ANNEX H TO SMALLPOX RESPONSE PLAN 29 September 2002
MEDICAL CARE OF ADVERSE EVENTS AFTER SMALLPOX VACCINATION.

REFERENCES.

a. CDC Smallpox Response Plan, Annex 4. Vaccine Adverse Event Reporting, 23 September 2002. http://www.bt.cdc.gov/DocumentsApp/Smallpox/RPG/annex/annex-4.doc.

b. Advisory Committee on Immunization Practices. Vaccinia (smallpox) vaccine. *MMWR* 2001;50(RR-10):1-25. http://www.cdc.gov/mmwr/PDF/rr/rr5010.pdf [Appendix J-5].

c. United States Army Medical Command. Clinical Guidelines For Managing Adverse Events After Vaccination. Falls Church, VA, June 2002.

d. United States Army Medical Command. “How-To” Guide for Command Surgeons: Implementation Guidelines for Investigational New Drug (IND) Protocols. Falls Church, VA, May 2002.

e. United States Army Medical Command. “How To” Guide for Unit Leaders and Unit Health Care Providers: Implementation Guidelines for Investigational New Drug (IND) Protocols. Falls Church, VA, May 2002.

f. United States Army Medical Command. “How To” Guide for Investigational New Drug (IND) Protocols, Supplement: Vaccinia Immune Globulin (IND # 10664). Falls Church, VA, publication pending.

g. United States Army Medical Command. “How To” Guide for Investigational New Drug (IND) Protocols, Supplement: Cidofovir (Vistide®, Gilead) To Treat Vaccinia Reactions (IND # pending). Falls Church, VA, publication pending.

1. General. This DoD Annex augments CDC Annex 3. Appendix H-1 summarizes CDC Annex 3 and this DoD Annex on one page.

a. Mission. Health-care workers will take actions warranted to treat people who develop severe adverse events after smallpox vaccination.

b. Assumptions.

(1) An increased use of smallpox vaccine is expected, as part of the national program to prepare for the contingency of a smallpox outbreak. Mild to moderate adverse events after smallpox vaccination can be managed according to guidelines in references a, b, and c.

(2) Serious adverse events (AEs) associated with smallpox vaccine are expected, with an overall frequency of ~ 50 serious AEs per 1,000,000 vaccinations. Mild and moderate AEs occur more frequently after smallpox vaccination. The unique adverse events that follow smallpox vaccination chiefly involve progressive or complicated disease with this live-virus vaccine.

(3) Vaccinia immune globulin (VIG) was FDA-licensed until the 1990s as an effective treatment for some adverse events after smallpox vaccination (e.g., eczema vaccinatum, progressive vaccinia, severe generalized vaccinia) and ocular vaccinia (Appendix H-4). VIG is currently available only under an investigational new drug (IND) protocol (references b and f). VIG is in short supply.

(4) Although no human efficacy data are available yet, cidofovir (*Vistide*, Gilead Sciences, www.gilead.com/wt/sec/vistide, Appendix H-5) may be effective in treating adverse events associated with invasive or progressive disease after smallpox vaccination.

c. Planning Factors.

(1) Education and Awareness. Prompt recognition of serious adverse events after smallpox vaccination, especially those that benefit from specific therapy, is integral to the training of people who will administer smallpox vaccine and others who provide primary care. Appendix H-2 summarizes early symptoms of adverse reactions that warrant treatment with vaccinia immune globulin. Once a possible serious adverse event is recognized, vaccination staff and primary-care providers must have access to specialists in infectious diseases, dermatology, and/or allergy-immunology.

(2) Ophthalmic Antiviral Medications. The current status and clinical utility of antiviral medications intended for ophthalmic administration are summarized in Appendix H-3.

(3) Access to VIG and Cidofovir.

(a) MTFs will not use on-hand stocks of VIG or cidofovir to treat patients infected with variola virus, nor order them from other sources, without first coordinating with the US Army Medical Research Institute of Infectious Diseases (USAMRIID).

(b) USAMRIID will establish a common point of access for telephonic requests for use of VIG or cidofovir for a named patient by a physician willing to comply with IND requirements (references d, e, f, and g). Access to cidofovir for eligible patients will be facilitated by specialized treatment teams (T-Teams). Healthcare providers from civilian institutions should contact the CDC Drug Service for VIG or cidofovir: CDC Drug Service, National Center for Infectious Diseases, Mail stop D-09, Atlanta, GA 30333; 404-639-3670, fax 404-639-3717.

