

Smallpox Vaccination: A Review, Part I. Background, Vaccination Technique, Normal Vaccination and Revaccination, and Expected Normal Reactions

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Because smallpox could be a factor in bioterrorism, the United States has provided guidelines for smallpox vaccination of certain members of the population, including health care workers and first responders, as well as military personnel. A plan for more extensive vaccination, if it is needed in the event of a bioterrorist attack, is being developed under the aegis of the Centers for Disease Control and Prevention. The characteristics of smallpox vaccine, the technique of administration, and the expected reactions to primary vaccination and revaccination are outlined in this article.

Smallpox in nature was eliminated from the world in 1977 by a concerted effort organized by the World Health Organization [1]. The last cases occurred in persons who acquired smallpox from an adjacent laboratory source in Birmingham, England, in 1978 [2, 3]. Smallpox vaccination was discontinued in the United States in 1972, except for vaccination of a few laboratory workers and, until 1983, military personnel. The terrorist attack on the World Trade Center in New York City in 2001 caused the US government to reevaluate the possibility of the reintroduction of smallpox. There is now renewed interest in smallpox vaccine and vaccination. This article reviews information about the vaccine, its application, and expected normal reactions. A second article addresses the spectrum of adverse events that could occur after vaccination [4].

Many of the observations described here are based on ex-

tensive experience with routine vaccination against smallpox in the period 1950–1970. New information gathered from experiences with reinstatement of vaccination programs and newer vaccines and screening methods may require modification of the statements made in this article. Many more images can be found at <http://www.bt.cdc.gov/training/smallpoxvaccine/reactions>; the images included here are limited and in most instances give only a single example.

THE BIOTERRORIST THREAT

The World Health Organization mandated that only 2 laboratories in the world would retain variola virus: one in the Union of Soviet Socialist Republics, and one in the United States [5]. The virus was not destroyed but has been retained at these 2 sites. Recently, there has been some evidence that other countries—perhaps as many as 7—possess variola virus [6]. These include, but are not limited to, North Korea and Iraq. These suspicions suggest that variola virus may be available to bioterrorists and could be used in an attack on the United States and other Western democracies. The risk is small but not negligible. Variola virus is easily transportable in a temperature-stable lyophilized state, and it is conceivable that it might be aerosolized to cause infection of many individuals

Received 20 February 2003; accepted 4 April 2003; electronically published 10 July 2003.

Financial support: Office of Bioterrorism Preparedness, US Department of Health and Human Services (grant to V.A.F.).

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Clinical Infectious Diseases 2003;37:241–50

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1058-4838/2003/3702-0013\$15.00

within the United States and elsewhere [5]. The United States government has, therefore, undertaken a series of steps to protect its residents against this risk. These include building an adequate supply of vaccine and bifurcated needles, enhancing the laboratory capacity for diagnosis of variola and vaccinia virus infection, and enacting a variety of training efforts directed toward health care and public health personnel. The United States is now ready to initiate the use of smallpox vaccine in a deliberate fashion.

SMALLPOX

There are many strains of variola virus, which manifest 2 clinically distinct illnesses: variola major and variola minor [5, 7]. Both can produce human disease, and neither has animal reservoirs. Variola minor produces a mild illness with a 1%–3% case-fatality rate. The clinical presentations of variola major range from a relatively benign pustular skin rash to fatal flat and hemorrhagic forms with overwhelming viremia leading to toxic/septic shock and disseminated intravascular coagulation.

Variola virus infection results from inhalation of infectious particles, usually from an infected person but occasionally from infected fomites. The incubation period after exposure is ~12 days (range, 7–17 days). A prodromal period follows, which is characterized by high fever, fatigue, headache, and backache. This lasts 2–3 days and is followed by an enanthem that heralds the infectious stage. Coincident with or within 24 h after the onset of the enanthem, an exanthem develops, predominately on the face, arms, and legs. This rash begins with erythematous macular lesions that progress to vesicles and then to pustules, crusts, and scabs. The distribution is characteristic; first lesions appear on the face, trunk, and extremities and progress centrifugally, all in the same stage of development. As the lesions become filled with pus, they develop a central umbilication and begin to crust and scab early in the second week. The scabs separate and fall off after ~3–4 weeks. More-serious forms of the disease include (1) confluent forms, in which a large part of the body is covered with lesions that coalesce; (2) a flat form, in which pustular lesions never develop; and (3) a hemorrhagic form, in which disseminated intravascular coagulation produces life-threatening hemorrhages throughout the body. In all 3 of these forms, the mortality rate approaches or equals 100%.

