

Review Article

*Current Concepts***DIAGNOSIS AND MANAGEMENT
OF SMALLPOX**JOEL G. BREMAN, M.D., D.T.P.H.,
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THE last case of endemic smallpox occurred in Somalia in 1977, and eradication of the disease was declared in 1980. With no natural reservoir, variola virus, which causes smallpox, has existed only in laboratories; indeed, the last case of smallpox was due to infection acquired in a laboratory in the United Kingdom in 1978. During the global program of smallpox eradication, the World Health Organization (WHO) made concerted efforts to decrease the number of laboratories retaining variola virus. On the basis of contacts with all countries and a total of 823 microbiology institutions, 76 such laboratories had been identified by 1978.^{1,2} By 1984, only the Centers for Disease Control and Prevention (CDC), in Atlanta, and the Research Institute of Viral Preparations, in Moscow, retained variola virus isolates. In 1994, the Russian isolates were moved to the State Research Center of Virology and Biotechnology (the Vektor Institute), in Novosibirsk, Russia.

There is concern that variola virus resides outside these laboratories and could be used as a weapon by terrorists. Possible sources are virus in countries that claim that they destroyed their stocks but did not and virus acquired from laboratories in the former Soviet Union.^{3,4} An accidental or deliberate release of smallpox could cause a major epidemic.⁵⁻⁷ Because vaccination against smallpox has not been performed routinely in the United States since 1972 and in the rest of the world since about 1982, there is now a large population of susceptible persons.¹ Thus, if an outbreak occurred, prompt recognition and institution of control measures would be important.

VIROLOGY

Variola virus belongs to the family Poxviridae, subfamily Chordopoxvirinae, and genus orthopoxvirus,

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which includes vaccinia (smallpox vaccine), monkeypox virus, and several other animal poxviruses that cross-react serologically.^{8,9} The poxviruses contain single, linear, double-stranded DNA molecules of 130- to 375-kb pairs and replicate in cell cytoplasm. They are shaped like bricks on electron micrographs and measure about 300 by 250 by 200 nm.

PATHOGENESIS

Studies of mousepox, rabbitpox, and monkeypox have provided information about the pathogenesis of poxviruses.⁹⁻¹³ The virus enters the respiratory tract, seeding the mucous membranes and passing rapidly into local lymph nodes. After a brief period of viremia, there is a latent period of 4 to 14 days, during which the virus multiplies in the reticuloendothelial system. Another brief period of viremia precedes the prodromal phase. During the prodromal phase, mucous membranes in the mouth and pharynx are infected. The virus invades the capillary epithelium of the dermal layer in skin, leading to the development of lesions (Fig. 1).¹⁴ Oropharyngeal and skin lesions contain abundant viral particles, particularly early in the illness. Virus is also present in urine and conjunctival secretions, with the levels decreasing during convalescence.^{15,16} The spleen, lymph nodes, liver, bone marrow, kidneys, and other viscera may contain large quantities of virus.

The migration of infected macrophages to lymph nodes after the initial infection elicits the production of cytotoxic T cells and B cells; these responses limit the spread of infection. Neutralizing antibodies appear during the first week of illness but are delayed if the infection is severe; hemagglutination-inhibition antibodies are detectable by day 16 of the infection, and complement-fixation antibodies by day 18. Neutralizing antibodies remain present for many years, whereas levels of hemagglutination-inhibition and complement-fixation antibodies begin to decrease after one year.¹ The correlation between humoral antibodies and protection from smallpox is not entirely clear.