(3) Training. Specialized treatment teams will be trained in the requirements of IND protocols in general and the cidofovir treatment protocol in particular, to allow prompt use of this agent. The US Army will coordinate training.

(4) Personnel Resources. If warranted by available resources, a specialized treatment team may travel to the MTF to assist with cidofovir administration. The gaining MTF will assign additional personnel to the team, as requested by the treating physician(s). Additional DoD assets will be assigned, if requirements extend beyond the capabilities of the local MTF. Additional details about composition of specialized treatment teams appear in Annex G.

(5) Other Medications. If therapeutic approaches with VIG or cidofovir are inadequate, clinicians may be inclined to try other therapeutic modalities unavailable when routine smallpox vaccinations ceased in the 1970s and 1980s (e.g., immune globulin intravenous as an immunomodulator to treat encephalitis). Little or no data may exist to support the safety or effectiveness of such approaches and no Federal agency sanctions their use. Nonetheless, DoD clinicians reserve their individual prerogatives and responsibilities in the clinical practice of medicine for individual patients.

d. Coordinating Instructions.

(1) Command Relationships. The specialized treatment team will be assigned under the operational control (OPCON) of the local MTF commander.

(2) Communication. No information will be conveyed to other external sources, including the media, without command approval. If working in coordination with local clinicians, no information will be conveyed to other external sources, including the media, without approval of, or simultaneous presentation with, the coordinating agency (CONUS--CDC, OCONUS--WHO).

(3) VIG investigators and cidofovir investigators will coordinate with the Walter Reed National Vaccine Healthcare Center (VHC, 202-782-0411, DSN 662-0411) on status of individuals treated with VIG or cidofovir under IND protocol. Specialized treatment teams, investigators, and the VHC will assist in centralized tracking and case management and provide coordination with CDC's Clinical Immunization Safety Assessment (CISA) centers of excellence.

e. Legal Considerations.

(1) All use of IND agents will be performed in accordance with IRB-approved guidelines and FDA regulations (see references d, e, f, and Appendix G-4). MTFs will provide personnel and supply resources to the specialized treatment teams to satisfy regulatory requirements.

(2) Adverse events due to vaccination for occupational purposes are covered under provisions of the military medical review evaluation process and worker's

compensation benefits. Civilian employees should seek counsel from occupational health clinics in this regard.

2. Execution.

a. Concept of Operations.

(1) Recognition of a serious adverse event after smallpox vaccination will be infrequent, but of high consequence to the patient affected. Based on criteria in references a and b, the attending physician will consult with an infectious-disease, dermatology, and/or allergy-immunology specialist. If warranted the specialist may request use of either VIG or cidofovir, according to clinical circumstances, from USAMRIID, the unit staffed with the principal investigators for the IND protocols for these agents.

(2) Patients will be treated by a physician registered as a subinvestigator on the applicable IND protocol. Patients will be treated at the earliest possible opportunity, at the closest MTF possible. Movement of patients to capable MTFs, and specialized treatment teams to the same MTFs, will be expedited. Patient consent must be obtained before administration. See also Appendix G-4, for exceptions for unconscious patients.

(3) Patients with appropriate indications (i.e., not encephalitis, not keratitis) will be treated using available supplies of VIG under IND until the VIG supply is exhausted. Cidofovir, also under IND, will then be used for any subsequent serious adverse events (Appendix H-5). The rationale for this approach is that less effectiveness data is available for cidofovir, which is more prone to inducing adverse events than VIG. Nonetheless, cidofovir is in greater supply than VIG.

(4) Actual protocol use of these agents is specified in the pertinent treatment protocols (references f and g), including dosage, expected side effects, and regulatory and reporting issues.

(5) Because of the administrative burden of implementing an IND protocol, and cidofovir’s intravenous route of administration, multidisciplinary specialized treatment teams may travel to an MTF to administer the IND product and assist with patient care. During a smallpox outbreak, prior vaccination against smallpox will be a condition of membership on these teams.

b. Tasks and Responsibilities.

