SMALLPOX

AUGUST 2005

Outline

By law, health care providers must report suspected or confirmed Smallpox to the local health department immediately (within 1 hr).

Even a single case of Smallpox is considered an outbreak and is a public health emergency.

To report: call SFDPH communicable disease control (24/7 Tel: 415-554-2830).

Upon receipt, SFDPH will initiate the public health response and can facilitate lab testing.

AGENT

Smallpox is caused by variola virus, a large, enveloped, single-stranded DNA virus of the Poxvirus family and the *Orthopoxvirus* genus. One strain of virus is responsible for variola major, the more lethal form of the disease, while several additional strains comprise variola minor.

Variola replicates in the host cell cytoplasm, forming inclusion bodies, unlike varicella which replicates in the cell nucleus. There is extensive cross-neutralization between orthopoxviruses, and this accounts for the protection against smallpox after vaccination by vaccinia virus.

EPIDEMIOLOGY

Smallpox as a Biological Weapon

Variola virus is believed to have been weaponized by the former Soviet Union to be mounted in missiles and bombs. Currently, variola virus is stored in two known facilities, one at the CDC, and the other in a Russian research laboratory, but may exist in other, covert, locations as well. Even if all stocks of naturally occurring smallpox virus are destroyed, it is now possible to genetically engineer a similar viral agent in the laboratory setting. This capability requires that the medical and public health communities maintain smallpox preparedness into the foreseeable future.

Smallpox is of concern as a biological weapon because:

- Much of the population (80%) is susceptible to infection
- The virus has a low infectious dose and carries a high rate of morbidity and mortality
- Vaccine is not yet available for general use
- Experience has shown that introduction of the virus creates havoc and panic.

Aerosol release of virus (such as into a transportation hub) would likely result in a high number of cases. Other possibilities include use of "human vectors" (i.e. persons who have been deliberately infected with smallpox) and use of fomites (e.g. contamination of letters sent through the mail).

Naturally Occurring Smallpox

Smallpox was eradicated globally by means of a 12-year, international campaign involving mass vaccination programs combined with surveillance and containment of outbreaks. The last reported case of endemic smallpox occurred in Somalia in 1977, and there have been no additional cases since a laboratory accident in 1978.

Infectivity

Before global eradication, the only reservoir for variola virus was humans. Vectorborne transmission does not occur. Smallpox is transmitted person-to-person mainly via inhalation of droplet nuclei, though inhalation of airborne particles and direct contact with skin lesions or infected body fluids have also been shown to transmit disease. Typically, smallpox transmission requires close face-to-face contact with an infected patient.

Historically, infectiousness in smallpox was correlated with rash onset, and patients in the prodromal phase were generally not considered infectious. However, variola virus is now known to be shed from oral lesions during the 1-2 days of fever preceding rash onset. Infectiousness is highest during the first week after rash onset when lesions in the mouth ulcerate and release large amounts of virus into the saliva.

Secondary attack rates among unvaccinated close contacts range from 30-80% and the average number of cases infected by a primary case is estimated at 3.5-6. In populations with little herd immunity, this transmission potential of smallpox has the capability to create a rapid rise in outbreak cases before control measures can be applied.

Communicability lasts until all the lesions have scabbed over and the scabs have fallen off. Viable viral particles can be detected in scabs, however scabs are considered relatively noninfectious since the viral particles are bound in the fibrin matrix of the scab. No chronic viral carrier state occurs.

CLINICAL FEATURES

The variola virus typically enters the body via respiratory or oral mucosa. The virus is carried by macrophages to regional lymph nodes where a primary viremia develops on the 3^{rd}-4^{th} day after infection. The reticuloendothelial organs are invaded and overwhelmed leading to a secondary viremia around the 8^{th}-12^{th} day after infection; this is followed by onset of fever and toxemia. Death most commonly results from overwhelming toxemia, probably associated with circulating immune complexes.

Variola Major

Historically there were 3 serious and 2 less-serious forms of variola major. The most common form, **ordinary smallpox**, occurred in 90% of cases and had case-fatality rates of 15-45%.