The majority of patients with smallpox recover, but death occurs in up to 50% of cases in unvaccinated individuals and, much less frequently, in vaccinated individuals, yielding an overall mortality rate of ~30%. Young children, elderly individuals, pregnant women, and (presumably) immunocompromised persons have the highest rates of morbidity and mortality. Vaccination within 2–3 days of exposure may protect against disease, and vaccination within 4–5 days may protect against death [5, 7].

Smallpox is most likely to spread from one person to another during the early phases of the rash, at which time viral shedding from the ulcerative lesions in the oral and pharyngeal mucosa is greatest. Some risk of transmission lasts until all scabs have fallen off, but epidemiologic evidence suggests that most transmission occurs in the first week of illness. Patients with smallpox are quite ill and, beginning soon after the onset of the prodrome, rarely circulate widely outside of home or the hospital sickbed. The reader is referred to other sources for a complete review of the virus and the disease forms that it produces [5, 7].

IMMUNITY AGAINST SMALLPOX

Ancient healers knew that smallpox could be prevented by transferring pustular material from a patient with the disease to an uninfected individual. Many methods were used, and the term “variolation” was applied to the technique [7]. The Chinese used bamboo splinters or batting dipped in pus and placed under or into the nasal mucosa; others placed a scab from an infected patient over the scarified skin of a recipient to effect transfer. This practice, which was in use before the late 18th century, was controversial, because some who were variolated developed fatal smallpox or transmitted the infection to other persons. Eventually, the practice was discontinued, and vaccination became the vogue.

The principle behind vaccination was first reported by Jenner [8] in 1796 after the observation that milkmaids infected with cowpox virus were resistant to infection with smallpox virus (i.e., that infection with a related, but not identical, virus affords protection against the natural disease). In the interim between that epochal discovery and the later practice of vaccination, the virus used underwent multiple transfers. The strains of vaccinia virus in current use are quite unlike cowpox, but their origin is unclear [8]. In the 20th century, strains of vaccinia virus were administered throughout the world, and this practice resulted in the eradication of smallpox [1].

The specific mechanisms that result in immunity have not been well documented. Studies conducted in an era with less sophisticated immunologic techniques have suggested that both antibody and cell-mediated immune function are stimulated by smallpox vaccination, but no surrogate test for clinical protection has been established [9–11]. It is clear that both antibody and cell-mediated immunity result from successful vaccination; >95% of primary vaccinees have detectable neutralizing antibody at a titer of $\geq 1:10$ within 1–2 weeks after immunization, and strong vaccinia virus-specific CD8⁺ cytotoxic T lymphocytes and IFN- γ -producing T cell responses have been detected [12]. The current idea that recovery from smallpox is associated with intact cell-mediated immune (T cell/cytokine) function is based on laboratory studies and clinical experience with vaccinia. Viremia

is diminished or eliminated by intact antibody or B cell immune competence [12, 13].

Protection against disease after primary vaccination begins to fade after 5 years and is probably negligible after 20 years, if the individual has not received additional vaccinations [5, 7]. Successful revaccination on ≥ 1 occasion probably provides residual immunity that may persist for ≥ 30 years [14–16]. Although such immunity may protect against a fatal outcome, it may not protect against the development of a milder form of smallpox. Mack and colleagues [17, 18] studied 680 patients with smallpox and found that the mortality rate was 52% among those who had never been vaccinated, 1.7% among those who had been vaccinated within 10 years, and 11% among those who had been vaccinated ≥ 20 years ago. Earlier studies cited by Fenner et al. [5] and Dixon [7] indicate similar trends. It appears that significant residual immunity is present in any group of vaccinees after primary immunization and reimmunization but that it is impossible to document any given individual's degree of immunity with currently available techniques.

Epidemiological evidence indicates that vaccination within 2–3 days after exposure to smallpox can result in protection against the disease and that vaccination within 4–5 days may protect against a fatal outcome [5, 7]. The rapid replication of the vaccinia virus dermally and in regional lymph nodes, with resultant rapid induction of immunity, may account for this protection.

SMALLPOX VACCINE(S)

Smallpox vaccine is used only to protect against orthopoxviruses, including smallpox. The idea that it may be used to treat such conditions as warts and recurrent herpes has no basis in fact. Use of vaccine for these reasons is fraught with the possibility of adverse events and is of no benefit to the patient. Smallpox vaccine must not be used for these purposes.