(1) Recognition of serious adverse events after smallpox vaccination is the responsibility of smallpox vaccination staff and primary-care providers. Any member of the medical team or the patient or patient’s contacts can alert the system to the possible presence of a vaccine-related adverse event.

(2) Once a definite or probable diagnosis of a medication-indicating adverse event has been made by a qualified provider (e.g., infectious-disease, dermatology, allergy-immunology physician), that provider may request use of VIG or cidofovir for a named patient by telephoning USAMRIID at 1-888-USA-RIID or 301-619-2257. Alternately, page the USAMRIID staff duty officer at 301-631-4393 or the USAMRMC staff duty officer at 301-619-6092. Healthcare providers from civilian institutions should contact the CDC Drug Service for VIG at 404-639-3670. USAMRIID will coordinate with specialized treatment teams, which will travel to the MTF caring for the diagnosed smallpox patient. These teams will be responsible for the treatment of patients with the indicated medications. IND-specific procedures will be followed carefully.

(3) The MTF will provide routine medical care in accordance with standard practice, with laboratory, radiology, and pathology support. If the patient is treated with an IND agent, the treating team will have responsibility for the completion and maintenance of records and reports, as well as the processing or packaging of pathologic or autopsy materials.

(4) MTF commanders will be responsible for transporting patients between MTFs; provision of ancillary supply and personnel resources to specialized treatment teams; pharmacy and laboratory support; and communication support.

(5) The service member's unit will be responsible for initial transportation to the first-level MTF. Once within the medical system, it will be the responsibility of the medical-evacuation system for further patient transportation as needed.

c. Reporting.

(1) T-team leaders will periodically brief the MTF commander on the status of patients with post-vaccination adverse events, at a frequency directed by the commander. Similar briefings will occur for and at the direction of the commander, USAMRIID.

(2) IND protocol reports will be submitted as detailed in the protocols.

(3) There is no need to report adverse events to VAERS that involve smallpox vaccine treated with vaccinia immune globulin (VIG) or cidofovir under IND protocol. The FDA will review all clinical data for patients treated with VIG or cidofovir under IND protocol under separate report filings. Filing reports to the Vaccine Adverse Event Reporting System (VAERS) in cases involving VIG or cidofovir under IND protocol is inappropriate, because filing a VAERS report will lead to double-counting of the case.

(4) Local requirements for reporting under quality-assurance programs (e.g., Patient Safety Program) will be observed.

3. Operational Constraints.

a. Equipment. No specialized equipment other than routine medical care in MTFs will be required.

b. Training. Specialized treatment teams will be trained in the requirements of IND protocols in general and the VIG and cidofovir treatment protocols in particular, to allow prompt use of this agent. The US Army will coordinate such training. Periodic alert exercises, without travel, will be performed to sustain team proficiency. During smallpox outbreaks, prior vaccination against smallpox will be a condition of membership on these teams.

c. Control of IND Agents. MTF pharmacy support to specialized treatment teams will include storage (see below), control, and security for both cidofovir and locally available medications. Pharmacy assets on the teams will prepare and dispense cidofovir for the team's use. Emergency use of an investigational drug for a named patient will comply with notification requirements to U.S. Army Medical Command, in accordance with Army Regulation 40-7 (Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances, 4 January 1991), paragraph 4-9, and comparable regulations in other military Services.

d. Medical Care of the Patient. General medical supportive care to a patient with an adverse event after vaccination will be given by the attending team organic to the MTF, supplemented by the specific therapy given by the treatment team, supplemented with MTF personnel as needed.

4. Administration and Logistics.

a. Shipping and Distribution. Either the T-Teams will transport the VIG or cidofovir themselves, or they will coordinate with the US Army Medical Materiel Agency (USAMMA) for transportation (see Annex I).

b. Supply and Storage. Supplies of VIG or cidofovir, delivered from USAMRIID, will be stored and maintained by the MTF pharmacy under the appropriate environmental conditions.

c. MTFs will provide administrative support for protocol performance by the specialized treatment teams (e.g., office space, copying, automation, communication support).

5. Special Situations.

a. Healthcare providers will attempt to periodically observe smallpox vaccine recipients through the duration of vaccine take and injection-site resolution. Nevertheless, recipients may be required to travel before this vulnerable window for complications has passed.

b. All situations in which a potential adverse event after vaccination is recognized in a recipient while outside of CONUS, or underway either in CONUS or outside of CONUS, should be handled by directing or transporting the recipient to the nearest MTF in an expedited manner. Once arrived, the medical consultation process described above will be implemented.

