



HUMBOLDT COUNTY PUBLIC HEALTH BRANCH DEPARTMENT OF HEALTH & HUMAN SERVICES

Medical Treatment and Response to Suspected Smallpox: Information for Health Care Providers During Biologic Emergencies

OCTOBER 2001

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**ALL SUSPECT CASES OF SMALLPOX MUST BE REPORTED IMMEDIATELY TO
HUMBOLDT COUNTY PUBLIC HEALTH BRANCH**

During Business Hours:

707-445-6200

After Hours (Nights, Weekends and Holidays):

Sheriff's Dispatch, (ask for the Health Officer), 707-445-7251

I. KEY SUMMARY POINTS

Epidemiology:

- Highly infectious after aerosolization
- Person-to-person transmission can occur via droplet nuclei or aerosols expelled from the oropharynx and by direct contact
- Contaminated clothing or bed linens can also spread the virus
- About 30% of susceptible contacts will become infected

Clinical:

- Incubation period is 12-14 days (ranges 7-17 days)
- Characteristic rash appears 2-3 days after nonspecific, flu-like prodrome (fever and headache)
- Maculopapular rash begins on mucosa of mouth and pharynx, face, hands, forearms and spreads to legs and centrally to trunk; lesions are more predominant on the face and extremities than on the trunk.
- Lesions progress synchronously on any given part of the body from macules to papules to vesicles to pustules to crusty scabs

Laboratory Diagnosis:

- Mask and gloves should be worn by person obtaining specimen, preferably a person who has been recently vaccinated
- Vesicular fluid is obtained by opening lesions with the blunt edge of a scalpel, harvesting fluid with a cotton swab; scabs can be removed by forceps. Swabs and scabs should be placed in a vacutainer, sealed with tape, and placed in a second, durable, watertight container
- Laboratory specimens must be handled in a Biosafety Level 4 facility (e.g. CDC) and will be evaluated with electron microscopy and cell culture

Patient Isolation:

- Strict isolation in negative pressure room (high efficiency particulate air filtration ideal) from onset of rash until all scabs separate
- Laundry and waste should be autoclaved before being laundered or incinerated

Treatment:

- Supportive care is the mainstay of therapy

- In-vitro antiviral activity against poxviruses has been shown with adefovir, cidofovir, dipivoxil, and ribavirin. (Animal studies suggest that cidofovir may be most effective).

Prophylaxis:

- Smallpox vaccine would be required for all persons exposed at the time of the bioterrorist attack or anyone with close personal contact with a smallpox case
- Vaccine is most effective if given before or within 3 days of exposure
- Ideally, all exposed persons should be placed in strict quarantine for 17 days after last contact with a smallpox case

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II. Introduction/Epidemiology

Smallpox is caused by an *Orthopoxvirus*, variola, a large enveloped DNA virus. The last occurrence of endemic smallpox was in Somalia in 1977 and the last human cases were laboratory-acquired infections in 1978. Smallpox was declared eradicated in 1980 by the World Health Organization.

Variola is infectious only for humans; there is no animal reservoir. Other key epidemiologic points include:

- The virus is highly stable and retains infectivity for long periods outside the host. Historically, smallpox was more common in the winter and spring; with aerosol infectivity decreasing with higher temperatures and humidity.
- Approximately 30% of susceptible contacts became infected during the era of endemic smallpox.

- Smallpox is transmitted by respiratory secretions, most efficiently during the early stages of the rash illness; it is generally believed that close person-to-person proximity is required for reliable transmission to occur. Patients are considered infectious from the time of development of the eruptive exanthem (usually 2-3 days after fever begins) until all scabs separate. In addition, virus can readily be recovered from scabs throughout convalescence.
- Fomites and inanimate objects are considered potential vehicles of transmission. However, since laundry from infected patients may contain viable virus, bedding and clothing of smallpox patients should be autoclaved.
- **Patients with confirmed or suspected smallpox should be placed on strict isolation until no longer considered infectious.**
- **Strict quarantine with respiratory isolation for 17 days is recommended for all persons in direct contact with a case.** In the setting of a large outbreak due to bioterrorism, this may not be possible - in which case, quarantine of exposed persons in their home with a daily fever watch may be an alternative public health measure.

During the past century, the prototypical disease, variola major, caused mortality of 3% and 30% in the vaccinated and unvaccinated, respectively. The key to control and eventual eradication of endemic smallpox was vigorous case identification, followed by quarantine and immunization of contacts. Routine smallpox vaccination was discontinued in the United States in 1972. Immunity from prior smallpox vaccination wanes with time and at this point, the entire United States' civilian population is likely susceptible. However, persons who have been vaccinated in the past may experience less severe disease.

