition, the authors reported 3 patients with Darier disease who developed a condition similar to EV after contact with a family member.

The CDC conducted 4 large studies in the United States to assess the incidence of adverse events following smallpox vaccination in 1963 and 1968. Neff et al⁸ conducted a national survey of patients from 3 sources: all individuals who had received vaccinia immune globulin in 1963 as treatment for a complication of vaccination (429 cases); death reports that listed postvaccinal complications as a principal cause of death (1 case) as well as cases of encephalitis reported to the CDC (2 cases); and reports received by Kempe,²⁰ who had surveyed all pediatricians (1 case). In a separate study, Neff et al⁹ surveyed all physicians in 4 states

for adverse events observed in 1963. Lane et al¹⁰ repeated these studies in 1968 in a prospective design, adding surveillance reports of patients from whom specimens had been sent to the CDC laboratory for vaccinia diagnosis and patients with suspected adverse events who had been reported to vaccine manufacturers and the maker of the antiviral compound *N*-methylisatin beta-thiosemicarbazone (Marboran). A survey of all physicians in 10 states (11.6% of the national population) also was performed, in which individual physicians were contacted by mail to learn about possible adverse events following vaccination.¹¹

The national surveys in both years provided remarkably similar results, especially with respect to EV (TABLE). In the United States, 11.8 million persons received primary vaccination during 1963 and 1968. The number of primary vaccinations is important because virtually all of those from whom vaccinia virus was transferred were primary vaccinees. The national surveys documented 54 cases of EV, with 2 deaths, in contacts of vaccinees in 1963 and 60 cases with 1 death in 1968. The frequencies of documented cases of contact EV for these 2 years were 8.7 and 10.7 cases per million primary vaccinees, respectively. These cases accounted for approximately half of all cases of EV identified in the 2 national surveys. Reported incidence of contact EV in the state surveys was approximately twice that reported in the national studies (16.8 and 20 cases per million primary vaccinations), perhaps representing more complete reporting of less severe cases.

One of us (J.M.N.) recently reviewed the US national data on patients with EV from 1968 and found that 13 (23%) of the 58 cases in vaccinated individuals and 2 (3%) of the 60 cases of contact vaccinia were reported by the physician to have had no active lesions of eczema at the time of exposure but to have had a history of eczema. These cases had a generally less serious secondary infection than those with active skin lesions at the time of exposure (unpublished data, available from the author).

Contact infection in individuals without a history of or active eczema at the time of exposure (contact AI) resulted

in less severe infection than those with a history of or active eczema (contact EV). There were reports of 3.5 and 7.9 cases of contact AI per million primary vaccinees in the national studies^{8,10} and 44.6 per million in the 1968 state survey.¹¹ The occurrence of 44.6 cases per million from the 1968 state survey suggests that this condition may have been significantly underreported in the national studies. The contact AI cases occurred in healthy children and the infections were self-limited.

The age distribution of all contact cases from the US studies (excluding the 5 cases from the 1963 study⁹ because of incomplete data) was as follows: younger than 1 year, 25 cases; 1 to 4 years, 113 cases; 5 to 19 years, 40 cases; and 20 years or older, 44 cases. Sixty-two percent of cases occurred in children younger than 5 years and 19.8% occurred in those 20 years or older. Of the 127 cases with contact EV, 87 (68.5%) were younger than 5 years and 20 (15.7%) were 20 years or older. Of the 95 cases with contact AI, 51 (53.7%) were younger than 5 years and 24 (25.3%) were 20 years or older.

In a separate analysis of deaths during a 9-year period (1959-1968), Lane et al¹² showed that all of the deaths attributed to EV occurred in contacts. The contacts between those who were infected and the primary vaccinees were quite close, generally among family members. There was no secondary spread of vaccinia beyond the initial contact.

