

*Sounding Board***THE CASE FOR VOLUNTARY SMALLPOX VACCINATION**

**T**HE former Soviet Union developed variola virus, which causes smallpox, for use as a biologic weapon, and supplies may have fallen into other hands. As Lev Sandakhchiyev, the director of Russia's Vektor Institute, has warned, "All you need is a sick fanatic to get to a populated place."<sup>1</sup> U.S. experts agree.<sup>2,3</sup> The benefits of preemptive, voluntary vaccination are great. One immediate outcome is deterrence. Vaccination before exposure dramatically reduces the value of smallpox as a weapon; in the case of an attack, the number of unimmunized persons will be greatly reduced, and the outbreak will be much easier to manage. The United States is the most likely target of bioterrorism, and preexposure vaccination in this country reduces the risk of secondary exposure elsewhere in the world. A survey has shown that 61 percent of Americans would want to be vaccinated if smallpox vaccine were available, and the public thus appears to be ready for this approach.<sup>4</sup>

The risk of an attack involving variola virus is impossible to quantify, but the vulnerability of the U.S. population is evident. The 119 million U.S. residents born after the program of mass vaccination was terminated in 1972 lack immunity. Moreover, the immunity of the 157 million U.S. residents who were born earlier is waning and therefore uncertain. The federal government recognizes the risk and has ordered the production of sufficient supplies of vaccine to immunize the entire U.S. population.<sup>5</sup>

The responsibility for deciding how to administer vaccine rests with the Centers for Disease Control and Prevention (CDC). The CDC currently recommends post-exposure "ring vaccination," an approach that requires rapid identification and quarantine of exposed persons, with immunization of their contacts and the contacts' contacts.<sup>6</sup> Ring vaccination is an effective strategy for the eradication of small, localized outbreaks in a population with widespread immunity. In a largely nonimmune and highly mobile population, however, epidemic control after multiple simultaneous exposures is a vastly different challenge. The CDC's strategy of post-exposure ring vaccination is predicated on certain assumptions that merit scrutiny. One assumption is that smallpox makes patients so visibly sick that infected persons can be identified, diagnosed, and quarantined within the four-day period after exposure during which vaccination may be ef-

fective.<sup>2,3</sup> Smallpox is "most contagious during the preeruptive period by aerosol droplets from oropharyngeal lesions."<sup>7</sup> A person may be infective for several days before smallpox is clinically obvious.<sup>8</sup> Infected terrorists could expose people in several cities (and on public transportation between cities) before becoming visibly ill. Identifying such cases of exposure within the four-day period is logistically impossible. Furthermore, aerosolized dispersion of the virus could make the situation much worse.

The CDC strategy also appears to be based on the assumption that each infected person will infect only two or three others: "Our data suggest that the lowest rate (2 persons infected per infectious person) is the most accurate representation of previous transmission rates."<sup>9</sup> But in the Yugoslav and German smallpox outbreaks in the 1970s, for each case of infection, the number of infected contacts ranged from 11 to 38.<sup>8</sup> A single case of smallpox in the Yugoslav outbreak required the administration of 18 million doses of vaccine to arrest the spread of disease in a population with substantial immunity.<sup>10</sup> Moreover, the deliberate exposure of a population to smallpox introduces multiplicative factors with effects that are unforeseeable.

Finally, the logistic complexity of administering millions of vaccine doses in a crisis is daunting. An epidemic is highly likely to outrun the vaccinators. Effective enforcement of quarantine is also difficult.<sup>11</sup> Official reassurances followed by further uncontrolled outbreaks could provoke panic, flouting of authority, and even the breakdown of medical and public health services. In June 2001, the Johns Hopkins Center for Civilian Biodefense Studies sponsored a simulation exercise, called *Dark Winter*, in which experienced officials used a containment-after-exposure strategy in response to a smallpox attack.<sup>12</sup> There was logistic havoc. It was attributed to the unclear and conflicting authority of competing jurisdictions, a shortage of vaccine, weak information-sharing mechanisms, and inadequate crisis capacity in the health care system.

