THE ASSISTANT SECRETARY OF DEFENSE

1200 DEFENSE PENTAGON
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

APR - 1 2008

MEMORANDUM FOR SECRETARIES OF THE MILITARY DEPARTMENTS
CHAIRMAN OF THE JOINT CHIEFS OF STAFF
UNDER SECRETARIES OF DEFENSE
GENERAL COUNSEL OF THE DEPARTMENT OF DEFENSE
INSPECTOR GENERAL OF THE DEPARTMENT OF DEFENSE
DIRECTORS OF DEFENSE AGENCIES
COMMANDANT OF THE U.S. COAST GUARD

SUBJECT: Update to Clinical Policy for the Department of Defense Smallpox Vaccination Program

This Health Affairs policy memorandum supersedes Health Affairs memorandum, "Clinical Policy for the Department of Defense (DoD) Smallpox Vaccination Program (SVP)," dated November 26, 2002. This memorandum updates policy on medical issues involving smallpox vaccination: Education, medical screening before immunization, pregnancy screening, vaccination-site selection, vaccine delivery, medical exemptions, and adverse-event management.

This memorandum applies primarily to the ACAM2000-brand smallpox vaccine manufactured by Acambis Incorporated, when administered in its original full-strength concentration. ACAM2000 was licensed by the U.S. Food and Drug Administration (FDA) on August 31, 2007. Supplemental policies will be issued, if warranted, for other circumstances or other vaccine formulations.

Education

All personnel will be educated about smallpox and smallpox vaccination before vaccination. Educational materials provided shall address the rationale, contraindications, criteria for medical exemptions for Service members or their household contacts, benefits, expected response at the vaccination site, side effects, risks to household contacts, vaccination-site care, and other medical information concerning the vaccine.

The ACAM2000-brand smallpox medication guide and the most current DoD version of the Smallpox Vaccine Trifold Brochure (available under "Education Toolkit"

at *www.vaccines.mil*) will be provided to vaccinees prior to vaccination (Attachments 1 and 2). The ACAM2000 package insert will also be provided to health care providers (Attachment 3).

Health care providers will remain alert to modifications in clinical recommendations as the smallpox vaccination program continues. Personnel involved in this program should regularly review the following Web sites for new clinical information and educational resources: Military Vaccine (MILVAX) Agency Web site at *www.vaccines.mil*, the Vaccine Health Centers (VHC) Network at *www.vhcinfo.org*, and the Centers for Disease Control and Preventions (CDC) at *www.bt.cdc.gov/agent/smallpox*. However, nothing in this memorandum will be superseded except by subsequent memoranda from the Assistant Secretary of Defense (Health Affairs).

Medical Screening Before Immunization

Medical screening before vaccination for contraindications in vaccine recipients and their household contacts is essential to prevent serious complications. Contraindications will be documented in the medical record and the automated immunization tracking system. Screening must be conducted in a manner that Service members can freely ask questions and get reliable answers. The standard of practice for all immunizations includes medical screening before immunization. Unique for the smallpox vaccine is the need to screen for risks among household contacts. Education and screening shall be conducted to document medical conditions for which immunization exemption (temporary or permanent) or further medical evaluation before immunization is indicated. Standardized screening tools and a follow-up questionnaire is provided (Attachment 4).

Infection with the human immunodeficiency virus (HIV) is a contraindication to smallpox vaccination. Service members will be up to date in accordance with Service HIV-screening policies before smallpox vaccination. Service members who are concerned that they could have HIV may request additional HIV testing. DoD civilian employees and contractors to be vaccinated against smallpox will be offered HIV testing in a confidential setting, with results communicated to the potential vaccinee before vaccination. HIV testing is recommended for anyone who has a history of a risk factor for HIV infection, especially since his or her last HIV test, and who is not sure of his or her HIV-infection status. Because known risk factors cannot be identified for some people infected with HIV, people concerned that they could be infected should be tested.

Pregnancy Screening

DoD policy is to defer smallpox vaccinations until after pregnancy, except in emergencies where personal benefit from vaccination outweighs the risks. During a smallpox outbreak, pregnant women with a high-risk exposure to smallpox may be vaccinated because the benefits of vaccination would outweigh its risks.

In accordance with the FDA and Advisory Committee on Immunization Practices (ACIP) recommendations, all appropriate efforts will be taken to avoid unintended vaccination during pregnancy. On rare occasions, typically after primary (first) vaccination, vaccinia virus has been reported to cause fetal vaccinia infection. Fetal vaccinia usually results in stillbirth or death of the infant shortly after delivery. Since the inception of the DoD smallpox vaccination program, there have been no reported cases of fetal vaccinia. Vaccinia vaccine is not known to cause congenital malformations.

All immunization clinics will display in a prominent place a written warning against unintentionally vaccinating pregnant women. This warning must be visible during the screening process. Women of childbearing potential are to be questioned/screened for pregnancy before receiving immunizations. Women who are uncertain about their pregnancy status shall be medically evaluated for pregnancy before immunization. Because the requirement for smallpox vaccination is based largely on occupational risk, defer vaccination for pregnant women at least until the resumption of full duties following pregnancy, or later as postpartum care may require. In addition, all women receiving a smallpox vaccination will be instructed to avoid becoming pregnant for at least four weeks after their smallpox vaccination. All cases of pregnant women being inadvertently vaccinated will be referred to the DoD Smallpox Vaccine Pregnancy Registry at the Naval Health Research Center, San Diego, California. The Web site is *www.nhrc.navy.mil/department164/projects/birthdefects.htm*, or call (619) 553–8400. (Attachment 5).

Vaccination Site Selection

The preferred site for smallpox vaccination is the skin over the insertion of the deltoid. Other optional sites are described in the vaccine package insert (Attachment 3). As always, appropriate clinical judgment is warranted. Do not vaccinate near the site of an active skin lesion or rash. Tattooed skin is not a contraindication for site selection, but should be considered where evaluation of a take may be impaired. Avoid skin folds where drying is impeded. Any skin condition that may interfere with the immune response to vaccination should be carefully evaluated before vaccination.

Vaccination

Only appropriately trained and qualified medical personnel, upon the order of an appropriately privileged health care provider, will administer the smallpox vaccine. People who administer the smallpox vaccine must be vaccinated themselves. While it is not a contraindication, pregnant females with a current smallpox status are discouraged from administering the smallpox vaccine. The preference to vaccinate smallpox vaccinators is based on the risk of inadvertent inoculation from repetitive handling of the vaccine. People may administer the smallpox vaccine promptly after being personally vaccinated.

Smallpox vaccination shall consist of 15 punctures (jabs) with a bifurcated needle for a primary (first) vaccination and for revaccination (see package insert). People vaccinated with the smallpox vaccine in the past 10 years do not require revaccination, except specific laboratory workers involved with orthopox virus research, who may require more frequent vaccination.

Assessment of vaccine take is required for health care workers and members of smallpox response teams who will travel into a smallpox outbreak area. Other persons receiving the vaccine should also have their vaccine take assessed. To assess vaccine take, medical personnel trained in vaccination evaluation will inspect the vaccination site six to eight days after vaccine administration. Reactions will be categorized as "Major Reaction" or "Equivocal," in accordance with the World Health Organization criteria (Attachment 6). To accommodate individuals for whom "take" assessment is not feasible, all persons receiving the smallpox vaccine will be instructed to report to the vaccination clinic if they do not develop a characteristic smallpox vaccination reaction.

Formation of a major cutaneous reaction by days six to eight is evidence of a successful "take" and acquisition of protective immunity. An equivocal reaction is any reaction that is not a major reaction, and indicates a non-take due to impotent vaccine or inadequate vaccination technique. Individuals who are not successfully vaccinated (i.e., equivocal after primary vaccination) may be revaccinated in an attempt to achieve a satisfactory take. If a repeat vaccination is given and no visible cutaneous reaction is noted, individuals should be referred for immunologic evaluation.

Accurate documentation of both vaccination and take is required. Vaccination will be documented in both individual health records and automated immunization tracking systems. In addition, vaccination take will be documented in individual health records immediately beneath the vaccination entry by writing the date of assessment and the type of reaction: Major Reaction or Equivocal.

Persons administering vaccines will follow necessary precautions to minimize risk of spreading diseases. Because of the nature of the vaccine container and method of administration, personnel preparing and administering the vaccine should wear surgical or protective gloves and avoid contact of the vaccine with skin, eyes, or mucous membranes. Special consideration should be observed while adding diluent to the vaccine vial to prevent spraying in the eyes. Gloves should be changed between patients.

Needles should be discarded in labeled, puncture-proof containers to prevent inadvertent needle-stick injury or reuse. Standard needle-stick-injury procedures will be followed if a vaccinator is inadvertently stuck with a used bifurcated needle.

No skin preparation should be performed unless the skin at the intended site of vaccination is obviously dirty, in which case an alcohol swab(s) may be used to clean the area. If alcohol is used, the skin must be allowed to dry thoroughly to prevent inactivation of the live vaccine virus by the alcohol.

Revaccination

Prior vaccination may modify (reduce) the cutaneous response upon revaccination such that the absence of a cutaneous response does not necessarily indicate vaccination failure. If a previously vaccinated person does not manifest a characteristic vaccination reaction six to eight days after smallpox vaccination, that person does not require revaccination in an attempt to elicit a cutaneous response.

Individuals should be revaccinated if more than 10 years have elapsed since the last smallpox vaccination. Persons at continued high risk of exposure to smallpox (e.g., research laboratory workers handling variola virus) should receive ACAM2000 vaccinations every three years.

Quality Assurance

Medical commanders will use standardized materials to train smallpox vaccinators. Medical commanders will assess vaccination technique by evaluating the vaccination take rates among the first cohort of people (e.g., 50 to 100) vaccinated by each vaccinator. Published studies found take rates > 95% with appropriate technique.

Medical commanders will assure that proper screening of vaccine recipients occurs before vaccination. Access to providers experienced in benefit-risk assessment will be made available to vaccine recipients and vaccinators. Medical commanders will facilitate prompt evaluation of vaccine recipients with adverse events or side effects that

interfere with the ability to work. The DoD's Clinical Guidelines, "Guide for Managing Adverse Events After Vaccination," was created to help medical personnel individually manage and document adverse events after vaccination. This document can be found under "Safety/Adverse Events" on the MILVAX Web site *(www.vaccines.mil)*, or under "Providers," "Management of Adverse Events" on the VHC Web site at (*www.vhcinfo.org*).

Timing and Spacing of Other Vaccinations

General recommendations from the ACIP accept administration of live and inactivated vaccines simultaneously, or at any interval. The only major restriction to combining vaccinations is with multiple live-virus vaccines, which should either be given simultaneously or separated by 28 days or more. There are limited data evaluating the simultaneous administration of the smallpox vaccine with other live-virus vaccines. It is desirable to separate varicella (chicken pox) and smallpox (vaccinia) vaccinations by 28 days, because of the potential to confuse attribution of lesions that may result in vaccine recipients.

Do not administer other vaccines near the smallpox vaccination site.

Care of the Vaccination Site

Vaccinia virus is present on the skin at the vaccination site up to 30 days after vaccination and until the site is healed. During that time, care must be taken to prevent the spread of the virus to another area of the body or to another person by inadvertent contact. Disease transmission from intact scabs is unlikely, but high-risk individuals may be vulnerable to scab particles. The DoD's goal is to reduce this risk as much as possible.

The most important measure to prevent the inadvertent-contact spread from smallpox vaccination sites is thorough hand washing (e.g., alcohol-based waterless antiseptic solution, soap, and water) after contact with the vaccination site.

To avoid secondary infection, commanders and other leaders will direct physical activities so that smallpox vaccination sites are not subject to undue pressure (likely to burst a pustule), rubbing, or immersion sufficiently prolonged to cause tissue breakdown or secondary infection. Activities that complicate vaccine site care and cleanliness should be avoided during the postvaccination healing period. For example, clothing and load-bearing equipment will be arranged in a manner to avoid excessive pressure or rubbing at the vaccination site. Avoid contact sports, such as wrestling. Avoid immersion in public pools or spas.

Appropriate care should be taken to prevent the spread of vaccinia virus from the vaccination site. The following special precautions will be observed. The vaccination site must be completely covered with a semipermeable bandage. Keep the site covered for 30 days and until the site is healed. Wearing clothing with sleeves covering the vaccination site and/or using a loose, porous bandage (e.g., standard Band-Aid®, a piece of gauze attached with adhesive, or paper tape around each edge) to make a touch-resistant barrier can reduce the opportunity for contact transfer until the scab falls off on its own. The vaccinee should change the bandage every one to three days, as this will keep skin at the vaccination site intact and will minimize softening. Do not apply salves or ointments on the vaccination site.

Used bandages, along with the vaccination scab, should be disposed of as biohazardous waste. If biohazardous waste receptacles are not available, these items should be disposed in sealed plastic bags (e.g., Ziploc® bag) with a small amount of bleach. Clothing, towels, sheets, or other cloth materials that have had contact with the site can be decontaminated with routine laundering in hot water with detergent and/or bleach. Normal bathing can continue, but it is best to keep the vaccination site dry by using a waterproof bandage during bathing. Avoid rubbing the vaccination site.

Close physical contact with infants less than 1-year of age should be minimized for 30 days after vaccination and the vaccine site is healed. If unable to avoid infant contact, wash hands before handling an infant (e.g., feeding, changing diapers) and ensure that the vaccination site is coved with a semipermeable bandage and clothing. It is preferable to have someone else handle the infant. The smallpox vaccine is not recommended for use with a nursing mother under nonemergency conditions.

Recently vaccinated health care workers should minimize contact with unvaccinated patients, particularly those with immunodeficiencies and those with current skin conditions, such as burns, impetigo, contact dermatitis, chicken pox, shingles, psoriasis, or uncontrolled acne. Contact with the above individuals should be minimized for 30 days after vaccination and the vaccine site is healed. Even patients vaccinated in the past may be at increased risk due to current immunodeficiency. If contact with unvaccinated patients is essential and unavoidable, health care workers can continue to have contact with patients, including those with immunodeficiencies, as long as the vaccination site is well-covered and thorough hand hygiene is maintained. In this setting, a more occlusive dressing might be appropriate. Semipermeable polyurethane dressings (e.g., Opsite®, Tegaderm®) are effective barriers to vaccinia and recombinant vaccinia viruses. However, exudate may accumulate beneath the dressing, and care must be taken to prevent viral contamination when the dressing is removed. In addition, accumulation

of fluid beneath the dressing may increase tissue breakdown at the vaccination site. To prevent accumulation of exudates, cover the vaccination site with dry gauze, and then apply the dressing over the gauze. The dressing should be changed every one to three days (according to the type of bandaging and amount of exudate), such as at the start or end of a duty shift. Military treatment facilities (MTFs) should develop plans for site-care stations, to monitor workers' vaccination sites, promote effective bandaging, and encourage hand hygiene. Wearing long-sleeve clothing can further reduce the risk for contact transfer. The most critical measure in preventing inadvertent contact spread is thorough hand hygiene after changing the bandage, or after any other contact with the vaccination site.

Medical Exemptions

Some individuals will have either acute or chronic pre-existing conditions that may warrant medical exemption from smallpox vaccination. In some cases, vaccination should be withheld if the individual cannot avoid household contact with another person with contraindicating conditions. Furthermore, a small proportion of individuals will develop a more serious reaction after vaccination that may warrant medical exemptions, temporary and permanent, from further smallpox vaccination.

In a smallpox emergency, there are no absolute contraindications to vaccinating people with a high-risk exposure to an infectious case of smallpox (e.g., face-to-face contact). Prior contraindications to vaccination could be overshadowed by personal risk of smallpox disease. The smallpox vaccine would be made available for people exempted during pre-outbreak vaccination programs. People at greatest risk for experiencing serious vaccination complications are often those at greatest risk for death from smallpox. If a relative contraindication to vaccination exists, the risk for experiencing serious vaccination complications must be individually weighed against the risks for experiencing a potentially fatal smallpox infection.

Granting medical exemptions is a medical function performed by a privileged health care provider. The provider will grant individual exemptions when medically warranted, with the overall health and welfare of the patient clearly in mind, balancing potential benefits with the risks while taking into consideration the threat situation. Medical exemptions are not based on preferences of the prospective vaccinee for or against vaccinations.

The two most common annotated medical exemption categories are Medical Temporary and Medical Permanent. Annotate the Service member's records and the immunization tracking system with these codes, and update them as appropriate. In the event of a confirmed smallpox outbreak, permanent exemptions could be lifted, based on individual risk.

People who have household contact with a person who has a contraindication to smallpox vaccination (e.g., immune-suppressed people, people with atopic dermatitis or eczema, pregnant women) shall either have alternative housing arrangements or be exempted from smallpox vaccination until the household-contact situation is no longer applicable. Avoidance of contact should continue for 30 days after vaccination and until the vaccine site is healed.

Military-unique berthing settings require similar precautions. Exempt individuals should be physically separated and exempt from duties that pose the likelihood of contact with potentially infectious materials (e.g., clothing, towels, linen) from recently vaccinated people. This separation will include not having the vaccine recipient share or alternate use of common sleeping space (e.g., cot, bunk, berth) with people with contraindications to vaccination.

Temporary medical exemptions are warranted when a provider has a concern about the safety of immunizations in people with certain clinical conditions. The vaccine's package insert contains examples of situations that warrant a temporary medical exemption (e.g., immune-suppressed people and pregnant women). The ACIP notes that people with acute, chronic, or exfoliative skin conditions (e.g., burns, impetigo, varicella zoster, herpes, psoriasis, severe or uncontrolled acne) may also be at higher risk for inadvertent inoculation and should not be vaccinated until the condition resolves or a provider affirms it is under maximal control.

In situations where a medical condition is being evaluated or treated, a temporary deferral of smallpox vaccination may be warranted, up to a maximum of 12 months. This would include significant vaccine-associated adverse events that are being evaluated, or while awaiting specialist consultation. The attending physician will determine the deferral interval, based on individual clinical circumstances.

Medical Permanent exemptions are generally warranted if the medical condition or adverse reaction is so severe or unremitting that the risk of subsequent immunization is not justified. In the case of the smallpox vaccine, these permanent exemptions could be lifted if the individual had face-to-face contact with someone contagious with smallpox. Examples of situations warranting a permanent medical exemption appear in the vaccine's package insert (e.g., life-threatening allergy to vaccine component, immune-suppressed people, people infected with HIV, people with atopic dermatitis or eczema or a past history of those disorders). People with contraindicating skin conditions who received the smallpox vaccine earlier in life may be revaccinated after medical consultation for individual risk-benefit decision making.

If a permanent medical exemption is indicated, follow appropriate DoD and Service-specific policies for granting such exemptions. If the situation changes, an appropriate medical specialist can remove a medical exemption.

