

CDC Interim Guidance for Revaccination of Eligible Persons who Participated in the US Civilian Smallpox Preparedness and Response Program

October 2008

Purpose: The purpose of this document is to propose a recommendation for an appropriate time-interval for revaccination of public health and health care volunteers who were vaccinated as responders in the US Civilian Smallpox Preparedness and Response Program. This document addresses only the revaccination of public health and healthcare volunteers and does not address routine revaccination guidance for laboratory workers or primary vaccination of emergency responders.

BACKGROUND: With the eradication of naturally-occurring smallpox in 1977 and destruction or transfer to 1 of 2 WHO reference laboratories of viral stockpiles, the potential threat of smallpox as a bioweapon was greatly diminished. However, verification of destruction or transfer was not systematically obtained from all countries with viral stockpiles and the possibility exists that *Variola* virus may be acquired and used by a terrorist organization.

Because of this possibility and the anthrax bioterrorism attacks that occurred in 2001, CDC asked the Advisory Committee on Immunization Practices (ACIP) to review its recommendations for smallpox vaccination regarding recommendations for vaccination of persons designated to respond to or care for a suspected or confirmed case of smallpox.¹ Supplemental recommendations were developed after formation of a joint working group of ACIP and the National Vaccine Advisory Committee in April 2002 and joined in September 2002 by the Healthcare Infection Control Practices Advisory Committee. A series of public meetings and forums also were held to review available data related to smallpox, smallpox vaccine, smallpox-control strategies, and other concerns related to smallpox vaccination.

The supplemental recommendations published in 2003 recommend that each acute-care hospital identify health-care workers who can be vaccinated and trained to provide direct medical care for the first smallpox patients requiring hospital admission and to evaluate and manage patients who are suspected of having smallpox. When feasible, the first-stage vaccination program should include previously vaccinated health-care personnel to decrease the potential for adverse events. Additionally, persons administering smallpox vaccine in this pre-event vaccination program should be vaccinated.²

Through December 2003, approximately 40,000 civilian personnel from 50 states received licensed smallpox vaccine as part of state and local smallpox preparedness programs. Of those vaccinated for whom complete data were available, approximately 17,000 were hospital health care staff, 13,000 were public health response team personnel, and 10,000 were defined as other personnel (most of whose occupations were listed as other health care). At least one employee was vaccinated in 2,137 acute care hospitals (43% of all United States acute care hospitals). At least 2,900 of these other personnel were first responders such as law enforcement, fire fighters, and emergency medical technicians. Subsequent to 2003, vaccination of response team members has

continued, although in much lower numbers. Unfortunately there is no registry which has current information regarding the number of public health and healthcare volunteers vaccinated within the states.^{3,4}

The 2003 ACIP supplemental recommendations for using smallpox vaccine in a prevent vaccination program did not address the issue of revaccination. State and local health departments have requested that CDC provide guidance regarding appropriate interval for revaccination of individuals who participate in the civilian smallpox responder vaccination program. Therefore, this interim guidance is intended to assist state and local health departments determine the appropriate revaccination schedule for eligible individuals in their jurisdiction who received smallpox vaccination as part of the US Civilian Smallpox Preparedness and Response, while considering the risks and benefits of alternate revaccination approaches.

Smallpox vaccine is made from live vaccinia virus and protects against smallpox disease but has rare but well-described adverse reactions. Serious complications and sequelae that may follow either primary smallpox vaccination or revaccination include: myocarditis and/or pericarditis, post-vaccinial encephalitis, progressive vaccinia, generalized vaccinia, erythema multiforme major (including Stevens-Johnson syndrome), eczema vaccinatum, contact transmission of vaccinia virus, and fetal death in pregnant women.⁵ Historically, death following smallpox vaccine is a rare event; approximately 1-2 death per 1 million vaccinations has occurred.^{6,7} This surveillance data, however, represented primarily the pediatric population. Using strict criteria for vaccination, designed to exclude those with conditions which were recognized to predispose to adverse events, a recent study conducted among adults, vaccinated after 2001, indicated an overall adverse event rate of 217 per 10,000 vaccinees; the rate of serious adverse events was 26 per 100,000.⁸ A joint CDC and Department of Defense smallpox vaccination safety-monitoring system found serious adverse events were rare because of careful education, prevaccination screening, and strict attention to vaccination-site management. In addition this monitoring system found that recent vaccinees could safely care for high-risk patients by adhering to recommended site care and that human immunodeficiency virus-infected individuals without severe immunosuppression had uncomplicated vaccination reactions. However; epidemiological studies did supported a causal relationship between myocarditis and/or pericarditis and smallpox vaccination. No new smallpox vaccine-associated clinical syndromes were identified.⁹

