

CORRESPONDENCE



Smallpox and Smallpox Vaccination

TO THE EDITOR: In the January 30 issue, a laudable attempt was made to come to grips with the many issues surrounding terrorist use of variola. An essential point remains unclear, however. How easily is variola transmitted? In the model of Bozzette et al.,¹ no control measures are taken until 26 days after the initial infection, 11 days after the expected development of rash. Mack,² however, argues persuasively that secondary spread takes place only after the characteristic rash is evident; thus, all infection takes place during those 11 days. Once the rash is evident, I presume that control procedures would be rapidly instituted, particularly in our era of heightened awareness and instantaneous transcontinental communication. This would decrease the number of days after the initial infection (T) in the model of Bozzette et al. to a number closer to 16 days and would drastically reduce the number of deaths expected from a smallpox attack predicted by their model. Can these views be reconciled?

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1. Bozzette SA, Boer R, Bhatnagar V, et al. A model for a smallpox-vaccination policy. *N Engl J Med* 2003;348:416-25.
2. Mack T. A different view of smallpox and vaccination. *N Engl J Med* 2003;348:460-3.

TO THE EDITOR: In their model for a smallpox-vaccination policy, Bozzette et al. make assumptions that decrease the perceived value of pre-exposure vaccination. Successful pre-exposure vaccination and post-exposure vaccination are assumed to provide equal benefit. This assumption is not supported by the literature. An expert working group concluded, "Vaccination administered within 4 days of first exposure has been shown to offer some protection against acquiring infection and significant protection against a fatal outcome."¹

In the model of Bozzette et al., a death rate of 0.225 is assumed for unvaccinated persons with smallpox. Historically, this rate has varied widely, largely due to differences in virulence among strains of variola major.² Mack's review of smallpox in Europe between 1950 and 1971³ showed a crude case fatality rate of 52 percent among unvaccinated persons.

Through simple strain selection, or through use of recombinant technology,¹ terrorists can control viral characteristics related to virulence and infectivity. The resulting epidemic would not resemble the "average" historical experience portrayed by this model, but rather — at a minimum — the worst historical experience. Credible alternative assumptions lower the threshold for pre-exposure vaccination.

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THIS WEEK'S LETTERS

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- 1925 Smallpox Vaccination
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- 1928 Off-Pump Coronary Bypass Surgery
- 1931 Widespread Coronary Inflammation in Unstable Angina
- 1931 Easy to See but Hard to Find
- 1932 Bromoderma after Ingestion of Ruby Red Squirt

1. Henderson DA, Inglesby TV, Bartlett JG, et al. Smallpox as a biological weapon: medical and public health management. *JAMA* 1999;281:2127-37.
2. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication. Geneva: World Health Organization, 1988.
3. Mack T. Smallpox in Europe, 1950-1971. *J Infect Dis* 1972;125:161-9.

TO THE EDITOR: Having seen "natural" epidemics of smallpox during my work in the Democratic Republic of Congo,¹⁻³ I believe the potential danger of disease and deaths associated with a terrorist attack far exceeds even the worst projections of Bozzette et al. It is extremely important that we put in place a core of persons who are protected (i.e., immunized) against smallpox as soon as possible. You have made an excellent contribution to stimulating discussions and review of this terrorist threat.

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2. *Idem*. Four dictators and one free man. Aberdeen, Wash.: Utterance Press, 1999.
3. Dr. James Fett: a passion for medicine. *Daily World*. January 25, 2003:24-31.

TO THE EDITOR: Since vaccination of health care workers with vaccinia virus may result in nosocomial transmission to immunocompromised patients, spread to family members, disseminated infections, and deaths, as discussed by Sepkowitz in the January 30 issue,¹ antiviral agents that are active against vaccinia are urgently needed. Cidofovir is active in vitro against poxviruses and is recommended for serious vaccinia infections, but it may cause renal failure, neutropenia, metabolic acidosis, and uveitis.²

An older antiviral agent, vidarabine (adenine arabinoside), is a selective inhibitor of vaccinia DNA polymerase. Originally approved for the treatment of herpesvirus infections, vidarabine actually is 10 times as potent against vaccinia as it is against herpes simplex virus type 1 or type 2.³ Vidarabine has been shown to be beneficial in animal models of vaccinia infection. Treatment with vidarabine was highly effective in preventing death from disseminated vaccinia infection in mice with immunosuppression induced by the administration of antithymocyte globulin.⁴

The safety profile of vidarabine is excellent and was similar to that of acyclovir in clinical trials com-

paring the two drugs.⁵ It is worthwhile to reevaluate vidarabine for the treatment of severe vaccinia infection in humans and as a potential treatment for smallpox.