If an individual's clinical case is complex or not readily definable, health care providers should consult an appropriate medical specialist with vaccine safety-assessment expertise, before granting a permanent medical exemption. In addition, providers may consult with physicians in the VHC Network (*www.vhcinfo.org*). In such cases, providers will document specialty consultation in the individual's health record, including the considerations and reasons why a temporary or permanent medical exemption is or is not granted.

An individual who disagrees with a provider's recommendation regarding an exemption may request a referral for a second opinion. In such cases, the individual will be referred to a provider experienced in vaccine adverse-event management who has not been involved in the decision-making to this point. This provider may be at the same facility or, when applicable, at a referral facility. If the patient disagrees with the second opinion, he or she may be referred directly to the VHC Network. Medical commanders retain authority to review all appealed exemption determinations and may delegate this authority to individuals with appropriate expertise within their organization.

Each MTF commander will assist people in obtaining appropriate specialty consultations expeditiously and in resolving patient difficulties. Specialists may grant permanent medical exemptions. Return of the patient to his or her primary care provider is not required if the referring specialist deems a permanent medical exemption is warranted. A Vaccine Adverse Event Reporting System (VAERS) report should be filed for any permanent medical exemption due to a vaccine-related adverse event. The following medical exemption codes relate to all vaccines.

Medical Exemption Codes:

Code	Meaning	Explanation or Example	Duration
MA	Medical Assumed	Prior immunization reasonably inferred from individual's past experiences (for example, basic military training), but documentation is missing. Code used to avoid superfluous immunization. Code can be reversed upon further review.	Indefinite
MI	Medical Immune	Evidence of immunity. For smallpox, documented infection (indefinite exemption) or documented confirmed "take" in medical records within the past 10 years.	Up to 10 years
MR	Medical Reactive	Permanent restriction from receiving additional doses of smallpox vaccine. Severe adverse reaction after immunization (e.g., anaphylaxis). File VAERS report.	Indefinite
MT	Medical Temporary	Pregnancy, hospitalization, temporary immune suppression, convalescent leave, pending medical evaluation board, events referred for medical consultation, any temporary contraindication to immunization, (e.g., smallpox vaccine and household-contact situation).	Up to 365 days
MP	Medical Permanent	HIV infection, atopic dermatitis, certain cardiac conditions, prolonged or permanent immune suppression, other condition determined by physician. Can be reversed if the condition changes.	Indefinite
MD	Medical Declined	Declination of optional vaccines (not applicable to many military vaccinations), religious waivers.	Indefinite
MS	Medical Supply	Exempt due to lack of vaccine supply.	Indefinite

Adverse-Event Management

As with any vaccine, some individuals receiving the smallpox vaccine will experience side effects or adverse events. Adults vaccinated for the first time may develop a clinical illness with injection-site inflammation, muscle aches, and fatigue, most often on days eight to nine after vaccination. This illness may interfere with work. In addition, the smallpox vaccine exhibits a unique adverse-event profile, including myocarditis and/or pericarditis, encephalitis, progressive vaccinia, eczema vaccinatum, and other serious conditions.

Ongoing evaluation of health outcomes among Armed Forces personnel indicates individuals vaccinated for smallpox are at higher risk for myocarditis and/or pericarditis than those not vaccinated. The CDC ACIP recommends exempting individuals with known cardiac condition(s) and persons with three or more known major cardiac risk factors. The Services should exempt personnel with the following cardiac conditions: Myocardial infarction, angina pectoris, cardiomyopathy, congestive heart failure, stroke, transient ischemic attacks, chest pain or shortness of breath with activity associated with a heart condition, other coronary artery diseases, and other heart conditions under the care of a physician. Persons with any of the listed conditions should be exempted from smallpox vaccination.

The following cardiac risk factors should be identified during pre-immunization processing: Current cigarette smoking, hypertension, hypercholesterolemia, diabetes mellitus, and family history of heart disease in first degree relative with onset before age 50. Persons with three or more of the above referenced risk factors should be exempted from receiving the smallpox vaccine. Along with the ACIP, Health Affairs recommends that recent smallpox vaccine recipients who have a cardiac condition or three or more major cardiac risk factors be evaluated by a health care professional if they develop any symptoms of chest pain, shortness of breath, or other symptoms of heart disease. All people with heart disease or risk factors should receive the routine care recommended for persons with these conditions (Attachment 7).

All DoD beneficiaries, including Reserve Component personnel who received their smallpox vaccine while in a duty status, with a clinically verified diagnosis of post-smallpox vaccine myopericarditis, will be enrolled in the central registry maintained by the VHC network and be followed for a minimum of 24 months from the date of initial diagnosis. Patient-informed consent is not required as part of enrollment. Identified cases should be submitted to VAERS. Upon enrollment, VHC staff help ensure appropriate follow-up in coordination with the patient's case manager (Attachment 8).

Those individuals requiring medical treatment/evaluation should be retained on Active Duty pending resolution of the medical condition or completion of the disability evaluation. Each Service will coordinate with the Military Medical Support Office (MMSO) (1-888-MHS-MMSO), as needed, to provide appropriate civilian medical follow-up and payment arrangements for Reserve Component personnel.

To support clinicians seeking multidisciplinary consultation, the MILVAX Agency established a 24/7 toll-free number for short-notice teleconferencing. Clinicians wishing to consult via this teleconference bridge with VHC staff and/or

military cardiologists regarding optimal care should call the DoD Vaccine Clinical Call Center at (866) 210–6469. Additional consultative support is available via e-mail at *ASKVHC@amedd.army.mil.*

DoD Clinical Guidelines for Management of Adverse Events After Vaccination offers useful advice. These clinical guidelines are available at the MILVAX Agency Web site at *www.vaccines.mil*, and at the VHC Web site at *www.vhcinfo.org*.

Vaccinia Immune Globulin (VIG) is indicated for the treatment or modification of certain conditions induced by the smallpox vaccine. Consultation with a board-certified infectious disease or allergy-immunology specialist is required prior to administration. The VHC Network will provide and coordinate professional consultation services to optimize clinical use of VIG, and then maintain a registry of patients treated with VIG. Long-distance consultations will be arranged via the VHC Network's Vaccine Clinical Call Center ((866) 210–6469). An infectious disease or allergy immunologist, in consultation with the VHC, and CDC physician, authorizes release of VIG. VIG is requested directly from the CDC by calling the CDC Director's Emergency Operation Center at (770) 488-7100 and request to speak with the Division of Bioterrorism Preparedness and Response on-call person. The CDC is the release authority for VIG (Attachment 9).

Adverse reactions from DoD-directed immunizations are line-of-duty conditions.

Immunizations are provided as part of the DoD's Force Health Protection program. At the time of immunization, personnel are to be provided documentation that identifies date and location of immunization, general information on typical responses to vaccination, common and serious adverse events, location of the nearest MTFs, and the toll-free telephone number ((888) MHS-MMSO) of the MMSO, in the event medical treatment is required from non-MTFs. Emergency-essential DoD civilian employees and contractor personnel carrying out mission-essential services are entitled to the same treatment and necessary medical care as given to the Service members. This includes follow-up and/or emergency medical treatment from the MTF or treatment from their personal health care providers or non-MTFs for emergency medical care as a result of immunizations required by their DoD employment.

When a vaccine recipient presents at an MTF, expressing a belief that the condition for which treatment is sought is related to an immunization received during a period of duty, the person must be examined and provided necessary medical care. Once treatment has been rendered or the individual's emergent condition is stabilized, Line of Duty and/or Notice of Eligibility will be determined as soon as possible. Reserve Component members and their family members, who seek medical attention as a result of

adverse reactions from DoD-directed immunizations should 1) immediately seek medical attention if an emergency and contact MMSO and their command as soon as possible, or 2) contact MMSO and their unit command for referral to the nearest treatment facility and to ensure payment for care and entitlements.

In the case of emergency-essential civilian employees presenting to a MTF or occupational health clinic, the initial assessment and any needed emergency care should be provided consistent with applicable occupational health program procedures. In the case of contractor personnel covered by the vaccination policy presenting to a military treatment facility or occupational health clinic, Secretarial-designee authority shall be used, consistent with applicable DoD policy, to allow an initial assessment and needed emergency care. This policy will facilitate awareness by our medical professionals of adverse events and provide the patient with medical expertise regarding vaccine events not necessarily available in the civilian medical community. This use of Secretarial-designee authority does not change the overall responsibility of the contractor under the workers' compensation program for all work-related illnesses, injuries, or disabilities.

A privileged health care provider and any specialists, as indicated, should immediately evaluate any vaccinee with a serious adverse event temporally associated with receiving smallpox vaccination.

VAERS reports shall be filed using Service reporting procedures for those events resulting in hospital admission, lost duty time, or work of 24 hours or more, adverse event suspected to result from contamination of a vaccine vial, or death. Further, health care providers are encouraged to report other adverse events that in the provider's professional judgment appear to be unexpected in nature or severity. This is to include autoinoculation (or inadvertent infections). In other situations in which the patient wishes a VAERS report to be submitted, the health care provider will work with the patient to submit one without regard to causal assessment. VAERS report forms may be obtained by accessing *www.vaers.org*, or by calling (800) 822-7967. The DoD forwards all VAERS reports to the FDA and the CDC without restriction.

Adverse-event management should be thoroughly documented in medical records. Medical record coders should use precision in coding medical encounters, noting coded specific to the smallpox vaccine (Attachment 10). A copy of the VAERS report will be filed in an individual's medical record after submitting the original form through DoD reporting channels, as discussed above. Providers are encouraged to provide a copy of the VAERS report to the patient.

Blood Donor Deferral

Because there is a significant donor deferral period associated with smallpox vaccination, it is critical that vaccination schedules be closely coordinated with local military and civilian donor center collection schedules to reduce the impact on the readiness and availability of the military blood supply. Individuals who receive the vaccination and have no complications will be deferred from donating blood for 30 days after vaccination and until the vaccination site is healed. Individuals with vaccine complications will be deferred for 14 days after all vaccine complications have resolved.

Policy

These policies are effective immediately and should be communicated to appropriate commanders, health care providers, and others involved in implementation. If the FDA-approved labeling for the smallpox vaccine changes, corresponding aspects of these policies will be superceded. Any recommendations from the ACIP will be taken into account in providing vaccination and clinical care.

S. Ward Casscells, MD

Attachment:
As stated

cc:
Chief of Staff of the Army
Chief of Naval Operations
Chief of Staff of the Air Force
Commandant of the Marine Corps
Surgeon General of the Army
Surgeon General of the Navy
Surgeon General of the Air Force
Director of Health & Safety, U.S. Coast Guard

Attachment 1

Medication Guide
ACAM2000™

Smallpox (Vaccinia) Vaccine, Live

Please read this Medication Guide before you receive a vaccination with ACAM2000. This Guide does not take the place of talking to your healthcare provider about ACAM2000 and the smallpox disease.

What is the most important information I should know about the ACAM2000 smallpox vaccine?

- **If you are at a high risk for being exposed to smallpox, you should be vaccinated even if you have health problems, unless you have certain problems with your immune system.** People who have health problems may have a higher chance of getting serious side effects from vaccination but are also those who have a higher chance of dying from the smallpox disease.
- **ACAM2000 may cause serious heart problems called myocarditis and pericarditis, or** swelling of the heart tissues. In studies, about 1 in every 175 persons who got the vaccine for the first time may have experienced myocarditis and/or pericarditis. On rare occasions these conditions can result in an irregular heart beat and death. Your chances of getting heart problems from the vaccine are lower if you have already had this vaccine before. You can have myocarditis and/or pericarditis even if you have no symptoms. **Call your healthcare provider or get emergency help right away if you have:**
    - **chest pain or pressure**
    - **fast or irregular heartbeat**
    - **breathing problems**

  See "**What are the possible side effects of ACAM2000?**"
- **Because the vaccine has a live virus, it can spread to other parts of your body or to other people if you touch the vaccination site and then touch other parts of your body or other people.** The vaccine virus can spread until the vaccination scab falls off (2 to 4 weeks after vaccination). **If the virus is spread to a person who should not get the vaccine, the side effects can be very serious and life-threatening.**

  See "**How do I care for the smallpox vaccination site?**"

What is the ACAM2000 smallpox vaccine?

ACAM2000 is a prescription vaccine used to protect people against smallpox disease. It is for use in people who have a high chance of getting the disease.

ACAM2000 contains live vaccinia virus (a "pox"-type virus) to protect against smallpox disease.

Who should not get the ACAM2000 smallpox vaccine?

- **In an emergency, you should be vaccinated if you are at high risk for getting smallpox disease even if you have health problems (except if you have certain problems with your immune system as discussed below).**

Attachment 1

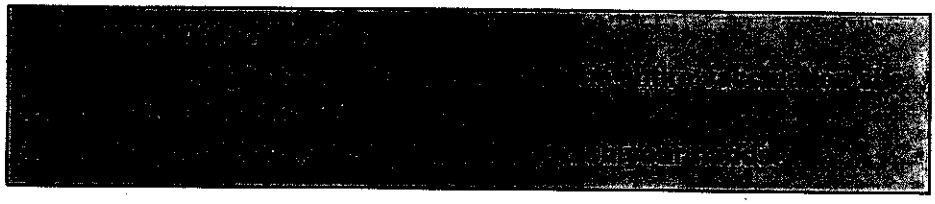
- Your healthcare provider may not give you ACAM2000 if you have problems with your immune system. You may have immune system problems if you:
    - have leukemia
    - have lymphoma
    - have had a bone marrow or organ transplant
    - have cancer that has spread
    - have HIV, AIDS
    - have cellular or humoral immune deficiency
    - are being treated with radiation
    - are being treated with steroids, prednisone, or cancer drugs

How do I receive ACAM2000?

ACAM2000 smallpox vaccine is not a shot like other vaccines. Your healthcare provider will make 15 pokes in the skin of your upper arm with a needle containing ACAM2000. The pokes are not deep, but will cause a drop of blood to form. This is called the vaccination site.

It is important to care for the vaccination site properly so that the virus doesn't spread to other parts of your body or to other people. You can infect another part of your body or other people until the scab falls off.

How do I care for the ACAM2000 vaccination site?



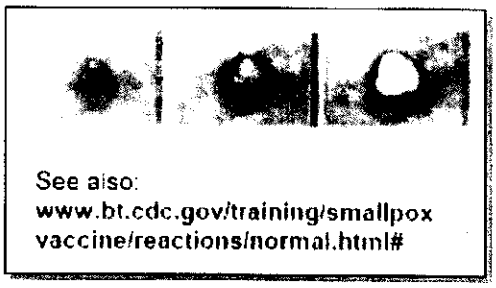
- **When changing bandages or caring for your vaccination site, wear gloves. Use an absorbent bandage or Band-Aid to completely cover your vaccination site.**
    - Change your bandage when it begins to soak through (at least every 1 to 3 days).
    - Throw away gloves and used bandages in sealed or double plastic bags. A small amount of bleach can be added to the bag to kill the virus.
- **Wear clothes with sleeves to cover the site and prevent scratching the vaccination site.** It is especially important to wear a bandage and sleeves to bed to avoid scratching.
- **Wash your hands frequently** with alcohol-based cleansers or soap and water.
    - Be sure to wash your hands each time you change your bandage or if you touch the vaccination site.

- Do not use creams or ointments on the vaccination site because they will delay healing and can spread the virus.
- Do not scratch or pick at the vaccination site.
- You can take a bath or shower, but don't touch or scrub the vaccination site.
    - It is best to cover the vaccination site with a waterproof bandage.
    - If the vaccination site gets wet, dry the site with toilet paper and flush it. (Do not use a cloth towel because it can spread the virus.)
    - Cover the vaccination site with a loose gauze bandage after bathing to allow it to dry out.
- Do not use a bandage that blocks air from the vaccination site. This could cause the skin at the vaccination site to soften and wear away.
- If you exercise enough to cause sweat to drip, use a waterproof bandage on the vaccination site when exercising.
- Wash clothing, towels, bedding or other items that may have come in contact with the vaccination site separately from other wash. Use hot water with detergent and bleach.
- When the scab falls off, throw it away in a sealed plastic bag with a small amount of bleach. Wash your hands afterwards.

What should I expect at the vaccination site and in the weeks following vaccination?

- If vaccination is successful, a red and itchy bump forms at the vaccination site in 2 to 5 days. Over the next few days, the bump becomes a blister and fills with pus. During the second week, the blister dries up and a scab forms. The scab falls off after 2 to 4 weeks, leaving a scar. People vaccinated for the first time may have a larger reaction than those being revaccinated. See expected responses below:

Smallpox Vaccination Site:
expected response after vaccination



See also:
www.bt.cdc.gov/training/smallpox vaccine/reactions/normal.html#

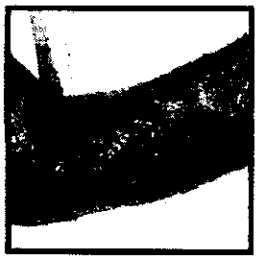
Note: After 6 to 8 days, check to be sure that your vaccination site looks like one of the pictures above. If is does not look like this, see your healthcare provider because you may need to be revaccinated.

- If you need medical care in the month after your vaccination, tell your healthcare provider you just got a smallpox vaccination.

- Certain people, such as laboratory workers who work with smallpox, are at risk of being exposed to smallpox over a long period of time. These people may need a booster vaccination every 3 years to maintain protection against smallpox.

What should I avoid after getting vaccinated with the ACAM2000 smallpox vaccine?

- **For 4 weeks after vaccination AND until the vaccination site has healed, you should avoid:**
    - **getting pregnant.** Smallpox vaccine may rarely cause infection in an unborn baby if the mother is vaccinated during pregnancy. This infection usually results in stillbirth or death.
    - **handling babies or breastfeeding.**
    - **swimming or hot tub use.**
    - **donating blood**
    - **Tuberculin (TB) testing. Smallpox vaccine may cause the TB test to give the wrong result.**
- Avoid rubbing, scratching or touching the vaccination site.
- Until the vaccination scab falls off, do **NOT**:
    - have contact with people who cannot get the vaccine to prevent accidental spread of the vaccine virus. This includes physical contact and household contact. If there is someone in your household who should not get the vaccine, such as a pregnant woman, an infant, or someone who has an illness, you should not stay in the house until the vaccination scab falls off.
    - share a bed, clothes, towels, linen, or toiletries with unvaccinated people



Don't scratch that itch.

Vaccine virus can accidentally spread to a family member, close contact, or another part of your body.

- We don't know if the vaccine virus can be spread to cats, dogs, or other household pets, or whether pets can spread the virus to other people in the household. Try to keep the vaccine virus from reaching your pet. See "**How do I care for the smallpox vaccination site?**"

What are the possible side effects of ACAM2000?

