INFORMATION PAPER

Military Vaccine Agency
10 January 2008

SUBJECT: Smallpox Disease and Smallpox Vaccine

1. Purpose. To describe smallpox disease and the smallpox vaccine.

2. Facts.

a. Microbiology. Variola virus causes the contagious disease smallpox in humans. The smallpox virus (variola) is a poxvirus of the genus *Orthopoxvirus*. *Orthopoxviruses* are large, complex, brick-shaped, double-stranded DNA viruses that cause infections characterized by a rash. Poxviruses have a highly specialized mode of replication and pathogenesis that allows them to replicate in the cytoplasm of infected cells. Because of the cytoplasmic site of replication, the poxvirus has no access to the cellular transcription and DNA replication apparatus, and therefore, has a large genome to support all of its nuclear-replication processes.

b. Disease. Smallpox was a serious, contagious, and sometimes fatal infectious disease. Typical smallpox disease (variola major) was characterized by fever followed by the development of pocks (raised bumps) through various stages (macules, papules, vesicles, and pustules) on the face and body of the infected person. The word 'pox' comes from the Latin word for 'spotted', referring to the raised bumps that occur during infection with these viruses. The pustules progress from being filled with fluid to umbilication (shrinking in the center), scabbing over, and falling off. After these scabs fall off and the skin underneath is healed, a person is then considered no longer contagious. It is important to know the key differences between smallpox and chickenpox. Smallpox spreads from the extremities towards the center of the body; chickenpox spreads from the center of the body outward. During smallpox infection, lesions usually appear 1-2 days after a high fever and are all in the same stage of development. Chickenpox lesions also appear a few days after a high fever, but emerge in various stages or crops, and typically are more concentrated on the trunk. Historically, untreated smallpox infection killed an average of 30% of those infected, with higher mortality rates among the young. Death often occurred from respiratory or cardiac arrest or hemorrhage due to complications of the disease. Smallpox survivors were often scarred and/or, less often, blinded. A milder case of smallpox was called variola minor. The mortality rate for variola minor was under 1%. There is no Food and Drug Administration (FDA)-approved treatment for smallpox and the only prevention is vaccination. Global eradication of smallpox disease in 1980 was the result of rigorous use of smallpox vaccines since 1944.

c. Epidemiology. The last natural case of smallpox occurred in 1977; however, increasing concerns exist about the potential deliberate use of variola virus as a deadly bioterror weapon. Naturally occurring smallpox was highly contagious, and was transmitted from an infected person to a susceptible (unvaccinated) person by respiratory secretions or through contact with infected skin. Transmission usually occurred after prolonged face-to-face contact with a contagious person for three or more hours at a distance of ≤ 6.5 feet. Although less common, transmission through contact with infected skin or inanimate objects (e.g., clothing, towels, bed linens) occurred. Once infected, a person usually began to experience symptoms in 7 to 17 days and was most contagious during the early rash stage following a fever that typically exceeded 101°F (38.3°C). On average, each contagious person infected about 3 to 5 other close contacts such as household members. When smallpox disease was circulating, the only

known reservoir for the virus was humans; no known animal or arthropod reservoirs existed.

d. Vaccine. The current smallpox vaccine, ACAM2000™, manufactured by Acambis, contains live vaccinia virus derived from the only other smallpox vaccine licensed by the FDA, Dryvax®, which is no longer manufactured. Wyeth, the manufacturer of Dryvax®, intends to withdraw the license for its smallpox vaccine soon after 31 March 2008. The vaccinia virus used in both vaccines cross-protects against the variola virus by causing a mild infection that stimulates an immune response to smallpox without actually causing the disease. About 95% of primary vaccine recipients are protected for 3 to 10 years or more depending on product and exposure. Individuals at high risk for exposure, such as research laboratory personnel handling variola virus, or in the event of an outbreak, revaccination is recommended every 3 years. For individuals deemed to be at an increased risk, such as segments of the military, revaccination is recommended every 10 years.