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1. Sepkowitz KA. How contagious is vaccinia? *N Engl J Med* 2003; 348:439-46.
2. Smallpox vaccine. *Med Lett Drugs Ther* 2003;45:1-4.
3. De Clercq E. Vaccinia virus inhibitors as a paradigm for the chemotherapy of poxvirus infections. *Clin Microbiol Rev* 2001;14:382-97.
4. Worthington M, Conliffe M. Treatment of fatal disseminated vaccinia virus infection in immunosuppressed mice. *J Gen Virol* 1977;36:329-33.
5. Whitley R, Arvin A, Prober C, et al. A controlled trial comparing vidarabine with acyclovir in neonatal herpes simplex virus infection. *N Engl J Med* 1991;324:444-9.

TO THE EDITOR: Sepkowitz's article may be misleading. He describes 85 cases of nosocomial spread of vaccinia in 12 instances, all but 1 before 1958. He states that little is known about the risk of transmission of vaccinia in a hospital and that vaccinia may be transmitted by aerosol. Two of us analyzed cases of adverse reactions reported from a variety of sources, including all cases involving treatment with vaccinia immune globulin.^{1,2} There were 462 patients with dermal vaccinia infections who were hospitalized for an average of 7.5 days. There was one instance of nosocomial infection in a child with eczema who was infected from a vaccinated licensed practical nurse.³ There were no cases of patient-to-patient spread. One of us (Dr. Fulginiti) hospitalized many patients with infectious cases of vaccinia in the 1960s, with no instance of nosocomial spread. In all our collective experience, there was no aerosol spread, and nosocomial infection occurs possibly once in 3000 to 4000 hospital days.

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Editor's note: Drs. Neff and Lane report having served as consultants to Acambis and Dynport on the data and safety monitoring boards for their smallpox-vaccine trial, and Dr. Neff is chair of the data and safety monitoring board for both companies. Neither Dr. Neff nor Dr. Lane has any financial interests in the vaccine product.

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2. Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccinations, 1968: national surveillance in the United States. *N Engl J Med* 1969;281:1201-8.
3. Neff JM, Lane JM, Fulginiti VA, Henderson DA. Contact vaccinia — transmission of vaccinia from smallpox vaccination. *JAMA* 2002; 288:1901-5.

TO THE EDITOR: Mack cites reports on two studies as evidence that variola was not grown from exhaled air.^{1,2} The earlier study¹ used inadequate methods of air sampling.² The later study recovered virus in 5 of 47 attempts. Another study,³ in which more efficient sampling methods were used and patients were studied late in the course of disease, when they were probably not infectious, still found positive air samples. Thus, variola has been grown from exhaled air. Airborne variola had an infectious half-life similar to that of vaccinia^{4,5} — about six hours, not a few minutes.

These reports suggest that, ordinarily, patients with smallpox have generated small numbers of infectious droplet nuclei. Such patients were too ill to go out in public when they were most infectious. Thus, the literature on airborne variola is consistent with a risk of infection that is greatest at the bedside, except in rare cases of dissemination, and does not rule out frequent airborne transmission. The possibility of frequent airborne transmission, however, reinforces the importance of Mack's recommendation that plans to prevent in-hospital transmission not rely solely on the vaccination of health care workers.

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1. Meiklejohn G, Kempe CH, Downie AW, Berge TO, St Vincent L, Rao AR. Air sampling to recover variola virus in the environment of a smallpox hospital. *Bull World Health Organ* 1961;25:63-7.
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3. Thomas G. Air sampling of smallpox virus. *J Hyg (Lond)* 1974; 73:1-7.

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5. Harper GJ. Airborne micro-organisms: survival test with four viruses. *J Hyg (Lond)* 1961;59:479-86.

DRS. BOZZETTE AND BOER REPLY: Dr. Letai and Dr. Snyder identify some of the key parameters of concern. We stand by our best estimates of these parameters. We doubt that today's providers will be better at quick recognition of smallpox than doctors and nurses who had first-hand experience with the disease, especially since the number and geographic extent of exposures will not be immediately apparent in any but the simplest attack. We do not make the assumption, attributed to us by Dr. Snyder, that pre-exposure vaccination and post-exposure vaccination are equally effective. Rather, we assume that the overall efficacy of prior vaccination is considerably higher than that of ring vaccination. We are aware of Dr. Mack's estimate of the case fatality rate, but our best point estimate did not agree with it.