CLINICAL MANIFESTATIONS

The incubation period for smallpox is 7 to 17 days (mean, 10 to 12). The prodromal phase, which lasts for two or three days, is characterized by severe headache, backache, and fever, all beginning abruptly.¹⁷ The temperature often rises to more than 40°C and then subsides over a period of two to three days. Enanthema over the tongue, mouth, and orophar-

ynx precedes the rash by a day. The rash begins as small, reddish macules, which become papules with a diameter of 2 to 3 mm over a period of one or two days; after an additional one or two days, the papules become vesicles with a diameter of 2 to 5 mm. The lesions occur first on the face and extremities but gradually cover the body. Pustules that are 4 to 6 mm in diameter develop about four to seven days after the onset of the rash and remain for five to eight days, followed by umbilication and crusting. There may be a second, less pronounced temperature spike five to eight days after the onset of the rash, especially if the patient has a secondary bacterial infection. The crusts begin separating by the second week of the eruption. Smallpox lesions have a peripheral or centrifugal distribution and are generally all at the same stage of development. Lesions on the palms and soles persist the longest. Death from smallpox is ascribed to toxemia, associated with immune complexes, and to hypotension.

After severe smallpox, pockmarks, or pitted lesions, are seen in 65 to 80 percent of survivors.¹ These lesions are common on the face because the large sebaceous glands tend to become infected. Panophthalmitis and blindness from viral keratitis or secondary infection of the eye occurs in about 1 percent of patients. Arthritis develops in up to 2 percent of children who have smallpox; viral infection of the metaphysis of growing bones is thought to be the cause. Encephalitis occurs in less than 1 percent of patients with smallpox. Although cough is not a prominent symptom, the more severe the disease, the greater the likelihood of respiratory complications; pneumonia or bacteremia may result in high mortality.

A useful classification proposed by WHO encompasses five types of smallpox.¹ The classification is based on a study of 3544 patients in India. In that study, the "ordinary" type of smallpox, *variola major* (described above), accounted for nearly 90 percent of cases, with a case fatality rate of 30 percent.^{15,17} The milder, "modified" type accounted for 2 percent of cases in unvaccinated persons and for 25 percent in previously vaccinated persons. The modified cases were rarely fatal; the lesions were fewer, smaller, and more superficial than those in patients with the first type, and they evolved more rapidly. Seven percent of cases were characterized by flat lesions that evolved more slowly than those of *variola major* and that coalesced; the case fatality rate for the flat type was 97 percent among unvaccinated patients. Hemorrhagic smallpox, which is difficult to diagnose, accounted for less than 3 percent of cases; almost all patients with this type of smallpox died within the first seven days of illness. In the Yugoslav outbreak of 1972, a fatal case of hemorrhagic smallpox was misdiagnosed as a penicillin-associated drug eruption. The patient

was treated in four medical institutions and infected 38 persons, 8 of whom died.¹

The last type of smallpox, *variola sine eruptione*, occurs in previously vaccinated contacts or in infants with maternal antibodies. Affected persons are asymptomatic or have a brief rise in temperature, headache, and influenza-like symptoms¹⁸; the transmission of clinical smallpox has not been documented with *variola sine eruptione*.¹⁹ In cases of *variola minor*, which occurs mainly in the Americas and parts of Africa, the disease is mild, causing death in less than 1 percent of patients.²⁰ Infection with smallpox confers lifelong immunity.

DIAGNOSIS

Many eruptive illnesses can be misdiagnosed as smallpox (Table 1). Severe chickenpox is most frequently misdiagnosed as smallpox, especially in adults who have an extensive rash (Table 2). The prodromal phase of chickenpox lasts for one or two days, fever occurs with the onset of the rash, and the eruption is concentrated over the torso; individual lesions are present at different stages and progress from vesicles, crusting within 24 hours. The interval from the initial appearance of lesions to the crusting of all lesions is about four to six days. Although about 75 percent of children in the United States are immunized against chickenpox, more than 1 million cases occur yearly. Human monkeypox, a zoonotic disease, has never occurred outside west and central Africa. The rash of human monkeypox resembles that of smallpox clinically, but patients with monkeypox often have lymphadenopathy, unlike those with smallpox, and monkeypox is not spread easily between humans, although up to four human-to-human chains of transmission have been reported in rare cases.²¹⁻²³

Drug-induced rashes, including erythema multiforme exudativum (the Stevens-Johnson syndrome), can be diagnosed by a careful history taking and examination; sulfonamides cause severe vesicular and bullous rashes. A morbilliform rash on the face due to measles virus (rare in the United States) or coxsackievirus may be confused with early smallpox. Insect bites are often linear, and allergic responses can occur. Patients with the acquired immunodeficiency syndrome may have widespread molluscum contagiosum lesions. Lesions associated with secondary syphilis vary in size and distribution, and the papules do not evolve.