CDC has begun distribution of a new-generation smallpox vaccine, ACAM2000™ (Acambis, Inc., Cambridge, Massachusetts), to civilian laboratory personnel, the military, and state public health preparedness programs. ACAM2000 is a live, vaccinia virus smallpox vaccine that was licensed for use in the United States by the Food and Drug Administration in August 2007. ACAM2000 will be replacing Dryvax® smallpox vaccine (Wyeth Pharmaceuticals, Inc., Marietta, Pennsylvania) because of withdrawal of the Dryvax license. ACAM2000 is a live vaccinia virus derived from plaque purification cloning from Dryvax. The safety data available from the ACAM2000 clinical trials indicate a similar safety profile to Dryvax.¹⁰

The decision to provide smallpox revaccination in the pre-event setting to individuals who were vaccinated as part of the US Civilian Smallpox Preparedness and Response Program involves consideration of several factors:

1. **Smallpox threat and risk of exposure if outbreak occurs.** The risk of a deliberate release of smallpox by terrorist is real; however, this risk is low, and the population at risk for such an exposure cannot be determined. In addition, health-care workers and others would be afforded a certain level of protection from infection through appropriate infection-control measures, including use of appropriate personal protective equipment.
2. **The risk of having an unvaccinated or partially immune cadre of initial first responders.** During the smallpox era, the overall mortality rate among unvaccinated individuals was approximately 30%. Smallpox vaccine can prevent or decrease the severity of clinical disease, even when administered 3-4 days after exposure to the smallpox virus. Data emerging from recent studies examining the duration of immunologic markers in humans (and animals) vaccinated long ago suggest that some degree of protection against smallpox may be maintained for decades after vaccination. There is however, no assurance of absolute protection from acquiring disease.
3. **Expected severe adverse reactions to vaccination.** Severe adverse reactions are expected to be similar to or less than historical rates. Appropriate screening for contraindications to vaccination among vaccinated persons as well as their household contacts and recommended precautions should minimize both the risk for adverse events among vaccinees as well as the risk for transmission of vaccinia to their contacts (e.g., patients or household members). However, the risk of adverse events following multiple revaccinations is not well defined. In the event of confirmed smallpox reintroduction, vaccine benefit versus risk ratio increases greatly.
4. **Liability issues for vaccine administrators.** On October 10, 2008, the Secretary of the Department of Health and Human Services issued a Declaration for Utilization of Public Readiness and Emergency Preparedness Act for Smallpox Countermeasures. This declaration pursuant to section 319F-3 of the Public Health Service Act (42 U.S.C. 247d-6d) provides targeted liability protection for smallpox countermeasures include vaccines.
5. **Full benefit of recombinant vaccinia vaccines.** Vaccinia virus can be genetically engineered to contain and express foreign DNA. Recombinant vaccinia viruses have been engineered to express immunizing antigens of herpesvirus, hepatitis B, rabies, influenza, human immunodeficiency virus (HIV), and other viruses. Persons with preexisting immunity to vaccinia might not receive the full benefit of recombinant vaccinia vaccines developed for immunization against other infections.

The following recommendations are based upon balancing the risks and benefits of continuing pre-event smallpox revaccination. In the event of confirmed smallpox reintroduction, vaccine benefit versus risk ratio increases greatly.

RECOMMENDATION: After consideration of available scientific evidence and the

practical issues relevant to pre-event vaccination, CDC recommends revaccination of volunteer responders from the pre-event smallpox program on an as-needed, “out-the-door” basis. “Out-the-door” basis is defined as receiving revaccination only after there is determination of a credible smallpox threat to public health and prior to engaging in activities involving a risk for exposure to smallpox virus. “Out-the-door” revaccination would only apply to first responders who had been vaccinated as part of the US Civilian Smallpox Preparedness and Response and had a documented vaccine ‘take’. A “take” typically appears as a vesicle surrounded by a red areola, which becomes umbilicated and then pustular by days 7-11 after vaccination. Skin reactions after revaccination are typically less pronounced with more rapid progression and healing than those after primary vaccinations.