One of us (J.M.L.) performed a separate analysis of the characteristics of the individuals who were responsible for transmitting vaccinia from 1964 to 1968 (unpublished data, available from the author). This analysis includes all individuals documented as having contact vaccinia in the 1968 national survey (104 cases), the case reports still available from the 1968 state survey (23 cases), and the vaccinia immune globulin reports still available from 1964 to 1967 (16 cases). Sixty-seven (46.9%) of these 143 cases were EV. Ages of cases ranged from 6 weeks to 80 years. Sixty-three percent were younger than 4 years, 18% were between 5 and 19 years, 16% were between 20 and 39 years, and 3% (4 cases) were older than 40 years. Only 3 had no known contact source, and 1 acquired vaccinia from an unknown contact during a communitywide vaccination campaign. Of the 139 known contacts, 70% were siblings (81 cases) and playmates (16 cases). Nine percent of transmissions (13 cases) were from parents or adult close relatives. Seventeen percent of cases were adults who had close contact with a child (21 parents and 3 grandparents). Five (4%) had contact with an individual other than a family member or playmate. One was a 17-month-old child admitted to a hospital with severe eczema. Five days after admission, the child developed EV; the apparent source was a licensed practical nurse who had just been vaccinated. Another case was an adult woman who slept with a recently vaccinated serviceman. Yet another case was a 17-year-old baby-sitter who cared for a recently vaccinated child. Two cases were children who acquired vaccinia from unidentified contacts in day care.

None of the studies documented cases of progressive vaccinia or postvaccinal encephalitis among contacts of vaccinees.

Perspectives on Risk of Transmission

The available data from the 1950s and 1960s show that there is a risk of vaccinia transfer from a primary vaccinee to an unimmunized individual in contact with the vaccinee, but the risk is not large. This risk needs to be kept in perspective. The US studies indicate that transfer of vaccinia virus from contacts that resulted in EV occurred at a frequency of about 1 to 2 per 100 000 primary vaccinations, and the overall transmission of contact vaccinia occurred in the range of 2 to 6 per 100 000 primary vaccinations. In all of the studies, contact vaccinia required close contact, was an unusual occurrence outside of the home, and occurred rarely as a result of a hospital-related contact.

It is important to note the limitations of studies conducted in the 1960s. All of the studies depended on appropriate recognition and reporting of adverse reactions to vaccination. The state studies included more cases, but it is likely that the adverse reactions, especially mild cases, were underreported. This would be true, for example, for cases in which the contact was unknown and the illness not recognized. In addition, EV was a poorly defined condition and depended on physician interpretation of what constitutes eczema or a history of eczema, and atopic dermatitis was not distinguished from other eczematous lesions. Only in the study by Copeman and Wallace¹⁹ did dermatologists attempt to define the underlying skin conditions (including atopic dermatitis) of these cases. Finally, the population that would be vaccinated today represents different targeted age groups with different baseline immunity to vaccinia and different underlying conditions than the populations of the 1960s.

What might be expected if widespread vaccination were to be conducted today? The population of 2002 differs from that of the 1960s in several respects. Smallpox vaccination was stopped in 1972. This means that the entire population younger than 30 years now has no immunity to vaccinia. Those aged 30 years or older (except clinical personnel and students in health care during and before the 1960s, smallpox researchers, the military before 1984, and travelers to countries requiring smallpox vaccination before the 1980s) in all probability had only a single vaccination in childhood. Individuals vaccinated many years after a primary vaccination react much like primary vaccinees and can be expected to shed virus from the vaccination site or be susceptible to contact infection.^{22,23} It can be assumed that all of the population younger than 30 years who might be vaccinated would respond with a primary type reaction and could shed virus from the vaccination site for up to 19 days.²³ The amount of virus that would be shed by vaccinees aged 30 years or older who had had previous vaccination depends on the length of time since vaccination and the number of previous vaccinations. The proportion or number of indi-

viduals who would respond this way is unknown, but presumably, a high percentage would be expected to respond similarly to those who had never been vaccinated. Thus, a higher incidence of contact vaccinia most likely would occur (especially in the age group younger than 30 years) than might be expected based on the 1960s experience.

There are other reasons to suggest the possibility of a higher frequency of adverse events, both in recipients and contacts. The prevalence of atopic dermatitis among children in the United States may have increased from 3%-6% to 6%-22% in the past 3 decades.^{24,25} A Canadian study conducted in 1999 showed a lifetime prevalence among children of between 14% and 22%.²⁶ In Oregon schoolchildren, the prevalence was estimated in 1996 to be between 6.8% and 17.2%.²⁷

Today, there are more individuals who are immunocompromised than during the 1960s. Although no cases of progressive vaccinia were reported as a result of contact vaccinia in the 1960s, it is uncertain what the experience might be today. In the 1960s, there were no known cases of human immunodeficiency virus (HIV) infection, and patients receiving immunosuppressive drugs because of cancer or organ transplantation were many fewer in number. In 1984, at the beginning of the AIDS epidemic and the end of vaccination for the US military, there was a case of disseminated vaccinia that occurred in an apparently healthy military recruit who was later diagnosed as having HIV/AIDS.²⁸ Now HIV/AIDS is relatively common, and some patients may not be aware of or may conceal their infection. The CDC recently estimated that 300 000 individuals in the United States remain unaware of their HIV infection.²⁹ In addition, HIV has cutaneous manifestations that can serve as a site of infection.³⁰ Contact vaccinia in this population could be especially serious.