VARIOLA MAJOR: CLINICAL FEATURES OF 'ORDINARY SMALLPOX'	
Incubation Period	• 10-13 days (range 7-19 days)
Signs & Symptoms	Prodromal Phase • 2-4 days of fever, chills, headache, backache, and often GI symptoms Rash Phase • Enanthem (papules, vesicles, then ulcers) of oropharyngeal mucosa beginning 1 day before skin lesions appear • First few skin lesions often appear on face ("herald spots") • Lesions spread centrifugally from trunk to proximal then distal extremities • Palms and soles are usually involved, while truncal rash is usually sparse • Lesions initially maculopapular (days 1-2), then vesicular (days 3-5), then pustular (days 7-14) • Vesicles and pustules often have central umbilication • Pustules often called "shotty" (i.e. like small, embedded hard balls) • Lesions tend to progress at same rate • Are typically painful, cause pitted scars as they heal • May be discrete, semiconfluent, or confluent • Gradually scab over during days 13-18
Complications	• Viral bronchitis/pneumonitis • Third spacing with resulting electrolyte and renal abnormalities • Massive skin desquamation • Secondary bacterial infection, particularly skin and pulmonary • Spontaneous abortion, stillbirth • Rarely: corneal ulceration, encephalitis, osteomyelitis or arthritis, orchitis • Death may occur during 2nd week of illness, from high-level viremia and circulating immune complexes
Laboratory Findings	• Lymphocytopenia and/or granulocytopenia

Flat-type smallpox (also known as malignant smallpox) occurred in about 6% of cases in the pre-vaccination era, and more commonly in children. The lesions do not progress to the pustular stage, instead remaining soft and flattened. There tends to be more systemic toxicity and higher mortality (>90%), and may be related to impaired host cell-mediated immunity.

Hemorrhagic smallpox occurred in about 3% of cases. It presented with severe systemic toxicity and case-fatality rates >95%. The rash begins as a dusky erythema, followed by extensive petechiae, mucosal hemorrhage, and intense toxemia. Thrombocytopenia and coagulopathy may be present. These patients usually died during week 1 of illness, often before the development of the typical pox lesions.

Two additional forms, **modified smallpox** and **variola without eruption**, were milder forms of disease that occurred in persons with some immunity from past infection or vaccination.

Variola Minor

Variola minor is a milder form of smallpox caused by distinct strains of variola virus. In the early 20th century, it was the most prevalent form of smallpox in the USA. Compared with variola major, the disease results in milder constitutional symptoms, typically discrete lesions that evolve a bit more rapidly, lower rates of hemorrhagic disease, and only rarely fatal (<1%) outcomes. The illness may be difficult to distinguish clinically from modified smallpox and variola without eruption.

DIFFERENTIAL DIAGNOSIS

The characteristic features of smallpox need to be differentiated from other illnesses that present with vesicular or pustular rash. The one disease that is most likely to be misidentified as smallpox in the setting of an outbreak is chicken pox. These may be differentiated clinically, as follows:

CLINICAL DIFFERENTIATION OF VARIOLA VS. VARICELLA

Feature	Variola	Varicella
Prodrome	• Lasts 2-4 days • High fever, headache, backache, severe prostration	• Often absent • If present, mild and brief (1 day)
Rash Distribution	• Begins on oropharyngeal mucosa • Expands to face • Then expands centrifugally – most dense on distal extremities • Commonly affects palms and soles • More involvement of back than abdomen	• Begins on trunk • Expands centripetally – most dense on trunk • Spares palms and soles • Back and abdomen equally involved
Lesion Evolution	• Emerge widely over 1-2 days, then progress at same rate • Progress slowly (7-14 days) from macules to papules to vesicles to pustules to scabs	• Emerge in crops, often at different stages of evolution at any given time • Progress quickly (1-2 days) from macules to papules to vesicles to scabs
Lesion Attributes	• May be semiconfluent or confluent • May be umbilicated • Often painful; pruritic only as scabs	• Usually discrete • Do not umbilicate or dimple • Typically painless; intensely pruritic

CDC has developed criteria for determining the risk of smallpox when evaluating patients with generalized vesicular or pustular rash. An online version of the algorithm is available at: www.bt.cdc.gov/agent/smallpox/diagnosis/riskalgorithm/index.asp