The “out-the-door” recommendation would be activated only after a smallpox outbreak is confirmed or highly suspected, or there is credible evidence of a release or imminent release of smallpox virus. The use of the “out-the-door” policy is also dependent on several assumptions:

- state or local health agencies maintain a sufficient supply of smallpox vaccine on hand to initiate revaccination and they have a mechanism in place to allow for quick revaccination of the responders if needed,
- state and local agencies have maintained a sufficient number and accurate registry of responders with documented takes after vaccination
- vaccine will be given to response members immediately regardless of interval from last vaccination, and
- screening for risk factors for adverse events and education must continue for every participant.
- Under the guidance of occupational health a system should be in place that is capable of monitoring all participants and has the ability to report vaccine adverse events to a vaccine safety monitoring system (e.g., Vaccine Adverse Events Reporting System [VAERS]).¹¹

CDC also recommends that personnel whose only occupational exposure to orthopoxviruses is through administering smallpox vaccine to others, (e.g., people who administer vaccine to poxvirus researchers, lab workers, etc.) be revaccinated every 10 years. Historically, vaccinators were administering smallpox vaccine as part of a disease control or eradication program and were revaccinated frequently. No data exist regarding the risks for inadvertent inoculation of vaccinia among susceptible vaccinators, but they are assumed to have some level of risk. The risk might be analogous to that observed among laboratory workers handling nonhighly attenuated vaccinia strains. During a smallpox outbreak, individuals likely to be administering vaccine in larger vaccination efforts, should receive “out-the-door” revaccination, without regard to interval from last vaccination, as outlined in this policy in order to also provide protection against smallpox exposure.

This interim guidance from CDC is based on the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including

peer-reviewed science and supporting studies when available. However, data on duration of protection and recommendations on periodicity of vaccinations are limited and based to a large extent on historic precedent and expert opinion used to develop previous ACIP recommendations for smallpox vaccination for laboratory workers using orthopoxviruses. This interim guidance balances overall risk for adverse events in the revaccinee (and their contact) populations with the public health need for a sufficient number of public health first responders available to rapidly respond to a smallpox outbreak. Implementation of this interim guidance should minimize the probability of adverse events by minimizing the number of times public health responders need to be revaccinated.

Considerations for state or local public health agencies who wish to maintain some individuals with more recent vaccination status

After consideration of the risk to benefit ratio regarding vaccination or revaccination of first responders against smallpox in the pre-event setting, some state and local public health agencies may have circumstances (e.g., perceived higher risk of targeted bioterrorism attack, inadequate number of previously vaccinated first responders), which lead them to determine that the above recommendations do not meet their specific needs.

In this situation, state and local public health officials who feel they need to go beyond the CDC recommendations and maintain a certain number of responders with a more recent vaccination status than provided by the current CDC recommendation should consider the following issues:

- Public health agencies should carefully consider if there is added benefit for more frequent revaccination given that out the door vaccination will, most likely, be recommended regardless of the time since last smallpox vaccination.
- If state and local public health agencies feel that more frequent vaccination is needed, they may want to consider whether the risk to their responders is analogous to that of laboratory workers who handle virulent strains of orthopoxviruses. ACIP recommends that these laboratory workers be revaccinated every three years.¹

-

References

- CDC. Vaccinia (smallpox) vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2001. MMWR 2001;50:1-25.
- CDC. Recommendations for Using Smallpox Vaccine in a Pre-Event Vaccination Program: Supplemental Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR 2003;52:1-16.

- Chapman LE, Mootrey GT, Neff LJ. Introduction: vaccination against smallpox in the posteradication era. *Clin Infect Dis*. 2008;46:S153-6
- Strikas RA, Neff LJ, Rotz L, et al. US Civilian Smallpox Preparedness and Response Program, 2003. *Clin Infect Dis* 2008;46:S157-67.
- CDC. Smallpox Vaccination and Adverse Reactions. *MMWR* 2003;52:1-28.
- Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination: national surveillance in the United States, 1968. *N Engl J Med* 1969;281:1201-7.
- Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys. *J Infect Dis* 1970;122:303-9
- Casey CG, Iskander JK, Roper MH, et al. Adverse events associated with smallpox vaccination in the United States, January-October 2003. *JAMA* 2005;294:2734-43.
- Neff J, Modlin J, Birkhead GS, et al. Monitoring the Safety of a Smallpox Vaccination Program in the United States: Report of the Joint Smallpox Vaccine Safety Working Group of the Advisory Committee on Immunization Practices and the Armed Forces Epidemiological Board. *Clin Infect Dis* 2008;46:S258-70.
- CDC. Notice to Readers: Newly Licensed Smallpox Vaccine to Replace Old Smallpox Vaccine. *MMWR* 2008; 57;207-8
 - Thomas TN, Reef S, Neff L, Sniadack MM, Mootrey GT. A Review of the Smallpox Vaccine Adverse Events Active Surveillance System. *Clin Infect Dis* 2008;46:S212-20.