Smallpox vaccine is prepared solely from live vaccinia virus and does not contain variola virus (the virus that causes smallpox) or the cowpox virus [5]. Vaccinia virus is a member of the orthopox virus family, which also includes smallpox (variola), cowpox, monkeypox, camelpox, gerbilpox, and mousepox (ectromelia) viruses and others. The origin of the many current strains of vaccinia virus is obscure; further details can be found in Fenner et al. [5] and Dixon [7]. When vaccinia virus is inoculated into the superficial layers of the skin, the virus grows and induces an immune reaction that protects against smallpox. The reaction that follows is termed “a take,” or “primary reaction” from the first vaccination and a “major reaction” from additional vaccinations. Virus implanted too deeply or without sufficient penetration of the external layer of the skin does not result in infection, a circumstance that is termed “no take.”

Currently, only calf-lymph vaccine (Dryvax; Wyeth Laboratories) is licensed in the United States. Acambis/Baxter and other companies are preparing tissue culture vaccines that are anticipated to be licensed by 2004, if clinical testing demonstrates equivalency to the calf-lymph vaccine. The licensed vaccine to be used in current vaccination efforts is a stored calf-lymph vaccine manufactured in the 1970s (Dryvax) that is freeze dried (lyophilized) [19]. Dryvax was produced by infection of skin of calves using the New York City Board of Health (NYCBOH) strain as seed virus. Present stocks of vaccine are held by the Centers for Disease Control and Prevention (CDC) in the National Stockpile and are distributed as indicated. The lyophilized undiluted vaccine, when reconstituted, contains ~ 100 million living vaccinia viruses/mL and not more than 10 nonpathogenic viable bacteria/mL. Dryvax must be reconstituted before use. The licensed diluent contains 50% glycerin and 0.25% phenol.

There are 15 million doses of undiluted vaccine stored at the CDC. Although Dryvax will be used in its undiluted concentration, it can be diluted 1:5; recent experimental evidence has shown that this strength of vaccine is sufficient to ensure take rates of almost 100% among previously unimmunized individuals [20, 21]. The 14 million doses stored at the CDC, if diluted in this fashion, could immunize as many as 70 million persons. A similarly prepared calf-lymph vaccine (85 million doses) was produced by Aventis-Pasteur in the 1950s. It has been tested and found to be fully potent, and, like Dryvax, it can be diluted 1:5. It is a liquid preparation and is in the National Stockpile. Together, these vaccine preparations could provide protection for the entire population if a smallpox outbreak occurred before licensure of the tissue culture vaccine(s). The CDC has distributed vaccine to strategic holding centers throughout the United States. These supplies of vaccine are being used currently to vaccinate those for whom the vaccine is recommended. Dryvax has been used in the recent past to immunize laboratory workers.

The packaging of the vaccine could be mistaken for a parenteral dosage form. *Smallpox vaccine must not be injected subcutaneously, intramuscularly, or intravenously.* Each vaccine lot may contain antibiotics and preservatives. Specific allergies to these products may occur. An appropriate history of such allergies should be obtained from prospective vaccinees and may indicate against vaccine administration if no smallpox outbreak is taking place. If smallpox is present and the risk of contact is great, the vaccine could be administered to individuals with a history of allergies to these components in combination with an appropriate antihistamine or other medication. Currently, Dryvax contains not more than 100 U of polymyxin B sulfate, 200 μg of dihydrostreptomycin sulfate, 200 μg of chlortetracycline hydrochloride, and 100 μg of neomycin sulfate.

Acambis/Baxter Laboratories is manufacturing 2 tissue cul-

ture cell vaccines [19, 22]. The 2 cell lines selected are Vero monkey kidney and human fibroblast (MRC5) tissue cultures. The NYCBOH vaccinia virus strain is the seed virus. The Vero cell culture vaccine is now undergoing phase II testing and is expected to be licensed in 2004. This preparation will supplant the calf-lymph vaccine for future use.

RECOMMENDED VACCINATION METHOD

Screening

Before any smallpox vaccination is done, all potential vaccinees and their contacts must be screened for contraindications to smallpox vaccination. The first step is to obtain an adequate history from the potential vaccinee to identify the major areas of susceptibility to adverse events. For a more complete discussion, refer to the individual descriptions of adverse events elsewhere [4, 23]. Individuals with whom the potential vaccinee has had contact and who are susceptible to adverse events must be identified to avoid inadvertent contact transplantation to that individual from the vaccinee and to ensure that the vaccinee avoids intimate contact with the individual until scar tissue forms, generally 2–3 weeks after vaccination [24].

