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## The Risks and Benefits of Pre-event Smallpox Vaccination: Where You Stand Depends on Where You Sit

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**See related article by Thorne et al,  
and editorial by Darling et al.**

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In this issue of *Annals*, Thorne et al<sup>1</sup> present a comprehensive review of smallpox vaccination complications, as well as special issues related to smallpox vaccine programs and transmission of vaccinia. This topic is of importance to emergency physicians, who have a special role in the medical and public health response to microbial threats such as smallpox. In an outbreak, persons with smallpox are likely to seek care at emergency care settings even before an outbreak or release has been recognized. Like severe acute respiratory syndrome,<sup>2</sup> health care workers may be infected with smallpox at higher rates unless they recognize this contagious threat and practice good infection control or are immune through prior successful smallpox vaccination. To prepare for such a scenario, the federal government initiated the Smallpox Vaccination Program and recommended pre-event smallpox vaccination of up to 440,000 civilian public health and hospital-based personnel during the winter and spring of 2003 (Phase 1).<sup>3</sup> This was to be followed by Phase 2, where an additional 10 million public safety and health care workers would be offered vaccine.<sup>3</sup>

Despite federal support of this program, 37,802 civilians had been vaccinated as of June 20, 2003,<sup>4</sup> less than 10% of the anticipated number. Clearly, health

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care workers have voted with their arms on this initiative despite recommendations to get vaccinated by the Advisory Committee on Immunization Practices (ACIP).<sup>5</sup> There are medical, financial, and employment consequences should an individual have a severe adverse reaction to the vaccine. Thus, a primary determinant of the number of civilians who volunteer to get vaccinated against smallpox is their assessment of the risks and benefits to them. In other words, where you stand (on the risks and benefits of pre-event smallpox vaccination) depends on where you sit (Table). From an individual risk perspective, the decision to be vaccinated or not is influenced by 3 factors<sup>6</sup>:

1. What are the risks of adverse vaccine reactions?
2. What is the risk of an intentional smallpox release?
3. What is the risk of being among the first exposed

to an unrecognized case of smallpox or to an initial smallpox release before it is recognized and mass vaccination begins?

First, the risks of smallpox vaccine adverse reactions have been well summarized.<sup>1</sup> In the pre-event smallpox vaccination program, the most important adverse reactions for a potential vaccinee are those associated with significant morbidity and those for which there are no screening criteria to reduce risk. On the basis of these criteria, postvaccinial encephalitis and the newly appreciated cardiac complications, especially myopericarditis, are of greatest concern. Before routine smallpox vaccination ended in the early 1970s, postvaccinial encephalitis occurred in about 1 in 300,000 primary vaccinees older than 1 year and was more than 15 times less common in revaccinees. About 1 in 3 vaccinees

**Table.**

*Direct risks and benefits of pre-event smallpox vaccination before and after a smallpox outbreak.*

Perspective	Risks Realized Before an Outbreak	Benefits Realized Before an Outbreak	Benefits Realized After an Outbreak
<b>Individual</b>			
Individual (vaccinees)	Severe adverse reactions, including death* Employment risks* Financial risks*	Psychological benefits ("peace of mind," sense of contributing to public good)	Protection against smallpox, including death
Contact (eg, patient)	Contact vaccinia <sup>†</sup>	None	Protection against smallpox from vaccinated contact
<b>Population</b>			
Public health and medical sectors	Contact vaccinia (low risk) <sup>†</sup>	Increased preparedness, practice, and readiness from administering the vaccine and running vaccination clinics Increased clinical knowledge from management of adverse events Increased availability of vaccinia immune globulin Increase in scientific knowledge from studying vaccinees	Prevaccinated vaccinators <sup>§</sup> More efficient and timely mass vaccination campaign <sup>§</sup> Prevaccinated medical care teams to care for smallpox patients <sup>§</sup> Prevaccinated public health response teams (investigation, contact tracing, vaccination) <sup>§</sup> Better clinical management of adverse reactions from mass vaccination Better availability of vaccinia immune globulin
General public	Contact vaccinia (very low risk) <sup>†</sup> Possible decreased trust in health authorities <sup>‡</sup>	Increase in scientific knowledge from studying vaccinees Possible increased trust in health authorities <sup>‡</sup> Deterrent to terrorists	All benefits described previously Some herd immunity Increased trust in health authorities

\*The informed consent process emphasizes the disclosure of the individual health, employment, and financial risks to the vaccinee.

<sup>†</sup>The risk of contact vaccinia will increase as vaccination becomes more widespread among vaccinees not well trained in infection control practices.

<sup>‡</sup>The level of trust or mistrust of health authorities will depend on several factors, including how honestly and effectively health officials communicate the risks, benefits, and trade-offs from the different stakeholder perspectives summarized in this Table.