ACAM2000 may cause serious heart problems, including myocarditis and pericarditis. This can happen within 3 to 4 weeks after you get the vaccine. Call your healthcare provider or get emergency help right away if you have:

- **chest pain or pressure**

- **fast or irregular heartbeat**
- **breathing problems**

Most people who get myocarditis and/or pericarditis seem to get better after a few weeks. But heart problems may last longer in some people, and in rare cases, could lead to death.

Other serious side effects include:

- swelling of the brain or spinal cord
- problems with the vaccination site blister, such as it becoming infected
- spreading of the vaccine virus to other parts of your body or to another person
- severe allergic reaction after vaccination
- accidental infection of the eye (which may cause swelling of the cornea causing watery painful eyes and blurred vision, scarring of the cornea, and blindness)

Common side effects include:

- itching
- swollen lymph nodes
- sore arm
- fever
- headache
- body ache
- mild rash
- fatigue

The risks for serious vaccine side effects are greater for people who:

- have skin problems called eczema or atopic dermatitis
- have skin problems, such as burns, impetigo, contact dermatitis, chickenpox, shingles, psoriasis, or uncontrolled acne
- have had heart problems
- have serious heart or blood vessel problems including angina, previous heart attack, artery disease, congestive heart failure, stroke, or other cardiac problems
- smoke or have high blood pressure, high cholesterol, diabetes, high blood sugar, or a family history of heart problems
- are breastfeeding
- are pregnant, could be pregnant, or plan to become pregnant
- are less than 1 year old
- are taking steroid eye drops or ointment
- have had problems after previous doses or are allergic to ACAM2000 or any part of ACAM2000 such as antibiotics neomycin or polymixin B

Tell your healthcare provider if you have any of the above conditions.

The virus from your vaccination can spread to other people and cause serious side effects. It is important to tell your healthcare provider if you:

- live or work with a person who has skin problems (like eczema, dermatitis, burns, psoriasis, bad acne) or is suffering from impetigo, chicken pox or shingles

- live or have close contact with a baby, or a person who is pregnant or breastfeeding
- live or have close contact with a person who has an immune deficiency or cardiac disease

See **"How do I care for the ACAM2000 vaccination site?"**

Tell your healthcare provider about any side effect that bothers you or that does not go away.

To report SUSPECTED ADVERSE REACTIONS, contact your health provider and Acambis Inc. at 866-440-9440 (toll free) or 617-866-4500 or VAERS at 800-822-7967 and https://.vaers.hhs.gov

General information about the safe and effective use of ACAM2000

This Medication Guide provides a summary of the most important information about ACAM2000. Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. If you would like more information or have any questions, talk to your healthcare provider. You can ask your healthcare provider for information about ACAM2000 that is written for healthcare professionals. You can also visit **http://www.acambis.com/ACAM2000**. The vaccine should not be used for a condition other than that for which it is prescribed.

What are the ingredients in ACAM2000?

ACAM2000: live vaccinia virus derived from plaque purification cloning from Dryvax® (Wyeth Laboratories, Marietta, PA, calf lymph vaccine, New York City Board of Health Strain) and grown in African Green Monkey kidney (Vero) cells

Inactive ingredients: 6-8 mM HEPES (pH 6.5-7.5), 2% human serum albumin USP, 0.5 – 0.7% sodium chloride USP, 5% mannitol USP, and trace amounts of the antibiotics neomycin and polymyxin B

Diluent for ACAM2000: 50% (v/v) Glycerin USP, 0.25% (v/v) Phenol USP in Water for Injection USP

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Attachment 2

Smallpox vaccine prevents smallpox, but requires very careful use.

What side effects should I expect?

Most reactions are mild, such as:

- Itching at vaccination site
- Swollen and/or sore lymph nodes
- Arm may become sore and red
- Fever, headache, and body ache
- Fatigue

These symptoms usually peak 3 to 12 days after vaccination and rarely last more than 30 days.

Myopericarditis is a serious adverse event that may cause chest pain/pressure/tightness, shortness of breath, or other heart symptoms within 30 days after vaccination. Seek immediate medical care if you experience these symptoms. Inform your doctor that you recently received a smallpox vaccination. Register with the VHC at 202-782-0411

More serious reactions that require medical attention may occur, such as:

- Accidental spread of virus elsewhere on body or to another person (prevented by handwashing)
- Widespread vaccine rash where sores break out away from vaccination site
- Allergic rash after vaccination

Life-threatening reactions that need immediate medical attention include:

- Chest pain or shortness of breath which may indicate an inflammation around the heart
- Serious skin rashes in people such as those with eczema or atopic dermatitis
- Ongoing infection of skin with tissue destruction

Attachment 2

Don't scratch that itch.
Vaccine virus can accidentally spread to a family member, close contact, or another part of your body

How should I care for the vaccination site?

Three Key Points:

1. **Wear bandages to cover vaccine site.**
2. **Wear sleeves to cover the site.**
3. **Wash your hands, wash your hands!!**

Vaccine virus (vaccinia) is present at the vaccination site for up to 30 days after vaccination and until site is healed. Other people can get infected by contact with the vaccinia virus from your vaccination site.

Use a non-sticking bandage. Do not use gauze. Change your bandages frequently so surface remains dry. Dispose of bandages in sealed or double plastic bags. You may add bleach, alcohol or soap to kill the virus.

Wear sleeves to cover the site and prevent scratching. Minimize close contact with infants for 30 days after vaccination and site is healed.

When not around others, you can leave the site uncovered. Air drying is helpful because it will speed healing. Only do this when you are not around others; make sure you wear a bandage and sleeves to bed to avoid scratching.

Do not use creams or ointments; they will delay healing and can spread the virus.

Vaccine recipients should place laundry in hot soapy water directly to avoid handling by others who could be infected. Don't share towels or clothes.

Normal bathing can continue, but don't touch or scrub the vaccination site. Dry the site last, with a paper towel or toilet paper and flush down the toilet.

If you exercise enough to cause sweat to drip, use a waterproof bandage. Avoid swimming and hot tubs.

Don't let your guard down at home! Although rare, spread of the vaccine virus happens most often with spouses and intimate partners.

8

- *For information about vaccine or policy.*
  Military Vaccine (MILVAX) Agency:
  www.smallpox.mil **www.vaccines.mil**
  E-Mail: **vaccines@amedd.army.mil** Toll-Free: **877.GET.VACC**
- *For medical advice about your smallpox vaccination,*
  DoD 24/7 Vaccine Clinical Call Center: Toll-Free **866 210 6469**
- *For clinical consultation or exemption assistance*
  DoD Vaccine Healthcare Centers: www.vhcinfo.org
  E-Mail: **askvhc@amedd.army.mil** Phone: **202.782.0411**
- **CDC National Immunization Hotline: 800 232 2522**

Civilian Healthcare Providers: If a Reservist or Active Duty Military Member presents to you for a condition that may be an adverse event caused by a military vaccination, please provide the appropriate care. For authorization and payment contact:

The Military Treatment Facility (MTF) where the member is enrolled. OR contact **The Military Medical Support Office (MMSO) 888 647-6676** if not enrolled to an MTF.

6

WHAT YOU NEED TO KNOW ABOUT SMALLPOX VACCINE

For more information visit
www.smallpox.mil
or
Contact us at:
vaccines@amedd.army.mil
877-GET-VACC
DSN 761-4245

1 August 2007

Smallpox is a contagious and deadly disease that would greatly disrupt mission capability.

What is smallpox and how does it spread?

Smallpox is a serious, contagious and sometimes fatal infectious disease.

Smallpox is caused by the variola virus. In unvaccinated individuals, about 3 out of 10 people will die. Survivors are often scarred and, in rare cases, may be blinded.

Smallpox (the disease not the vaccine) is usually spread by prolonged face-to-face contact with a contagious person.

Smallpox can also be spread by contact with infected body fluids and contaminated objects such as clothing, towels, linens.

A person with smallpox is sometimes contagious with onset of fever, but the person becomes most contagious with the onset of rash. They stay contagious until their last scab falls off.

The symptoms of smallpox begin with a high fever, head and body aches, and fatigue. A rash follows that spreads and progresses to raised bumps that crust, scab, and fall off after about three weeks, sometimes leaving pitted scars.

There is no specific treatment for smallpox disease, and the only prevention is vaccination.

Preserving the health and safety of our people are our top concerns.

What is the smallpox vaccine?

Smallpox vaccine contains live vaccinia virus (not smallpox virus) to protect against smallpox.

The vaccine is made from a virus called *vaccinia*, which is another "pox"-type virus related to smallpox but does NOT cause the disease.

After a single smallpox vaccination, about 95% of people develop protection within 5-10 days.

In the United States, most individuals born after 1970 have never received a smallpox vaccination. A booster dose is recommended every 10 years to maintain immunity.

Who should not get smallpox vaccine?

Some people should not get smallpox vaccine, including people:

- Whose immune system is not working normally due to disease, medication, or radiation.
- With a current and/OR childhood history of eczema (also known as atopic dermatitis, persistent rashes).
- With current skin conditions, such as burns, impetigo, contact dermatitis, chickenpox, shingles, psoriasis, or uncontrolled acne, until the condition clears up. Any skin problem should be evaluated.
- Who are pregnant or could be pregnant.
- With a household or intimate contact who meets any of the above conditions.
- With serious heart or blood vessel conditions (such as angina, heart attack, coronary artery disease, congestive heart failure, stroke, other cardiac problems).
- With 3 cardiac risk factors (smoking, high blood pressure or cholesterol, diabetes, family history of heart disease).
- Using steroid eye drops or ointment.
- Who are breastfeeding mothers.
- Who had problems after previous doses or are allergic to the vaccine or any of its components.

Women should avoid getting pregnant for 4 weeks after smallpox vaccination.

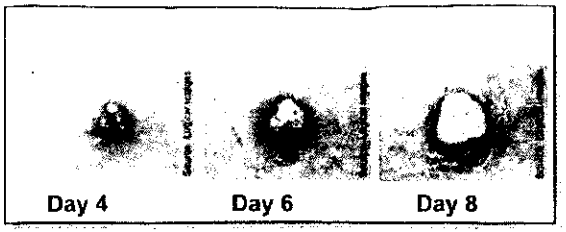
Protection against smallpox is essential for fighting the Global War on Terror.

How do you care for the smallpox vaccination site?

- ✓ *ALWAYS* wear bandages, wear sleeves and wash your hands
- ✓ Dispose of bandages in sealed or double plastic bags
- ✓ Don't touch any smallpox vaccination site. *Don't let other people touch your site or materials that touched it.*
- ✓ Avoid close contact with people who cannot receive the vaccine for 28 days after vaccination AND the vaccine site has healed. Do not share a bed or bunk with them. Do not share clothes, towels, linen or toothpaste.
- ✓ Keep site dry. With bathing, keep covered or dry fast avoiding spread of virus. Avoid rubbing, swimming, contact sports, and topical medications.
- ✓ Launder clothing, towels, & sheets in hot water with detergent or bleach.

Follow these instructions, or you could harm yourself or others. Adverse events after vaccination should be reported to the vaccine adverse events reporting system (VAERS). Submit VAERS reports at http://vaers.hhs.gov or call 1-800-822-7967.

Smallpox Vaccination Site



Note: If your vaccination site does **NOT** look like one of the pictures above on Days 6 to 8 after vaccination, see your healthcare provider.

What should I expect after vaccination?

If vaccination is successful, a red and itchy bump forms at the vaccination site in 2 to 4 days. Over the next few days, the bump becomes a blister and fills with pus. During the second week, the blister dries up and a scab forms. The scab falls off after 2 to 4 weeks, leaving a scar. People vaccinated for the first time may have a larger reaction than those being revaccinated.

Anyone who does not get the expected reaction needs to be revaccinated. If you have a question or concern about the smallpox vaccination site, contact your primary-care manager or healthcare provider.

Virus is present on the skin at the vaccination site up to 30 days after vaccination and until the site is healed. Be careful not to touch the vaccination site, so you don't spread virus elsewhere, especially to the eyes, nose, mouth or genitalia (or to others).

Always wear bandages, wear sleeves and wash your hands frequently with alcohol-based hand sanitizer or soap and warm water.

If you develop chest pain, shortness of breath, or other heart symptoms within 30 days after vaccination, seek immediate medical care.

If you need medical care in the month after your vaccination, tell your provider you just received a smallpox vaccination.

Inform your civilian employer that you were recently vaccinated.

Attachment 3

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all information needed to use ACAM2000 safely and effectively. See full prescribing information for ACAM2000.

ACAM2000™ (Smallpox (Vaccinia) Vaccine, Live)

Lyophilized preparation for percutaneous scarification

Initial U.S. Approval: 2007

WARNING:

See full prescribing information for complete boxed warning

- **Myocarditis and pericarditis (suspect cases observed at a rate of 5.7 per 1000 primary vaccinees (95% CI: 1.9-13.3)), encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including STEVENS-JOHNSON SYNDROME), eczema vaccinatum resulting in permanent sequelae or death, ocular complications and blindness and fetal death, have occurred following either primary vaccination or revaccination with live vaccinia virus smallpox vaccines. These risks are increased in certain individuals and may result in severe disability, permanent neurological sequelae and/or death [see Warnings and Precautions (5)].**

INDICATIONS AND USAGE

ACAM2000 is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection.

DOSAGE AND ADMINISTRATION

- ACAM2000 must be administered only by vaccine providers with training to safely and effectively administer the vaccine by the percutaneous route (scarification). The manufacturer is responsible for ensuring that such training is available to all vaccine providers, as required by the manufacturer's Risk Management Plan. (2.3)
- A droplet of ACAM2000 is administered by the percutaneous route (scarification) using 15 jabs of a bifurcated needle. ACAM2000 should not be injected by the intradermal, subcutaneous, intramuscular, or intravenous route. (2.3)
- The droplet (0.0025 mL) of reconstituted vaccine is picked up with a bifurcated needle by dipping needle into ACAM2000 vial. (2.3)
- See full prescribing information for instructions for vaccine preparation (2.2), administration including provision of the Medication Guide to vaccinees and instruction to vaccinees about vaccination site care, (2.3) and interpretation of response to vaccination. (2.4)
- Re-vaccination may be recommended (e.g. every 3 years). (2.5)

DOSAGE FORMS AND STRENGTHS

- Lyophilized powder reconstituted with packaged diluent. After reconstitution, each vial has approximately 100 doses of 0.0025 mL of live vaccinia virus containing 2.5 – 12.5 x 10^5 plaque forming units. (3)

CONTRAINDICATIONS

- Individuals with severe immunodeficiency who are not expected to benefit from the vaccine. These individuals may include persons who are undergoing bone marrow transplantation or persons with primary or acquired immunodeficiency states who require isolation (4).

WARNINGS AND PRECAUTIONS

- Myocarditis and/or pericarditis, ischemic heart disease and non-ischemic dilated cardiomyopathy (5.1, 5.2)
- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson syndrome), eczema vaccinatum, fetal vaccinia and fetal death. (5.1)
- Ocular vaccinia and blindness (5.3)
- These risks, including risks of severe disability and/or death, are increased in vaccinees with:
  - Cardiac disease (5.2)
  - Eye disease treated with topical steroids (5.3)
  - Congenital or acquired immune deficiency disorders (5.4)
  - History or presence of eczema and other skin conditions (5.5)
  - Infants < 12 months of age (5.6)
  - Pregnancy (5.7)
- ACAM2000 is a live vaccinia virus that can be transmitted to persons who have close contact with the vaccinee and the risks in contacts are the same as those stated for vaccinees. (5.10)

ADVERSE REACTIONS

Common adverse events include inoculation site signs and symptoms, lymphadenitis, and constitutional symptoms, such as malaise, fatigue, fever, myalgia, and headache (6.1). These adverse events are less frequent in revaccinated persons than persons receiving the vaccine for the first time.

Inadvertent inoculation at other sites is the most frequent complication of vaccinia vaccination. The most common sites involved are the face, nose, mouth, lips, genitalia and anus.

Self-limited skin rashes not associated with vaccinia replication in skin, including urticaria and folliculitis, may occur following vaccination.

To report SUSPECTED ADVERSE REACTIONS, contact Acambis Inc. at 617-866-4500 or 866-440-9440 (toll-free within the U.S.) or VAERS at 800-822-7967 and https://vaers.hhs.gov.

USE IN SPECIFIC POPULATIONS

- ACAM2000 may rarely cause fetal infection, usually resulting in stillbirth or death. (8.1)
- ACAM2000 live vaccinia virus may be transmitted from a lactating mother to her infant causing complications in the infant from inadvertent inoculation. (8.3)
- ACAM2000 may be associated with an increased risk of serious complications in children, especially in infants younger than 12 months. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE

Revised: [8/2007]

Attachment 3

FULL PRESCRIBING INFORMATION: CONTENTS*

BOXED WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Instructions for Vaccine Preparation

2.2 Preparation / Handling Precautions and Instructions for Disposal

2.3 Vaccination Instructions

2.4 Instructions for Interpreting Vaccination Response

2.5 Booster Schedule

2.6 Smallpox Vaccination Recommendations from U.S. Government Agencies

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Serious Complications and Death

5.2 Cardiac Disease

5.3 Ocular Complications and Blindness

5.4 Presence of Congenital or Acquired Immune Deficiency Disorders

5.5 History or Presence of Eczema and Other Skin Conditions

5.6 Infants (<12 months of Age) and Children

5.7 Pregnancy

5.8 Allergy to ACAM2000 Smallpox Vaccine or its Components

5.9 Management of Smallpox Vaccine Complications

5.10 Prevention of Transmission of Live Vaccinia Virus

5.11 Blood and Organ Donation

5.12 Limitations of Vaccine Effectiveness

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

6.2 ACAM2000 Clinical Trial Experience

7 DRUG INTERACTIONS

7.1 Simultaneous Administration with Other Live Virus Vaccines

7.2 Interference with Laboratory Tests

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

17.1 Serious Complications of Vaccination

17.2 Protecting Contacts at Highest Risk for Adverse Events

17.3 Self-inoculation and Spread to Close Contact

17.4 Care of the Vaccination Site and Potentially Contaminated Materials

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING:

- Suspected cases of myocarditis and/or pericarditis have been observed in healthy adult primary vaccinees (at an approximate rate of 5.7 per 1000, 95% CI: 1.9-13.3) receiving ACAM2000 [see Warnings and Precautions (5.1)].
- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, and erythema multiforme major (including STEVENS-JOHNSON SYNDROME) and eczema vaccinatum resulting in permanent sequelae or death, ocular complications, blindness, and fetal death have occurred following either primary vaccination or revaccination with smallpox vaccines [see Warnings and Precautions (5)].