EMERGENCY REPORTING

A possible case of smallpox is a public health emergency and of utmost international concern.^{5,24,25} State health officials should be contacted immediately, and the diagnosis confirmed in a Biological Safety Level 4 laboratory where staff members have been vacci-

nated. The state officials should contact the CDC at any time of the day or night (telephone number, 770-488-7100). The CDC, in turn, will inform the WHO Department of Communicable Diseases Surveillance and Response Unit in Geneva, Switzerland.

After the patient has been isolated, interviews should be conducted to identify contacts. The contacts should be vaccinated as soon as possible and not more than two or three days after exposure. Smallpox vaccination within this period offers substantial protection, which is the rationale, in part, for the current policy of not launching a program of widespread vaccination of health care personnel before an outbreak has occurred.

All health care providers, regardless of their immunization status, should use airborne and contact precautions.^{25,26} Scrapings of skin lesions, papular, vesicular, or pustular fluid, crusts, blood samples, and tonsillar swabbings must be sent to the CDC (or a designated laboratory) after public health officials have been notified.²⁵

There are several methods for confirming the diagnosis; some are specific for variola virus, and others are for orthopoxviruses in general.^{27,28} Specimens can be examined directly for the presence of virions by electron microscopy, and viral antigen can be identified by immunohistochemical studies; the brick shape of the variola virus distinguishes it from varicella-zoster virus (Fig. 2). A polymerase-chain-reaction assay for orthopoxvirus genes can be used to identify variola virus.²⁹⁻³² Isolation of the virus on live-cell cultures, followed by nucleic acid identification of orthopoxvirus species, or growth on chorioallantois, is confirmatory. The results of serologic testing do not differentiate among orthopoxvirus species, and paired serum samples are required to distinguish recent infection from vaccination in the remote past. Newer methods, which detect IgM responses, may enhance the sensitivity and specificity of serologic tests.

EPIDEMIOLOGY

Smallpox spreads primarily through respiratory-droplet nuclei, but infected clothing or bedding can also spread infection.^{1,17} Although smallpox is less transmissible than measles, chickenpox, or influenza,³³ secondary attack rates among unvaccinated contacts range from 37 to 88 percent.^{1,34} Patients are most in-

fectious from the onset of the enanthema through the first 7 to 10 days of rash. Secondary cases are often limited to family members or health care personnel. Patients who have severe disease or who are coughing can transmit large quantities of virus. In Meschede, Germany, 17 persons on three floors of a hospital contracted smallpox from 1 patient during the incubation period³⁵; this extensive outbreak was ascribed to the patient's cough and the low relative humidity and the air currents in the hospital.

The incidence of smallpox is highest during winter and early spring, because aerosolized orthopoxviruses survive longer at lower temperatures and low levels of humidity.^{36,37} Virtually no persons in the United States under the age of 30 years have been vaccinated, and therefore, all such persons are susceptible to smallpox. Some persons who were born before 1972 and were vaccinated may still be partially protected; if exposed, they may have milder disease and may be less likely to transmit it to others.

TREATMENT

A suspect case of smallpox should be managed in a negative-pressure room, if possible, and the patient should be vaccinated, particularly if the illness is in an early stage. Strict respiratory and contact isolation is imperative. When there are many patients, an isolation hospital or other facility should be designated.²⁵ There is no treatment approved by the Food and Drug Administration for orthopoxviruses. Penicillinase-resistant antimicrobial agents should be used if smallpox lesions are secondarily infected, if bacterial infection endangers the eyes, or if the eruption is very dense and widespread. Daily eye rinsing is required in severe cases. Patients need adequate hydration and nutrition, because substantial amounts of fluid and protein can be lost by febrile persons with dense, often weeping lesions. Topical idoxuridine (Dendrid, Herplex, or Stoxil) should be considered for the treatment of corneal lesions, although its efficacy is unproved for smallpox. Cidofovir has been licensed for the treatment of cytomegalovirus.³⁸ Recent studies in animals suggest that cidofovir and its cyclic analogues, given at the time of or immediately after exposure, have promise for the prevention of cowpox, vaccinia, and monkeypox.^{39,40} The drug decreases pulmonary viral levels and pneumonitis in animals with vaccinia or

Figure 1 (facing page). Clinical Manifestations and Pathogenesis of Smallpox and the Immune Response.

