

Editorial

Risks of smallpox vaccination: 200 Years after Jenner

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It has been more than 200 years since Dr Edward Jenner performed the first experiment to demonstrate the efficacy of cowpox in preventing smallpox.¹ Jenner realized that his approach might eventually lead to the eradication of smallpox; indeed, this vision did come true. Because of immunologic cross-reactivity among orthopox viruses, inoculation of cowpox or vaccinia virus protects against smallpox, and smallpox was eradicated throughout the world by 1980. The risk of vaccination exceeded the benefits in the United States, and routine vaccination was discontinued in 1972.

Unfortunately, events early in the 21st century have raised the possibility that terrorists will initiate epidemics of smallpox or other severe infectious diseases. Ironically, the remarkable success of vaccination has led to the current situation, in which most of the world has never been vaccinated against smallpox. If terrorists have access to viable smallpox, then much of the world's population is once again at risk for acquiring this contagious disease, which has a mortality rate of 20% to 40%.² Vaccinia immunization is also needed for laboratory workers exposed to vaccinia and for protection against other orthopox viruses, such as monkeypox.

Effective vaccination against smallpox requires epicutaneous administration of viable vaccinia virus ("scarification"). Immunization results in both an antibody response and a cell-mediated immune response, including cytotoxic T cells.³ The relative roles of innate immunity, antibody immunity, and cell-mediated immunity in protection from adverse effects of inoculated vaccinia and smallpox exposure are uncertain.

Abbreviations used

EV: Eczema vaccinatum
PDC: Plasmacytoid dendritic cells
MVA: Modified vaccinia Ankara

The virulence of vaccinia virus and its epicutaneous route of administration result in a number of adverse effects, including life-threatening complications. The current issue of this Journal presents 4 reviews of topics central to an understanding of the risk of smallpox vaccination. Mullin¹ provides a historical perspective on Jenner's contributions to the development of an effective vaccine for smallpox. Gruchalla and Jones⁴ review the adverse events associated with prevention and treatment of infectious diseases induced by agents of bioterrorism; they include a discussion of allergic reactions to antibiotics and of adverse reactions to smallpox and other vaccines. Hackett⁵ reviews the role of innate immunity in protection against infectious agents. Wollenberg⁶ reviews cutaneous viral infections in patients with atopic dermatitis (AD) and the abnormalities in cutaneous immunity in these patients that enhance their risk of eczema vaccinatum (EV) from immunization with vaccinia.

The adverse effects associated with vaccinia administration have been reviewed by Engler et al,³ by Bray,² and, in this issue of the Journal, by Gruchalla.⁴ Careful epidemiologic studies in the 1960s identified 3 major life-threatening reactions: postvaccinial encephalitis, progressive vaccinia, and EV. Recent studies have identified a fourth adverse event that is potentially life-threatening: myopericarditis.⁷ Progressive vaccinia occurs in immune-deficient recipients of vaccinia. Much of the risk is associated with a cellular immunodeficiency, though rare individuals with apparent B-cell deficiency are also at risk.^{3,8} The prevalence rates of at-risk individuals, such as those who are carriers of HIV and those who are on immunosuppressive medications, are much higher than they were 30 to 40 years ago.³ Most cases of EV occurred in individuals with histories of "eczema," and most of these individuals probably had what would now be diagnosed as AD. The prevalence of AD has increased substantially in recent years; more than 10% of the population might have histories of this disease, and even greater numbers have household contacts with AD.³

EV was the most common life-threatening complication of smallpox vaccination, occurring in approximately

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10 vaccinees per million in a national survey⁹ and in approximately 40 vaccinees per million in a more detailed survey that probably identified milder cases.¹⁰ EV is 10-fold more frequent in primary vaccinees than in those revaccinated.^{9,10} The mortality estimates from untreated EV vary widely—from 1% to 6% to 30% in children under the age of 2 years.^{3,8} Deaths from EV were among children less than 9 years of age, and nearly all cases were from exposure to a vaccinated household contact.¹¹ There are limited treatments available for life-threatening complications of vaccinia immunization. Whereas anecdotal data suggest that vaccinia immune globulin is effective in treating EV, there are no controlled studies to demonstrate the efficacy of vaccinia immune globulin or of antivirals for EV or other adverse effects of vaccinia.²

Recent studies have not identified any cases of EV among 450,000 military personnel and 37,000 civilian personnel.^{12,13} This low rate might reflect the modified vaccination scheme (only 3 punctures for primary vaccinees), better postvaccination care of the scarified site, and better screening for individuals with AD and individuals with household contacts with AD. In 2003, the clinical diagnosis of AD is defined by a set of questionnaires, and recent military experience demonstrates that 11% to 34% of eligible personnel deferred vaccination, skin condition being the major reason for deferral.¹² However, the success of the military experience might need to be interpreted cautiously, inasmuch as recent civilian surveys suggest that 30% to 40% of individuals with histories of AD will not correctly report this history.¹⁴