Known Contraindications to Vaccination

Contraindications to smallpox vaccination apply only if the virus has not been introduced into the environment; if a bioterrorist attack has occurred, there are no contraindications to vaccination of exposed individuals.

Immunodeficiency. Any immune defect is an absolute contraindication to vaccination in the absence of a smallpox outbreak. T cell defects appear to be the major susceptibility factor, although it has been reported that some individuals with pure B cell defects have experienced major complications. Most of what is known about adverse events is based on rudimentary information obtained at a time when there were fewer susceptible persons in the population, when much less was known about immunologic systems, and when methods of measuring immune function were less sophisticated than they currently are.

Certain skin disorders. Much of the older literature on diffuse vaccinia virus infection in diseased skin uses the term “eczema” to describe a number of dermatoses that make a patient susceptible to implantation of vaccinia virus. True atopic dermatitis, as well as other widespread skin disruptions, is a contraindication to smallpox vaccination in the absence of a smallpox outbreak. There is evidence that some individuals with inactive or “healed” atopic dermatitis could become infected through exposure to vaccinia virus. Vaccinia virus infections may be less serious in individuals with skin disorders of a lesser magnitude than florid atopic dermatitis. This is a difficult clinical decision, and clear guidelines are desirable. However, there are none that have been developed on the basis

of prior experience. Clinical judgment about risks and benefits must be exercised to determine whether such individuals should be vaccinated. The degree of skin involvement, the proximity of disrupted skin to the vaccination site, and the capacity of the individual to exercise restraint in manipulating the vaccination site and in practicing good hygiene are factors that may be taken into account in making a decision.

Ocular or periorbital disease. Any inflammatory or disruptive disorder of the cornea, conjunctiva, or periorbital skin may predispose the individual to implantation of vaccinia virus. Pruritic lesions of eye structures or surrounding skin, because of the tendency of persons with such lesions to rub the eye area, might increase the chance that contact transfer of vaccinia virus will occur. The use of cortisone to treat such inflammatory disorders constitutes a contraindication to vaccination.

Immunosuppressive therapy. Drugs that diminish T cell capacity can predispose the individual to adverse events. Because so many of these medications were not in use during the smallpox vaccination era, little specific information is available about dosage, type, and routes of administration in relation to susceptibility to an adverse event. Judgments will have to be made on the basis of the degree of T cell deficiency resulting from such treatment.

HIV infection and AIDS. HIV infection did not occur when smallpox vaccination was prevalent. Individuals with HIV infection and AIDS can be assumed to be at some undetermined risk for adverse events. Limited information is available about the specific immunologic susceptibility of these individuals to vaccination. There is a report of progressive vaccinia in a soldier who was HIV positive; neither his HIV status nor the degree of T cell deficiency at the time that he was vaccinated is known [25]. Bartlett [26] has suggested that the CD4⁺ cell count may be the best measure that is currently available for predicting risk. Judging by experience with other infectious agents, a CD4⁺ cell count of <200 cells/mm³ is the accepted threshold for defining susceptibility.

Other possible susceptibility factors. There are no certain contraindications or precautions associated with the use of smallpox vaccine other than those listed above. In the 1960s, cardiac complications after smallpox vaccination were not thought to be significant, although they were reported in some European literature. The emergence of myopericarditis in a number of individuals who received vaccine as part of the vaccination of civilians and military personnel in 2002 has led to the belief that these events truly are adverse outcomes of smallpox vaccination [27]. Most of these patients had very mild disease and returned to normal activities within 7–10 days. Whether long-term consequences exist is not known. None have been identified so far, and no susceptibility criteria are known.

On the other hand, some deaths resulting from coronary



Figure 1. Bifurcated needle for smallpox vaccination. A needle is shown both empty and containing vaccine in the bifurcation.

artery-related disease occurring within 1 month after vaccination appear to be only temporally related to vaccination, rather than being caused by the vaccine itself. The CDC has cautiously recommended that individuals at increased risk of cardiac disease be granted medical deferrals for smallpox vaccination.

Pregnancy. Pregnant women should not receive the vaccine unless the risk of contracting smallpox is high.