APPENDIX H-1
Medical Care Of Adverse Events After Smallpox Vaccination – Summary.

1. Recognition of a serious adverse event after smallpox vaccination will be infrequent, but of high consequence to the patient. The attending physician will consult with an infectious-disease, dermatology, and/or allergy-immunology specialist. If warranted, the specialist may request use of either vaccinia immune globulin (VIG) or cidofovir.

2. The US Army Medical Research & Materiel Command (USAMRMC) is applying to the Food & Drug Administration (FDA) for permission to use cidofovir (*Vistide*, Gilead Sciences, Appendix G-5, Appendix H-5) under an investigational new drug (IND) protocol to treat adverse events after smallpox vaccination. This annex assumes FDA will accept this IND protocol.

3. Patients with appropriate indications (e.g., eczema vaccinatum, progressive vaccinia, ocular vaccinia, febrile-"toxic" generalized vaccinia) (i.e., not encephalitis, not keratitis) will be treated using available supplies of VIG under IND until the VIG supply is exhausted. Cidofovir will then be used under IND for any subsequent serious adverse events. Less effectiveness data is available for cidofovir, which is more prone to inducing adverse events than VIG. Nonetheless, cidofovir may be in greater supply than VIG.

4. Because of the administrative burden of implementing an IND protocol, and cidofovir's intravenous route of administration, multidisciplinary specialized treatment teams may travel to an MTF to administer cidofovir and assist with patient care. During a smallpox outbreak, prior vaccination against smallpox will be a condition of membership on these teams.

5. Once a definite or probable diagnosis of a medication-indicating adverse event has been made by a qualified provider (e.g., infectious-disease, dermatology, allergy-immunology physician), that provider may request use of VIG or cidofovir for a named patient by telephoning USAMRIID at 1-888-USA-RIID or 301-619-2257. Alternately, page the USAMRIID staff duty officer at 301-631-4393 or the USAMRMC staff duty officer at 301-619-6092.

6. USAMRIID will coordinate with these specialized treatment teams (T-teams), which will travel to the MTF caring for the patient. IND-specific procedures will be followed carefully. The treatment team will be assigned under the operational control (OPCON) of the local MTF commander.

7. Specialized treatment team leaders will periodically brief the MTF commander on the status of patients, at a frequency directed by the commander. Team leaders and IND investigators will submit IND protocol reports as required by the FDA. VIG investigators and cidofovir investigators will coordinate with the Walter Reed National Vaccine Healthcare Center (VHC) on status of individuals treated with VIG or cidofovir.

APPENDIX H-2
Initial Symptoms of Conditions Warranting VIG Therapy.

1. In 1968, the Food & Drug Administration licensed vaccinia immune globulin intramuscular (VIG-IM) as a safe and effective treatment for some adverse events after smallpox vaccination, including eczema vaccinatum, progressive vaccinia, severe generalized vaccinia). VIG may be useful in treating ocular vaccinia resulting from inadvertent inoculation. VIG is neither effective nor indicated in treating post-vaccinial encephalitis. VIG is the immunoglobulin (antibody) fraction of plasma obtained from people vaccinated with smallpox (vaccinia) vaccine (Appendix H-4).

2. Current supplies of VIG-IM are limited, and limited supplies of an intravenous formulation of VIG (VIG-IV) are just becoming available. At present, both VIG-IM and VIG-IV are available only under investigational new drug (IND) protocols for patients who meet specific inclusion and exclusion criteria. Both forms of VIG should be reserved for treatment of vaccine complications with serious clinical manifestations. The recommended dosage of the currently available VIG for treatment of complications is 0.6 mL/kg of body weight. Because therapeutic doses of VIG might be substantial (e.g., 42 ml for a person weighing 70 kg), the product should be given in divided doses over a period of 24 to 36 hours. Doses can be repeated, usually at intervals of 2 to 3 days, until recovery begins.

3. VIG should be given as early as possible after the onset of symptoms. Consider hospitalization of any patient who requires VIG treatment. To assist primary-care providers in recognizing early symptoms of these conditions, the following information is provided.