Panel A shows the initial phases of infection and the clinical manifestations, which include temperature spikes and progressive skin lesions (photographs of lesions courtesy of Dr. David Heymann, World Health Organization). Panel B shows the pathogenesis of the infection. The photographs at the right-hand side of the panel show the characteristic features of the vesicles caused by smallpox (hematoxylin and eosin, $\times 1040$; reprinted from Strano¹⁴). Panel C shows the immune response to smallpox and the period of infectiousness. HI denotes hemagglutination inhibition, and CF complement fixation.

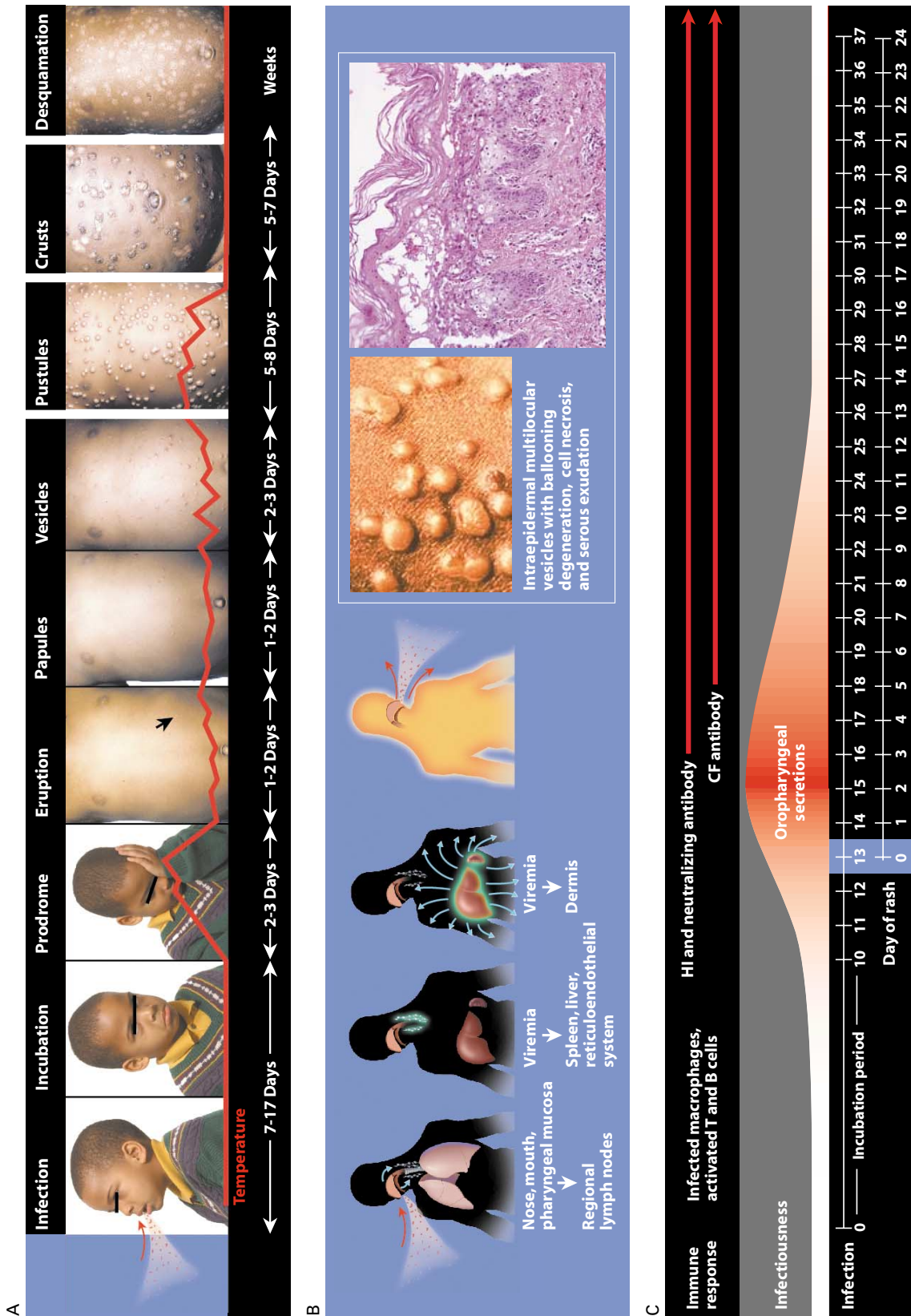


TABLE 1. CAUSES OF PAPULOVESICULAR AND MACULOPAPULAR ERUPTIONS.*

CAUSES OF PAPULOVESICULAR ERUPTIONS	CAUSES OF MACULOPAPULAR ERUPTIONS
Atypical measles (rubeola)	AIDS (HIV)
Acne†	Adenoviruses
Chickenpox (varicella)†	Arboviruses (dengue, chikungunya, and o'nyong-nyong)
Coxsackievirus infections (hand-foot-and-mouth disease and coxsackievirus A16)	Atypical measles (rubeola)
Dermatitis herpetiformis	Cytomegalovirus infection
Drug eruptions†	Drug eruptions†
Eczema herpeticum (herpes simplex virus)	Epstein-Barr virus
Generalized vaccinia and eczema vaccinatum (vaccinia)†	Enteroviral infections (echoviruses 1-7, 9, 11, 12, 14, 16, 18-20, 25, 30 and coxsackieviruses A4, A6, A10, A16, B2, B3, B5)
Impetigo	Erythema infectiosum (parvovirus B19)
Insect bites†	Exanthem infectiosum (herpesvirus 6)
Molluscum contagiosum	German measles (rubella)
