Smallpox 2003

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Infectious disease physicians are schooled in the triumphant saga of smallpox eradication (1). The milestones are well known – the last human-to-human case in 1977 in Bangladesh, a human case from laboratory exposure in England shortly after, and then transmission stopped worldwide. Laboratories in Russia and the United States maintained smallpox virus stocks, but with use restricted to genetic studies. The world was forever safe from smallpox! – only the social and financial benefits of smallpox eradication remained to be measured. Even the military stopped vaccination.

But then murmurings began – were there smallpox virus stocks in North Korea? Iraq? (2). And what exactly had the Russians done with their virus? As the bioterrorism drumbeats increased in intensity throughout the late 1990's, smallpox was back – prominent in the list of top bioterrorist agents (3). Following September 11th and anthrax, there was no escaping smallpox. Of the eight class A bioterrorism agents on the Centers for Disease Control and Prevention (CDC) list, smallpox seemed the most immediate threat. Only smallpox and plague have a record of repeatedly emerging in world-wide human epidemics with high mortality and great social upheaval. They have changed the course of history. But for smallpox, unlike plague, there is still no specific therapy.

Smallpox now seems to be on everyone's mind, despite several decades of celebrating disease eradication. Clinical pictures and case discussions at professional meetings and on websites remind us of the disease manifestations – how is smallpox not chickenpox? Hopeful discussions of potentially beneficial antiviral therapies continue. But the most insistent topic has been smallpox vaccination (4,5). How extensive should vaccine programs be in 2003? How much vaccine is enough? Are the vaccines stockpiled several decades ago still useful? Can the number of doses be extended by dilution? What is the optimal method of vaccination? What are the vaccine risks in 2003? And the military has reinstituted vaccination programs.

Canada has been an observer as the Americans rolled out a program for the wide-scale vaccination of civilian populations, primarily health care personnel, in preparation for a potential bioterrorist event (4). The United States' approach was supported at a high political level, with substantial resources. Each state, community, and facility has identified persons for vaccination. Voluntary vaccination under this program was initiated early in 2003. While concerns about the balance of benefits and potential adverse effects of vaccination were occasionally raised before initiating the program, no strong voice opposing wide-scale pre-emptive vaccination nor any critical discussion of alternate approaches was heard. The American vaccination program has subsequently progressed more slowly than planned. Questions of liability for adverse events of vaccination, and reimbursement for healthcare workers placed on work restriction because they are potentially infectious post-vaccination, were not adequately addressed before implementation. In addition, some individuals and health care organizations did not accept the rationale for such an intensive pre-event vaccination program.

The CDC began shipping smallpox vaccine to the states on January 22, 2003. Less than 10% of the anticipated 500,000 persons had been vaccinated by the beginning of the summer. Even this more restricted vaccination activity is of substantial scientific and clinical interest as a description of a large vaccination experience in a developed country in 2003. Vaccinia virus inoculation is associated with many side effects, some of which are severe. The opportunity of discontinuing universal smallpox vaccination to avoid these adverse effects was seen as a prominent benefit of the global smallpox eradication program. What would be the complications of widespread vaccination in a developed population of the early 2000's, given the increased number of immunocompromised individuals and the high proportion of the population not previously vaccinated? The vaccine has not disappointed. By late August, the CDC reported three cases of generalized vaccinia, three of inadvertent ocular and 21 of inadvertent nonocular inoculation, and one postvaccinal encephalitis. There were also 22 cases of myocarditis/pericarditis (6). This cardiac complication had been previously described, but the frequency or severity evidenced by the current American vaccination program was not appreciated. Overall, this is a substantial rate of adverse events, given that only 38,257 individuals had been vaccinated by the beginning of August (4). On March 25th, only two months after vaccinations began, revised recommendations by the National Advisory Committee on Immunization advised a temporary medical deferral from smallpox vaccination for all persons diagnosed with heart disease (7).

The Canadian smallpox plan is more restrictive in recommendations for pre-event vaccination (5). The current draft of the Canadian plan proposes the development of teams of vaccinated persons within Health Canada and at the provincial level to provide an initial response in any smallpox event. The numbers of vaccinated individuals in such teams would be small. Should a smallpox episode occur, the major control activities will be ring vaccination and isolation of contacts.

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This approach has been previously successful as the major strategy leading to the ultimate success of the global eradication program. The pre-vaccinated team would also provide immediate inoculation of local individuals who could provide additional assistance in responding to the episode.

The next smallpox vaccine chapter opened with the monkeypox epidemic in the United States – Gambian rats, prairie dogs, and about 70 human cases (8)! Monkeypox is an orthopoxvirus, as is vaccinia and smallpox. There was no evidence for person-to-person transmission in the United States outbreak, although this could not be fully excluded for many cases with both animal and human contact. In previous African monkeypox outbreaks, person-to-person transmission was uncommon, although as many as 10% of cases may have acquired infection from humans (9). Limited experience in African outbreaks also suggested some efficacy of smallpox vaccination in preventing monkeypox. In the American outbreak, smallpox vaccination was recommended to prevent transmission to health care workers, laboratory workers and household contacts. By the end of July, residents of six states had received smallpox vaccine for the monkeypox outbreak. Some vaccinated individuals acquired monkeypox. Again, the question arises – is this an appropriate use of smallpox vaccination in a public health response?

Despite smallpox vaccination being 'front and centre' for almost a year, there is no smallpox. Is the disease a phoenix rising from the ashes of global eradication, or just a ghost that continues to haunt us? The American program committed extraordinary resources and accepted considerable risk to address a problem that may not exist. Aggressive promotion of widespread smallpox vaccination to respond to a potential problem of uncertain probability or impact requires somber analysis – is it sensible from a public health or, for that matter, a political, perspective? But the positive spinoffs, including a reassessment and updating of vaccine stockpiles, an expanded clinical and scientific understanding of the adverse effects of smallpox vaccination and, perhaps, an advance in our knowledge of antiviral agents, must also be acknowledged. The experience is a potent brew of science, public health, politics, and the military imperative.

What is an appropriate response to a potential concern of high profile but low probability and unknown severity should it occur? There is no specific answer. But consider also that any individual or organization with the laboratory sophistication to successfully mount a smallpox bioterrorist attack would also likely be capable of propagating attacks with other potential bioweapons, including bioengineered strains of microorganisms. A focus of proactive preventive interventions on smallpox may deter smallpox attacks, but it may also shift perpetrators to other agents where vulnerability remains. Intense pre-event interventions to minimize the specific risk of smallpox will not necessarily improve safety from the larger bioterrorism perspective. From this perspective, excessive focus on smallpox is shortsighted, and may even be counterproductive. The major focus of bioterrorism response planning must be the general response for minimization of the impact of any potential known or unknown agent – the surveillance, emergency response, laboratory facilities, containment facilities and clinical capacity. Specific smallpox prevention efforts are one small part of this.

The other inescapable observation is the shambles which the 'success' of global smallpox eradication has become. Instead of a benefit for society through discontinuing smallpox vaccination, some governments are now vaccinating widely in populations without disease, thus creating vaccine-associated illness. Political and economic progress towards global security has not matched the scientific and public health progress achieved in understanding and controlling communicable diseases. The smallpox experience is a compelling reminder of the imperative to think and act beyond the laboratory, the bedside, or outbreak management, to address the broader issues of global security and causes of terrorism. Otherwise, the triumphs of infectious disease eradication are hollow.

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