4. Eczema Vaccinatum.

a. Eczema vaccinatum is a localized or systemic dissemination of vaccinia virus, seen especially among people who have atopic dermatitis or eczema or a history of these conditions or other chronic exfoliative skin conditions. Usually, the illness is mild and self-limited, but can be severe or occasionally fatal. The most serious cases occur with primary vaccination and are independent of the activity of the underlying skin condition. Severe cases have also occurred after contact of recently vaccinated people with people who have active atopic dermatitis or eczema. Patient management includes supportive care as if the patient suffered extensive burns that denuded the skin, posing problems for secondary infection and fluid or electrolyte imbalances.

b. “Either concurrently with or shortly after the development of the local vaccinial lesion (or after an incubation period of about 5 days in unvaccinated eczematous contacts) a vaccinial eruption occurred at sites on the body that were at the time eczematous or had previously been so. These areas became intensely inflamed, and sometimes the eruption later spread to healthy skin. Constitutional symptoms were severe, with high temperature and generalized lymphadenopathy, and the prognosis

was grave in infants in whom large areas of skin were affected." Fenner, page 299. [Sic, atopic dermatitis rather than eczema.]

c. "Vaccinial lesions either generalized or as individual lesions elsewhere than at the vaccination site in a person who has eczema or a past history of eczema." Neff, et al., page 126. [Sic, atopic dermatitis rather than eczema.]

5. Progressive Vaccinia.

a. Progressive vaccinia (vaccinia necrosum) is a severe, potentially fatal illness characterized by progressive necrosis in the area of vaccination and other tissues at the vaccination site, often with metastatic lesions. It occurred almost exclusively among people with cellular immunodeficiency. Progressive vaccinia starts as a painless progressive enlargement of the vaccination site with scant inflammation and little or no discomfort. It is characterized by a vaccine site that fails to heal properly. The site may enlarge deeply, widely, and relentlessly with an ultimately fatal outcome.

b. "In these case the local lesion at the vaccination site failed to heal, secondary lesions sometimes appeared elsewhere on the body and all lesions spread progressively until—as was likely—the patient died, usually 2-5 months later." Fenner, page 299.

c. "Vaccinia necrosum (progressive vaccinia) is a rare, often fatal complication of vaccination, characterized by progressive necrosis in the area of vaccination, often with metastatic lesions. Although the lesions can be extensive, patients may not have fever, erythema, pain, or regional lymphadenopathy, and may not come to their physician's attention until several weeks after vaccination." Lane, et al., page 260.

d. "On very rare occasions, the growth of vaccinia virus in the skin is not halted at about the eighth or tenth day by the development of antibodies and the cellular reaction against the virus. The virus continues to grow for many weeks, producing large, destructive ulcers, the advancing edge being studded with typical primary-type vesicles, apparently growing in a fully susceptible skin. Although in the first few weeks the lesion may be limited to progress from the primary site, towards the end of the condition, which may last as long as three or four months, numerous secondary lesions occur on the face and on other parts of the body, which are most probably blood-borne, but may also be inoculated, and these again have all the appearances of primary vaccinations." Dixon, pages 153-154.

6. Severe Generalized Vaccinia.

a. Other less serious complications include generalized vaccinia, with a vesicular or pustular rash of varying extent away from the vaccination site, possibly the result of viremia. Lesions occur 6 to 9 days after vaccination and can be few or generalized. Generalized vaccinia in people without underlying illness is generally self-limiting and

requires little or no therapy. VIG is indicated for severe generalized vaccinia if the patient is extremely ill or has a serious underlying disease.

b. “Very rarely a generalized vaccinial rash, sometimes covering the whole body, occurred 6-9 days after vaccination. The course of the individual skin lesions resembled that of the lesion at the vaccination site, but if the rash was profuse the lesions sometimes varied greatly in size. The generalized eruption usually did not have the “centrifugal” distribution which was characteristic of the rash of smallpox.” Fenner, page 299.

c. “When systemic signs and symptoms lead one to suspect blood-borne virus dissemination, VIG may be of benefit.” Lane, et al., pages 258-259.

d. “There is general enlargement of the lymphatic glands, and the lesions normally commence in the abnormal areas of skin, but in this malignant form always involve normal skin as well. Usually, large areas of the skin are infected simultaneously, with a uniform development of the rash, not at all unlike that of malignant smallpox. Although in some areas the rash may be confluent, in closely adjoining areas of skin there may be no rash at all, and the characteristic centrifugal distribution of smallpox is absent, although the rash may be more developed on the limbs than on the trunk. The abrupt change in density is probably more characteristic than anything else. Although the rash on the face at first sight resembles smallpox, the absence of rash on the tip of the nose compared with the density on the cheeks rules this out.” Dixon, pages 151-152.

