SOUNDING BOARD

A Different View of Smallpox and Vaccination

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According to federal,[1] academic,[2] and lay[3] observers, smallpox might be used as a weapon of terrorism. Variola virus is presumed to be available,[4] and a terrorist could introduce it, leading to secondary spread and deaths. Current policy is to promote vaccination, initally to ½ million hospital-selected health care providers[5] and subsequently to as many as 10 million others.[6] This policy should be compared with alternatives in the light of the likely outcome of an introduction of variola virus into this country. Three decades ago, I was among those who investigated the dynamics of smallpox transmission by direct observation in Pakistan.

RISK OF SMALLPOX

Smallpox was eradicated because its chain of transmission is inherently vulnerable. The clinical characteristics of an infectious patient restrict spread, because most virus shedding[7] and almost all transmission[8] occur during the first week of florid rash, and this period coincides with rapidly evolving symptoms severe enough to keep infectious patients in bed. Although the virus can be isolated from pharyngeal washings at the onset of rash and from month-old scabs,[9] neither of these seems to be important in practice.[8] Moreover, the physical appearance of an unvaccinated person with variola major is alarming and quite unlike anything else, including the appearance of persons with varicella. Once they are infectious, 98 percent of previously unvaccinated patients have disease severe enough[10] to be recognized by any professional or layperson familiar with the characteristic appearance (Fig. 1). Whether clustered densely or sparsely, the lesions, uniform in stage and set deeply in the dermis of the face and extremities,[11] are unmistakable.

Transmission would not be expected to occur over more than very short distances. Although virus can be grown from pharyngeal washings and the face and bedding of infectious patients,[12] attempts to grow it from exhaled air or from unbroken vesicles have been unsuccessful,[12,13] suggesting that virus is usually discharged not in droplet nuclei but in saliva droplets too large to be wafted long distances. Moreover, the viability of artificially airborne virus is measured in minutes.[14]

Smallpox is not as infectious as its reputation would suggest. Whether in Punjab,[15] Bengal,[16] or Europe,[17] variola major was almost always transmitted at the bedside of the source, not at an external location. The source of infection was reported for about 96 percent of the cases that resulted from 51 introductions into highly susceptible European populations after World War II.[17-19] Among the 18 cases, on average, per introduction, 3.8 occurred among household contacts and only 1.1 appeared among the multitude of community residents with no acknowledged exposure. None of the 945 cases involved disease contracted on an airplane, train, or bus. Any spread into the community from an introduction would thus be limited. Past experience is likely to be a more accurate predictor of future events than models based on arbitrary assumptions.[20]

Enhancing the vulnerability of the smallpox chain is the interval of one to three weeks[8,17] between exposure and infectiousness. This interval provides the time to intervene and limit secondary spread. Close contacts of each case patient can be listed, located, given postexposure prophylaxis, placed under surveillance for symptoms, and isolated, if symptoms occur (and infectiousness is anticipated). If a case is identified only after contacts would have become symptomatic, attention can turn to the contacts of these contacts.

A generation ago, such control efforts were effective. Of the case patients known to be responsible for European outbreaks,[17-19] 84 percent had consulted physicians. Even without a terrorist threat or an alert public, 78 percent of those patients, many with vaccine-modified disease, were correctly diagnosed and isolated. Twenty-five percent of the introductions into those susceptible European populations resulted in no transmission at all, 60 percent were controlled before a third indigenous generation of cases,[17] and smallpox always disappeared within a few months.

Disappearance was facilitated, not impeded, by economic development. Long before the World Health Organization's Smallpox Eradication Pro-

gram began, and despite low herd immunity, unsophisticated public health facilities, and repeated introductions, smallpox disappeared from many countries as they developed economically, among them Thailand, Egypt, Mexico, Bolivia, Sri Lanka, Turkey, and Iraq.[9] The largest and longest outbreak in postwar Europe occurred in Kosovo, in the least developed corner of the continent.[19]

In the United States, secondary spread would probably be greatly limited by our high level of literacy, efficient means of personal and public communication, and organized public health services. Graphic photographs would saturate the media, and subsequent infectious patients would be recognized, avoided, and reported. Contacts would seek, not avoid, medical assistance and could be efficiently kept under surveillance wherever they were. Few new diagnoses would be expected more than a month or so after an introduction.