SMALLPOX VACCINATION IN THE PRESENCE AND ABSENCE OF SMALLPOX IN THE ENVIRONMENT

In the absence of smallpox in the community, smallpox vaccine should not be administered to any individual with known contraindications or who has close contact with anyone with known contraindications. If reintroduction of smallpox occurs, these recommendations may be modified, depending on the risk of infection of individuals with known contraindications. Exposure to a patient with smallpox and high risk of exposure are the criteria used to determine whether an individual with a known contraindication should be vaccinated. This is a complicated issue that requires clinical judgment to balance the risk of an adverse event against the risk of smallpox in an individual who has a contraindication to vaccination. For example, a pregnant woman has little risk associated with vaccination, and her fetus has a remote risk. On the other hand, smallpox that occurs during pregnancy can result in hemorrhagic disease and death. In this instance, it may be prudent to vaccinate a woman who is exposed to smallpox, despite the small risk to her fetus.

Individuals with atopic dermatitis who are exposed to smallpox may be vaccinated, with the prospect of vaccinia immune globulin administration if they develop eczema vaccinatum; the risk of smallpox is greater than the anticipated risk of vaccinia, given that the latter can be treated. Persons with severe T cell deficiencies almost certainly will develop progressive vaccinia if vaccinated, but it is assumed that smallpox also poses a major risk. Such individuals must be counseled to avoid exposure at all costs, so that the need for vaccination can be avoided. If necessary, they should be sequestered for the duration of the outbreak.

As can be seen from this brief discussion, decisions about whether to vaccinate are complex and must be based on individual risk/benefit ratios balancing vaccination against smallpox. A prudent and careful assessment is necessary in each instance to make this decision.

Vaccination Method: Primary Vaccination and Revaccination

Multiple-puncture vaccination. In the past, vaccination was performed by the scratch or multiple-puncture method. In some mass-vaccination situations, a compressed-air “gun” device was used, but this is not contemplated for modern vaccinations. During the global eradication effort, the bifurcated needle was universally used for multiple-puncture vaccination [1, 5]. This method is recommended for use in the United States and by the World Health Organization [19]. Each bifurcated needle is sterile and individually wrapped. The needle is designed to hold a minute drop of vaccine (figure 1). Sufficient supplies of needles are available for all contemplated vaccination plans.



Figure 2. The correct sequence for smallpox vaccination. *Upper left*, Dipping of the needle into a vaccine vial. *Upper right*, Proper position for 3–15 insertions. *Middle left*, Appearance of site after successful vaccination. *Middle right*, Wiping of excess vaccine. *Lower left*, Safe discarding of gauze. *Lower right*, Appropriate covering for vaccination site (semipermeable membrane shown) for health care workers. Others need nothing or a loosely applied sterile gauze pad.

Site of vaccination. The preferred site for vaccination is the deltoid area on the upper arm. Traditionally, the vaccination is done on the nondominant arm to avoid limitation of use, should there be a local reaction of sufficient severity. In the past, other sites were sometimes used because of cosmetic concerns. Placement of the vaccination at sites likely to be heated or constrained (such as those under several layers of clothing) may result in maceration and increased local reactions. Place-

ment of the vaccination in areas of the skin likely to be contaminated by bacteria (e.g., the buttock or inner thighs) could result in bacterial infection.

Preferred technique. Figure 2 shows the preferred technique for both primary vaccination and revaccination.

1. Skin preparation. The site for insertion should be clean, with no other skin preparation required. During the eradication



Figure 3. Progression of primary vaccination. *Upper left*, Lesion at day 5 after vaccination; *upper right*, day 8; *lower left*, day 10; *lower right*, day 14.

campaign, almost all were vaccinated with no skin preparation. In the past, some vaccinators used acetone to clean the skin (the acetone should be given time to evaporate before vaccination); others have used soap and water. Under no circumstances should alcohol be applied to the skin before vaccination. Skin preparation with alcohol may result in fewer takes, because residual amounts of alcohol on the skin inactivate the vaccine virus.

2. Preparation of needle. The needle simply is dipped into a multiple-dose vial; the bifurcated needle is designed to hold a droplet of vaccine by capillary action of sufficient size to ensure a take.

3. Insertion of needle. Three to 15 perpendicular insertions within an area ~5 mm in diameter are made. Three insertions are recommended for primary vaccination and 15 for revaccination. The needle is held perpendicular to the site of insertion. The wrist of the vaccinator should be maintained in a firm position, which can be accomplished by resting the wrist on the arm of the vaccinee or another firm support. Perpendicular insertions are made in rapid succession in an area ~5 mm in diameter. Strokes should be vigorous enough to evoke a trace of blood at the site after 15–30 s. When infants or

children are vaccinated, it may be necessary to restrain the child to avoid accidents during administration.