  These risks are increased in vaccinees with the following conditions and may result in severe disability, permanent neurological sequelae and/or death:
  - Cardiac disease or a history of cardiac disease
  - Eye disease treated with topical steroids
  - Congenital or acquired immune deficiency disorders, including those taking immunosuppressive medications
  - Eczema and persons with a history of eczema or other acute or chronic exfoliative skin conditions
  - Infants less than 12 months of Age
  - Pregnancy

ACAM2000 is a live vaccinia virus that can be transmitted to persons who have close contact with the vaccinee and the risks in contacts are the same as those for the vaccinee.

The risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox infection.

1 INDICATIONS AND USAGE

ACAM2000 is indicated for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection.

2 DOSAGE AND ADMINISTRATION

ACAM2000 must be administered only by vaccine providers with training to safely and effectively administer the vaccine by the percutaneous route (scarification). ACAM2000 should not be injected by the intradermal, subcutaneous, intramuscular, or intravenous route.

2.1 Instructions for Vaccine Preparation

2.1.1 Reconstitution

ACAM2000 is reconstituted by addition of 0.3 mL of diluent to the vial containing lyophilized vaccine. ACAM2000 should only be reconstituted with 0.3 mL of the diluent provided. The vaccine vial should be removed from cold storage and brought to room temperature before reconstitution. The flip cap seals of the vaccine and diluent vials are removed, and each rubber stopper is wiped with an isopropyl alcohol swab and allowed to dry thoroughly. Using aseptic technique and a sterile 1 mL syringe fitted with a 25 gauge x 5/8" needle (provided), draw up 0.3 mL of diluent and transfer the entire contents of the syringe to the vaccine vial. Gently swirl to mix but try not to get product on the rubber stopper. The reconstituted vaccine should be a clear to slightly hazy, colorless to straw-colored liquid free from extraneous matter. Reconstituted vaccine should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is observed, the vaccine should not be used and the vial should be disposed safely. [See Preparation / Handling Precautions and Instructions for Disposal (2.2)]

2.1.2 Storage following Reconstitution

After reconstitution, ACAM2000 vaccine may be administered within 6 to 8 hours if kept at room temperature (20-25°C, 68-77°F); it should then be discarded as a biohazardous material. Unused, reconstituted ACAM2000 vaccine may be stored in a refrigerator (2-8°C, 36-46°F) up to 30 days, after which it should be discarded as a biohazardous material. [See Preparation / Handling Precautions and Instructions for Disposal (2.2)] Exposure of reconstituted vaccine to room temperature during vaccination sessions should be minimized by placing it in refrigerator or on ice between patient administrations.

2.2 Preparation / Handling Precautions and Instructions for Disposal

Personnel preparing and administering the vaccine should wear surgical or protective gloves and avoid contact of vaccine with skin, eyes or mucous membranes.

The vaccine vial, its stopper, the diluent syringe, the vented needle used for reconstitution, the bifurcated needle used for administration, and any gauze or cotton that came in contact with the vaccine should be discarded in leak-proof, puncture-proof biohazard containers. These containers should then be disposed of appropriately.

2.3 Vaccination Instructions

All vaccine providers must receive education on the proper administration as required by the U.S. Food and Drug Administration. All vaccine providers also receive a Medication Guide to distribute to each vaccinee prior to administering the vaccine. In the event of an actual smallpox emergency, declared by the Secretary of the U.S. Department of Health and Human Services, vaccine providers may follow educational instructions they receive from the manufacturer, such as how to educate vaccinees without a Medication Guide.

The site of vaccination is the upper arm over the insertion of the deltoid muscle.

No skin preparation should be performed unless the skin at the intended site of vaccination is obviously dirty, in which case an alcohol swab(s) may be used to clean the area. If alcohol is used, the skin must be allowed to dry thoroughly to prevent inactivation of the live vaccine virus by the alcohol.

Remove the vaccine vial cap. Remove bifurcated needle from individual wrapping. Submerge bifurcated end of needle in reconstituted vaccine solution. The needle will pick up a droplet of vaccine (0.0025 mL) within the fork of the bifurcation. Use aseptic technique, i.e., do not insert the upper part of the needle that has been in contact with fingers into the vaccine vial, and never re-dip the needle into the vaccine vial if the needle has touched skin.

Deposit the droplet of vaccine onto clean, dry skin of the arm prepared for vaccination. The needle is held between thumb and first finger perpendicular to the skin. The wrist of the hand holding the needle of the vaccinator rests against the patient's arm. Rapidly make 15 jabs of the needle perpendicular to the skin through the vaccine droplet to puncture the skin, within a diameter of about 5 mm. The jabs should be vigorous enough so that a drop of blood appears at the vaccination site.

Any excess droplets of vaccine and blood should be wiped off the skin using a dry gauze pad and discarded in a biohazard container. Discard the needle in a biohazard sharps container. Close the vaccine vial by reinserting the rubber cap and return to a refrigerator or place on ice unless it will be used immediately to vaccinate another subject. [See Storage Following Reconstitution (2.1.2)]

Cover the vaccination site loosely with a gauze bandage, using first aid adhesive tape to keep it in place. This bandage provides a barrier to protect against spread of the vaccinia virus. If the vaccinee is involved in direct patient care, the gauze should be covered with a semipermeable (semiocclusive) dressing as an additional barrier. A semipermeable dressing is one that allows for the passage of air but does not allow for the passage of fluids.

Wash hands with soap and warm water or with alcohol-based hand rubs such as gels or foams after direct contact with the vaccination site, the bandage or clothes, towels or sheets that might be contaminated with virus from the vaccination site. This is vital in order to remove any virus from your hands and prevent contact spread.

Put the contaminated bandages in a sealed plastic bag and throw them away in the trash.

Wash separately clothing, towels, bedding or other items that may have come in direct contact with the vaccination site or drainage from the site, using hot water with detergent and/or bleach. Wash hands afterwards.

Don't use a bandage that blocks air from the vaccination site. This may cause the skin at the vaccination site to soften and wear away. Use loose gauze secured with medical tape to cover the site.

Don't put salves or ointments on the vaccination site.

2.4 Instructions for Interpreting Vaccination Response

2.4.1 Primary Vaccinees

In an individual vaccinated for the first time (primary vaccination), the expected response to vaccination is the development of a major cutaneous reaction (characterized by a pustule) at the site of inoculation. The lesion evolves gradually, with appearance of a papule at the site of vaccination after 2-5 days. The papule becomes vesicular, then pustular, and reaches its maximum size at 8-10 days after vaccination. The pustule dries and forms a scab, which usually separates within 14-21 days, leaving a pitted scar. (See Figure 1) Formation of a major cutaneous reaction by day 6-8 is evidence of a successful 'take' and acquisition of protective immunity. An equivocal reaction is any reaction that is not a major reaction, and indicates a non-take (vaccination failure) due to impotent vaccine or inadequate vaccination technique.

2.4.2 Previously Vaccinated Individuals (Revaccination)

Successful vaccination in an individual previously exposed to vaccine is confirmed when a major cutaneous reaction [See Primary Vaccinees (2.4.1) and Figure 1) is observed 6 to 8 days post-vaccination. However any prior vaccination may modify (reduce) the cutaneous response upon revaccination (Figure 2) such that the absence of a cutaneous response does not necessarily indicate vaccination failure. Previously vaccinated individuals who do not have a cutaneous response on revaccination do not require revaccination to try to elicit a cutaneous response.

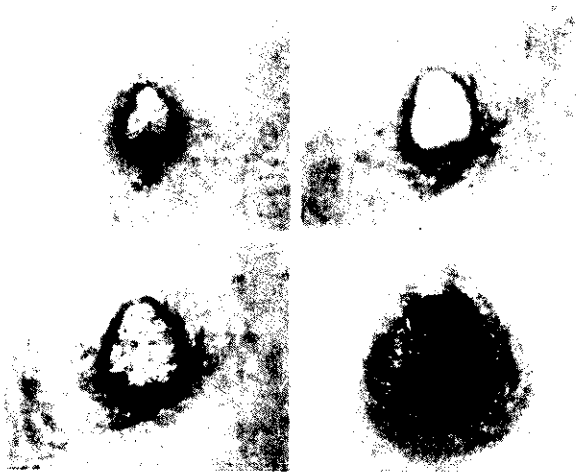
2.4.3 Vaccination Failures

Individuals who are not successfully vaccinated (i.e., vaccination failures) after primary vaccination may be revaccinated again in an attempt to achieve a satisfactory take. The vaccination procedures should be checked, and vaccination repeated with vaccine from another vial or vaccine lot, employing the same technique described in 2.3 [See Vaccination Instructions (2.3)].

If a repeat vaccination is conducted using vaccine from another vial or vaccine lot fails to produce a major reaction, healthcare providers should consult the Centers for Disease Control and Prevention (CDC) at (404) 639-3670 or their state or local health department before giving another vaccination.

Figure 1: Progression of major cutaneous reaction after primary vaccination[1]

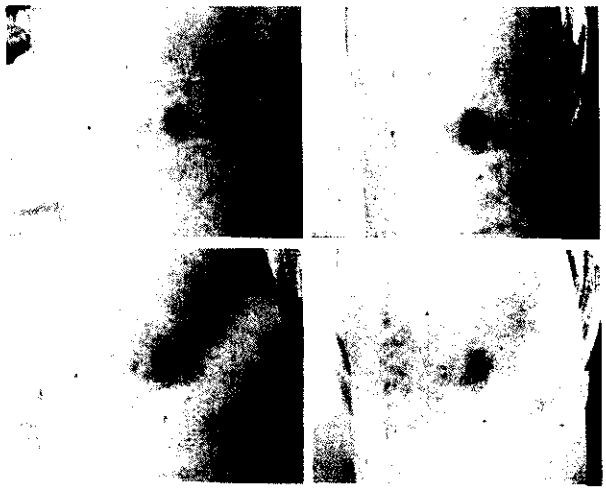
Day 5 Day 8



Day 10 Day 14

Figure 2: Progression of major cutaneous reaction after revaccination[1]

Day 3 Day 7



Day 10 Day 14

2.5 Booster Schedule

Persons at continued high risk of exposure to smallpox (e.g., research laboratory workers handling variola virus) should receive repeat ACAM2000 vaccination every three years.

2.6 Smallpox Vaccination Recommendations from US Government Agencies

Additional information may be obtained from U.S. Department of Defense (http://www.dtic.mil/whs/directives/corres/html/620503.htm) and U.S. Centers for Disease Control and Prevention (CDC) about smallpox vaccination (http://www.bt.cdc.gov/agent/smallpox/vaccination).

3 DOSAGE FORMS AND STRENGTHS

After reconstitution of the lyophilized preparation, each vial has approximately 100 doses of 0.0025 mL of vaccinia virus (live) containing 2.5-12.5x10^5 plaque forming units / dose.

4 CONTRAINDICATIONS

There are very few absolute contraindications to this vaccine for those who are at high risk for smallpox. The risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox infection. See *Warnings and Precautions* (5) for persons who are at higher risk of experiencing serious vaccination complications.

Severe Immune Deficiency

Severe localized or systemic infection with vaccinia (progressive vaccinia) may occur in persons with weakened immune systems. Individuals with severe immunodeficiency who are not expected to benefit from the vaccine should not receive ACAM2000. These individuals may include individuals who are undergoing bone marrow transplantation or individuals with primary or acquired immunodeficiency who require isolation.

5 WARNINGS AND PRECAUTIONS

Persons at greatest risk of experiencing serious vaccination complications are often those at greatest risk for death from smallpox. The risk for experiencing serious vaccination complications must be weighed against the risks for experiencing a potentially fatal smallpox infection.

5.1 Serious Complications and Death

Serious complications that may follow either primary live vaccinia smallpox vaccination or revaccination include: myocarditis and/or pericarditis, encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson syndrome) eczema vaccinatum, blindness, and fetal death in pregnant women. These complications may rarely lead to severe disability, permanent neurological sequelea and death. Based on clinical trials, symptoms of suspected myocarditis or pericarditis (such as chest pain, raised troponin/cardiac enzymes, or ECG abnormalities) occur in 5.7 per 1000 primary vaccinations. This finding includes cases of acute symptomatic or asymptomatic

myocarditis or pericarditis or both. Historically, death following vaccination with live vaccinia virus is a rare event; approximately 1 death per million primary vaccinations and 1 death per 4 million revaccinations have occurred after vaccination with live vaccinia virus. Death is most often the result of sudden cardiac death, postvaccinial encephalitis, progressive vaccinia, or eczema vaccinatum. Death has also been reported in unvaccinated contacts accidentally infected by individuals who have been vaccinated.

5.1.1 Incidence of Serious Complications in 1986 US Surveillance Studies

Estimates of the risks of occurrence of serious complications after primary vaccination and revaccination, based on safety surveillance studies conducted when live vaccinia virus smallpox vaccine (i.e., New York City Board of Health strain, Dryvax®) was routinely recommended, are as follows:

Table 1A - Rates of reported complications* associated with primary vaccinia vaccinations (cases/million vaccinations) †

Age (yrs)	<1	1-4	5-19	≥20	Overall rates‡‡
Inadvertent inoculation§	507.0	577.3	371.2	606.1	529.2
Generalized vaccinia	394.4	233.4	139.7	212.1	241.5
Eczema vaccinatum	14.1	44.2	34.9	30.3	38.5
Progressive vaccinia¶	--††	3.2	--††	--††	1.5
Post-vaccinial encephalitis	42.3	9.5	8.7	--††	12.3
Death#	5	0.5	0.5	unknown	--
Total**	1549.3	1261.8	855.9	1515.2	1253.8

† Adapted from Lane JM, Ruber FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys. J Infect Dis. 1970; 122:303-309.
* See article for descriptions of complications.
§ Referenced as accidental implantation.
¶ Referenced as vaccinia necrosum.
# Death from all complications.
** Rates of overall complications by age group include complications not provided in this table, including severe local reactions, bacterial superinfection of the vaccination site, and erythema multiforme.
†† No instances of this complication were identified during the 1968 10-state survey.
§§ Overall rates for each complication include persons of unknown age.

Table 1B - Rates of reported serious complications* associated with vaccinia revaccinations (cases/million vaccinations) †

Age (yrs)	<1	1-4	5-19	≥20	Overall rates†
Inadvertent inoculation§	--††	109.1	47.7	25.0	42.1
Generalized vaccinia	--††	--††	9.9	9.1	9.0
Eczema vaccinatum	--††	--††	2.0	4.5	3.0
Progressive vaccinia¶	--††	--††	--††	6.8	3.0
Post-vaccinial encephalitis	--††	--††	--††	4.5	2.0
Death#	--	--	--	--	--
Total**	--††	200.0	85.5	113.6	108.2

See Table 1A for explanation of footnotes.

5.1.2 Incidence of Serious Complications and Emergence of Myocarditis and/or Pericarditis in 2002-2005

Data on the incidence of adverse events among U.S. military personnel and civilian first responders vaccinated with Dryvax®, a licensed live vaccinia virus smallpox vaccine, during vaccination programs initiated in December 2002 are shown below in Table 2. The incidence of preventable adverse events (eczema vaccinatum, contact transmission, and auto-inoculation) were notably lower in these programs when compared with data collected in the 1960s; presumably because of better vaccination screening procedures and routine use of protective bandages over the inoculation site. Myocarditis and pericarditis were not commonly reported following smallpox vaccination in the 1960s, but emerged as a more frequent event based on more active surveillance in the military and civilian programs.

Table 2 - Serious adverse events in 2002-2005 [5]

Adverse event	Department of Defense program (n=730,580[1]) as of Jan05		Department of Health and Human Services program (n=40,422) as of Jan04[2]	
	N	Incidence /million	N	Incidence /million
Myo/pericarditis	86	117.71	21	519.52
Post-vaccinal encephalitis	1	1.37	1	24.74
Eczema vaccinatum	0	0.00	0	0.00
Generalized vaccinia	43	58.86	3	74.22
Progressive vaccinia	0	0.00	0	0.00
Fetal vaccinia	0	0.00	0	0.00
Contact transmission	52	71.18	0	0.00
Auto-inoculation (nonocular)	62	84.86	20	494.78
Ocular vaccinia	16	21.90	3	74.22

[1] 36% primary vaccination; 36% male; median age 47.1 yr
[2] 71% primary vaccination; 89% male; median age 28.5 yr

5.1.3 Myocarditis and Pericarditis in the ACAM2000 Clinical Trial Experience

In clinical trials involving 2983 subjects who received ACAM2000 and 868 subjects who received Dryvax®, ten (10) cases of suspected myocarditis [0.2% (7 of 2983) ACAM2000 subjects and 0.3% (3 of 868) Dryvax® subjects) were identified. The mean time to onset of suspected myocarditis and/or pericarditis from vaccination was 11 days, with a range of 9 to 20 days. All subjects who experienced these cardiac events were naïve to vaccinia. Of the 10 subjects, 2 were hospitalized. None of the remaining 8 cases required hospitalization or treatment with medication. Of the 10 cases, 8 were sub-clinical and were detected only by ECG abnormalities with or without associated elevations of cardiac troponin I. All cases resolved by 9 months, with the exception of one female subject in the Dryvax® group, who had persistent borderline abnormal left ventricular ejection fraction on echocardiogram. The best estimate of risk for myocarditis and pericarditis is derived from the Phase 3 ACAM2000 clinical trials where there was active monitoring for potential of myocarditis and pericarditis. Among vaccinees naïve to vaccinia, 8 cases of suspected myocarditis and pericarditis were identified across both treatment groups, for a total incidence rate of 6.9 per 1000 vaccinees (8 of 1,162). The rate for the ACAM2000 treatment group were similar: 5.7 (95% CI: 1.9-13.3) per 1000 vaccinees (5 of 873 vaccinees) and for the Dryvax® group 10.4 (95% CI: 2.1-30.0) per 1000 vaccinees (3 of 289 vaccinees). No cases of myocarditis and/or pericarditis were identified in 1819 previously vaccinated subjects. The long-term outcome of myocarditis and pericarditis following ACAM2000 vaccination is currently unknown.

5.2 Cardiac Disease

Ischemic cardiac events, including fatalities, have been reported following smallpox vaccination; the relationship of these events, if any, to vaccination has not been established. In addition, cases of non-ischemic, dilated cardiomyopathy have been reported following smallpox vaccination; the relationship of these cases to smallpox vaccination is unknown.

There may be increased risks of adverse events with ACAM2000 in persons with known cardiac disease, including those diagnosed with previous myocardial infarction, angina, congestive heart failure, cardiomyopathy, chest

pain or shortness of breath with activity, stroke or transient ischemic attack, or other heart conditions. In addition, subjects who have been diagnosed with 3 or more of the following risk factors for ischemic coronary disease: 1) high blood pressure; 2) elevated blood cholesterol; 3) diabetes mellitus or high blood sugar; 4) first degree relative (for example mother, father, brother, or sister) who had a heart condition before the age of 50; or 5) smoke cigarettes may have increased risks.