7. Ocular or Peri-ocular Vaccinia.

a. Vaccinia virus can be inadvertently transferred from the vaccination site to other parts of the body. A common site of autoinoculation is to the cutaneous surfaces surrounding the eye (the peri-ocular region). These lesions may occur either in vaccinees or close contacts. Usually these lesions heal without treatment, but severe untreated disease may heal with scarring of the lids causing subsequent ophthalmologic problems. Vaccinial infection of the cornea may cause blindness.

b. VIG was frequently used to treat peri-ocular vaccinia and possibly helps reduce its untoward consequences. On the other hand, VIG should be avoided if there is keratitis or corneal involvement because it increases the risk of corneal scarring. About 5 to 7% of patients with peri-ocular vaccinia developed corneal involvement (i.e., vaccinial keratitis), with resultant pain and significant blurring of the vision. These lesions usually result in scarring of the cornea. Use of VIG is generally contraindicated in vaccinial keratitis because it can lead to increased scarring. Therefore, VIG should be used with extreme caution is cases of ocular vaccinia and only after consultation with an ophthalmologist.

8. References.

a. American Academy of Dermatology. Smallpox vaccine primer. www.aad.org. Accessed September 2002.

b. Dixon CW. *Smallpox*. London: J&A Churchill, 1962.

c. 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.

d. Lane JM, Millar JD, Neff JM. Smallpox and smallpox vaccination policy. *Annu Rev Med* 1971;22:251-272.

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APPENDIX H-3
Ocular Vaccinia & Ophthalmic Antiviral Medications.

1. Inadvertent Inoculation. Other than local pain, fever, and constitutional symptoms occurring in the first two weeks after smallpox vaccination, inadvertent inoculation (i.e., accidental infection) is the most frequently occurring type of adverse reaction. The most representative data regarding complications come from the 10-state survey of physicians in 1968 (Lane, et al., 1970). In that study, the overall rate of inadvertent inoculation was 529 cases per million people primarily vaccinated, and 42 cases per million for those re-vaccinated. Seven percent of all people with inadvertent inoculation were actually close contacts of vaccinees and not directly vaccinated. Of all complications recorded in the survey, 42% were due to inadvertent inoculation.

2. Inadvertent inoculation occurs on almost any part of the body, but the most frequently described areas include the face (particularly around the eye, nose or mouth), buttocks, and genitalia (ACIP, 2001; Goldstein, et al., 1975). In the 1963 and 1968 national studies, largely based on cases identified from vaccinia immune globulin (VIG) records, 308 cases of inadvertent inoculation were identified, of which 246 involved the eye (80%) (Neff, et al., 1967; Lane, et al., 1969).

3. Most ocular vaccinia presents as a few vesicular lesions with inflammation and swelling of the eyelids or conjunctiva. The cornea was affected in six percent (22/348) of the ocular vaccinia cases series from the 1960's (Ruben & Lane, 1970). Of six patients with keratitis from 1963 who could be followed up by slit-lamp examination in 1969, only two had no residua. The remainder had varying degrees of minor to more bothersome corneal and eyelid or eyelash abnormalities. There was also one case of chronic iritis. No other lasting problems were reported in the group with initial corneal involvement. The rate of residual complications in cases of ocular vaccinia without a history of keratitis was 2%. Most of these individuals either lost eyelashes or had other eyelid deformities.

4. Given the frequency of inadvertent inoculation and the potential sequelae of vaccinial keratitis, it is prudent to attempt to prevent this complication. As previously described, smallpox vaccination involves inoculation of a small amount of live virus into the skin. The potential exists for that virus to be disseminated directly to other areas of the body or even to other individuals. Current recommendations for smallpox vaccination recommend that recipients practice good hand hygiene to limit spread from the area of vaccination to themselves or others (ACIP, 2001). Simple detergent-type hand cleaners are adequate for this purpose, but alcohol-based gels are better as antiseptics, because alcohol inactivates vaccinia virus. These gels also cause less skin irritation after repetitive washing (Larson, 1995; Larson, 2001).