4. Absorption of excess vaccine. After vaccination, excess vaccine should be absorbed with sterile gauze. The gauze should be discarded in a safe manner (usually in a hazardous-waste receptacle) to avoid contaminating the site or infecting others. In young children, many autoinoculations have occurred at the time of vaccination from droplets of vaccine left on the skin.

5. Covering the vaccination site. Although some prefer to leave the vaccination site uncovered, exudate from the lesion may soil clothing and is infectious. Therefore, some covering is now recommended. Sterile gauze can be loosely held down by tape. In recent trials, use of a semipermeable occlusive dressing without underlying gauze appears to have resulted in a macerated lesion in a number of vaccinees and may increase the risk of satellite lesions at the primary site and, possibly, secondary bacterial infection [20].

The currently recommended method for health care workers is the use of a doubled-over sterile gauze pad placed directly over the vaccination site and covered by a semipermeable membranous covering. This technique allows absorption of purulent material, both reducing maceration and diminishing viral yield

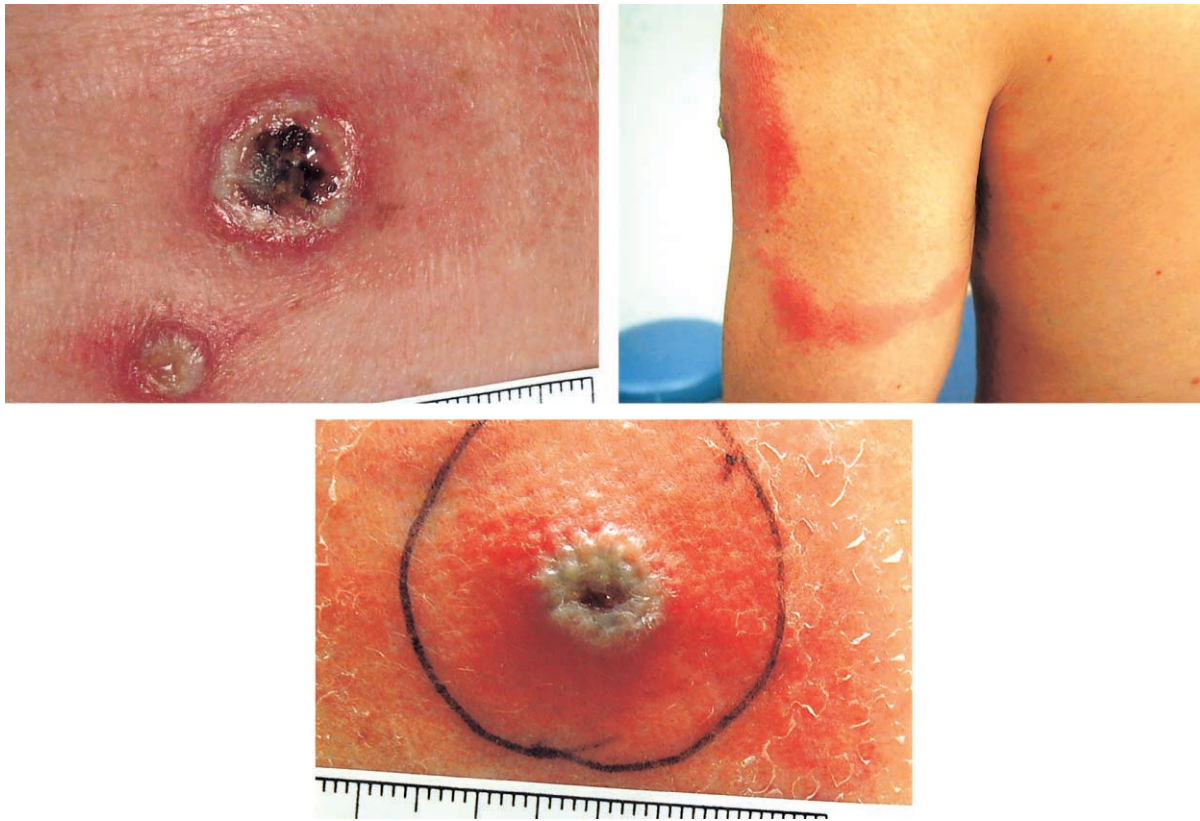


Figure 4. Normal reactions after primary vaccination. *Top left*, Satellite lesions at site; *top right*, viral lymphangitis; *bottom*, robust reaction and extensive edema of the upper arm.

at the surface of the overlying covering. The dressing should be examined by the patient and changed several times, depending on the amount of exudate and skin irritation. This technique may help eliminate dissemination of infection in high-risk areas, such as a health care setting. Normally, only a single, loosely applied gauze pad is necessary.