Although virus might be weaponized for mass delivery or even altered genetically to enhance virulence or resistance to vaccine-induced immunity, such changes would not impair our ability to limit secondary spread. Even if multiple cases were produced by the same introduction,[4,21] there is no reason to expect disease to persist longer, although more teams would be required to establish control. Smallpox as a terrorist weapon corresponds more closely to a grenade than to a catastrophic "dirty" bomb or even a dissemination of anthrax spores.

Our greatest concern should be about transmission within hospitals. In postwar Europe, 4.4 cases per introduction occurred among caregivers and related professionals, and 6.7 cases occurred among hospital patients and visitors — numbers that together represent over 60 percent of the total. Only in hospitals has substantial transmission occurred at some distance from the beds of the source patients. Contact with infected linens has been responsible,[22] as has, in one case, air recycled from a coughing patient to other rooms.[18] Hospital spread also has been responsible for protracted outbreaks in Kuwait[23] and Brazil,[23] and it was responsible for the majority of cases in each of the last three outbreaks in the United States — in Seattle,[24] New York City,[25] and the Rio Grande valley.[26]

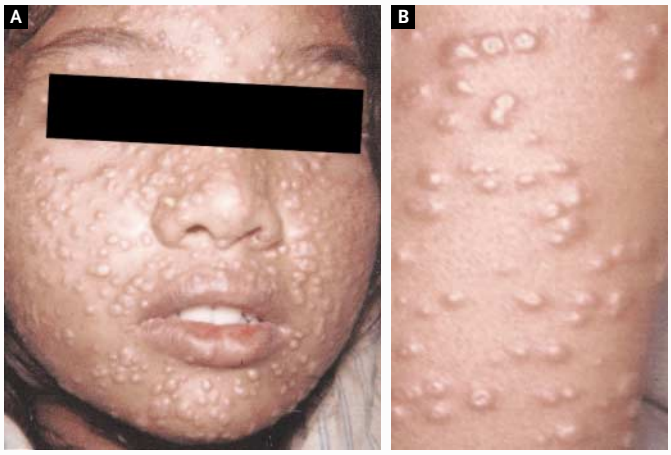

Figure 1. Smallpox in Pakistan, 1967.
Panels A and B are photographs of a young, unvaccinated woman in about the seventh day of fever and fourth day of rash.

VACCINATION POLICY

Prophylactic vaccination of contacts is an important containment strategy, although the actual effectiveness depends on the timing[17,27] of the vaccination in relation to exposure. Nearly twice as effective as vaccine alone, however, is vaccination followed by the administration of vaccinia immune globulin.[28-30]

Vaccination before importation offers the only possible protection to households directly targeted by an introduction (assuming that genetic engineering has not rendered the strain of virus resistant[31]). However, we cannot identify those households in advance, and vaccinia is a dangerous live vaccine. It causes substantial morbidity among both healthy vaccinees and their pregnant or eczematous contacts.[32] Despite recommendations for screening and treatment with vaccinia immune globulin, deaths from complications occurred at a rate of 1 to 2 per million primary vaccinees.[33] Today, immunosuppressed patients with chronic disease or transplanted organs and carriers of the human immunodeficiency virus with or without AIDS, especially those with skin lesions, constitute additional vulnerable groups.[34] Complications today will surely be several times as common as previously. Even with a rate of 3 deaths per million, primary vaccination of 250,000 persons would be more likely than not to cause death. Moreover, liability for complications is unclear, marketing prophylaxis to adults is generally unsuccessful, and herd immunity will be difficult to achieve. Vaccine complications will be quickly, widely, and graphically reported in the media. Americans are better informed and less trusting than in the past, and noncompliance will be common.