Risk of Smallpox in Patients with Generalized Vesicular or Pustular Rash	
High	All 3 'major criteria' present: a) Febrile prodrome 1-4 days before rash onset, with fever >101°F, plus 1 or more of the following: Prostration, headache, backache, chills, vomiting, severe abdominal pain b) Classic smallpox lesions present (vesicles or pustules that are deep-seated, firm or hard, round, and well-circumscribed; sharply raised and feel like 'BB pellets' under the skin; may become umbilicated or confluent as they evolve) c) Lesions on any one part of the body are in the same stage of development
Moderate	Febrile prodrome as in (a) above, plus either (b) or (c) above *OR* Febrile prodrome as in (a) above, plus at least 4 of the following 'minor criteria': • Centrifugal distribution • First lesions appeared on the oral mucosa/palate, face, or forearms • Patient appears toxic or moribund • Slow evolution of lesions from macules to papules to pustules over several days • Lesions on the palms and soles
Low	No viral prodrome *OR* Febrile prodrome as in (a) above, plus < 4 'minor criteria' above
Source: CDC (www.bt.cdc.gov/agent/smallpox/diagnosis/rashtestingprotocol.asp)	

Additional considerations in the differential diagnosis of smallpox include:

- Disseminated herpes zoster
- Hand, foot & mouth disease - (Coxsackie virus)
- Disseminated herpes simplex
- Molluscum contagiosum
- Human monkey pox*
- Erythema multiforme major - (Stevens-Johnson syndrome)
- Bullous pemphigoid
- Miscellaneous drug eruptions
- Impetigo (*Strep, Staph*)
- Secondary syphilis

Hemorrhagic smallpox may resemble:

- Meningococcemia
- Rocky Mountain spotted fever
- Ehrlichiosis
- Gram-negative septicemia

* In June 2003, an outbreak of monkeypox virus occurred among 71 persons in several Midwestern US states. There were no fatalities. The outbreak was traced to contact with prairie dogs which had been infected through contact with rodents from Ghana. Monkeypox in humans is similar to discrete or semiconfluent ordinary smallpox, but is generally milder than smallpox, and is distinguished by the presence of prominent lymphadenopathy.

LABORATORY DIAGNOSIS

Laboratory diagnosis is confirmatory, as smallpox can most often be diagnosed clinically. Once smallpox has been confirmed in a geographic area, additional cases can be diagnosed clinically, and specimen testing can be reserved for specific cases in which the clinical presentation is unclear, to identify an index case, or to assist with law enforcement activities.

If you consider testing for Smallpox, you should IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830) to facilitate specimen processing and public health response.

Per CDC guidelines, only personnel vaccinated within 3 years, wearing appropriate barrier protection (gloves, gown, shoe covers, and face shields) should be involved in specimen collection for suspected Smallpox.

If vaccinated personnel are not available, only those without contraindications to vaccination should be utilized as they would require immediate vaccination if the diagnosis of Smallpox is confirmed. Appropriate respiratory as well as barrier protection should be worn.

Basic confirmation relies upon electron microscopic examination of vesicular or pustular fluid or scabs, which can rapidly confirm the presence of *Orthopoxvirus* in the specimen but does not prove that *variola* is the species. Definitive laboratory identification and characterization of the variola virus requires several days, and involves growth of the virus in cell culture or on chorioallantoic egg membrane and characterization of strains by use of various biologic assays (including PCR techniques) and restriction fragment-length polymorphisms.

Specimen Collection from Patients with Vesicles or Pustules

Use the protective equipment described above.

Lesion Specimens. Sanitize skin with an alcohol wipe and allow it to dry. Unroof the lesion with a sterile scalpel and place the skin into a dry, sterile, capped plastic tube. Scrape the base of the vesicle or pustule with the blunt edge of the scalpel. Apply a microscope slide to the vesicular fluid multiple times, with progressive movement of the slide, to make a touch prep. Allow the fluid to air-dry 10 minutes without smearing. Store the dried slide in a plastic slide container. If available, lightly touch an electron microscope grid to the unroofed base of the lesion and allow to air dry. Repeat this procedure two more times, varying the pressure applied to the unroofed lesion (lighter or firmer pressure). Place in gridbox and record which slot is used for each patient specimen. Biopsy vesicles (2) with 3.5- or 4-mm punch biopsy kit. Place one biopsy in formalin and the other in a dry, screw-capped container.

Blood Samples. Draw 10 cc of blood into a plastic marble-topped tube or plastic yellow-topped serum separator tube. If plastic tubes are not available, glass tubes may be used, but should be placed in Styrofoam protector for packaging and shipping.