6. Instructions to the vaccinee. The vaccinee should minimize the risk of contact transmission of the virus by avoiding rubbing or scratching of the vaccination site. Gauze used to cover the site must be discarded in a safe fashion. The gauze must be put into a plastic bag and placed in the trash.

Each vaccinee and anyone caring for the vaccination site should wash their hands thoroughly after handling gauze or otherwise touching the site. Vaccinia virus can contaminate the vaccinee's hands or the skin and mucosa of others with whom the vaccinee comes into contact. Advise vaccinees or guardians that virus can be transmitted until a scab has formed at the vaccination site.

7. Inspection of the vaccination site. The vaccination site should be inspected 6–8 days after vaccination of both primary vaccinees and revaccinees, to ensure that a take has occurred. In the past, when vaccination was routine, a verbal report was sufficient to record a take; currently, in the context of pre-event

limited vaccinations, the practice is to have the vaccinee revisit for inspection. Should mass vaccination be reinstated, a return to verbal reporting may become necessary because of the sheer volume of vaccinations performed in a short period of time.

8. Record keeping. Accurate records must be maintained of the timing, site, vaccine, and outcome of vaccination (e.g., successful) for each vaccinee. This information should be readily available to both the individual vaccinee and public health departments, should smallpox be introduced into the environment at any time in the future, so that immune status and the potential need for revaccination can be determined

NORMAL VACCINATIONS, EXPECTED EVENTS, AND ADVERSE EVENTS

The normal progression of a primary vaccination (figure 3) is as follows: There is no visible skin reaction for the first 3–4 days. On approximately day 3–4, a papule appears, which progresses to a vesicle with surrounding erythema at approximately day 5–6. By day 7–9, the center of the vesicle umbilicates and pustulates. The pustule crusts, and a dark brown or black scab

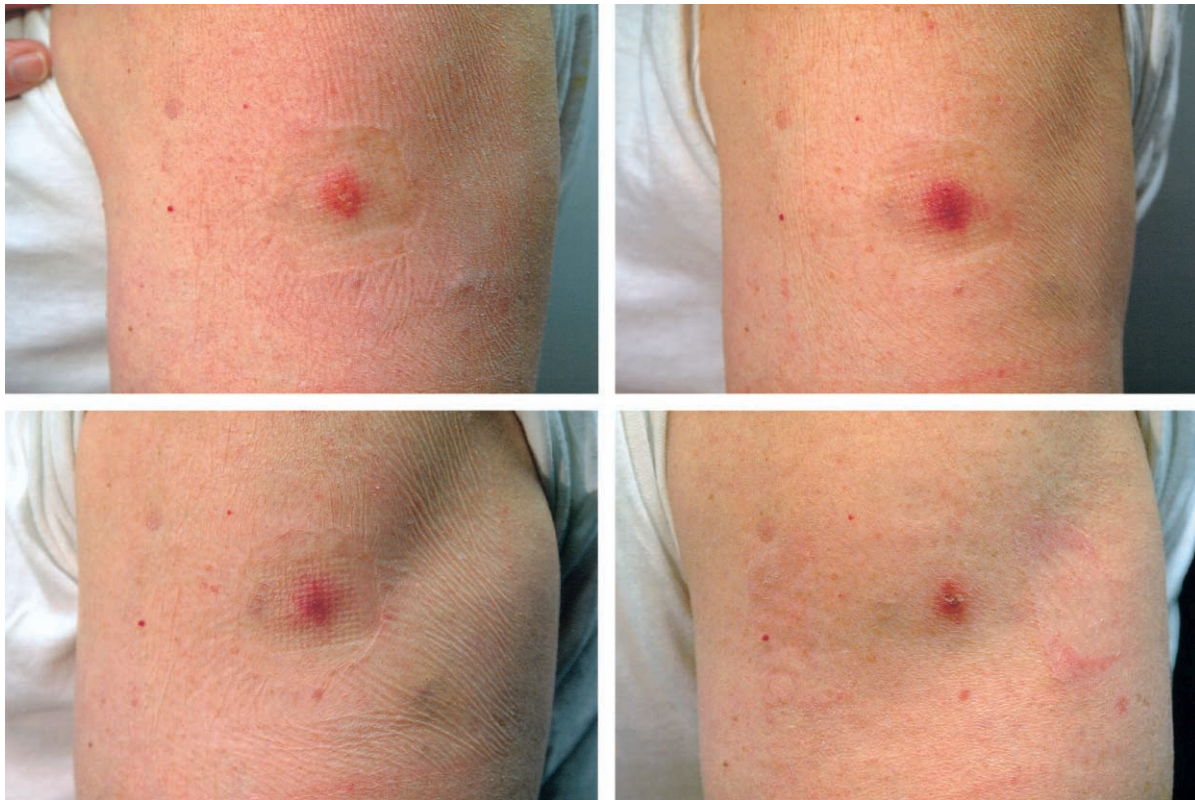


Figure 5. Major reaction after revaccination (in a 69-year-old patient who received primary vaccination 60 years before revaccination). *Upper left*, 3 days after revaccination; *upper right*, 7 days; *lower left*, 10 days; *lower right*, 14 days.