5.3 Ocular Complications and Blindness

Accidental infection of the eye (ocular vaccinia) may result in ocular complications including keratitis, corneal scarring and blindness. Patients who are using corticosteroid eye drops may be at increased risk of ocular complications with ACAM2000.

5.4 Presence of Congenital or Acquired Immune Deficiency Disorders

Severe localized or systemic infection with vaccinia (progressive vaccinia) may occur in persons with weakened immune systems, including patients with leukemia, lymphoma, organ transplantation, generalized malignancy, HIV/AIDS, cellular or humoral immune deficiency, radiation therapy, or treatment with antimetabolites, alkylating agents, or high-dose corticosteroids (>10 mg prednisone/day or equivalent for ≥2 weeks). The vaccine is contraindicated in individuals with severe immunodeficiency [See Contraindications (4)]. Vaccinees with close contacts who have these conditions may be at increased risk because live vaccinia virus can be shed and be transmitted to close contacts.

5.5 History or Presence of Eczema and Other Skin Conditions

Persons with eczema of any description such as, atopic dermatitis, neurodermatitis, and other eczematous conditions, regardless of severity of the condition, or persons who have a history of these conditions at any time in the past, are at higher risk of developing eczema vaccinatum. Vaccinees with close contacts who have eczematous conditions, may be at increased risk because live vaccinia virus can shed and be transmitted to these close contacts. Vaccinees with other active acute, chronic or exfoliative skin disorders (including burns, impetigo, varicella zoster, acne vulgaris with open lesions, Darier's disease, psoriasis, seborrheic dermatitis, erythroderma, pustular dermatitis, etc.), or vaccinees with household contacts having such skin disorders might also be at higher risk for eczema vaccinatum.

5.6 Infants (< 12 months of Age) and Children

ACAM2000 has not been studied in infants or children. The risk of serious adverse events following vaccination with live vaccinia virus is higher in infants. Vaccinated persons who have close contact with infants, e.g., breastfeeding, must take precautions to avoid inadvertent transmission of ACAM2000 live vaccinia virus to infants.

5.7 Pregnancy

ACAM2000 has not been studied in pregnant women. Live vaccinia virus vaccines can cause fetal vaccinia and fetal death. If ACAM2000 is administered during pregnancy, the vaccinee should be apprised of the potential hazard to the fetus [See Use in Specific Populations (8.1)]. Vaccinees with close contacts who are pregnant may be at increased risk because live vaccinia virus can shed and be transmitted to close contacts.

5.8 Allergy to ACAM2000 Smallpox Vaccine or its Components

ACAM2000 contains neomycin and polymyxin B. Persons allergic to these components may be at higher risk for adverse events after vaccination.

5.9 Management of Smallpox Vaccine Complications

The CDC can assist physicians in the diagnosis and management of patients with suspected complications of vaccinia (smallpox) vaccination. Vaccinia Immune Globulin (VIG) is indicated for certain complications of vaccination live vaccinia virus smallpox vaccine. If VIG is needed or additional information is required, physicians should contact the CDC at (404) 639-3670, Monday through Friday 8 AM to 4:30 PM Eastern Standard Time; at other times call (404) 639-2888.

5.10 Prevention of Transmission of Live Vaccinia Virus

The most important measure to prevent inadvertent auto-inoculation and contact transmission from vaccinia vaccination is thorough hand washing after changing the bandage or after any other contact with the vaccination site.

Individuals susceptible to adverse effects of vaccinia virus, i.e., those with cardiac disease, eye disease, immunodeficiency states, including HIV infection, eczema, pregnant women and infants, should be identified and measures should be taken to avoid contact between those individuals and persons with active vaccination lesions.

Recently vaccinated healthcare workers should avoid contact with patients, particularly those with immunodeficiencies, until the scab has separated from the skin at the vaccination site. However, if continued contact with patients is unavoidable, vaccinated healthcare workers should ensure the vaccination site is well covered and follow good hand-washing technique. In this setting, a more occlusive dressing may be used. Semipermeable polyurethane dressings are effective barriers to shedding of vaccinia. However, exudate may accumulate beneath the dressing, and care must be taken to prevent viral spread when the dressing is changed. In addition, accumulation of fluid beneath the dressing may increase skin maceration at the vaccination site. Accumulation of exudate may be decreased by first covering the vaccination with dry gauze, then applying the dressing over the gauze. The dressing should be changed every 1-3 days [See Self Inoculation and Spread to Close Contacts (17.3) and Care of the Vaccination Site and Potentially Contaminated Materials (17.4)].

5.11 Blood and Organ Donation

Blood and organ donation should be avoided for at least 30 days following vaccination with ACAM2000.

5.12 Limitations of Vaccine Effectiveness

ACAM2000 smallpox vaccine may not protect all persons exposed to smallpox.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia (vaccinia necrosum), generalized vaccinia, severe vaccinial skin infections, erythema multiforme major (including Stevens-Johnson syndrome) and eczema vaccinatum. Severe disability, permanent neurological sequelae, and/or death may occur. Death of unvaccinated individuals who have contact with vaccinated individuals. [See Warnings and Precautions (5.1)]
- Myocarditis and/or pericarditis, ischemic heart disease and non-ischemic, dilated cardiomyopathy [See Warnings and Precautions (5.1)]
- Ocular complications and blindness [See Warnings and Precautions (5.3)]

6.1 Overall Adverse Reaction Profile

Information regarding the safety of ACAM2000 has been derived from three sources, 1) ACAM2000 clinical trial experience (Phase 1, 2 and 3 clinical trials), 2) data compiled during the era of routine smallpox vaccination using other NYCBH vaccinia vaccines and 3) adverse event data obtained during military and civilian smallpox vaccination programs (2002-2005) that used Dryvax®, a licensed live vaccinia virus smallpox vaccine.

- General Disorders and Administrative Site Conditions: In the ACAM2000 clinical studies 97% and 92% of vaccinia-naïve and previously vaccinated subjects, respectively, experienced one or more adverse event. Common events included injection site reactions (erythema, pruritus, pain and swelling) and constitutional symptoms (fatigue, malaise, feeling hot, rigors and exercise tolerance decreased). Across all ACAM2000 studies 10% of vaccinia-naïve and 3% of previously vaccinated subjects experienced at least one severe adverse event (defined as interfering with normal daily activities).
- Nervous System Disorder: Overall, 51% and 35% of vaccinia-naïve subjects and previously vaccinated subjects, respectively, reported headaches in ACAM2000 studies. There have been reports of headache following smallpox vaccination which required hospitalization. Although <1% of the subjects in the ACAM2000 program experienced severe headaches, none required hospitalization.

  Neurological adverse events assessed among the 2002 - 2005 military (n=590,400) and DHHS (n=64,600) programs temporally associated with smallpox vaccination included headache (95 cases), non-serious limb paresthesias (17 cases) or pain (13 cases) and dizziness or vertigo (13 cases). Serious neurologic adverse events included 13 cases of suspected meningitis, 3 cases of suspected encephalitis or myelitis, 11 cases of Bell palsy, 9 seizures (including 1 death), and 3 cases of Guillain-Barre syndrome. Among these 39 events, 27 (69%) occurred in primary vaccinees and all but 2 occurred within 12 days of vaccination. There have also been cases of photophobia following smallpox vaccination, some of which required hospitalization.
- Musculoskeletal and Connective Tissue Disorders: Across all ACAM2000 studies, severe, vaccine-related myalgia was seen in 1% of vaccinia-naïve subjects and <1% of previously vaccinated subjects. Other adverse events included back pain, arthralgia and pain in

extremity and none occurred with a frequency of more than 2% in either the vaccinia-naïve or previously vaccinated populations.

- Blood and Lymphatic System Disorders: The only adverse event occurring at ≥5% in the ACAM2000 studies were lymph node pain and lymphadenopathy. The incidence of severe lymph node pain and lymphadenopathy was <1%.
- Gastrointestinal (GI) Disorders: Commonly reported GI disorders among ACAM2000-treated subjects included nausea and diarrhea (14%), constipation (6%), and vomiting (4%). Severe abdominal pain, nausea, vomiting, constipation diarrhea and toothache accounted for all the severe adverse events reported and occurred in <1% of subjects.
- Skin and Subcutaneous Tissue Disorders: Erythema and rash were noted in 18% and 8% of subjects respectively. In ACAM2000 subjects 1% of vaccinia-naïve and <1% of previously vaccinated subjects experienced at least one severe adverse event. With the exception of one case of contact dermatitis and one case of urticaria, erythema and rash accounted for all severe events.

  Generalized rashes (erythematous, papulovesicular, urticarial, folliculitis, nonspecific) are not uncommon following smallpox vaccination and are presumed to be hypersensitivity reactions occurring among persons without underlying illnesses. These rashes are generally self-limited and require little or no therapy, except among patients whose conditions appear to be toxic or who have serious underlying illnesses.

  Inadvertent inoculation at other body sites is the most frequent complication of vaccinia vaccination, usually resulting from autoinoculation of the vaccine virus transferred from the site of vaccination. The most common sites involved are the face, nose, mouth, lips, genitalia and anus. Accidental infection of the eye (ocular vaccinia) may result in ocular complications including, but not limited to, keratitis, corneal scarring and blindness.

  Major cutaneous reactions at the site of inoculation, characterized by large area of erythema and induration and streaking inflammation of draining lymphatics may resemble cellulitis. Benign and malignant lesions have been reported to occur at the smallpox vaccination site.

6.2 ACAM2000 Clinical Trial Experience

Two randomized, controlled, multi-center Phase 3 trials enrolled 2244 subjects that received ACAM2000 and 737 that received a comparison licensed live vaccinia virus vaccine, Dryvax®. Study 1 was conducted in male (66% and 63% for ACAM2000 and Dryvax®, respectively) and female (34% and 37% for ACAM2000 and Dryvax®, respectively) subjects who previously had not been vaccinated with smallpox vaccine (i.e., vaccinia-naïve subjects). The majority of subjects were Caucasian (76% and 71% for ACAM2000 and Dryvax®, respectively) and the mean age was 23 in both groups with an age range from 18-30 years. Study 2 was conducted in male (50% and 48% for ACAM2000 and Dryvax®, respectively) and female (50% and 52% for ACAM2000 and Dryvax®, respectively) subjects who had been vaccinated with smallpox vaccine >10 years previously (i.e., previously vaccinated subjects). The majority of subjects were Caucasian (78% for both groups) and the mean age was 49 years in both groups with an age range of 31 to 84 years.

6.2.1 Common Adverse Events Reported in ACAM2000 Clinical Program

Adverse events reported by ≥5% of subjects in either the ACAM2000 or the comparison treatment group during Phase 3 studies are presented by type of adverse events, by baseline vaccination status (vaccinia-naïve versus previously vaccinated) and by treatment group. Severe vaccine-related adverse events, defined as interfering with normal daily activities, in vaccinia-naïve subjects were reported by 10% of subjects in the ACAM2000 group and 13% in the comparison group. In the previously vaccinated subjects, the incidence of severe vaccine-related adverse events was 4% for the ACAM2000 groups and 6% for the comparison group.

Table 3 - Adverse Events Reported by ≥5% of Subjects in ACAM2000 or Dryvax®

	Study 1 Vaccinia-Naive Subjects		Study 2 Previously Vaccinated Subj	
	ACAM2000 N=873 n (%)	Dryvax® N=289 n (%)	ACAM2000 N=1371 n (%)	I
At least 1 adverse event	864 (99)	288 (100)	1325 (97)	443 (99)
Blood and lymphatic system disorders	515 (59)	204 (71)	302 (22)	133 (30)
Lymph node pain*	494 (57)	199 (69)	261 (19)	119 (27)
Lymphadenopathy	72 (8)	35 (12)	78 (6)	29 (6)
Gastrointestinal disorders	273 (31)	91 (31)	314 (23)	137 (31)
Nausea*	170 (19)	65 (22)	142 (10)	63 (14)
Diarrhea*	144 (16)	34 (12)	158 (12)	77 (17)
Constipation*	49 (6)	9 (3)	88 (6)	31 (7)
Vomiting*	42 (5)	10 (3)	40 (3)	18 (4)
General disorders and administration site conditions	850 (97)	288 (100)	1280 (93)	434 (97)
Injection site pruritus*	804 (92)	277 (96)	1130 (82)	416 (93)
Injection site erythema*	649 (74)	229 (79)	841 (61)	324 (72)
Injection site pain*	582 (67)	208 (72)	505 (37)	209 (47)
Fatigue*	423 (48)	161 (56)	468 (34)	184 (41)
Injection site swelling	422 (48)	165 (57)	384 (28)	188 (42)
Malaise*	327 (37)	122 (42)	381 (28)	147 (33)
Feeling hot*	276 (32)	97 (34)	271 (20)	114 (25)
Rigors*	185 (21)	66 (23)	171 (12)	76 (17)
Exercise tolerance decreased*	98 (11)	35 (12)	105 (8)	50 (11)
Musculoskeletal and connective tissue disorders	418 (48)	153 (53)	418 (30)	160 (36)
Myalgia*	404 (46)	147 (51)	374 (27)	148 (33)
Nervous system disorders	444 (51)	151 (52)	453 (33)	174 (39)
Headache*	433 (50)	150 (52)	437 (32)	166 (37)
Respiratory, thoracic, and mediastinal disorders	134 (15)	40 (14)	127 (9)	42 (9)
Dyspnea*	39 (4)	16 (6)	41 (3)	18 (4)
Skin and subcutaneous tissue disorders	288 (33)	103 (36)	425 (31)	139 (31)
Erythema*	190 (22)	69 (24)	329 (24)	107 (24)
Rash*	94 (11)	30 (10)	80 (6)	29 (6)

* Event was listed on a checklist included in subject diaries; therefore should be considered sc
addition to events listed above the following were also included as part of the checklist: chest
palpitations, but these events did not occur ≥5% of subjects.

7 DRUG INTERACTIONS

7.1 Simultaneous Administration with Other Vaccines

There are no data evaluating the simultaneous administration of ACAM2000 with other vaccines.

7.2 Interference with Laboratory Tests

ACAM2000 may induce false-positive tests for syphilis. Positive RPR tests results should be confirmed using a more specific test, such as the FTA assay.

ACAM2000 may induce temporary false-negative results for the tuberculin skin test (purified protein derivative [PPD]) and possibly, blood tests for tuberculosis. Tuberculin testing should be delayed if possible for 1 month following smallpox vaccination.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

ACAM2000 has not been studied in pregnant women. Live vaccinia virus vaccines can cause fetal harm when administered to a pregnant woman. Congenital infection, principally occurring during the first trimester, has been observed after vaccination with live vaccinia smallpox vaccines, although the risk may be low. Generalized vaccinia of the fetus, early delivery of a stillborn infant, or a high risk of perinatal death has been reported.

The only setting in which vaccination of pregnant women should be considered is when exposure to smallpox is considered likely. If this vaccine is used during pregnancy, or if the vaccinee lives in the same household with or has close contact with a pregnant women, the vaccinee should be apprised of the potential hazard to the fetus. Healthcare providers, state health departments, and other public health staff should report to the National Smallpox Vaccine Pregnancy Registry all cases in which persons who received ACAM2000, or were exposed to a woman who received ACAM2000 within 28 days after vaccination, during pregnancy, or within 42 days prior to conception. Civilian women should contact their healthcare provider or state health department for help enrolling in the registry. Clinicians or public health staff should report civilian cases through their state health department or to CDC, telephone 404-639-8253 or 877 554 4625. Military cases should be reported to the DoD, telephone 619 553-9255, Defense Switched Network (DSN) 553-9255, fax 619 553 7601 or e-mail code 25@nhrc.navy.mil.Labor and Delivery.

8.3 Nursing Mothers

ACAM2000 has not been studied in lactating women. It is not known whether vaccine virus or antibodies are secreted in human milk. Live vaccinia virus can be inadvertently transmitted from a lactating mother to her infant. Infants are at high risk of developing serious complications from live vaccinia smallpox vaccination.

8.4 Pediatric Use

The safety and effectiveness of ACAM2000 have not been established in the age groups from birth to age 16. The use of ACAM2000 in all pediatric age groups is supported by evidence from the adequate and well-controlled studies of ACAM2000 in adults and with additional historical data with use of live vaccinia virus smallpox vaccine in pediatrics. Before the eradication of smallpox disease, live vaccinia virus smallpox vaccine was administered routinely in all pediatric age groups, including neonates and infants, and was effective in preventing smallpox disease. During that time, live vaccinia virus was occasionally associated with serious complications in children, the highest risk being in infants younger than 12 months of age. [See Warnings and Precautions (5.6)].

8.5 Geriatric Use

Clinical studies of ACAM2000 did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There are no published data to support the use of this vaccine in geriatric (persons >65 years) populations.

11 DESCRIPTION

ACAM2000, Smallpox (Vaccinia) Vaccine, Live, is a live vaccinia virus derived from plaque purification cloning from Dryvax® (Wyeth Laboratories, Marietta, PA, calf lymph vaccine, New York City Board of Health Strain) and grown in African Green Monkey kidney (Vero) cells and tested to be free of adventitious agents.

ACAM2000 is provided as a lyophilized preparation of purified live virus containing the following non-active excipients: 6-8 mM HEPES (pH 6.5-7.5), 2% human serum albumin USP, 0.5 – 0.7% sodium chloride USP, 5% mannitol USP, and trace amounts of neomycin and polymyxin B.

Diluent for ACAM2000 contains 50% (v/v) Glycerin USP, 0.25% (v/v) Phenol USP in Water for Injection USP, supplied in 3 mL clear glass vials containing 0.6 mL of diluent.

After reconstitution, each vial of ACAM2000 vaccine contains approximately 100 doses (0.0025 mL/dose). The concentration of vaccinia virus is 1.0-5.0 x 10^8 plaque-forming units (PFU)/mL or 2.5-12.5 x 10^5 PFU/dose determined by plaque assay in Vero cells. ACAM2000 is administered by the percutaneous route (scarification) using 15 jabs of a stainless steel bifurcated needle that has been dipped into the vaccine.

12 CLINICAL PHARMACOLOGY

Smallpox vaccine does not contain smallpox virus (variola) and cannot spread or cause smallpox.