The number of patients with AD who were vaccinated is unknown, so the risk of EV among these patients is also unknown. Although individuals with “eczema” were supposed to be excluded from mass vaccination campaigns, approximately one half to one third of individuals who developed EV acquired it after vaccinia immunization,^{9,15} suggesting that substantial numbers of patients with AD must have been vaccinated inadvertently. The remaining one half to two-thirds of EV cases developed after exposure to household contacts who had been vaccinated.^{9,15} It is likely that only a small subset of patients with AD develop EV after exposure to vaccinia. Unfortunately, there are no biomarkers to identify this high-risk subpopulation. The most intriguing approach to identifying the subpopulation is suggested by the data of Wollenberg.⁶ Individuals with AD who are infected with cutaneous viruses, including both eczema molluscum due to chronic molluscum contagiosum and eczema herpeticum due to disseminated herpes simplex, represent a subset of patients with AD who are likely to be at increased risk for EV, and this subset should be compared with patients with AD who do not have such viral infections.

There are at least 4 abnormalities in cutaneous and/or immune function in patients with AD that might be markers of predisposition to EV: defective skin barrier, high T_H2 responses, decreased antimicrobial peptides, and decreased plasmacytoid dendritic cells (PDCs). Defective barrier properties of the stratum corneum are

associated with greater skin irritancy and inflammation and a lower irritancy threshold. The lower irritancy threshold is attributed in part to the increased number of cutaneous nerve fibers found in AD skin. The increased sensation of itch might cause scratching of the skin and mechanical release of Substance P from nerve endings, which in turn induces cutaneous mast cell release of histamine.¹⁶ Other results have identified an increase in T_H2 cytokines in acute AD lesions, and these cytokines inhibit antiviral defense in the skin. Furthermore, antimicrobial peptides, a major component of innate antimicrobial/antiviral lytic mechanisms, are relatively diminished in AD skin.¹⁷

Through their overlapping inflammatory and antigen-presenting properties, dendritic cells link innate and adaptive immunity. One subpopulation of dendritic cells, the PDCs, is thought to be viral antigen-presenting cells. PDCs are markedly reduced in the skin of patients with AD, possibly because IL-4 and IL-10, 2 cytokines that are increased in the AD skin, inhibit PDC recruitment.¹⁸

Poxvirus-induced blockade of immune pathways might act synergistically with AD-induced compromise of adaptive and innate immune pathways to predispose patients with AD to cutaneous viral infections. For example, vaccinia produces homologs of the host interferon pathway, viral IFN α/β binding protein and a soluble viral IFN receptor, that block IFN signaling and promote a virally permissive environment.⁵

New generations of vaccines are intended to protect against threats of bioterrorism and be safe for immunocompromised individuals. Attempts to improve the safety of vaccination against smallpox have focused on developing attenuated versions of vaccinia. One attenuated virus, modified vaccinia Ankara (MVA), is derived from a vaccinia virus that was passaged more than 500 times. Compared to wild-type vaccinia, MVA has many gene deletions and has limited ability to proliferate in mammalian tissue.¹⁹ MVA underwent clinical trials in Europe in the 1970s with some success, but it is difficult to determine which at-risk groups received the vaccine. Should attenuated vaccinia preparations induce adequate immune responses, they might be useful either as an alternate vaccine to wild-type vaccinia or as a pretreatment. Administration of attenuated vaccinia might induce protective antivaccinia immune responses that would permit safer administration of wild-type vaccinia several weeks after administration of the attenuated virus.

The effectiveness and long-term protective value of attenuated viruses directed against smallpox in patients with AD and other immunocompromised individuals remain to be determined. It is noteworthy that current research into improvement of smallpox vaccination is limited by our success in eradicating smallpox. Until the 1970s, smallpox vaccine efficacy was evaluated in populations naturally exposed to smallpox. Since then, vaccine efficacy has not been evaluated because there has been no population exposed to smallpox. In contrast, in the late 1700s the only available protection against smallpox was variolation, or inoculation of a small amount of smallpox.

The mortality rate from variolation was initially approximately 2% and subsequently somewhat lower, but variolation apparently protected against the high mortality of natural exposure to smallpox.¹ Jenner evaluated the success of his new therapy by a challenge with live smallpox, an approach that would now be considered unethical.

The complexity of vaccine development for immunocompromised individuals is highlighted by the inability of the at-risk population to mount an adequate antivaccinia immune response, so they almost certainly do not make an adequate anti-smallpox response. Research on smallpox vaccination had been performed before recent advances in immunology. New immunologic knowledge, as well as substantial technical advances in fields such as genomics, molecular biology, and bioinformatics, should in the future provide an array of tools by which we can understand the immune and gene expression response to viruses of normal and susceptible individuals, including responses in subsets of patients with AD.²⁰ These data should result in the identification of biomarkers of susceptibility to adverse events and in the development of improved vaccines. Although the reemergence of smallpox is potentially devastating to the world community, future research promises to develop new immunotherapeutic approaches so that even at-risk individuals will be able to be protected from smallpox.

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