forms by approximately day 12, which detaches in 2.5–3 weeks, leaving a scar.

In some previously unvaccinated individuals, vaccination may result in no reaction. It should be assumed that the individual is not immune, and at least 3 attempts should be made to achieve a primary take, with careful attention to correct technique.

Approximately 1 week after successful vaccination, certain systemic symptoms are expected in some vaccinees [7, 20, 21]. These include a temperature $>37.7^{\circ}\text{C}$ in the first 3 weeks after vaccination (2%–16%); malaise, myalgia, headache, chills, nausea, and fatigue (0.3%–37%); soreness at the vaccination site (almost universal); local lymphadenopathy (25%–50%); and intense erythema ringing the vaccination site (common).

Expected and normal local events occur infrequently after vaccination (in 2%–6% of vaccinees in clinical trials) and require only symptomatic treatment (figure 4) [20, 21]. These include the appearance of satellite lesions within ~ 2.5 cm (1 in) of the primary vaccination site; viral lymphangitis with a visible track toward regional lymph nodes in the axilla (which must be differentiated from bacterial infection); local edema, often enlarging the upper arm's circumference and causing discomfort and pain; and intense inflammation surrounding the papule (viral cellulitis).

REVACCINATION SEQUENCES

The response to revaccination depends on the degree of residual immunity. The following classification is slightly modified from the World Health Organization definitions [28].

The patient may experience a normal primary take, indicating no residual immunity. Most revaccinees will have a major reaction—an area of definite induration or congestion surrounding a central lesion that may scab or ulcerate 6–8 days after vaccination (figure 5). Erythema observable on days 6–8 after revaccination is proof that viral replication has taken place and is counted as a major reaction. The presence of induration, ulceration, or a scab is even stronger evidence of a major reaction. Studies are under way that are using modern immunologic techniques to increase understanding of the meaning of these various reactions. A transient erythema that is not observable on day 6–8 probably represents a hypersensitivity reaction, and the vaccinee should be considered not immune. Any other reaction or no reaction at the site should be considered equivocal and reimmunization attempted.

Equivocal reactions do not imply immunity. In a highly immune individual, a red, itchy papule, similar that seen after a positive response to tuberculin skin testing, will occur, demonstrating a vigorous cell-mediated immune response without

viral replication. This will resolve fully within 3–4 days. Unfortunately, a similar reaction can occur when poor technique or low-potency vaccine is used or when the vaccinia virus is inactivated by alcohol preparation of the skin. Revaccination using recently reconstituted vaccine of assured potency, 15 multiple punctures, and vigorous technique is indicated; at least 1 attempt should be made, and some recommend 3 attempts. The CDC suggests expert consultation if the first additional attempt fails.

Lack of a take does not imply immunity; poor technique, low-potency vaccine, and inactivation of the virus (e.g., through use of alcohol to prepare the site) are common causes. Revaccination using vaccine of known potency is indicated.

MAINTAINING IMMUNITY

Routine revaccinations were recommended routinely every 3–10 years in the past, because immunity waned after an indefinite period for any given individual to a point at which immunity was no longer protective. Currently, public health personnel, health care workers, and first responders are being vaccinated. Vaccination of the civilian population in the absence of a smallpox outbreak is not recommended. If no smallpox outbreak occurs, it would be prudent to maintain immunity of those immunized at present by revaccination every 5–10 years. Of course, if a smallpox outbreak were to occur and mass immunization were done, then all primary vaccinees would be revaccinated, to maintain immunity.

Acknowledgments

We appreciate the assistance of John Treanor (Departments of Medicine and Microbiology/Immunology, University of Rochester, Rochester, NY); Cynthia Fay and the staff at LogicalImages, Inc. (Rochester); Shirley Fulginiti; and the Department of Family and Community Medicine and the Dean's Office, University of Arizona Health Sciences Center (Tucson).

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