Labeling and Shipping. Label all specimens with patient name, date of collection, and specimen source. Place specimens from a single patient into a biohazard bag labeled with the above information. Ship all specimens, packaged to avoid shocks and breakage, within 24 hours of collection. All samples should be stored at 4°C, except formalin-fixed biopsy (room temperature) and non-formalin fixed biopsy (dry ice).

Specimen Collection from Patients with Scab Lesions

Use the protective equipment described above.

Scab Specimens. Sanitize skin with an alcohol wipe and allow it to dry. Use a 26-gauge needle to pry off as many scabs as possible (at least four). Place two scabs in each of two dry, screw-capped plastic vials. Biopsy lesions (2) with 3.5- or 4-mm punch biopsy kit. Place one biopsy in formalin and the other in a dry, screw-capped container.

Blood Specimens. As above.

Labeling and Shipping. As above.

TREATMENT AND PROPHYLAXIS

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfdph.org/cdcp).

Treatment

The management of confirmed or suspected cases consists of supportive care, with careful attention to electrolyte and volume status, and ventilatory and hemodynamic support. General supportive measures include ensuring adequate fluid intake (difficult because of the enanthem), alleviation of pain and fever, and keeping skin lesions clean to prevent bacterial superinfection.

Currently there are no antivirals with proven activity against smallpox in humans, though several agents have shown in vitro activity and are undergoing testing in animal models.

Vaccine Supply, Administration, and Efficacy

The smallpox vaccine used in the USA (Dryvax) is a lyophilized (freeze-dried) preparation of live attenuated Vaccinia virus, an *Orthopoxvirus* closely related to cowpox that induces antibodies that are protective against smallpox. The preparation also contains the antibiotics polymyxin B, streptomycin, tetracycline and neomycin. The diluent used to reconstitute the vaccine is 50% glycerin and a small amount of phenol as a preservative. The vaccine vial stopper contains natural rubber.

The Dryvax vaccine was produced by Wyeth in the 1970's and existing supplies have been maintained in storage since that time. Evaluation has shown that the vaccine is still potent.

Although there are about 15 million full-strength doses remaining, studies have shown that the vaccine is capable of eliciting adequate immune responses in most vacinees at dilutions of up to 1:10 (Frey, JAMA 2003). It is licensed by the FDA and distributed by the CDC.

An additional 85 million doses of a similar smallpox vaccine produced by Aventis were stored frozen. This preparation is not currently licensed, but has shown >99% vaccination success rates at 1:10 dilution (Talbot, JAMA 2004). Efforts to develop new smallpox vaccines are in progress.

Technique. Dryvax vaccine is administered using a droplet of the vaccine applied to a bifurcated needle. The needle is dipped into the vaccine vial and stroked against the skin with sufficient vigor that a trace of blood appears at the vaccination site. The site is then covered with sterile gauze dressing underneath a semipermeable dressing. Since the vaccine contains live Vaccinia virus, vaccinees must be instructed to keep the site dry and covered, to avoid touching the site, and to thoroughly launder or carefully discard any materials that come into contact with the site. (**Note: vaccine should be administered by persons trained in its administration, who have themselves been successfully vaccinated. Should smallpox vaccination be necessary in San Francisco, it will be coordinated by SFDPH.)** For additional information on vaccine administration, see www.bt.cdc.gov/agent/smallpox/vaccination.

Assessment. Under optimal conditions, Dryvax vaccinees must return 6-8 days after vaccination for a "take check." Successful primary vaccination is demonstrated by occurrence of a pustular or vesicular skin lesion at the site of vaccination. Successful revaccination (in persons who received $\geq$1 prior dose of vaccine) is indicated by palpable inflammation at the site. The presence of a successful "take" correlates with the development of neutralizing antibody, which appears about 10 days after primary vaccination and about 7 days after revaccination.

Protection. Antibody titers of 1:10 or higher develop in 95% of primary vaccinees after a single inoculation, a level believed to confer adequate protection. Protection against smallpox persists for 5 to 10 years after primary vaccination. Antibody titers of 1:10 or higher are found in 75% of persons up to 10 years after receiving two doses of vaccine and up to 30 years after receiving three doses. Probably fewer than 20% of persons vaccinated before the early 1970s have immunologic protection today. It is not clear whether a remote history of receiving one dose of smallpox vaccine will modulate disease severity in the event that infection occurs.