Monkeypox†	Infectious mononucleosis
Papular urticaria	Measles (rubeola)
Pemphigus	Meningococemia
Rickettsialpox (<i>Rickettsia akari</i>)	Mucocutaneous lymph-node syndrome (Kawasaki's disease)
Shingles (varicella-zoster virus)	<i>Mycoplasma pneumoniae</i>
Yaws (<i>Treponema pallidum</i> , subspecies <i>pertenue</i>)	Roseola infantum
Smallpox (<i>Variola major</i> and <i>V. minor</i>)	Scalded skin syndrome (<i>Staphylococcus aureus</i>)
	Scarlet fever (<i>Streptococcus pyogenes</i>)
	Sunburn
	Secondary syphilis (<i>T. pallidum</i> subspecies <i>pallidum</i>)†
	Rat-bite fever (<i>Streptobacillus moniliformis</i>)
	Reoviruses
	Rocky Mountain spotted fever (<i>R. rickettsii</i>)
	Toxic erythemas
	Toxic shock syndrome (<i>S. aureus</i> , phage group I)
	Toxoplasmosis
	Typhus and tick fevers (<i>R. prowazekii</i> , <i>R. typhi</i> , <i>Coxiella burnetii</i>)
	Typhoid
	Vaccine reactions (live virus)†

*AIDS denotes the acquired immunodeficiency syndrome, and HIV human immunodeficiency virus.

†This condition has frequently been confused with smallpox.

cowpox. In the event of a smallpox outbreak, the drug could be made available under an investigational-new-drug protocol for smallpox or adverse effects of vaccine. There is no evidence that prophylaxis with the use of vaccinia immune globulin, given early in the incubation period along with vaccination, has a greater survival benefit than vaccination alone¹; vaccinia immune globulin has no benefit in patients with clinical smallpox.