Preexposure vaccination does not pose the logistic difficulties of vaccination during an outbreak and is less expensive. It also reduces the risk of infection among immunocompromised persons.<sup>10</sup> The primary objection to voluntary preexposure vaccination is the risk of serious complications, but exposure of immunocompromised persons to vaccinia is much easier to control in a noncrisis setting than during an outbreak.<sup>3,10</sup> An increased level of immunity in the population would reduce the overall risk of infection among immunocompromised persons in the event of an attack.

In 1968, the last year for which we have data on mass vaccination, 14.2 million persons in the United States were vaccinated. Nine deaths resulted — six primary vaccinees and three revaccinees — for a death rate of less than 1 per million. Complications included

postvaccinal encephalitis (16 cases, 4 of which were fatal), progressive vaccinia (11 cases, 4 fatal), eczema vaccinatum (126 cases, 1 fatal), and generalized vaccinia (143 cases, none fatal). Vaccinia immune globulin is effective for the treatment of eczema vaccinatum and certain cases of progressive vaccinia, and it is also recommended for severe generalized vaccinia but not for all complications.<sup>2,10</sup>

Applying the 1968 data to today's population suggests that there would be 180 deaths from vaccination nationwide, which is approximately the number of deaths from traffic accidents every 1.5 days.<sup>13</sup> Since there are many more immunocompromised persons today than there were in 1968, complication rates may be higher, but vigilance, voluntary testing for human immunodeficiency virus before vaccination, wide availability of vaccinia immune globulin, and good medical care should help keep the rates of death and serious complications close to those in 1968.<sup>3</sup> These rates, which the American public accepted before 1972, must be weighed against the possibility of a much higher rate of death from a well-coordinated terrorist attack.

Consider the hypothetical case of an attack on numerous cities that put 50 percent of the U.S. population at risk. If we applied the lowest historical case fatality rates (3 percent among persons with partial immunity and 5 percent among nonimmune persons) and also assumed (optimistically) that an intensive post-exposure vaccination program and good medical care would further reduce the rates of transmission and death by 90 to 95 percent, there could still be 100,000 to 1 million deaths.<sup>8,14</sup> In comparison, the influenza pandemic of 1918–1919 caused about 500,000 deaths in the United States.<sup>15</sup>

Voluntary smallpox vaccination requires precise planning. As soon as sufficient supplies of vaccine are available, first responders and other key public-safety and public health personnel should be offered voluntary immunization. (The CDC has already vaccinated its own smallpox-response teams.) Vaccinia immune globulin should be stockpiled rapidly by initially immunizing first responders who have a history of smallpox vaccination and then obtaining blood from them for the production of vaccinia immune globulin. Immunized personnel should be monitored for adverse reactions before a program of widespread voluntary vaccination is initiated. This approach will also facilitate the evaluation of any new vaccine derived from tissue culture.<sup>10</sup>

An aggressive educational campaign will be needed to inform the public about the risks and benefits of smallpox vaccination. Guidelines for the protection of immunocompromised persons and infants should be formulated and publicized. When there are sufficient supplies of vaccinia immune globulin, the vaccine

should be made available to the entire population on a voluntary basis through ambulatory care providers and public health departments. The CDC guidelines indicate that federal support to the states in the form of staffing will be limited. The CDC director will maintain control of the distribution of vaccine, but the states should insist that vaccine purchased with tax dollars be made available to them promptly, without restrictions on its use for preexposure vaccination.

Post-exposure containment of a terrorist-induced smallpox outbreak is unlikely to be successful. Widespread, voluntary vaccination before exposure will greatly reduce the number of victims, if an attack occurs, and it will be much easier to protect unimmunized persons through additional ring vaccination. With a reduced risk of infection in the United States, secondary epidemics in other countries will be less likely. Speaking as a former commissioner of the Massachusetts Department of Public Health, I would underscore that the assessment of risk entails a value judgment that belongs in the public forum. It is time for a full and open debate about the best protection against the possible reappearance of smallpox.

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