Smallpox Vaccination in the Pre-Event and Post-Exposure Settings

Routine vaccination of the US population ended in the 1970's. Vaccination is currently required for most military personnel and is recommended for select health care and emergency workers, described below. Due to the relative frequency and seriousness of vaccine-related complications and the low risk of smallpox outbreak in the US, routine vaccination is not recommended for the vast majority of healthcare workers or for the general US population.

In 2002, the CDC recommended pre-event vaccination for local smallpox response teams, consisting of public health, medical, nursing, and public safety personnel, who would conduct

investigation and management of initial smallpox cases. As of July 31, 2004, 39,579 healthcare workers and first-responders had been vaccinated nationally, including several in San Francisco.

Immunity to variola virus generally develops within 8 to 11 days after vaccination. Since the incubation period for smallpox averages about 12 days, vaccination within 4 days may confer some immunity to exposed persons and reduce the likelihood of a fatal outcome. Post-exposure vaccination may be particularly important for those vaccinated in the past, provided that revaccination is able to boost the anamnestic immune response.

An exposed person is defined as one who has been in close personal contact with a patient with suspected or confirmed smallpox. Close personal contact includes persons residing in the same household as the case-patient or persons with face-to-face contact with the case, once the case has developed febrile illness.

Vaccine Contraindications and Complications

The Dryvax vaccine does have serious complications with up to 3 in 100,000 vaccinees reporting significant adverse reactions and nearly 1 in 1,000,000 deaths. Likelihood of adverse effects is 3- to 4-fold higher in infants and in primary vaccinees.

Vaccination during the pre-exposure period is contraindicated for certain persons. **During a smallpox emergency, however, all contraindications would be reviewed in the context of the risk of smallpox exposure, and updated recommendations would be issued by SFDPH and other public health authorities.** Contraindications to vaccination are as follows (see www.bt.cdc.gov/agent/smallpox/vaccination for further description):

- Past or present eczema or atopic dermatitis (risk of eczema vaccinatum)
- Other acute or chronic exfoliative skin conditions (e.g. burns, impetigo, chicken pox, contact dermatitis, shingles, herpes, severe acne, psoriasis), until the condition resolves
- Immunodeficiency states, due to disease or treatment of disease
- Pregnancy or breastfeeding
- Hypersensitivity to vaccine components
- Under 18 years of age in nonemergency situations
- Household contacts who are immunodeficient, who have past or present eczema or atopic dermatitis, or who have an acute, chronic, or exfoliative skin condition
- Physician-diagnosed cardiac disease, or $\geq$3 major risk factors for cardiac disease

Well-documented adverse reactions to vaccination are listed below (photos of vaccine adverse events at www.bt.cdc.gov/training/smallpoxvaccine/reactions):

- Tenderness, erythema at the injection site, other localized reactions (including allergic reactions to tape adhesives and “robust takes”), and secondary bacterial infections
- Systemic reactions: fever of at least 100°F, malaise, myalgias, local lymphadenopathy
- Dermatologic reactions, including erythema multiforme and Stevens Johnson syndrome, urticaria, exanthems, contact dermatitis, and erythematous papules

- Focal and generalized suppurative folliculitis (without evidence of viral infection; may be mistaken for generalized vaccinia)
- Inadvertent autoinoculation of another body site (25-529 cases per 1M* primary vaccinees)
- Generalized vaccinia (GV): vesicles or pustules appearing on normal skin distant from the vaccination site (23-241 cases per 1M primary vaccinees)
- Eczema vaccinatum (EV): localized or systemic spread of vaccinia virus; may be severe and can be fatal; (10-38 cases per 1M primary vaccinees)
- Vaccinia keratitis
- Progressive vaccinia (PV): progressive necrosis in vaccination area, often with spread to other sites; can be severe and fatal; (0.9-1.5 cases per 1M primary vaccinees)
- Postvaccinial encephalitis (PVEM) (2.9-12.3 cases per 1M primary vaccinees)
- Fetal vaccinia: occurs after primary inoculation of the mother during pregnancy; usually results in stillbirth or death of the infant soon after birth
- Myopericarditis, identified among military personnel vaccinated 12/2002-12/2003 (124 cases per 1M vaccinees)
- Death: 1.1 deaths per 1M primary vaccinees
- Contact vaccinia: transmission of vaccinia virus from newly vaccinated persons to susceptible unvaccinated contacts (61-81 cases per 1M primary vaccinees; higher rates of transmission likely with immunocompromised contacts)

