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SMALLPOX VACCINE

Because of concerns about the possibility of bioterrorism involving smallpox, the US government is reinstating smallpox vaccination (www.bt.cdc.gov/agent/smallpox/index.asp; www.idsociety.org/bt/toc.htm). Vaccination is currently expected to proceed in three phases: the military and hospital smallpox response teams first, other health care workers, police and firefighters second, and the general public in the third phase. Except for the military, vaccination will be voluntary.

THE DISEASE – History – Smallpox was a world-wide infectious disease, affecting only humans, until it was eradicated in 1977 by intensive case finding and vaccination. The last case in the US occurred in 1949. Smallpox vaccination in the US was discontinued in civilians in 1972 and in the military in 1990.

Epidemiology – Smallpox is transmitted by inhalation of the causative variola virus (an orthopoxvirus) in droplets or aerosols from the respiratory tract, or by contact with skin lesions of infected patients or their bedding or clothing. The incubation period is 7 to 17 days, with an average of 12 days. The disease begins with fever and prostration for 2 to 4 days, followed by the rash, which lasts for weeks with slow evolution from papules to vesicles, then pustules and finally scabs, all at the same stage in any one area. Disease transmission may occur late in the prodrome but mainly occurs during the rash, and diminishes as the lesions scab. Transmission is most common in families; about 50% of unvaccinated family members become infected. In the past the mortality rate of smallpox was 20%-30% in unvaccinated populations; many survivors were left with severe scarring, and some with blindness from ocular involvement. Natural infection confers lifelong immunity.

SMALLPOX VACCINE – Formulations – Smallpox vaccine is a suspension of live vaccinia virus, a virus that apparently evolved from serial passage of cowpox. The vaccine to be used in the first and second phases of vaccination (*Dryvax* – Wyeth) is a lyophilized preparation derived from the lymph of calves that had been inoculated with vaccinia virus. According to the CDC, *Dryvax* is already available in adequate amounts for Phases I and II. It contains small amounts of polymyxin B, dihydrostreptomycin, chlortetracycline and neomycin to prevent bacterial contamination. A similar calf-derived vaccine produced by Aventis-Pasteur years ago is also available as a reserve supply. A third vaccine produced by Acambis-Baxter using the same strain of vaccinia virus as in *Dryvax*, but grown in monkey kidney and human fibroblast cells, is expected to be available in sufficient amounts to vaccinate the entire US population in 2004.

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Vaccination — Smallpox vaccine is administered by intracutaneous inoculation using a bifurcated needle to puncture the skin with 15 perpendicular strokes within an area 5 mm in diameter. The punctures are made with just enough pressure to produce a small amount of blood on the skin surface. In the past, the vaccination site was generally left uncovered, but current plans for Phase I call for it to be covered with both gauze to absorb liquid and a semi-permeable membrane such as an *Opsite* dressing to prevent spread of the virus. A successful ("primary") vaccination (called a "take", indicating that good immunity to variola infection will result) is suggested by the appearance of a well-formed pustule 6 to 11 days after vaccination followed by scabbing. A "major reaction" suggesting residual immunity in a previously vaccinated person is indicated by more rapid evolution of the lesion to a vesicle or pustule at 3 to 4 days with scabbing or ulceration at 6 to 8 days. Equivocal reactions, including rapid development of erythema without evolution to a definite vesicle or pustule, may indicate some residual immunity from past vaccination or an allergy to vaccine components.

Efficacy — No randomized prospective controlled trials have documented the efficacy of smallpox vaccine. Retrospective analyses in families with an index case have suggested greater than 90% protection against disease in those who were vaccinated before exposure. Vaccination can decrease the rate of severe or fatal smallpox if administered during the first 4 days, and possibly as late as 10 days, after exposure.

Duration of Immunity — Viral neutralizing antibodies appear in serum 10 to 13 days after vaccination and can persist for decades. Limited *in vitro* data indicate that cell-mediated immunity to vaccinia virus also persists for decades. The duration of clinical immunity induced by primary vaccination is uncertain. A study of an epidemic in Liverpool in 1902-03 suggested protection for decades against fatal or severe smallpox following one vaccination in childhood ([J Cohen, Science 2001; 294:985](#)), but the endemicity of smallpox during that time may have led to multiple natural boosts in immunity. Most experts believe that immunity after primary vaccination wanes after 5 years, but residual protection against fatal disease may persist for many years. Revaccination is considered likely to provide longer-lasting immunity.