Nonetheless, Dr. Letai, Dr. Snyder, and we suspect, others have reasonable and legitimate concerns about the conditions and parameters of our model. Our sensitivity analysis did include variations in these parameters that were more extreme than those suggested here, with effects in the expected directions as described in our article. None of the variations described would lead to a substantial change in the policy recommendations.

We certainly feel privileged that our sterile analyses have earned the thanks of Dr. Fett, who has cared for "victims of Mobutu's massacres in the Congo," "unaccompanied minors" on Cambodia's borders, and "peasants victimized by Baby Doc Duvalier." We believe that his interpretation is quite correct: raising the immune status of those in the population who are most likely to become ill in an attack is a prudent policy, the implementation of which deserves a high priority and therefore full funding as necessary.

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DR. MACK REPLIES: Dr. Letai is correct; surveillance of contacts would start within days after the first evidence of rash, especially after the initial report.

Dr. Snyder is also correct; pre-exposure vaccination is highly effective, and post-exposure vaccination is at best of limited effectiveness. Unfortunately the case fatality rate for variola major among unvaccinated persons is likely to be closer to 50 percent than 22.5 percent. Some historical observations were based on cases in smallpox hospitals — that is, cases in persons who made it to the hospital. Field investigators relied on the personal history and findings on physical examination to infer vaccination status, thus misclassifying some surviving vaccinees.

Although recombinant technology might alter virulence, a more virulent virus would probably lead to less contact with visitors, a more frightening appearance, and a shorter clinical course — a combination that would reduce transmission, not increase it. Since infectivity is already maximal at the bedside, an increase in this characteristic is more likely to occur as a function of human, rather than viral, behavior.

Dr. Milton takes me to task for indicating that attempts to grow airborne variola virus were “unsuccessful,” with viability “measured in minutes.” Of course, person-to-person transmission requires that some virus be airborne, at least temporarily. Capture at the bedside in about 10 percent of attempts¹ was not regarded as very successful, and the later success² was achieved only with equipment that screened very large volumes of air, captured droplets of variable size (unlikely to travel well), and used an extremely sensitive two-stage culture protocol. Even so, success was limited to periods when infected persons were physically active, suggesting that airborne virus emanated from clothing and bedclothes rather than directly from the enanthem. Moreover, infectiousness clearly is based on virion quantity as well as quality. Some virus can even be grown from the mouth of a healthy unvaccinated contact, who is not only unlikely to transmit the virus but also unlikely even to become symptomatic.³ Effective transmission probably requires a larger number of virions than a successful culture.

Vaccinia, not variola, survived for six hours, and it was in a small (75-liter), tightly regulated drum that rotated, possibly refreshing the aerosol.⁴ When variola virus itself was placed in a much larger (1500-liter) drum nine years later, no more than 20 to 30 percent survived for 60 minutes under similarly well-regulated conditions.⁵ The latter observation is consistent with the epidemiologic evi-

dence that suggests that this virus lives long enough when airborne near the bedside, but usually does not live long when subjected to the changing conditions of air currents.

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1. Downie AW, Meikeljohn M, St Vincent L, Rao AR, Sundara Babu BV, Kempe CH. The recovery of smallpox virus from patients and their environment in a smallpox hospital. *Bull World Health Organ* 1965;33:615-22.
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DR. SEPKOWITZ REPLIES: Letai asks if the contagiousness of variola is known. A table in the classic textbook by Fenner and colleagues summarizes the available information (Table 1), demonstrating an incidence of secondary infection among nonimmune close contacts of about 58 percent.¹

Worthington and Ross note that vidarabine has activity against vaccinia and suggest that this drug may have a role in the management of severe cases of vaccinia. I certainly agree that this and other compounds should be examined. Another nearly forgotten drug, methisazone (Marboran), a thiosemicarbazone, appeared to demonstrate activity against both viruses,² but development was not pursued, because the incidence of smallpox declined worldwide. This oral medication may cause severe nausea and vomiting, possibly limiting its practical use. A recent review has identified additional potentially active compounds.³

Neff et al. are correctly concerned that the older studies I cited will be misapplied to the current situation. My goal in this review was not to take a stand on one side or the other, but rather to provide a dispassionate summary of a pertinent and difficult-to-obtain literature. The single cardinal rule for those submerging themselves in the older literature is that one must take the original authors at their word and not question their observations, merely report them. In that spirit, I reported that several authors were concerned that vaccinia could be spread by the airborne route. Certainly, Dr. Fulginiti's observation (previously unreported) that no nosoco-