The primary therapy for adverse reactions to smallpox vaccination is vaccinia immunoglobulin (VIG). VIG is manufactured from plasma of persons vaccinated with vaccinia vaccine. An intravenous preparation (VIGIV) was recently licensed by the FDA. Antiviral agents with activity against vaccinia virus include cidofovir (a nucleotide analogue of cytosine), which may also be available from the CDC under an investigational protocol, and topical ophthalmic antiviral drugs (trifluridine or vidarabine) for vaccinia ocular involvement.

INFECTION CONTROL†

These recommendations are current as of this document date. SFDPH will provide periodic updates as needed and situational guidance in response to events (www.sfdph.org/cdcp).

Smallpox is transmissible from person-to-person by exposure to respiratory secretions, particulary during coughing, by contact with pox lesions, and by fomites. **Airborne and Contact Precautions in addition to Standard Precautions** should be implemented for patients with suspected smallpox. Healthcare workers caring for patients with suspected smallpox should be vaccinated immediately.

* 1M = 1 million
† For description of Precautions, see chapter on Infection Control

Standard disinfection/sterilization methods are deemed to be adequate for medical equipment used with smallpox patients. Standard hospital disinfectants or hypochlorite are adequate for cleaning surfaces potentially contaminated with the virus. Bedding and clothing of smallpox patients should be minimally handled to prevent re-aerosolization, and autoclaved or laundered in hot water to which bleach has been added. Since variola virus is rapidly inactivated in the environment, standard terminal cleaning practices are considered adequate for rooms that have housed smallpox patients. Airspace decontamination (fumigation) is not required.

Detailed instructions on infection control practices for smallpox have been prepared by the CDC and may be found at: www.bt.cdc.gov/agent/smallpox/response-plan/files/guide-f.doc.

REFERENCES

CDC. Evaluate a Rash Illness Suspicious for Smallpox. (Online Form) (www.bt.cdc.gov/agent/smallpox/diagnosis/riskalgorithm)

CDC. Acute, generalized vesicular or pustular rash illness testing protocol in the United States. (www.bt.cdc.gov/agent/smallpox/diagnosis/rashtestingprotocol.asp)

CDC. Adverse events following smallpox vaccination: United States, 2003. MMWR 2003 Apr 4;52(13):278-82

CDC. Cardiac and other adverse events following civilian smallpox vaccination—United States, 2003. MMWR 2003 Jul 11;52(27):639-42

CDC. Caring for the smallpox vaccination site. (www.bt.cdc.gov/agent/smallpox/vaccination)

CDC. Generalized vesicular or pustular rash illness protocol (www.bt.cdc.gov/agent/smallpox/diagnosis)

CDC. Medical management of smallpox (vaccinia) vaccine adverse reactions (www.bt.cdc.gov/agent/smallpox/vaccination/vaccinesafety.asp)

CDC. Multistate outbreak of monkeypox: Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. MMWR 2003 Jul 11;52(27):642-6

CDC. Smallpox response plan and guidelines. Nov 26, 2002.(www.bt.cdc.gov/agent/smallpox/prep)

CDC. Smallpox vaccination and adverse events training module (http://www.bt.cdc.gov/agent/smallpox/vaccination/training.asp)

CIDRAP. Smallpox: Current, comprehensive information on pathogenesis, microbiology, epidemiology, diagnosis, treatment, and prophylaxis. May 18, 2005. (www.cidrap.umn.edu/cidrap/content/bt)

Frey SE et al. Response to smallpox vaccine in persons immunized in the distant past. JAMA 2003 Jun 25;289(24):3295-9

Henderson DA et al, for the Working Group on Civilian Biodefense. Smallpox as a biological weapon: medical and public health management. JAMA 1999;281(22):2127-39

LA County DHS. Terrorism Agent Information and Treatment Guidelines for Clinicians and Hospitals. June 2003. (labt.org/Zebra.asp)

Talbot TR et al. Vaccination success rate and reaction profile with diluted and undiluted smallpox vaccine: a randomized controlled trial. JAMA 2004 Sep 8;292(10):1205-12