<sup>§</sup>The postoutbreak response benefits from pre-event vaccination could be small if pre-event planning, preparedness, and readiness are not optimal. For example, vaccinated but untrained public health response workers would still need to be trained, potentially delaying an effective response. Additionally, efficient postoutbreak mass and ring vaccination could mitigate the risks from lack of pre-event vaccination.

with encephalitis died. Today, results from the Phase 1 reporting of vaccine adverse events demonstrate a high occurrence of myopericarditis with smallpox vaccination (and possibly associated with myocardial ischemia and dilated cardiomyopathy).<sup>7,8</sup> Among 37,802 civilians and 450,293 military personnel vaccinated, 21 (1 in 1,800) and 37 (1 in 12,000) developed myopericarditis, respectively. This cardiac complication is much more common than previously recognized in the United States. Although the patients with myopericarditis recovered clinically and there were no deaths, the long-term health consequences of myopericarditis are not known.<sup>9</sup> From the military experience, their investigators assure us that smallpox vaccination is safe<sup>8</sup>: “Our experience suggests that broad smallpox vaccination programs may be implemented with fewer serious adverse events than previously believed.” However, if civilian medical care and public health workers were reluctant to get vaccinated in the face of a much smaller risk of postvaccinial encephalitis, will they be less reluctant and volunteer in the face of an additionally recognized myopericarditis risk of 1 in 1,800?

The second factor to consider is the risk of an intentional smallpox release. This risk is considered to be low but not zero.<sup>5</sup> In a policy decision model presented to ACIP, investigators assessed different release scenarios and probability of release thresholds above which the policy should be to vaccinate public health and medical care teams.<sup>10</sup> In their conclusions, they endorsed “a policy of vaccinating all eligible health care workers and first responders before an attack.” They assumed that these workers would accept the “risk of personal harm for the public good” and would volunteer to get vaccinated, which has turned out not to be the case. Fortunately, however, although we cannot quantify with confidence the probability of smallpox release, it is very likely that should a smallpox release and outbreak occur anywhere in the world, we would discover the outbreak within 2 to 3 weeks of the initial clinical cases as was the case with monkeypox.<sup>11</sup> Given a confirmed outbreak of smallpox, vaccination of targeted health care workers followed by mass vaccination

would occur. In addition, individuals exposed to a case of smallpox will likely be protected from disease if vaccinated within 3 to 4 days of exposure.<sup>12</sup>

The third and last factor to consider in weighing the individual risks and benefits of pre-event smallpox vaccination is assessing the likelihood that one would be exposed to an unrecognized case of smallpox or to the initial release of smallpox before an outbreak is recognized and large-scale vaccinations begin. In reality, the actual risk of contact begins after a release has occurred and would continue until the outbreak is recognized. Although this risk is difficult to quantify, certain medical professionals (eg, emergency medicine staff) and certain geographic regions (eg, metropolitan, densely populated cities) are likely at higher risk until the outbreak is recognized.

Taken together, if the risks of serious vaccine reactions were very low, the risk of a smallpox release was high, and risk of having contact with the initial cases or release was high, then from an individual potential vaccinee perspective, one should get vaccinated. Alternatively, if the risk of a serious vaccine reaction was relatively high, the risk of a smallpox release was low, and risk of having contact with the initial cases or release was low, then one should not get vaccinated. In an individual risk model, these same factors have been assessed quantitatively.<sup>6</sup> In addition, postevent strategies were considered. Once an outbreak occurs, ring and mass vaccination would occur. Using this type of quantitative risk approach, most individuals (including health care workers) should postpone smallpox vaccination (and the risk of adverse reactions) until there is a smallpox outbreak and the benefits of vaccination outweigh the risks. This analysis was completed before the myopericarditis complications were widely appreciated.

Although each individual must ultimately make the decision to be vaccinated or not as part of a voluntary program, there are several other relevant perspectives on smallpox vaccination. These are summarized in the Table and include contacts to vaccinated, still-infectious vaccinees (eg, household members, patients), institutions (eg, hospitals), public health systems, and society.

Close contacts to infectious vaccinees are at risk of unintentional infection and the development of contact vaccinia.<sup>13</sup> For these contacts, there is only risk and no immediate benefit. For those who are uninformed of their exposure, the risk is involuntary. This poses an ethical dilemma in the health care setting. In general, patients accept the risks of medical care because there is an expected benefit from this care. However, if a patient experiences an exposure to vaccinia and has not been informed, we have subjected the patient to potential harm with no clear benefit. It is unethical to submit a patient to a preventable exposure without their knowledge and/or consent. On ethical grounds, we agree with Thorne et al<sup>1</sup> that health care workers who were recently vaccinated should not have close and continuous contact with patients until they are noninfectious.

Hospitals and public health institutions benefit by pre-event vaccination in terms of smallpox preparedness. This includes having prevaccinated staff, practicing vaccine administration, increasing clinical knowledge and experience in the management of vaccinia adverse reactions, increasing availability of vaccinia immune globulin, and increasing scientific knowledge from studying vaccinees. However, there are also risks to participation that include an adverse reaction in a staff member, contact vaccinia, liability issues,<sup>1</sup> and the possibility of a diminution of trust in the institution should there be significant adverse reactions. Each of these risks and benefits must be considered as an institution decides if and how to participate in the smallpox vaccination program.

Finally, as a society, we must continue to evaluate the risks and merits of our smallpox vaccination program as additional information is gathered. Both ACIP<sup>14</sup> and the Institutes of Medicine<sup>15</sup> have recommended that the vaccination program be paused before expanding to Phase 2. A pause will provide federal, state, and local agencies an opportunity to review the risks and benefits of the program in the context of all smallpox preparedness activities. We agree with the Institutes of Medicine and ACIP that, given the unanticipated risks (myopericarditis) and uncertain benefit, the civilian smallpox vaccination program should not expand at this time, especially not to the general population.

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