12.1 Mechanism of Action

Vaccinia virus is a member of the same taxonomic group (the Orthopox genus) as smallpox (variola) virus, and immunity induced by vaccinia virus cross-protects against variola virus. Vaccinia virus causes a localized virus infection of the epidermis at the site of inoculation, surrounding dermal and subcutaneous tissues, and draining lymph nodes. Virus may be transiently present in blood and infects reticuloendothelial and other tissues. Langerhans cells in the epidermis are specific targets for the early stage of virus replication. The formation of a pustule ('pock' or 'take') at the site of inoculation provides evidence of protective immunity. The virus replicates within cells and viral antigens are presented to the immune system. Neutralizing antibodies and B and T cells provide long-term memory. The level of neutralizing antibody that protects against smallpox is unknown but >95% of persons undergoing primary vaccination develop neutralizing or hemagglutination inhibiting antibodies to vaccinia.

12.2 Pharmacodynamics

12.2.1 Cutaneous Response

The cutaneous responses following smallpox vaccination are dependent on the immune status of the individual, potency of the vaccine, and vaccination technique. Two types of responses have been defined by the WHO Expert Committee on Smallpox, and described by the Advisory Committee on Immunization Practices (ACIP). The responses include: a) major cutaneous reaction, which indicates that virus replication has taken place and vaccination was successful; or b) equivocal reaction. Equivocal reactions may be a consequence of pre-existing immunity adequate to suppress viral multiplication, vaccination technique failure, or use of inactive vaccine or vaccine that has lost potency.

Successful vaccination in persons who are naïve to smallpox vaccination, termed primary vaccination, is represented by a major cutaneous reaction, defined as a vesicular or pustular lesion or an area of definite palpable induration or congestion surrounding a central lesion that might be a crust or an ulcer.

Subjects who have been previously vaccinated and are revaccinated may manifest a reduced cutaneous response compared to vaccinia-naïve subjects, but still exhibit an immune response to the vaccine. [See Dosage and Administration (2.4)]

12.2.2 Neutralizing Antibody and Cellular Immune Responses

Neutralizing antibodies are known to mediate protection against smallpox. Neutralizing antibodies against vaccinia develop in >95% of individuals following primary vaccination, rise rapidly (by day 15-20 after vaccination) and may be boosted on revaccination. Antibody titers are highly variable. Titers may remain high for longer periods following two or more vaccinations than after a primary vaccination. The level of the neutralizing antibody response following primary vaccination is generally in proportion to the intensity of the cutaneous reaction. The level of neutralizing antibody that is required to protect against smallpox has not been clearly established, although some studies indicate that persons with antibody titers > 1:32 are protected. Cellular immune responses are also elicited by vaccination and may contribute to protection and immunological memory.

12.2.3 Virus Shedding

Virus is shed from the vaccination site during the period starting with the development of a papule (day 2-5); shedding ceases when the scab separates and the lesion is re-epithelialized, about 14-21 days after vaccination. Steps should be taken in clinical use to reduce the risk of accidental infection of other sites in the vaccinated patient or of contact spread to other individuals [See Vaccination Instructions (2.3)].

14 CLINICAL STUDIES

Vaccine efficacy was assessed by comparing the immunologic response of ACAM2000 to another US-licensed live vaccinia virus smallpox vaccine, Dryvax®, in two randomized, multi-center active-controlled clinical trials; one study in subjects who previously had not been vaccinated with smallpox vaccine (i.e., vaccinia-naïve subjects) and one study in subjects who had been vaccinated with smallpox vaccine >10 years previously (i.e., previously vaccinated subjects). In both trials, the co-primary efficacy endpoints were the proportion of subjects with a successful vaccination/revaccination and the geometric mean neutralizing antibody titer (GMT) on Day 30. Successful primary vaccination was defined as a major cutaneous reaction on Day 7 or 10 (Days 6 to 11, with allowable visit window). Successful revaccination was defined as development of any cutaneous lesion on Day 7 (± 1 day) of a measurable size. Successful revaccination was determined by a panel of experts who reviewed digital photographs of the cutaneous lesions.

The statistical method used to compare the proportion of subjects who were successfully vaccinated in the two treatment groups was a test of non-inferiority of ACAM2000 to the active comparator intended to rule out a greater than 5% margin of superiority of the comparator for successful primary vaccination (Study 1) and a 10% margin of superiority of the comparator for successful revaccination (Study 2). Non-inferiority was to be declared if the lower bound of the 1-sided 97.5% confidence interval (CI) for the percent difference between ACAM2000 and the comparator exceeded -5% in naïve subjects and -10% in previously vaccinated subjects.

Analysis of the GMT was performed using a test of non-inferiority of neutralizing antibody titer between ACAM2000 and the comparator, intended to ensure that the ratio of the GMTs of ACAM2000: comparator vaccine was at least 0.5 (equivalent to the difference of the $\log_{10}$ (GMT) being at least -0.301).

In Study 1, a total of 1037 male and female vaccinia-naïve subjects, aged 18 to 30 years inclusive, primarily Caucasian (76%) were randomized in a 3:1 ratio to receive ACAM2000 (780 subjects) or comparator (257 subjects). The ACAM2000 subjects were further stratified to receive one of three lots (Lots A, B and C) at a 1:1:1 ratio (258, 264, and 258 subjects, respectively). All subjects were to be evaluated for their cutaneous response and a random subset was selected for evaluation of neutralizing antibody response.

In Study 2, a total of 1647 male and female previously-vaccinated subjects, aged 31 to 84 years inclusive, primarily Caucasian (81%) were randomized in a 3:1 ratio to receive ACAM2000 (1242 subjects) or the comparator (405 subjects). The ACAM2000 subjects were further stratified to receive one of three lots (Lots A, B and C) at a 1:1:1 ratio (411, 417, and 414 subjects, respectively). All subjects were evaluated for their cutaneous response and a random subset was to be selected for evaluation of neutralizing antibody response.

Table 4 presents the results of the primary efficacy analyses for both studies.

Table 4 - – Cutaneous Response (Vaccination Success) and Neutralizing Antibody Response In Subjects Given ACAM2000 Vs. Comparator Vaccine

	Study Population / Treatment Group			
	Study 1 Vaccinia-Naïve Subjects		Study 2 Previously Vaccinated Subjects	
	ACAM 2000	Comparator	ACAM 2000	Comparator
Cutaneous Response (Vaccination Success)				
Size of Evaluable Population[a]	776	257	1189	388
Number of Vaccination Successes (%)	747 (96)[b]	255 (99)	998 (84)[h]	381 (98)
97.5% 1-sided CI by normal approx. on percent difference between ACAM2000-Comparator	-4.67%[c]		-17%[i]	
Non-Inferiority to Comparator	Yes		No	
Neutralizing Antibody Response (based on $PRNT_{50}$[d] Titer on Day 30)				
Size of Evaluable Population[e]	565	190	734	376
GMT[f]	166	255	286	445
$\log_{10}$ mean	2.2	2.4	2.5	2.6
97.5% 1-sided CI by ANOVA on difference between ACAM2000-Comparator	-0.307[g]		-0.275[j]	
Meets Non-Inferiority to Comparator	No		Yes	

a. Subjects who received study vaccine and were evaluated for a local cutaneous reaction within the protocol-designated timeframe were included in the efficacy evaluable (EE) population.

b. Results for vaccine lots, A, B and C were 95%, 98% and 96%.

c. Since the critical value for the evaluation was declared to be -5%, ACAM2000 is considered to be non-inferior to Comparator for this parameter

d. $PRNT_{50}$ – Vaccinia 50% plaque reduction neutralization test

e. A randomly selected sample of subjects who received study vaccine and had samples collected for neutralizing antibody response at Baseline and at the designated time-point post-treatment were included in the antibody evaluable (AnE) population

f. GMT – Geometric mean neutralizing antibody titer

g. Since the critical value for the evaluation was declared to be -0.301, ACAM2000 is not considered to be non-inferior to Comparator for this parameter

h. Results for vaccine lots, A, B and C were 79%, 87% and 86%.

i. Since the critical value for the evaluation was declared to be -10%, ACAM2000 is not considered to be non-inferior to Comparator for this parameter

j. Since the critical value for the evaluation was declared to be -0.301, ACAM2000 is considered to be non-inferior to Comparator for this parameter

The primary determinant for an effective immune response in those naïve to vaccine is a major cutaneous reaction. ACAM2000 was non-inferior to comparator in this population with regard to eliciting a major cutaneous reaction. The measure of the strength of the generated antibody response was similar but did not meet the predefined criterion for non-inferiority. Among subjects who were previously vaccinated, development of a major cutaneous response after revaccination with vaccinia-based smallpox vaccines may not provide an accurate measure of the strength of the immune response because the pre-existing immunity modifies the scope of the cutaneous response. In previously vaccinated subjects, ACAM2000 was non-inferior to the comparator with regard to the strength of the neutralizing antibody immune response. Therefore, ACAM2000 was non-inferior to the comparator in the rate of major cutaneous reaction in those naïve to the vaccine, and the strength of the neutralizing antibody immune response in those previously exposed to vaccinia-based smallpox vaccines.

15 REFERENCES

1 Fulginiti VA, Papier A, Lane JM, Neff JM, Henderson, DA. Smallpox vaccination: a review, part 1. background, vaccination technique, normal vaccination and revaccination, and expected normal reactions. *Clin Infect Dis.* 2003;37:241-250.

2 Centers for Disease Control and Prevention. Notice to readers: Supplemental recommendations on adverse events following smallpox vaccine in the pre-event vaccination program: recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep.* 2003;52(13):282-284.

3 Lane J, Millar J. Risks of smallpox vaccination complications in the United States. *Am J Epidemiol.* 1971;93:238-240.

4 Lane, JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: results of ten statewide surveys. *J Infect Dis.* 1970;122(4):303-309.

5 Poland GA, Grabenstein JD, Neff JM. The US smallpox vaccination program: a review of a large modern era smallpox vaccination implementation program. *Vaccine.* 2005;23:2078-2081.

6 Casey GC, Iskander JK, Roper MH, Mast EE, Wen X-J, Torok TJ, et al..Adverse events associated with smallpox vaccination in the United States, January-October 2003. *JAMA.* 2005;94(21):2734-2743.

7 Centers for Disease Control and Prevention.Update: Cardiac and other adverse events following civilian smallpox vaccination – United States, 2003. *MMWR Morb Mortal Wkly Rep.* 2003;52(27):639-42.

8 Centers for Disease Control and Prevention. Cardiac adverse events following smallpox vaccination – United States, 2003. *MMWR Morb Mortal Wkly Rep.* 2003; 52(12):248-50.

9 Centers for Disease Control and Prevention. Update: adverse events following smallpox vaccination – United States, 2003. *MMWR Morb Mortal Wkly Rep.* 2003; 52(13):278-282.

10 Neff JM, Lane JM, Pert JH, Moore R, Millar JD, Henderson DA. Complications of smallpox vaccination. National survey in the United States, 1963. *N Engl J Med.* 1967;276:125-132.

11 Centers for Disease Control and Prevention. Recommendations for Using Smallpox Vaccine in a Pre-event vaccination Program. Supplemental Recommendation of the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). *MMWR* 2003;52 (No. RR-7).

12 Centers for Disease Control and Prevention.Notice to Readers. National smallpox vaccine in pregnancy registry. *MMWR Morb Mortal Wkly Rep.* 2003;52(12):256.

13 Centers for Disease Control and Prevention. Vaccinia (smallpox) vaccine recommendation of the Advisory Committee in Immunization Practices (ACIP). 2001. *MMWR Morb Mortal Wkly Rep.* 2001;50 (RR10):1-25.

14 Sejvar J, Labutta RJ, Chapman LE, Grabenstein JD, Iskander J. Lane JM. Neurological adverse events associated with smallpox vaccination in the United States, 2002-2004. *JAMA.* 2005;294(24):2744-50.

15 Nagao S, Inaba S, Iijima S. Langerhans cells at the sites of vaccinia virus inoculation. *Arch Dermatol Res.* 1976;256(1):23-31.

16 Cole, G. Blanden R. Immunology of poxviruses. In: Nahmias AJ, O'Reilly RJ, eds *Comprehensive Immunology, Immunology of Human Infection, Part II, Viruses and Parasites.* Vol 9 New York, NY: Plenum; 1982:1-19.

17 Mack TM, Noble J, Thomas DB. A Prospective Study of Serum Antibody and Protection Against Smallpox. *Am. J Trop Med & Hygiene.* 1972: 21(2):214-218.

18 Department of Defense Directive. Number 6205.3 DoD immunization program for biological warfare defense. 1993. Available from http://www.dtic.mil/whs/directives/corres/html/620503.htm. Accessed July 17, 2007.

19 Centers for Disease Control and Prevention. Recommendations for use of smallpox vaccine for bioterrorism preparedness and response. Available from http://www.bt.cdc/gov/agent/smallpox/vaccination. Accessed July 17, 2007.

16 HOW SUPPLIED / STORAGE AND HANDLING

16.1 How Supplied

ACAM2000, Smallpox (Vaccinia) Vaccine, Live is supplied in multiple-dose 3 mL clear glass vials containing lyophilized powder (freeze-dried vaccine). After reconstitution with 0.3 mL of diluent, the vial contains approximately 100 nominal doses of 0.0025 mL of vaccinia virus (live,) 1.0 - 5.0×10^8 PFU/mL or 2.5-12.5×10^5 PFU/dose.

Diluent for ACAM2000, 50% (v/v) Glycerin USP 0.25% (v/v) Phenol USP in Water for Injection USP, is supplied in 3 mL clear glass vials containing 0.6 mL of diluent.

Bifurcated needles are supplied in boxes (5 x 5 x 1 in) containing 100 needles.

1 mL tuberculin syringes with 25 gauge x 5/8" needles are supplied for vaccine reconstitution.

16.2 Storage and Handling

ACAM2000 should be stored in a freezer with an average temperature of -15°C to -25°C (+5°F to -13°F).

Prior to reconstitution, ACAM2000 vaccine retains a potency of 1.0×10^8 PFU or higher per dose for at least 18 months when stored at refrigerated temperatures of +2-8°C (36-46°F).

During shipment, ACAM2000 should be maintained at a temperature of -15°C or colder.

After reconstitution, ACAM2000 vaccine may be administered during a 6 to 8 hour workday at room temperature (20-25°C, 68-77°F). Reconstituted ACAM2000 vaccine may be stored in a refrigerator (2-8°C, 36-46°F) no longer than 30 days, after which it should be discarded. [*See Dosage and Administration (2.3)*] Diluent for Smallpox Vaccine, (Vero Cells) Lyophilized, ACAM2000 should be stored at room temperature (15-30°C, 59-86°F). ACAM2000 contains live vaccinia virus that is transmissible, and should be handled as an infectious agent once vials are open. See 2.1 [Instructions for Vaccine Preparation] and 2.2 [Preparation / Handling Precautions and Instructions for Disposal] for details on handling and disposal.

17 PATIENT COUNSELING

Please refer patient to the Medication Guide prepared for ACAM2000 Smallpox Vaccine.

17.1 Serious Complications of Vaccination

Patients must be informed of the major serious adverse events associated with vaccination, including myocarditis and/or pericarditis, progressive vaccinia in immunocompromised persons, eczema vaccinatum in persons with skin disorders, auto- and accidental inoculation, generalized vaccinia, urticaria, and erythema multiforme major (including Stevens-Johnson syndrome) and fetal vaccinia in pregnant women.

17.2 Protecting Contacts at Highest Risk for Adverse Events

Patients must be informed that they should avoid contact with individuals at high risk of serious adverse effects of vaccinia virus, for instance, those with past or present eczema, immunodeficiency states including HIV infection, pregnancy, or infants less than 12 months of age.

17.3 Self-Inoculation and Spread to Close Contacts

Patients must be advised that virus is shed from the cutaneous lesion at the site of inoculation from approximately Day 3 until scabbing occurs, typically between Days 14-21 after primary vaccination. Vaccinia virus may be transmitted by direct physical contact. Accidental infection of skin at sites other than the site of intentional vaccination (self-inoculation) may occur by trauma or scratching. Contact spread may also result in accidental inoculation of household members or other close contacts. The result of accidental infection is a pock lesion(s) at an unwanted site(s) in the vaccinee or contact, and resembles the vaccination site. Self-inoculation occurs most often on the face, eyelid, nose, and mouth, but lesions at any site of traumatic inoculation can occur. Self-inoculation of the eye may result in ocular vaccinia, a potentially serious complication.

17.4 Care of the Vaccination Site and Potentially Contaminated Materials

Patients must be given the following instructions:

- The vaccination site must be completely covered with a semipermeable bandage. Keep site covered until the scab falls off on its own.
- The vaccination site must be kept dry. Normal bathing may continue, but cover the vaccination site with waterproof bandage when bathing. The site should not be scrubbed. Cover the vaccination site with loose gauze bandage after bathing.
- Don't scratch the vaccination site. Don't scratch or pick at the scab.
- Do not touch the lesion or soiled bandage and subsequently touch other parts of the body particularly the eyes, anal and genital areas that are susceptible to accidental (auto-) inoculation.
- After changing the bandage or touching the site, wash hands thoroughly with soap and water or >60% alcohol-based hand-rub solutions.
- To prevent transmission to contacts, physical contact of objects that have come into contact with the lesion (e.g. soiled bandages, clothing, fingers) must be avoided.
- Wash separately clothing, towels, bedding or other items that may have come in direct contact with the vaccination site or drainage from the site, using hot water with detergent and/or bleach. Wash hands afterwards.
- Soiled and contaminated bandages must be placed in plastic bags for disposal.
- The vaccinee must wear a shirt with sleeves that covers the vaccination site as an extra precaution to prevent spread of the vaccinia virus. This is particularly important in situations of close physical contact.
- The vaccinee must change the bandage every 1 to 3 days. This will keep skin at the vaccination site intact and minimize softening.
- Don't put salves or ointments on the vaccination site.
- When the scab fall off, throw it away in a sealed plastic bag and wash hands afterwards.

Attachment 4

CHRONOLOGICAL RECORD OF MEDICAL CARE

Smallpox Vaccination Initial Note Page 1 of 2

This page may be completed by potential vaccine recipient

Shade Circles Like This--> ●
Not Like This--> ⊗ ✓

1. Today's Date (MM/DD/YYYY) ☐☐ / ☐☐ / ☐☐☐☐

2a. GENDER ○ Male ○ Female 2b. First day of last normal menstrual period: ___/___/___

2c. FEMALES: Was your last menstrual period normal and on time? ○ Yes ○ No ○ Unsure

2d. Are you currently breastfeeding? ○ Yes ○ No

3. Could someone you LIVE WITH or YOU be pregnant? ○ Yes ○ No ○ Unsure

4. Did you ever receive smallpox vaccine? ○ Yes ○ No ○ Unsure

4a. IF YES: Were you vaccinated within the last 10 years? ○ Yes ○ No ○ Unsure

4b. IF UNSURE: Birth Year ☐☐☐☐ First Year in Military (if applicable) ☐☐☐☐

5. Have you ever had a serious problem after smallpox or other vaccination? (Describe below) ○ Yes ○ No ○ Unsure

6. Do you currently have an illness with fever? ○ Yes ○ No ○ Unsure

7. Are you allergic to any of these products: polymyxin B, neomycin, latex? ○ Yes ○ No ○ Unsure

Before vaccinating against smallpox, we want to know if you or your household close contacts have any of several medical conditions.