5. Historically, VIG was used with some success to treat ocular vaccinia. Because of currently limited supply, it is reserved for severe or life-threatening cases involving progressive vaccinia or eczema vaccinatum (ACIP, 2001; Henderson, et al., 1999). VIG

is contraindicated in cases of vaccinial keratitis, according to the Advisory Committee on Immunization Practices (ACIP, 2001), based on an animal study suggesting it may increase corneal scarring (Fulginiti, et al., 1965). At least one ophthalmologist specializing in viral diseases of the cornea disagrees with this position, advocating use of VIG to prevent progression to corneal melt with perforation.

6. Several pharmacologic agents show antiviral activity against orthopox and other DNA viruses, but few have been tested in either animals or humans, especially as an ophthalmic preparation (Clercq, 2001). The ACIP (2001) states that there is insufficient information to recommend any antiviral drug for treatment of complications of smallpox virus vaccination. Idoxuridine was the antiviral ophthalmic preparation typically used by clinicians for ocular vaccinia with keratitis in the past, but data on its efficacy were conflicting (Fulginiti, et al., 1965; Kaufman, et al., 1962; Kaufman, 1963; Jack & Sorenson, 1963; Focasi, et al, 1963). Breman & Henderson (2002) recently recommended idoxuridine topically to treat corneal lesions due to smallpox. However, this agent is no longer available in pharmacies in the United States, nor is vidarabine (Vira-A, Monarch Pharmaceuticals), both having gone out of production.

7. The FDA-approved therapeutic agent available for herpetic keratitis is trifluridine (Viroptic®, Monarch, also known as triflurothymidine), having displaced idoxuridine as a more effective treatment. Trifluridine is effective even in cases of idoxuridine-resistant herpetic keratitis. Trifluridine has been evaluated in animal models of experimentally induced vaccinial keratitis in comparison to idoxuridine or untreated controls and found to be significantly more effective in eliminating or reducing vaccinial ulcers on the cornea, as well as virus by culture (Hyndiuk, et al., 1976). The drug is administered in herpes simplex keratitis as a 1% ophthalmic solution, one drop every two hours while awake up to nine drops daily until the cornea is re-epithelialized, and then one drop every four hours up to five drops daily for seven more days. Ophthalmology consultation is warranted.

8. Use of trifluridine for ocular vaccinia (e.g., vaccinial conjunctivitis, vaccinial keratitis, vaccinial complications involving eyelid) would be off-label and, therefore, prescribed at the discretion of an individual physician after discussion with the patient. To change the product's FDA-approved labeling would require an investigational new drug (IND) protocol. Other antiviral agents have also been evaluated for use in vaccinia keratitis with promising results, but these are also not commercially available currently in the United States (Sidwell, et al, 1973). Cidofovir, active against some orthopox viruses and suggested for possible treatment of smallpox, has not been evaluated in ocular vaccinia or keratitis (ACIP, 2001; Clercq, 2001).

9. Summary. Inadvertent inoculation is one of the most common complications of smallpox vaccination and is usually manifested as a periorbital infection. Ocular vaccinia may result in deformities of the eyelid and eyelashes, and in the worst cases result in chronic iritis and or corneal scarring. Evidence of ocular vaccinia after vaccination should prompt ophthalmologic evaluation, including slit-lamp examination. Treatment of non-corneal ocular vaccinia may benefit from VIG if available, but until consensus is

obtained, VIG should not be used without advice of a corneal expert for vaccinial keratitis. Trifluridine ophthalmic solution is likely to be of benefit for this indication, but its use would be off-label.

10. References.

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APPENDIX H-4
Product Labeling for Vaccinia Immune Globulin (VIG).

[reprinted verbatim from Hyland Therapeutics Division's VIG product labeling, circa 1983. Note that production methods in that era did not include viral-inactivation steps.]