PREVENTION

If performed very early in the incubation period, vaccination can markedly attenuate or even prevent clinical manifestations of smallpox. Full protection occurs after a successful vaccination. Vaccinia multiplies in the basilar epithelium after vaccination, causing a local cellular reaction. At six to eight days, the lesion is a grayish-white, loculated pustule 1 to 2 cm in diameter, with central umbilication; it is called a Jennerian pustule. Central crusting begins and spreads

peripherally over a period of three to five days. Local edema and a dark crust remain until the third week. A Jennerian pustule is classified as a major reaction, indicating a successful primary vaccination; successful revaccination is indicated by palpable inflammation at six to eight days. Other reactions are classified as equivocal, and another vaccination is required in such cases. A successful primary vaccination confers full immunity to smallpox in more than 95 percent of persons for perhaps 5 to 10 years, and successful revaccination probably provides protection for 10 to 20 years or more.¹

Guidelines from the CDC address the release of vaccine in the event of bioterrorism.^{25,26} Because the risk of a deliberate release of variola virus is considered low, preexposure vaccination is not advised, except for clinical or laboratory personnel working with non-highly attenuated orthopoxviruses.²⁶ If the risk increased, expanded preexposure vaccination would be considered. According to the ring vaccination and

TABLE 2. DIFFERENTIAL DIAGNOSIS OF SMALLPOX AND CHICKENPOX.

DIAGNOSTIC CRITERIA	SMALLPOX	CHICKENPOX
History		
Recent contact with smallpox	Yes	No
Recent contact with chickenpox	No	Yes
Prior vaccination against smallpox*	In some cases	In some cases
Prior vaccination against chickenpox	In some cases	No
Incubation period (days)	10–12 (range, 7–17)	14–16
Prodromal phase†		
Duration (days)	2–4	0–2
Fever	Yes	In some cases
Headache, backache	Yes	In many cases
Muscle pain, malaise	Yes	In some cases
Pallor, transient rash	In some cases	No
Physical examination		
Scar from smallpox vaccination*	In some cases	In some cases
Skin lesions†		
Distribution	Centrifugal	Central
Peak (days after onset of eruption)	7–10	3–5
Evolution	Same stage	Different stages
Diameter (mm)	4–6	2–4
Shape	Round	Oval
Depth	Deep	Superficial
Desquamation (days after onset of eruption)	14–21	6–14
Lesions on palms and soles	Common	Uncommon
Complications		
Skin infection	In some cases	In some cases
Facial scarring	In most cases	In some cases (superficial)
Pneumonia	In some cases	Rare
Blindness	In some cases	No
Encephalitis	In some cases	Rare
Case-fatality rate (%)		
Chickenpox		<1 (2–3/100,000)
<i>Variola major</i>	30	
<i>V. minor</i>	<1	
Laboratory diagnosis		
Antigen or nucleic acid detection	Variola virus	Varicella–zoster virus
Electron-microscopical findings	Poxvirus particles	Herpesvirus–varicella virus
Results of culture on chorioallantois	Characteristic pocks	No growth
Serologic findings	Increase in antibody to orthopoxvirus	Increase in antibody to varicella virus

*Routine vaccination against smallpox stopped in 1972 in the United States and in the early 1980s in other countries, except in the case of laboratory personnel working with orthopoxviruses. The vaccination scar may fade with time.

†Patients who have undergone smallpox vaccination may have attenuated disease.

containment strategy, in the case of an international release of variola virus, the following groups would be vaccinated initially, depending on the supply of vaccine: persons directly exposed to the release; persons with face-to-face or household contact with an infected patient or in close proximity (within 2 m); personnel directly involved in the evaluation, care, or transport of infected patients; laboratory personnel involved in processing specimens; and others likely to have contact with infectious materials.^{25,26} Healthy persons with no contraindication to vaccination, who have been vaccinated immediately before or shortly after contact with infected patients, should provide care for patients or work with potentially infectious

materials. Those vaccinated before 1972 might have an accelerated immune response after revaccination or exposure.¹ A careful history of all persons and places in contact with patients within a period starting three weeks before the onset of the illness should be obtained for application of the ring vaccination and containment strategy.²⁵