Please answer the following questions to the best of your knowledge.	Myself	Close Contact
8. Do you OR someone you currently live with NOW HAVE any of the following skin problems: Psoriasis (scaly skin rash), Burns (other than mild sunburn), Impetigo (skin infection), Uncontrolled Acne, Shingles (herpes zoster), Chickenpox, Darier's disease or Other skin conditions (describe below)?	○ Yes ○ No ○ Unsure	○ Yes ○ No ○ Unsure
9. Do you OR someone you currently live with NOW HAVE or RECENTLY HAD a problem or take(s) medication that affects the immune system? For example: have or take medication for HIV, AIDS, leukemia, lymphoma, or chronic liver problem; have or take medication for Crohn's disease, lupus, arthritis, or other immune disease; have had radiation or X-ray treatment (not routine X-rays) within the last 3 months; have EVER had a bone-marrow or organ transplant (or take medication for that); or have another problem that requires steroids, prednisone or a cancer drug for treatment.	○ Yes ○ No ○ Unsure	○ Yes ○ No ○ Unsure
10. Have you OR someone you currently live with EVER HAD Eczema or Atopic Dermatitis? (Usually this skin condition involves an itchy, red, scaly rash that lasts more than 2 weeks. It often comes and goes.) IF YES or UNSURE: for either you or your close contact, Answer 10a-10e	○ Yes ○ No ○ Unsure	○ Yes ○ No ○ Unsure
10a. A doctor has made the diagnosis of eczema or atopic dermatitis.	○ Yes ○ No ○ Unsure	○ Yes ○ No ○ Unsure
10b. There have been itchy rashes that have lasted more than 2 weeks.	○ Yes ○ No ○ Unsure	○ Yes ○ No ○ Unsure
10c. At least once, there is a history of an itchy rash in the folds of the arms or legs.	○ Yes ○ No ○ Unsure	○ Yes ○ No ○ Unsure
10d. There is a history of eczema and food allergy during childhood.	○ Yes ○ No ○ Unsure	○ Yes ○ No ○ Unsure
10e. A doctor has made the diagnosis of asthma or hayfever (including first-degree relatives).	○ Yes ○ No ○ Unsure	○ Yes ○ No ○ Unsure

11. Are you being treated with steroid eye drops or ointment or have you had recent eye surgery? ○ Yes ○ No ○ Unsure

12. Do you have a heart or vessel condition, such as angina, earlier heart attack, coronary artery disease, congestive heart failure, cardiomyopathy, stroke, "mini stroke", chest pain or trouble breathing on exertion? ○ Yes ○ No ○ Unsure

13. Check EACH of the following conditions that apply to you: ○ Heart Condition before age 50 in mother, father, brother, sister
○ Smoke cigarettes now ○ High blood pressure ○ High cholesterol ○ Diabetes or high blood sugar

14. Do you have a child in home less one year of age? ○ Yes ○ No

15. Do you have other questions or have other concerns you would like to discuss? ○ Yes ○ No

Explain "other," "unsure," or additional concerns (may use additional page). NOTE: If you might have a risk factor for HIV infection, we can arrange for HIV testing. FOR FEMALES: If you might be pregnant, or likely to become pregnant, please tell us. You may need additional pregnancy testing.

Last Name ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

First Name ☐☐☐☐☐☐☐☐ MI ☐

Social Security Number ☐☐☐ ☐☐ ☐☐☐☐

Patient's identification (May use mechanical imprint)

RECORDS MAINTAINED AT:
RANK/GRADE
SEX
DATE OF BIRTH
SPONSOR NAME
(or Sponsor SSN)
RELATIONSHIP TO SPONSOR
(Or FMP)
ORGANIZATION
STATUS
DEPT/SVC

Standard Form 600 (Rev.6-97) Electronic Copy SVP Overprint (11-07)

Attachment 4

CHRONOLOGICAL RECORD OF MEDICAL CARE

Smallpox Vaccination Initial Note Page 2 of 2

This page may be completed by a healthcare provider

1. Provider Assessment Date (MM/DD/YYYY)

☐☐ / ☐☐ / ☐☐☐☐

If Provider Assessment Date or Action Taken Immunization Date is blank, Default is "Today's date" on page 1.

2. Reason for Vaccination (Indicate One):

- O Pre-outbreak: disease prevention
- O Post-outbreak: not exposed to virus
- O Post-outbreak: exposed to virus
- O Other reason (Describe)

3. Vaccine Risk Factors based on page 1 review and interview (Check all that apply):

	Self		Close Contact
No restriction	O		O
Pregnancy	O		O
Immune suppression	O		O
Skin condition	O		O
Relevant allergy	O		
Heart condition	O	3+ RF O	
Unsure	O		O (Describe)

4. Provider comment on any concerns about contraindications, need to defer, need to consult, and/or relevant diagnosis

5. Provider Decision and Plan (Check all that apply):

- ☐ Vaccinate: Primary (e.g. birth year >1972, military entry >1984)
- ☐ Vaccinate: Revaccination
- ☐ Medically immune: vaccinated within approp interval (MI)
- ☐ Vaccination deferred: Pending consult or lab test
- ☐ Vaccination deferred: Temporary contraindication (MT)
- ☐ Vaccination contraindicated unless exposed (MP)
- ☐ Vaccination not given (other reason specify below):

6. IF NOT IMMUNIZED, Check all that apply:

- ☐ Reason for non-immunization explained
- ☐ Lab test requested
- ☐ Consult request written/sent
- ☐ Follow up appointment planned
- ☐ Other reason (specify below):

List labs or consults requested, and length of temp referrals

VACCINE ADMINISTRATION

Vaccination Date (M M / D D / Y Y Y Y)

☐☐ / ☐☐ / ☐☐☐☐

7. Vaccination Action Taken:

Location: O Left Arm O Right Arm O Other Location (Describe)

Number of jabs: ☐☐

Lot # ☐☐☐☐☐☐☐ Mfr # ☐☐☐

For QA use: local vial serial # ☐☐☐

8. IF IMMUNIZED, Check all that apply

- ☐ Information sheet given to recipient
- ☐ Recipient advised about post-vaccination reaction and site care
- ☐ Reasons for follow-up clinic visit described
- ☐ Patient understands information given
- ☐ Bandages provided if needed.

Please assure that all actions taken and deferrals are updated into your service's electronic Immunization Tracking System (ITS) as soon as possible.

Provider Signature and Printed Name/Stamp:

Vaccine administered by: (Signature and Printed Name/Stamp)

Last Name

First Name MI

Social Security Number

Patient's identification (May use mechanical imprint)

RECORDS MAINTAINED AT:
RANK/GRADE
SEX
DATE OF BIRTH
SPONSOR NAME
(or Sponsor SSN)
RELATIONSHIP TO SPONSOR
(Or FMP)
ORGANIZATION
STATUS
DEPT/SVC

CHRONOLOGICAL RECORD OF MEDICAL CARE

Smallpox Vaccination Clinical/Sick-call Follow up Note

1. Today's Date (MM/DD/YYYY) ☐☐ / ☐☐ / ☐☐☐☐

2. Day 0 = Smallpox Vaccination Date ☐☐ / ☐☐ / ☐☐☐☐

2b. Days post vax ☐☐

3. Vital Signs Temp ☐☐☐ . ☐ Pulse ☐☐☐ Resp ☐☐ BP ☐☐☐ / ☐☐☐

4. Chief Compliant (Default = routine check)

5. Was there a bandage on the vaccination site? O Yes O No

5a. IF YES: How many days did patient use a bandage? ☐☐

5b. Did patient see the vaccination site every day or two? O Yes O No

6a. Vaccination site appearance today (Check all that apply)

- ☐ local redness
- ☐ bump
- ☐ reddish blister
- ☐ whitish blister
- ☐ scab or crust
- ☐ local itching
- ☐ local rash
- ☐ nothing

6a. Vaccination site appearance today (Check all that apply)

- ☐ local redness
- ☐ bump
- ☐ reddish blister
- ☐ whitish blister
- ☐ scab pr crust
- ☐ local itching
- ☐ local rash
- ☐ nothing seen
- ☐ patient did not remember/observe

7. Check anything else experienced after the smallpox vaccination (Check all that apply)

- ☐ headache
- ☐ body rash
- ☐ itchy all over
- ☐ eye infection
- ☐ fever (temp in box)
- ☐ muscle aches
- ☐ feeling lousy
- ☐ swollen lymph nodes
- ☐ bandage reaction
- ☐ chest pain
- ☐ shortness of breath
- ☐ other (describe in box)

8. Any problems following vaccination? (Check all they apply)

- ☐ Restricted activity — How many days? ☐☐
- ☐ Limited duty — How many days? ☐☐
- ☐ Missed work — How many days? ☐☐
- ☐ Took medication (list in box) — How many days? ☐☐
- ☐ Visited clinic or emergency room
- ☐ Hospitalized
- ☐ Other (described in box)

9. Vaccination Site measures (if indicated)

Erythema length (mm) ☐☐☐ X width ☐☐☐

Vesicle length (mm) ☐☐☐ X width ☐☐☐

Note any other reactions, problems or medications following vaccination:

10. Does the patient believe anyone might have become ill as a result of the vaccination? O Yes O No O Unsure

If YES or UNSURE describe in box (or on continuation page)

11. Assessment and Plan (check all that apply:

- ☐ Fully Immunized ("major reaction, "take")
- ☐ Equivocal response
- ☐ Referred to Vaccine Healthcare Centers
- ☐ Re-vaccination indicated
- ☐ Follow-up for events described
- ☐ Medication prescribed (list)
- ☐ No further follow up planned
- ☐ Consultation Allergy/Immunology/Dermatology/Cardiology/other_____)
- ☐ Other action (describe in box) Report to VAERS if warranted.

11a. Other assessment/plan related to evaluation

12. Duty limitations

- ☐ Full duty
- ☐ No direct patient care
- ☐ Quarters for ___ days
- ☐ Urgent/Emergent referral
- ☐ Routine referral

Provider Signature and Printed Name/Stamp

Patient's identification (May use mechanical imprint)

Last Name

First Name MI

Social Security Number

RECORDS MAINTAINED AT:
RANK/GRADE
SEX
DATE OF BIRTH
SPONSOR NAME
(or Sponsor SSN)
RELATIONSHIP TO SPONSOR
(Or FMP)
ORGANIZATION
STATUS
DEPT/SVC

CHRONOLOGICAL RECORD OF MEDICAL CARE

Smallpox Vaccination Clinical/Routine Follow up Note

1. Today's Date (MM/DD/YYYY) ☐☐/☐☐/☐☐☐☐

2. Smallpox Vaccination Date ☐☐/☐☐/☐☐☐☐

3. Did you put a bandage on the vaccination site ○ Yes ○ No

3a. IF YES: How many days did you use a bandage? ☐☐

3b. Did you see the vaccination site every day or two? ○ Yes ○ No

4a. Vaccination site appearance today (Check all that apply)

- ☐ local redness
- ☐ bump
- ☐ reddish blister
- ☐ whitish blister
- ☐ scab or crust
- ☐ local itching
- ☐ local rash
- ☐ nothing

4b. Vaccination site appearance today (Check all that apply)

- ☐ local redness
- ☐ bump
- ☐ reddish blister
- ☐ whitish blister
- ☐ scab pr crust
- ☐ local itching
- ☐ local rash
- ☐ nothing seen
- ☐ patient did not remember/observe

4c. Check anything else experienced after the smallpox vaccination (Check all that apply)

- ☐ headache
- ☐ body rash
- ☐ itchy all over
- ☐ eye infection
- ☐ fever (temp in box)
- ☐ muscle aches
- ☐ feeling lousy
- ☐ swollen lymph nodes
- ☐ bandage reaction
- ☐ chest pain
- ☐ shortness of breath
- ☐ other (describe in box)

5. Any problems following vaccination? (Check all they apply)

- ☐ Restricted activity — How many days? ☐☐
- ☐ Limited duty — How many days? ☐☐
- ☐ Missed work — How many days? ☐☐
- ☐ Took medication (list in box) — How many days? ☐☐
- ☐ Visited clinic or emergency room
- ☐ Hospitalized
- ☐ Other (described in box)

6. Note any other reactions, problems or medications following vaccination:

7. Does the patient believe anyone might have become ill as a result of the vaccination? ○ Yes ○ No ○ Unsure

If YES or UNSURE describe in box (or on continuation page)

8. Provider evaluation and action (check all that apply:

- ☐ Fully Immunized ("major reaction, "take")
- ☐ Equivocal response
- ☐ Referred to Vaccine Healthcare Centers
- ☐ Re-vaccination indicated
- ☐ Follow-up for events described
- ☐ Medication prescribed (list)
- ☐ No further follow up planned
- ☐ Consultation Allergy/Immunology/Dermatology/Cardiology/other_____)
- ☐ Other action (describe in box) Report to VAERS if warranted.

Provider Notes:

Provider Signature and Printed Name/Stamp:

Last Name

First Name MI

Social Security Number

Patient's identification (May use mechanical imprint)

RECORDS MAINTAINED AT:
RANK/GRADE
SEX
DATE OF BIRTH
SPONSOR NAME
(or Sponsor SSN)
RELATIONSHIP TO SPONSOR
(Or FMP)
ORGANIZATION
STATUS
DEPT/SVC

CHRONOLOGICAL RECORD OF MEDICAL CARE

Smallpox Vaccination Continuation Note

1. Today's Date (MM/DD/YYYY)

☐☐ / ☐☐ / ☐☐☐☐

Additional Notes on Problems, Issues or Concerns of Patient or Provider related to Vaccine Assessment or Follow-up. Subjective section may be filled out by either patient/vaccine or provider. Objective findings, Assessment and Plan should be completed by a provider.

Subjective: History of issues related to vaccination assessment or follow-up

Objective: Relevant exam, test or laboratory findings

Assessment: Integrated summary

Plan

Provider Signature and Printed Name/Stamp:

Last Name

First Name

MI

Social Security Number

Patient's identification (May use mechanical imprint)

RECORDS MAINTAINED AT:
RANK/GRADE
SEX
DATE OF BIRTH
SPONSOR NAME
(or Sponsor SSN)
RELATIONSHIP TO SPONSOR
(Or FMP)
ORGANIZATION
STATUS
DEPT/SVC

Symptom Diary After Smallpox Vaccination

a) Patient name: Last _____ First _____ MI ____ b) Social Security Number: _____-_____-_____

c) Date of Birth: Mo____/Day____/Yr_____ d) Age: ____years e) Gender: ☐ Male ☐ Female

f) Date of smallpox vaccine administration: Mo____/Day____/Yr_____ g) Clinic / site where vaccination was given: _____

h) Taken any steroids/pain/fever medications: ☐ 1-3 days before vaccine(_____) ☐ 0-30 days after vaccine(_____) ☐ None during this period (-3 to +30 days)

i) Ethnicity ☐ White/Caucasian ☐ Asian ☐ Black/African American ☐ Native Hawaiian/Other Pacific Islander
☐ Hispanic ☐ American Indian/Alaskan Native ☐ Do not want to provide ☐ Other (specify: _____)

THE FIRST 4 WEEKS AFTER SMALLPOX VACCINATION: Please check any symptoms present on each indicated day recording details below	Day 0 vaccination	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Week 4
1. Symptoms (Y or N)																						
2. Fever (record temperature, eg.101.2F)																						
3. Chills (Yor N)																						
4. Swelling at vaccination site (Y or N)																						
5. Cough/ difficulty breathing (Y or N)																						
6. Rash or vaccine-type reaction on body (Y or N, if Y describe rash and where, below)																						
7. Bandage used (Y or N, type below)																						
8. Did you seek medical care because of vaccination? (describe below)																						
9. Did you take any medications because of vaccination?(specify below)																						
10. Did you miss work/school because of vaccination?																						
11. Joint pain (0-9scale) (0=no, 9=worse)																						
12. Muscle pain (0-9 scale)																						
13. Headache (0-9 scale)																						
14. Pain at vaccination site (0-9 scale)																						
15. Swelling/tender lymph nodes (0-9 scale)																						
16. Itching at vaccination site (0-9 scale)																						
17. Chest pain (0-9 scale)																						
18. Shortness of breath (0-9 scale)																						
19. Other symptoms, illnesses, new medications, etc.(describe below)																						
20. Vaccination site appearance (using letter codes below)																						

Date scab fell off: Mo_____/Day_____/Yr_____

If at any time you have questions about your vaccination please contact the DoD Vaccine clinical Call Center at 1-866-210-6469 (24 hrs a day, 7 days a week) or email the vaccine Healthcare Centers Network at https://askvhc.wramc.amedd.army.mil

Use all the letter codes that apply to describe vaccination site for each day above:

1= red spot	2= bump	3=reddish blister	4=whitish blister	5=scab
6=ulcer, crater	w=warmth	sw=swollen>3 in.	st=streaks	dr=drainage

If medical care sought, where? Name of facility/MD: _____

Permission to acquire medical records? ☐ **Yes** ☐ **No**

Additional comments (use additional pages if necessary): _____

Signature of vaccinee:	Date completed:

DATA PRIVACY NOTICE: Data requested are being collected under the authority of The Privacy Act of 1974, 5 U.S.C. §552A. The SSN is being collected because it is a unique identifier that will better enable military staff to maintain contact with patients over time. Every effort will be made to safeguard the confidentiality of the information provided

Attachment 5

Smallpox Vaccine in Pregnancy Registry

INFORMATION PAPER:
When Pregnancy Is Discovered After Smallpox Vaccination

1. Purpose. This paper provides information for women who discover they are pregnant after receiving smallpox vaccination.

2. Current Recommendations on Vaccination and Pregnancy

Similar to other live virus vaccines, smallpox vaccine is not recommended for pregnant women in non-emergency situations. Further, it is recommended that women who receive the vaccine should avoid becoming pregnant for at least 4 weeks after vaccination.

Because it can be difficult to predict conception or diagnose early pregnancy, it is not surprising that some women may inadvertently receive smallpox vaccine shortly before or after becoming pregnant.

3. Historic Experience with Smallpox Vaccine in Pregnancy

Smallpox vaccine recommendations have changed over time. In the mid-20th century, when smallpox disease was still naturally occurring, billions of women around the world, both pregnant and not pregnant, received the vaccine. During smallpox outbreaks, health officials intentionally gave pregnant women smallpox vaccine to protect them from lethal infections.

There is no historic evidence that smallpox vaccine caused increased rates of spontaneous abortion (miscarriage). There is no historic evidence that the smallpox vaccine used in the United States caused birth defects.