Hyland®
Vaccinia Immune Globulin (Human)

DESCRIPTION

HYLAND Vaccinia Immune Globulin (Human) is a sterile 16.5 (±1.5) percent solution of the immunoglobulin fraction of plasma from individuals who were immunized with vaccinia virus. The solution is isotonic and contains 0.3M glycine as a stabilizer. It contains 0.01% thimerosal (a mercury derivative) as a preservative and 0 1% sodium chloride.

This product meets the FDA potency requirements for vaccinia antibody.

Each unit of plasma used in the preparation of this product has been found to be nonreactive for hepatitis B surface antigen (HBsAg) by counterelectrophoresis or radioimmunoassay. The product is prepared by the cold ethanol fractionation method; no instance of hepatitis transmission has been reported from the use of human immune globulins when prepared by this method.

This product has been processed and tested in accordance with requirements established by the Food and Drug Administration and is distributed under U.S. License No. 140.

INDICATIONS

Smallpox -Prevention or Modification:

Administration of Vaccinia Immune Globulin (Human) in conjunction with simultaneous vaccination or revaccination has been shown to reduce the incidence of smallpox in exposed individuals.[1]

Vaccinia Infections - Prevention or Modification:

Vaccinia Immune Globulin (Human) may be indicated in the following circumstances to prevent or modify aberrant infections induced by smallpox vaccine:[2-5]

a. Accidental implantation of vaccinia virus in eyes, mouth, or other areas where vaccinia infection would constitute a special hazard

b. Accidental vaccinia exposure of children who have extensive skin lesions such as eczema, burns, impetigo, or varicella.

c. Eczematous children where vaccination is indicated due to risk of exposure to smallpox.

Treatment of Postvaccinal Complications:

Vaccinia Immune Globulin (Human) may be effective for use in the following conditions: eczema vaccinatum, vaccinia necrosum, severe generalized vaccinia, vaccinia infections of the eyes or mouth, and vaccinia infections in the presence of other skin lesions such as burns, impetigo, varicella-zoster, or poison ivy.

This product is not of value in the treatment of postvaccinal encephalitis.

CONTRAINDICATIONS

Vaccinia Immune Globulin (Human) is contraindicated for use in the presence of vaccinal keratitis. The administration of a similar preparation in rabbits with vaccinal keratitis has been shown to cause increased scarring.[6]

WARNINGS

Do not give intravenously; this preparation is for intramuscular use only. Do not use if turbid.

PRECAUTIONS

A separate sterile syringe and needle or single-use disposable unit must be used for each individual patient to prevent the possible transmission of hepatitis or other infectious agents from one patient to another.

After cleansing the site for injection and inserting the needle in a muscle, draw back on the plunger of the syringe before injection in order to be certain that the needle is not in a blood vessel.

ADVERSE REACTIONS

A few instances of allergic or anaphylactoid systemic reactions have been reported following intramuscular injection of human immunoglobulin preparations. It is advisable that epinephrine or other suitable medication be available for treating such reactions should they occur.

Occasionally local tenderness and stiffness occur, persisting from a few hours to 1 to 2 days following injection (When the dosage is 10 ml or more, it should be divided and injected at 2 or more sites in order to reduce the trauma of injection).

DOSAGE

Smallpox - Prevention or Modification:

A dose of 0.3 ml per kg of body weight should be given within 24 hours of exposure. Exposed individuals should be simultaneously vaccinated or revaccinated with smallpox vaccine unless otherwise contraindicated.

Vaccinia Infections -Prevention or Modification:

A dose of 0.3 ml per kg of body weight should be given simultaneously with smallpox vaccination. In cases of accidental exposure to vaccinia virus, this dosage should be given as soon as possible after exposure has occurred.

Treatment of Postvaccinal Complications:

A dose of 0.6 ml per kg of body weight should be administered as soon as possible after symptoms appear. This dose may be repeated, depending upon the severity of symptoms and response to treatment.

No therapeutic effect may be expected from the use of this product in postvaccinal encephalitis.

ADMINISTRATION

Vaccinia Immune Globulin (Human) is to be administered intramuscularly, preferably in the buttock or the anterolateral aspect of the thigh.

When the dosage is 10 ml or more, it should be divided and injected at 2 or more sites.

HOW SUPPLIED

HYLAND Vaccinia Immune Globulin (Human) is available in a 5-ml size.

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APPENDIX H-5
Product Labeling for Cidofovir.

Vistide®, Gilead Sciences

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