The 15 million doses of smallpox vaccine in the United States were derived from the New York Board of Health vaccinia strain. Vaccine is administered with the use of a bifurcated needle, which is dipped into reconstituted vaccine. Fifteen assertive jabs into the dermis of the upper deltoid are given in an area with a diameter of about 0.5 cm; a small amount of

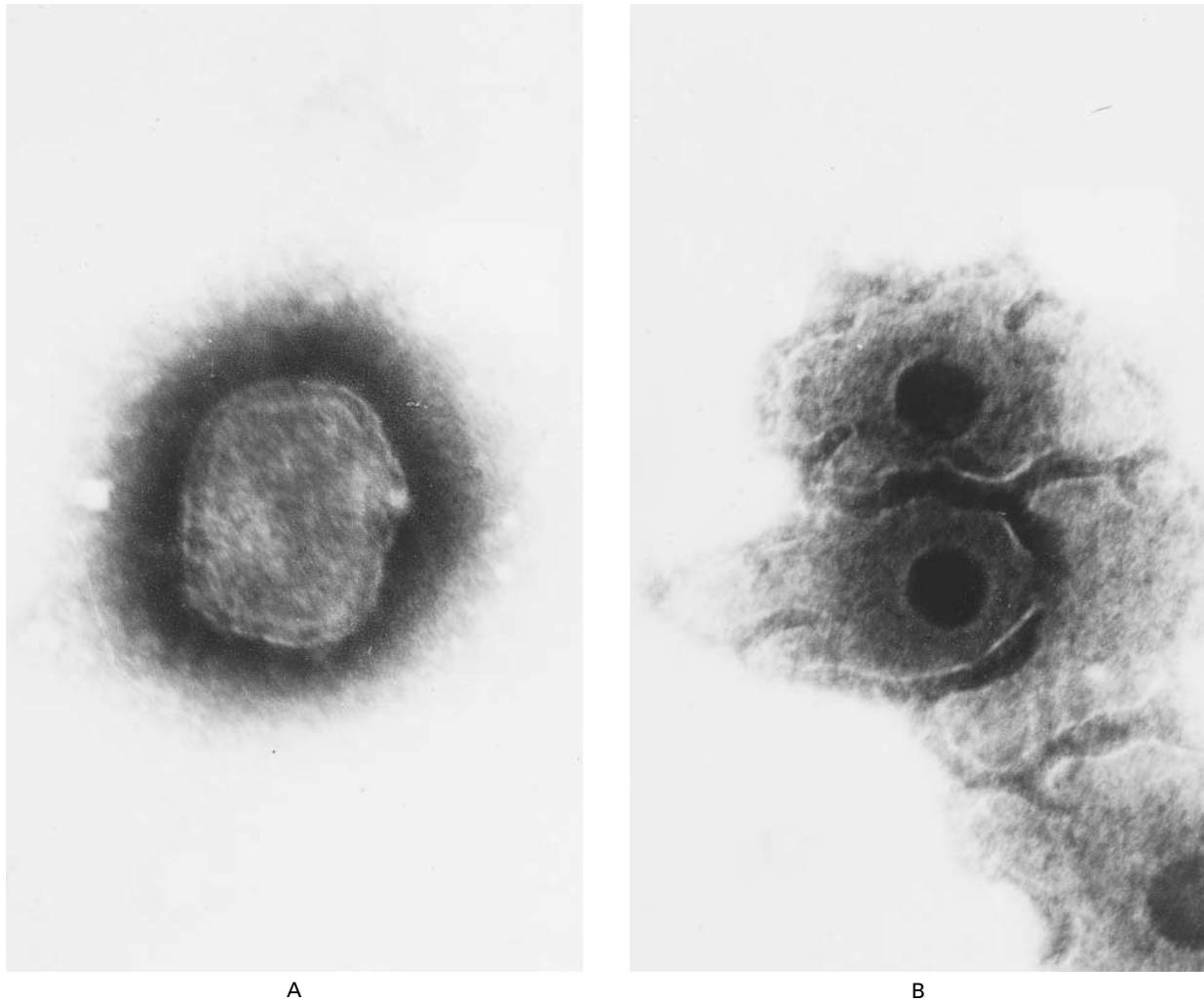


Figure 2. Electron Micrographs of Variola Virus (Panel A $\times 200,000$) and Varicella-Zoster Virus (Panel B $\times 200,000$). Photographs courtesy of Dr. Inger Damon, Centers for Disease Control and Prevention.