Caregivers, at high risk of secondary transmis-

sion, deserve preferential protection. However, we cannot predict which hospitals will be affected, and undertaking staff vaccination through programs at all hospitals poses serious problems. There is substantial turnover among emergency room personnel, and some caregivers will refuse to be vaccinated. It will be difficult to protect highly vulnerable inpatients and outpatients from the spread of vaccinia. Moreover, the existence of hospital-based vaccination programs may lead to the knowing admission of patients with smallpox, putting those who are not protected at very high risk.

COSTS AND BENEFITS

Extrapolating from the European experience, we can predict that an initial smallpox introduction is likely to result in substantially fewer than 20 cases[17] and 10 deaths[11,17]; experience would lessen the impact of subsequent introductions. Many well-informed members of the general public will refuse vaccination. Every million primary vaccinations will cause at least 3 deaths from vaccinia, and the chance of preventing deaths from smallpox would be less than 0.4 percent (1 in 275 million). To prevent all potential deaths from smallpox would require universal compliance with vaccination, with as many as 800 deaths from complications. Even after an introduction, mass vaccination would do more harm than good.

About 2½ million health care professionals and technicians work in U.S. hospitals[35] and are at some excess risk of caring for a patient with smallpox. Vaccination of the entire 2½ million, assuming 100 percent compliance, would prevent all deaths of caregivers from smallpox, but at a cost of at least 7 to 8 deaths from vaccinia. Risk to other members of the antiterrorist infrastructure is likely to be similar to that of the general public.

BETTER OPTIONS

A terrorist introduction of smallpox could produce a short outbreak of cases and deaths, but the current vaccination policy will provide little protection, and the cost in deaths from vaccine complications will outweigh any benefit. Only if evidence suggests that a massive attack or sustained biologic warfare is probable can such a vaccination policy be justified. Safer options would be more effective. I recommend the following.

Every effort should be made to facilitate rapid diagnosis. Posters with dramatic photographs of florid smallpox cases should be distributed widely. No suspicious patient should be admitted to or even knowingly examined at a general hospital, even one with isolation facilities and an already vaccinated staff. Alternative dedicated facilities, even National Guard field hospitals, should be identified and activated at first diagnosis. Limited numbers of preselected (preferably older, previously vaccinated) field investigators, diagnostic laboratory personnel, caregivers, and paramedics and some law-enforcement personnel should be recruited, vaccinated, and committed to serve wherever necessary in the event of an introduction. No more than 15,000 persons would be required. Reserves of vaccinia immune globulin should be large enough to meet the anticipated need for both treatment of complications and postexposure smallpox prophylaxis. Experts should be convened to develop protocols for postexposure prophylaxis and treatment. Finally, the authorities and the media should provide more detail about the dangers of vaccination and more accurate, less inflammatory information about the potential for the spread of smallpox.

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This article was published at www.nejm.org on December 19, 2002.

Preventing the Return of Smallpox

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> Each state party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain: (1) Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes; (2) Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.
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> — Biological and Toxin Weapons Convention, 1972, Article 1[1]

It is imperative and urgent that we prevent the intentional or unintentional release of variola (smallpox) virus into an essentially unprotected global population that continues to benefit from 25 years of freedom from smallpox. During the incubation period of 7 to 17 days, infected persons can travel virtually anywhere in the world before manifesting disease and then spreading it through close respiratory contact with others. In many low-income countries, the disease would be exceedingly difficult to contain. Establishment of smallpox transmission by bioterrorists in one or more countries, particularly low-income countries, would create a global public health emergency. The understandable response to this threat in the United States has been to manufacture and stockpile enough vaccine to cover the entire population, to vaccinate some medical and military staff members and others who will be among the first to respond in the event of bioterrorism, to develop detailed plans for distributing and using the vaccine when it is needed, to confirm the presence of smallpox virus in patients by laboratory testing should there be a bioterrorist event, and to investigate cases and contain the spread of the virus.[2] Similar preparations are beginning in countries of the European Union and other high-income countries.

The World Health Organization (WHO), concerned especially with helping low-income countries that have a poor health infrastructure, is fo-