Fetal vaccinia is a known, but extremely rare, complication that can occur after smallpox vaccine is given in pregnancy. Fetal vaccinia occurs when the virus used in smallpox vaccine infects the unborn baby (fetus). Cases of fetal vaccinia have been associated with stillbirth or infant death shortly after delivery. In the 20th century, 3 cases of fetal vaccinia were reported in the United States, and 47 cases were reported from other countries around the world. It is possible that other cases occurred, but were not reported. No cases of fetal vaccinia were reported after 173,000 pregnant women in New York City were vaccinated in 1947. It is estimated that 1 case of fetal vaccinia might occur for every 10,000 to 100,000 pregnant women who get smallpox vaccine for the first time.

4. Recent Experience with Smallpox Vaccine in Pregnancy

The Smallpox Vaccine in Pregnancy Registry, established in 2003 and managed by the Department of Defense Birth and Infant Health Registry, follows women who inadvertently receive smallpox vaccine while pregnant. The Registry collects confidential information to better understand if smallpox vaccine in pregnancy is associated with problems for mothers or infants in the modern era.

In the United States, approximately 17% of all recognized pregnancies end in miscarriage, and 3% to 5% of infants are born with birth defects. It is natural for parents who suffer a pregnancy loss, or have a baby with a birth defect, to want to know the cause. Unfortunately, the causes of most miscarriages and birth defects are unknown.

Thus far, information from the Smallpox Vaccine in Pregnancy Registry indicates that miscarriages and birth defects occur at rates similar to, or less than, rates seen in the general population. Women who inadvertently receive smallpox vaccine while pregnant may be reassured that current data support historic data, and do not suggest that they are at higher risk for pregnancy loss or giving birth to a child with a birth defect.

In addition, there have been no cases of fetal vaccinia among pregnancies followed by the Registry.

Attachment 5

5. Better Understanding Pregnancy Losses

It may be possible to know if smallpox vaccine was associated with a miscarriage or stillbirth by laboratory testing for vaccinia virus. In order to perform this testing, specimens must be brought to a special laboratory and preserved (without formalin) at –70C in viral transport media. Women who would like to have this testing performed should discuss with their healthcare providers as soon as possible after a miscarriage is diagnosed.

6. Resources for Additional Information

The Smallpox Vaccine in Pregnancy Registry was established to collect important confidential information from women who received smallpox vaccine in pregnancy. Professionals from the Registry can answer many questions from participants and their healthcare providers. The Registry may be contacted at:

National Smallpox Vaccine in Pregnancy Registry
c/o DoD Birth and Infant Health Registry,
NHRC Dept 164, 140 Sylvester Road, San Diego, CA 92106
Phone: 619-553-9255 (DSN 553-9255)
Fax: 619-553-7601
Email: NHRC-BirthRegistry@med.navy.mil

Additional resources include:

Vaccine Healthcare Center Network
c/o Walter Reed Army Medical Center, Washington, DC
Phone: 202-782-0411 (DSN 662)

Military Vaccine (MILVAX) Agency
Falls Church, VA
Phone: 877-GET-VACC or 703-681-5101 (DSN 761)

Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine
Madigan Army Medical Center, Tacoma, WA
Phone: 253-968-1710 or 1252 (DSN 782)

References

Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and Its Eradication. Geneva: World Health Organization 1988. http://www.who.int/emc/diseases/smallpox/Smallpoxeradication.html

CDC. Recommendations for Using Smallpox Vaccine in a Pre-Event Vaccination Program. MMWR 2003;52(RR07):1-16. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5207a1.htm

Levine MM, Edsall G, Bruce-Chwatt LJ. Live-virus vaccines in pregnancy: Risks and recommendations. Lancet 1974;2:34-8.

Naderi S. Smallpox vaccination during pregnancy. Obstet Gynecol 1975;46(2):223-6. (Note that the vaccine strain described here and used in Iran was different from the vaccine used in the United States.)

Stenchever MA, Droegemuller W, Herbst AL, Mishell DR. Comprehensive Gynecology, Mosby, 2001:414.

This document was last updated Sep 2007
M. Ryan, MD, MPH for the Natl Smallpox Vaccine in Pregnancy Registry team.

Attachment 6

VACCINATION-RESPONSE INTERPRETATION

Inspect the vaccination site 6 to 8 days after vaccination. Interpret the response at that time. The World Health Organization (WHO) Expert Committee on Smallpox defined two types of responses:

a) major reaction: virus replication took place and vaccination was successful; or

b) equivocal reaction: a possible consequence of immunity adequate to suppress viral multiplication or allergic reactions to an inactive vaccine without production of immunity.

Major Reaction:

A vesicular (blistery) or pustular (pus-filled) lesion or area of definite palpable induration or congestion surrounding a central lesion that might be a crust or an ulcer.

After primary (first) vaccination, the vaccination site usually progresses as follows:

- The inoculation site becomes reddened and pruritic 3 to 4 days after vaccination.
- A vesicle surrounded by a red areola then forms, which becomes umbilicated (collapsed center) and then pustular by days 7 to 11 after vaccination.
- The pustule begins to dry; the redness subsides; and the lesion becomes crusted between the second and third week. By the end of about the third week, the scab falls off, leaving a permanent scar that at first is pink in color but eventually becomes flesh-colored.
- After revaccination, skin reactions might be less pronounced with more rapid progression and healing than those after primary vaccination. Revaccination is successful if a pustular lesion or area of definite induration or congestion surrounding a central lesion (i.e., scab or ulcer) appears 6 to 8 days after revaccination.

Equivocal Reaction:

Equivocal reactions, including accelerated, modified, vaccinoid, immediate, early, or immune reactions, are all responses other than major reactions. If an equivocal reaction is observed, check vaccination procedures and repeat vaccination using another vial or vaccine lot, if available. A response to smallpox vaccination may be blunted by immunity, insufficiently potent vaccine, or vaccination technique failure. If repeat vaccination using vaccine from another vial fails to elicit a major reaction, consult public-health authorities before attempting another vaccination of that person.

Sources: Fenner et. al, 1988 (pp 296, 312-314); ACIP, 2001.

Attachment G

Attachment 7

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D. C. 20301-1200

HEALTH AFFAIRS

APR 1 0 2003

MEMORANDUM FOR ASSISTANT SECRETARY OF THE ARMY (M&RA)
ASSISTANT SECRETARY OF THE NAVY (M&RA)
ASSISTANT SECRETARY OF THE AIR FORCE (M&RA)
DIRECTOR, JOINT STAFF

SUBJECT: Policy for Smallpox Vaccine and Persons with Cardiac Conditions

On March 28, 2003, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) met to review data (summary attached) and consider recommendations for the use of smallpox vaccine in persons with known cardiac condition and/or known cardiac risk factors. After careful deliberation, the committee recommends: 1) add myopericarditis as an expected adverse event of smallpox vaccination, and 2) exempt from vaccination persons with known cardiac condition(s) and persons with three or more known major cardiac risk factors (summary of ACIP recommendations attached). The Services should exempt personnel with the following cardiac conditions: myocardial infarction, angina pectoris, cardiomyopathy, congestive heart failure, stroke, transient ischemic attacks, chest pain or shortness of breath with activity and associated with a heart condition, other coronary artery disease, and other heart conditions under the care of a physician. Persons with any of the listed conditions should be exempted from smallpox vaccination.

The following cardiac risk factors should be identified during pre-immunization processing: current cigarette smoking, hypertension, hypercholesterolemia, diabetes mellitus, and family history of heart disease in 1st degree relative with onset before age 50. Persons with three or more of the above referenced risk factors should be exempted from receiving smallpox vaccine. Along with the ACIP, Health Affairs recommends that recent smallpox vaccine recipients who have a cardiac condition or three or more major cardiac risk factors be evaluated by a health care professional if they develop any symptoms of chest pain, shortness of breath, or other symptoms of heart disease. All people with heart disease or risk factors should receive the routine care recommended for persons with these conditions.

I direct the Services to make appropriate adjustments to their smallpox vaccination programs to incorporate these recommendations. DoD smallpox vaccine education and screening materials will be modified accordingly and posted at www.smallpox.army.mil.

HA POLICY: 03-002

Attachment 7

My points of contact are COL Benedict Diniega ((703) 575-2669), and COL John Grabenstein (Military Vaccine Agency, (703) 681-5059).

William Winkenwerder Jr.

William Winkenwerder, Jr., MD

Attachments:
As stated

cc:
Joint Staff (J-4 (HSSD))
Surgeon General, Army
Surgeon General, Navy
Surgeon General, Air Force
Medical Officer, HQ, U.S. Marine Corps
Director of Health and Safety, U.S. Coast Guard

Attachment 8

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

JUN -9 2003

MEMORANDUM FOR DEPUTY SURGEON GENERAL OF THE ARMY
DEPUTY SURGEON GENERAL OF THE NAVY
DEPUTY SURGEON GENERAL OF THE AIR FORCE

SUBJECT: Establishment of Case Management Guidelines for Smallpox Vaccine Associated Myopericarditis

REFERENCES:

1. Deputy Secretary of Defense Memorandum, "Smallpox Vaccination Program," September 30, 2002
2. Under Secretary of Defense for Personnel and Readiness Memorandum, "Policy on Administrative Issues Related to Smallpox Vaccination Program (SVP)," December 13, 2002
3. Assistant Secretary of Defense for Health Affairs Memorandum, "Clinical Policy for the DoD Smallpox Vaccination Program (SVP)," November 26, 2002

Myopericarditis has historically been associated with vaccination for smallpox (vaccinia virus). Until recently, it has been a rare or unrecognized event after vaccination with the currently utilized strain of vaccinia virus (New York City Board of Health; Dryvax®, Wyeth Laboratories, Marietta, PA). Ongoing evaluation of health outcomes among Armed Forces personnel indicates individuals vaccinated for smallpox are at higher risk for myopericarditis than those not vaccinated. Ongoing review of cases diagnosed to date indicate a need to standardize evaluation and clinical management to decrease variation and provide ready access to clinical consultative services, assure access to care for longer-term follow-up for individuals separating from active duty, reserve component and National Guard personnel, and a need to document outcomes for future smallpox vaccine program management.

This memorandum provides a uniform approach for evaluation and establishes a program for consultation and long-term follow-up of individuals diagnosed with smallpox vaccine associated myopericarditis. A tri-service team supporting the DoD Vaccine Healthcare Center (VHC) Network developed the attached guidelines for clinicians. Forward deployed medical support units should be aware of and use the guidelines for the diagnosis and treatment of myopericarditis associated with smallpox vaccination. The guidelines will be modified in an iterative process as new information and clinical experience evolve, and will be available at www.vaccines.mil. To support clinicians seeking multi-disciplinary consultation, the Military Vaccine (MILVAX) Agency established a 24/7 toll-free bridge number for short-notice teleconferencing. Clinicians wishing to consult via this teleconference bridge with VHC staff and/or military cardiologists regarding optimal care should call the DoD Vaccine Clinical Call

Attachment 8

Center at (866) 210-6469. Additional consultative support is available via e-mail at ASkVHC@amedd.army.mil.

All DoD beneficiaries, including Reserve component personnel who received their smallpox vaccine while in a duty status, with a clinically verified diagnosis of post-smallpox vaccine myopericarditis will be enrolled in the central registry maintained by the VHC Network and be followed using the attached clinical guidelines for a minimum of 12 months from the date of initial diagnosis. The Vaccine Adverse Event Reporting System (VAERS) should be used according to service policy. Patient informed consent is not required as part of enrollment. Enrollment in this registry will facilitate long-term clinical follow-up, delivery of appropriate clinical care, and a greater understanding of potential sequelae of this clinical manifestation. Upon enrollment VHC staff should help ensure appropriate 6 and 12-month follow-up in coordination with the patient's case manager.

Those individuals requiring medical treatment/evaluation should be retained on Active Duty pending resolution of the medical condition or completion of the disability evaluation. Each Service will coordinate with the Military Medical Support Office (1-888-MHS-MMSO), as needed, to provide appropriate civilian medical follow-up and payment arrangements for Reserve Component personnel.

David N. Tornberg, MD, MPH
Deputy Assistant Secretary of Defense
Clinical and Program Policy

Attachment:
As stated

Attachment 9

INFORMATION PAPER

Military Vaccine Agency
9 November 2007

SUBJECT: Intra-Venous Vaccinia Immune Globulin (IV-VIG)

1. Purpose. Define procedures for ordering IV-VIG

2. Facts.

a. Smallpox immunizations are provided to designated at-risk military personnel, DoD civilian personnel classified as emergency-essential, and other civilian personnel. Some people are at greater than usual risk for serious side effects from the smallpox vaccine. IV-VIG is indicated for the treatment or modification of certain conditions induced by the smallpox vaccine.

b. Under routine circumstances, the need for VIG shall be validated by a board-certified infectious-disease or allergy-immunology specialist before administration. The Vaccine Healthcare Centers (VHC) Network will provide and coordinate professional consultation services to optimize clinical use of IV-VIG, and then maintain a case file of patients treated with IV-VIG.

3. Procedures

a. Clinician identifies smallpox vaccinee with adverse reaction that may benefit from IV-VIG administration This would include but is not limited to: aberrant infections induced by vaccinia virus that include accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard; eczema vaccinatum; progressive vaccinia; severe generalized vaccinia; or vaccinia infections in people who have skin conditions such as burns, impetigo, varicella-zoster, or poison ivy; or in people who have eczematous skin lesions because of either the activity or extensiveness of such lesions.

b. Clinician consults with infectious-disease (ID) or allergy-immunology (AI) specialist physician. Long-distance consultations will be arranged via the Vaccine Healthcare Centers (VHC) Network's Vaccine Clinical Call Center (866-210-6469). VHC will notify the Military Vaccine (MILVAX) Agency of case specifics.

c. ID or AI, in consultation with the VHC and Centers for Disease Control and Prevention (CDC) physician, authorizes release of IV-VIG from CDC's Strategic National Stockpile (SNS).

d. IV-VIG is requested directly from the CDC by calling the CDC Director's Emergency Operation Center (DEOC) at (770) 488-7100 and request to speak with the

Attachment 9

Division of Bioterrorism Preparedness and Response (DBPR) on-call person. The CDC is the release authority for IV-VIG.

e. Requestor notifies VHC Network (telephone 866-210-6469, email askvhc@amedd.army.mil); MILVAX (telephone 877-GET-VACC, DSN 761-4245, email patrick.garman@us.army.mil).

f. The attending clinician reads package insert and case-report form while considering the patient's clinical situation. The clinician then obtains needed specialty consults and administers IV-VIG if warranted. Clinician draws serum specimens before infusion and then 5 days after each IV-VIG dose. Freeze serum vials at -20°C until ready to ship. Obtain patient's consent to release serum samples. Ship serum vials at -20°C and case-report form to CDC in accordance with detailed instructions in the serum processing kit that accompanies IV-VIG. Send copy of case-report form to VHC.

4. References.

a. Advisory Committee on Immunization Practices. Smallpox Vaccinations and Adverse Reactions, MMWR 2003;52(RR04): 1-28: www.cdc.gov/mmwr/preview/mmwrhtml/rr5204a1.htm

b. CDC VIG information website: ww.bt.cdc.gov/agent/smallpox/vaccination/vig.asp

c. CDC disease information website. www.bt.cdc.gov/agent/smallpox/index.asp

d. Multiple resources (e.g., product insert, Vaccine Information Statements) assembled by Military Vaccine Agency: www.vaccines.mil/smallpox

Mr. William Watson/(703) 681-5101

Approved by: LTC Garman

Attachment 10

Precision in ICD9 Coding of Medical Encounters.

1. To increase the precision of automated analyses of vaccine safety, military treatment facilities should help medical-record coders find the most precise ICD9 codes to describe the patient's visit. Encourage precision by distributing lists of codes for common encounters related to vaccination.

2. For example, use consistent codes to identify visits to treat injection-site inflammation after vaccination. If the patient experiences a chief complaint of muscle ache, along with headache and swelling of the injection site, enter 729.1, 784.0, 729.81, and 995.2. This will allow visits for similar conditions to be grouped together, enhancing our ability to calculate how often they occur.

3. The following lines list common codes. As always, use the most specific codes clinically appropriate to the patient seen. When in doubt, consult with the coding specialists and the reference books in your Patient Administration Division.

a. Anaphylaxis -- 995.0 – including allergic shock and anaphylactic reaction due to adverse effect of correct medicinal substance properly administered
b. Angioedema – 995.1 – also called angioneurotic edema
c. Dizziness and giddiness – 780.4 – including light-headedness, vertigo not otherwise specified (NOS)
d. Edema -- 782.3
e. Fainting – 780.2 – including syncope and collapse, blackout, (near) (pre)syncope, vasovagal attack
f. Fever – 780.6 – including chills with fever
g. Headache -- 784.0
h. Infection following infusion, injection, transfusion, or vaccination – 999.3
i. Itching – 698.9 – pruritis
j. Malaise and fatigue – 780.7
k. Mylagia and myositis, unspecified – 729.1
l. Other general symptoms – 780.9 – including chill(s) NOS
m. Pain in joint – 719.4 – including arthralgia
n. Rash and other nonspecific skin eruption – 782.1 – including exanthem.
o. Skin sensation disturbance – 782.0 – including burning or prickling sensation, hyperesthesia, hypoesthesia, numbness, paresthesia, tingling
p. Subcutaneous nodules -- 782.2 – including localized superficial swelling, mass, or lump
q. Swelling of limb – 729.81
r. Unspecified adverse effect of drug, medicinal and biological substance (due) to correct medicinal substance properly administered -- 995.2 – including allergic reaction, hypersensitivity, and idiosyncrasy to correct substance properly administered
s. Unspecified erythematous condition – 695.9 – including erythema NOS

4. The following codes are specific to smallpox vaccination:

a. Encephalitis, postvaccinal -- 323.5

Attachment 10

b. Keratitis superficial without conjunctivitis -- 370.2
c. Keratitis or keratoconjunctivitis in exanthema -- 370.44
d. Infection following infusion, injection, transfusion, or vaccination – 999.3 (such as for inadvertent inoculation)
e. Generalized vaccinia -- 999.0
f. Adverse effects of correct medicinal substance properly administered, smallpox vaccine -- E949.0

5. According to the International Classification of Diseases, 9th edition (ICD9), "poisoning" codes from 960 to 979 exclude adverse effects ["hypersensitivity," "reaction," etc.] of correct substances properly administered. Such episodes should be classified according to the nature of the specific adverse effect.

6. "E" codes are appropriate in specific circumstances. For example, adverse effects of correct medicinal substance properly administered, bacterial vaccines should be coded as E948.8.

7. Coding conventions vary from time to time. Additional guidance on this topic will be issued periodically.