blood should appear at the vaccination site within 20 to 25 seconds. Studies by the National Institutes of Health indicate that vaccine diluted as much as 5 to 10 times can result in high rates of successful reactions.^{41,42} In this issue of the *Journal*, Frey et al. report a 97 percent success rate with a 1:10 dilution of the vaccinia vaccine.⁴¹ These data show that current supplies can be extended. Contracts with vaccine producers call for 280 million doses of vaccine to be available in the United States by late 2002. The newer vaccine will be produced on cell culture, in contrast to the previously used method of production in calves. Because of the different method of production, stud-

ies of the vaccine's reactogenicity and immunogenicity are required.

Complications from smallpox vaccination in the United States were closely scrutinized in the 1960s.^{43,44} Because of adverse reactions, termination of the vaccination program was advised, because the risk of complications outweighed the threat of endemic smallpox.¹ The most accurate data, from a 10-state study, indicated that there were 1254 complications per 1 million primary vaccinations (Table 3).⁴⁴ Children under the age of five years who were undergoing primary vaccination had the highest rates of complications, particularly for the complications that were most

TABLE 3. RATES OF COMPLICATIONS FROM VACCINIA, ACCORDING TO VACCINATION STATUS AND AGE.*

COMPLICATION	PRIMARY VACCINATION (N=650,000)				REVACCINATION (N=998,000)			
	0-4 YR	5-19 YR	≥20 YR	ALL AGES	1-4 YR†	5-19 YR	≥20 YR	ALL AGES
	no. of events/1 million vaccinations							
Accidental infection	564	371	606	529	198	48	25	42
Generalized vaccinia	263	140	212	242	0	10	9	9
Erythema multiforme	209	87	30	165	73	2	9	10
Eczema vaccinatum	39	35	30	39	0	2	5	3
Postvaccinal encephalitis	15	9	0	12	0	0	5	2
Progressive vaccinia	3	0	0	2	0	0	7	3
Other	222	214	636	266	18	24	55	39

*Data are from a 1968 survey of 10 states.⁴⁴ No deaths occurred.

†No children under the age of one year were revaccinated.

severe. A nationwide study showed that the case fatality rate was 1 per 1 million primary vaccinations⁴³; in 1968, there were 9 vaccine-associated deaths.

Persons who have immunologic disorders or severe eczema and pregnant women should not receive vaccinia or be in close contact with recent recipients. There are several million immunosuppressed persons in the United States, including those with human immunodeficiency virus infection and those with organ transplants, who may have vaccinia necrosum or other severe complications.⁴⁵ A limited supply of vaccinia immune globulin is available from the CDC through state health departments for the treatment of severe complications.²⁵ Two attenuated vaccine strains have been developed and tested: modified vaccinia Ankara (MVA) and a Japanese strain (LC16m8).^{46,47} Neither has been used in areas where smallpox is endemic, so their efficacy is unknown; MVA is of special interest as a vector for immunization against other infectious diseases.

RESEARCH ISSUES

Studies that might be undertaken with the use of variola virus have been described by the Institute of Medicine, the National Academy of Sciences, and the WHO Advisory Committee on Variola Virus Research.⁴⁸ These studies address DNA-sequence information,⁴⁹ the development of antiviral drugs,^{39,40} the development of an animal model for the evaluation of novel antiviral drugs and vaccines, validation of tests and equipment for early diagnosis,²⁷⁻³⁰ establishment of a program for the production of monoclonal antibody, and the development of new vaccines with few adverse events, especially for use in immunosuppressed persons.⁴⁶

The views expressed in this article are those of the authors and do not necessarily reflect those of the institutions with which they are affiliated or the U.S. government.

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