e. Vaccine Handling. ACAM2000™ is shipped and stored in the refrigerator at 2-8°C (36-46°F). Once ACAM2000™ is removed from long-term storage at the Centers for Disease Control and Prevention's (CDC) Strategic National Stockpile (SNS), the vials will be labeled with an 18-month expiration date. Un-reconstituted ACAM2000™ should not be exposed to room temperature conditions (23-27°C or 73-81°F) for more than 48 hours. During immunization clinic operating hours, reconstituted ACAM2000™ may be exposed to room temperatures (20-25°C, 68-77°F), not to exceed 6-8 hours per day. After reconstitution, use ACAM2000™ within 30 days. To prevent vaccine from spraying out of the vial during reconstitution, the vial's vacuum seal should be released with a 21 gauge (or smaller) needle inserted into the vial's rubber stopper prior to adding diluent. Gloves should be worn when reconstituting or administering the vaccine. Change gloves in between patients.

f. Immunization. Screen all potential vaccine recipients for eligibility for vaccination using standardized screening forms available from the Military Vaccine Agency at: www.vaccines.mil. Provide all eligible vaccinees a medication guide before vaccination to help educate them about proper care of the vaccination site and to minimize risks associated with the vaccine. For both primary (naïve) vaccinees and re-vaccinees, administer a droplet of ACAM2000™ by percutaneous route (scarification) using 15 jabs with a bifurcated needle into the skin of the arm just above the deltoid muscle insertion. Jabs should be vigorous enough to cause a drop of blood to appear at the vaccination site. After vaccination, individuals must follow specified site-care guidelines listed in the Medication Guide ACAM2000™ approved by the FDA.

g. Caution. ACAM2000™ is a live vaccinia virus that can be transmitted to persons who have close contact with the vaccinee. The risks in contacts are the same as those stated for vaccinees. Some people are at greater risk for developing serious side effects from the smallpox vaccine and should be deferred based on the risk of exposure to the smallpox (variola) virus. Smallpox vaccinations should be deferred during pregnancy and post-pregnancy period, and until a woman has returned to full duty. Screening for contraindications is required by DoD. In the event of a smallpox outbreak, weigh the risks of vaccination with the risks of exposure.

h. Adverse Events. Common adverse events include: inoculation site pain, redness, warmth, and itching. Lymphadenitis, malaise, fatigue, fever, myalgia, and headache also occur. These adverse events occur less frequently in revaccinated persons than persons receiving the vaccine for the first time. Inadvertent inoculation of other body sites such as the face, nose,

mouth, lips, genitalia, and anus are the most frequent complication. Rare serious adverse events, such as myocarditis and pericarditis, encephalitis, encephalomyelitis, encephalopathy, progressive vaccinia, generalized vaccinia, severe vaccinial skin infections, erythema multiforme major, eczema vaccinatum, ocular complications, and fetal death, have occurred following either primary vaccination or revaccination with live vaccinia virus smallpox vaccines.

i. DoD Policy. Because of concerns about the potential for deliberate use of variola virus as a bioterror weapon, the DoD requires smallpox vaccination of designated at-risk military personnel, DoD civilian personnel classified as emergency-essential per DoD Directive 1404.10, and members of smallpox response teams (e.g., smallpox epidemic response teams, treatment teams, and public health teams).

j. Special Considerations. Vaccinia virus can be spread from the vaccination site to other parts of the body or to nearby people through close physical contact. This can happen for up to 30 days after vaccination and until the site is healed. Do not touch a smallpox vaccination site; this is the best way to avoid spreading the virus. Frequent hand washing also helps prevent spreading the virus if the vaccination site is touched by accident. Dispose of used bandages in a sealed plastic bag with a little bleach or in a sealed double plastic bag.

3. References.

a. Acambis. ACAM2000™ (Smallpox (Vaccinia) Vaccine, Live) vaccine: Package insert. Cambridge, MA. 2007.

b. Acambis. ACAM2000™ (Smallpox (Vaccinia Vaccine, Live) vaccine: Deployment Guidance. Cambridge, MA, 20007.

c. Advisory Committee on Immunization Practices (ACIP). Vaccinia (Smallpox) Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2001; 50 (RR10):1-25.

d. Advisory Committee on Immunization Practices. Supplemental recommendations for using smallpox vaccine in a pre-event vaccination program. MMWR 2003;52(RR-7):1-16.

e. Brooks GF, Carroll KC, Butel JS, Morse SA. Poxviruses. *In* Jawetz, Melnick, & Adelberg's Medical Microbiology. The McGraw-Hill Companies, 24th (ed.) 2007.

f. Control of Communicable Diseases Manual. David L. Heymann. Washington DC, USA: American Public Health Association, 18th (ed.) 2004.

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

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