Health care workers for whom vaccination might be indicated pose a special risk. In the early 1960s, there were many programs to vaccinate large numbers of hospital staff because of concern about smallpox importations from other countries. During this time, hospitals took a variety of measures to guard against the spread of vaccinia, such as performing vaccination immediately before a holiday or not permitting staff to work in clinical services during the period they might be shedding vaccinia. These programs were conducted with varying care and intensity, and no known contact cases resulted. Today, even more caution should be exercised, for several reasons. The CDC estimates that as of June 2001, there were 23 473 health care workers with AIDS.³¹ Many hospital staff (eg, residents and nurses younger than 30 years) have not been vaccinated against smallpox. The rest of the staff in all likelihood have not been immunized for 30 years, many only once, and can expect to have minimal residual immunity to vaccinia. These personnel would be likely to shed more vaccinia virus from their vaccination site and are more likely to be in contact with patients who are immunocompromised than their counterparts would have before 1972.

Finally, sometimes a routine primary vaccination reaction may appear as if it were infected with a bacterial pathogen, and inappropriate use of antibiotics might result.

Implications for Current Vaccination Policy

The frequency of possible contact spread of vaccinia and the likelihood of adverse events cannot be predicted. In the 1960s, contact cases were infrequent and resulted almost entirely from exceptionally close contact. Even though more adults and school-aged children today can be expected to have primary reactions from vaccination than what was reported in the 1960s, close contact is still the expected mode of transmission. Critical attention must be given to screening, counseling, and monitoring. Screening must focus on both the individual vaccination candidate and the potential contacts. These include individuals with active or chronic dermatitis or a history of chronic dermatitis and individuals whose immune response may have been compromised as a result of disease or therapy. A carefully paced and limited vaccination program can be based on specific protocols that are developed to screen, counsel, and monitor for adverse reactions. Surveillance to document and track cases of contact vaccinia is also needed. Such a program could result in a limited number of cases of contact vaccinia. However, any large-scale response, such as the one proposed by the CDC,⁶ has the potential to result in more cases of contact vaccinia. An orderly, systematic approach along with careful screening to identify potential vaccinia-susceptible individuals and household contacts and close monitoring for adverse effects are essential to reduce the risk of transmission of vaccinia following smallpox vaccination.

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EDITORIAL

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Invasive vs Conservative Management of Acute Coronary Syndromes

Do the Data Support the Guidelines?

David J. Cohen, MD, MSc

ACU TE CORONARY SYNDROMES (ACSS) ACCOUNT FOR approximately 1.4 million hospitalizations each year in the United States alone, and more than 2 million worldwide.¹ Until recently, however, there was no consistent guidance as to how such patients should be optimally managed during the hospital phase. Some clinicians favored an early invasive strategy, with cardiac catheterization during the first 24 to 48 hours of presentation. Others favored a more conservative strategy with initial medical stabilization followed by cardiac catheterization only if the patient demonstrated high-risk features (such as recurrent myocardial ischemia or congestive heart failure) or significant myocardial ischemia on noninvasive testing. Although the invasive strategy offers the ability to identify patients with high-risk coronary anatomy quickly and definitively, several clinical trials suggested that these poten-

tial benefits were offset by the early risks of revascularization procedures in these high-risk subgroups.^{2,3}

Recently, however, 2 large-scale randomized clinical trials have demonstrated that advances in percutaneous coronary intervention (PCI) and adjunctive medical therapy have tipped the balance in favor of an early invasive strategy. In the Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC) II trial, 2457 patients with unstable angina or non-ST-segment elevation myocardial infarction (MI) were initially stabilized with dalteparin (5-7 days) and then were randomly assigned to an early invasive strat-

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See also p 1851.