Table 1. Rates of Disease among Persons Exposed to Measles, Chickenpox, or Smallpox.*

Disease and Locality (for Smallpox)	Vaccination Scar	Total No. of Household Contacts	Contacts in Whom Disease Developed	
			no.	%
Measles	NA	266	201	75.6
Chickenpox	NA	282	172	61.0
Chickenpox	NA	888	771	86.8
Variola				
Nigeria	Absent	27	12	44.4
Nigeria	Present	45	12	26.2
Benin	Absent	17	8	47.0
Benin	Present	13	2	15.4
Madras, India	Absent	103	38	36.9
Madras, India	Present	1146	14	1.2
Pakistan	Absent	45	33	73.3
Pakistan	Present	190	6	3.2
Pakistan	Absent	22	10	45.5
Pakistan	Present	338	3	1.3
Pakistan	Absent	43	38	88.4
Pakistan	Present	180	13	7.2
Calcutta, India	Absent	80	61	76.3
Calcutta, India	Present	661	47	7.1
Bangladesh	Absent	21	9	42.9
Bangladesh	Present	57	4	7.0
Average for variola†				
Vaccinated			58.4	
Unvaccinated			3.8	

* The data, which are based on several studies, are from Fenner et al.¹

† Persons with scars were considered to have been vaccinated, and those without scars were considered never to have been vaccinated.

mial transmission occurred during his years of caring for many patients with vaccinia, including eczema vaccinatum, is a very powerful indication of how unlikely airborne spread must be. This observation, coupled with the current, most favorable experience with the vaccine in the United States and Israel, serves to endorse the new, admirably sane infection-control guidelines for smallpox vaccina-

tion recently released by the Centers for Disease Control and Prevention.⁴

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Smallpox Vaccination

TO THE EDITOR: Rubins and Relman, in their Image in Clinical Medicine (Jan. 30 issue),¹ mention that a lymphangitic streak was present on day 9 and that “two physicians who examined the patient on day 10 . . . suspected bacterial cellulitis.” The lesion apparently resolved within two days after its appearance, without the use of antimicrobial agents. It is nonetheless a matter of concern that antimicrobial agents were withheld despite the clinical suspicion of cellulitis.

Although it is well known that lymphangitis and cellulitis may be seen during the major cutaneous reaction associated with successful smallpox vaccination (a “robust take”), it can be quite difficult clinically to discern a nonbacterial lesion from a secondary bacterial infection of the site. The Centers for Disease Control and Prevention (CDC) recently reported that 9 of 191 of its vaccinees (4.7 percent) met the criteria for a robust take; all 6 who sought medical attention were treated with systemic antibacterial agents.² My colleagues and I have had a similar recent experience with smallpox vaccination. Given the potentially dire consequences of an untreated, rapidly progressive, bacterial soft-tissue infection and the fact that clinicians may soon face this issue as the smallpox-vaccination program progresses, one must ask whether empirical antimicrobial agents are indicated.

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2. Smallpox vaccination and adverse reactions: guidance for clinicians. *MMWR Morb Mortal Wkly Rep* 2003;52(RR-4):1-28.

THE AUTHORS REPLY: We agree that bacterial soft-tissue infection, including bacterial cellulitis, can be difficult to distinguish on a clinical basis from a robust take to the Dryvax smallpox vaccine. Lymphangitis may occur with each. In cases with features that are strongly suggestive of bacterial infection, a decision to provide treatment with antibiotics may be unavoidable. In this particular case, antibiotics were in fact prescribed; however, the patient did not begin this therapy immediately, and by the next morning, the erythematous streak had already improved, even though the patient had not yet started taking the antibiotics.

We also wish to clarify another feature of this case. The persistence of an open cutaneous lesion on day 51, after detachment of the eschar, is not typical of smallpox-vaccination sites and may have resulted from daily application of topical antibacterial ointment, which is not included in standard recommendations for the care of robust takes (Table 2 in the CDC’s recommendations).¹ Besides drawing attention to these management issues, this case emphasizes the important need for newer-generation smallpox vaccines with less severe accompanying features.

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Multifactorial Intervention and Cardiovascular Disease in Type 2 Diabetes

TO THE EDITOR: Gæde et al. (Jan. 30 issue)¹ unintentionally demonstrate that for many patients, treatment of type 2 diabetes amounts to benign neglect.

This is illustrated by the absence of a meaningful reduction in glycosylated hemoglobin, total cholesterol, or systolic blood pressure in the convention-