ADVERSE EFFECTS — This live vaccine has the potential to cause many adverse effects ([SE Frey et al, N Engl J Med 2002; 346:1275](#); [KA Sepkowitz, N Engl J Med 2003; 348:5](#)). Historically, about one death occurred per million primary vaccinations. Local reactions include satellite lesions, focal inflammation and lymphadenopathy. Brief systemic reactions typical of a viral illness (fever, muscle aches, headache, nausea and fatigue) are common after primary vaccination. Accidental inoculation of the vaccine virus into other skin sites or into the eyes, where it may cause sight-threatening keratitis, can occur. Generalized vaccinia, erythema multiforme, post-vaccinial encephalitis (more common in infants) and eczema vaccinatum (occurring in areas of healed as well as active eczema/atopic dermatitis) can also occur ([RJ Engler et al, J Allergy Clin Immunol 2002; 110:357](#)). Among contacts of vaccinees, complications are most frequently the result of accidental inoculation. The risk of eczema vaccinatum may be greater than in the past because eczema/atopic dermatitis is more common, occurring in up to 10%-20% of the population. Progressive vaccinia (vaccinia necrosum), which occurs mainly in patients with depressed cell-mediated immunity, might also be more common now because of HIV infection and widespread use of immunosuppressive drugs. Rare cases of fatal vaccinia have been reported after vaccination during pregnancy.

EXCLUSIONS — Smallpox vaccine currently is not recommended for children less than 18 years old except in an emergency. Vaccination is contraindicated in infants, pregnant women, patients with immunodeficiencies or receiving immunosuppressive therapy, and

those with household members whose immunity is compromised. It is also contraindicated in patients with a history of atopic dermatitis/eczema, regardless of current activity, and those with household contacts who have eczema. Patients with other extensive skin diseases (acne, burns, wounds, recent incisions, impetigo, contact dermatitis or psoriasis), inflammatory eye diseases or allergy to the antibiotics contained in the vaccine also should not be vaccinated. However, there is no contraindication to use of smallpox vaccine in anyone who actually has been exposed to smallpox.

MANAGEMENT OF COMPLICATIONS – Vaccinia Immune Globulin – Vaccinia immune globulin (VIG – Baxter) is currently available in limited amounts from the CDC as an investigational drug. Its efficacy has never been evaluated in adequate controlled trials. VIG is injected into the buttocks or anterior/lateral thigh in doses of 0.6 ml/kg, and can be repeated every 2 to 3 days for severe vaccination complications with continued activity. There is little evidence that VIG is effective in patients with progressive vaccinia, and it is not useful for the treatment of post-vaccinial encephalitis. In vaccinia keratitis VIG may increase damage to the cornea; trifluridine (*Viroptic*), a pyrimidine nucleoside, has been used for this complication.

Cidofovir (*Vistide*) ([Medical Letter 1997; 39:14](#)) is a nucleotide analog that has been used to treat cytomegalovirus (CMV) infections and also has activity against pox viruses. Cidofovir is active *in vitro* against variola virus and has shown good activity in animals against vaccinia infections. Cidofovir is nephrotoxic, and can also cause neutropenia, metabolic acidosis, iritis, uveitis and ocular hypotony. It has a long half-life; for treatment of CMV infection in AIDS patients, it has been given IV once a week or every other week, with oral probenecid and IV saline to decrease the risk of nephrotoxicity. Its use should be strongly considered in patients with progressive vaccinia, severe eczema vaccinatum, generalized vaccinia or extensive accidental inoculation of vaccinia not responding to VIG, or to treat severe cases of smallpox in the event of an outbreak.

Ribavirin (*Virazole; Rebetol; Copegus*) is active against variola virus and vaccinia virus *in vitro* ([E De Clercq, Antiviral Res 2002; 55:1](#)). One case report suggested that IV ribavirin, which is not commercially available in the US, was effective in an immunocompromised patient with progressive vaccinia ([AM Kesson et al, Clin Infect Dis 1997; 25:911](#)).

CONCLUSION – Smallpox vaccination will begin in 2003 in the US military and health care workers. Historically, fatal complications of the vaccine occurred in about 1 per million primary vaccinees. Without vaccination, smallpox has a mortality rate of 20%-30%.

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