III. **Significance as a Potential Bioterrorist Agent**

- High aerosol infectivity; stability of virus in aerosols
- Infectious dose is thought to be low (as low as a few virions)
- Increasing susceptibility of the population
- High mortality rate in the non-immune

- Potential for significant ongoing transmission due to secondary spread
- Ease of large-scale virus production
- Existence of clandestine smallpox virus stockpiles outside the stockpiles at the Centers for Disease Control and Prevention (USA) and the State Center for Virology and Biotechnology (Koltsovo, Russia).
- Currently, worldwide supplies of smallpox vaccine are limited

IV. **Clinical Manifestations**

During an act of bioterrorism, release of an aerosol will be the most likely route of transmission.

A. Variola major

***Incubation period* - typically 12-14 days, can be 7-17 days**

Acute onset of malaise, fever, rigors, vomiting, headache and
Symptoms: Prodrome: backache. 15% develop delirium. 10% of light skinned patients have an erythematous rash.

Appears as soon as 2-3 days after prodrome, just as fever peaks.

Discrete maculopapular rash on face, hands, forearms, and mucous membranes of mouth and pharynx. Involvement of palms and soles is common.

Exanthem: Rash spreads to legs and then centrally to trunk during Week 2.

Lesions quickly progress from macules to papules to vesicles to pustular vesicles (umbilicated) to crusty scabs.

Scabs form 8-14 days after onset, leaving depressions and depigmented scars primarily on the face which has more sebaceous glands.

CLINICAL CLUES TO DISTINGUISH SMALLPOX FROM CHICKENPOX:

- Smallpox has many more lesions on face and extremities than trunk (Centrifugal spread).
- Smallpox lesions are synchronous in their stage of development.

- Smallpox lesions are more common on palms and soles.
- Smallpox lesions are more deeply imbedded in the dermis compared with the superficial lesions of chickenpox.

B. Variations in Variola Major

Flat-type/"malignant" smallpox: Occurs in 2-5% of smallpox cases due to lack of adequate cell-mediated immune response. Notable for severe systemic toxicity and slow evolution of flat, soft, focal skin lesions. These papules coalesce and never become pustular. Skin develops a fine-grained reddish color, resembling crepe rubber. The mortality among unvaccinated persons is 95%.

Hemorrhagic-type smallpox: Occurs in < 3% of smallpox cases. Notable for extensive petechia, mucosal hemorrhage and intense toxemia (high fevers, headache, backache and abdominal pain). Seen more commonly in pregnant women. Patients usually die before development of typical pox lesions. Differential diagnosis includes: meningococemia and acute leukemia.

C. Variola minor (alastrim)

Incubation period - 7-17 days

Symptoms - Clinically resembles variola major but with milder systemic toxicity and sometimes more diminutive pox lesions. Lesions on the face are typically more sparse and evolve more rapidly than those on the arms and legs. Mortality in the unvaccinated is usually less than 1%.

D. Clinical Complications of Smallpox

Arthritis and osteomyelitis:	Frequency is 1-2%. Occurs late in course; usually affects children; bilateral elbow joint involvement most common.
Cough and bronchitis:	Occasionally a prominent symptom. Pneumonia was unusual.
Pulmonary edema:	Common in hemorrhagic and flat-type smallpox.
Orchitis:	Noted in 0.1% of patients.
Encephalitis:	Developed in 1 in 500 patients with variola major.
Keratitis/corneal ulcers:	Progresses to blindness in about 1% of cases.
Disease during pregnancy:	Precipitated high perinatal mortality.

E. Monkeypox

A naturally-occurring relative of variola, monkeypox virus, is a rare zoonosis that occurs in the rain forest areas of Africa and is felt to be rodent borne. The disease it causes, monkeypox, is clinically indistinguishable from smallpox, except for notable swelling of cervical and inguinal lymph nodes.

V. Laboratory Diagnosis

If smallpox is suspected, please call the Humboldt County Public Health Branch at 707-445-6200 to arrange for submission of specimens to CDC for testing. After hours, please call Sheriff's Dispatch, (ask for the Health Officer), 707-445-7251.

The diagnosis of smallpox requires astute clinical evaluation. The clinical diagnosis may be confused with chickenpox, erythema multiforme with bullae or allergic contact dermatitis.

The diagnosis of smallpox is an international emergency and confirmation of the diagnosis by laboratory techniques requires coordination between the medical and laboratory community and local, state, federal and international agencies. **If you clinically suspect even a single case of smallpox, notify the Humboldt County Public Health Branch IMMEDIATELY at 707-445-6200 (AFTER HOURS : Sheriff's Dispatch, (ask for the Health Officer), 707-445-7251.** In the event of a bioterrorist release of smallpox, confirmation by a reference laboratory will be necessary for the earliest (index) cases. After a smallpox outbreak is confirmed, diagnosis of subsequent cases will need to be based on a compatible clinical presentation.

Opening the lesions with the blunt edge of a sterile scalpel and harvesting the fluid with a sterile swab should obtain vesicular fluid. The swab(s) should be placed in a cryo-safe 1-2 ml gasketed vial (the gasket on the vial prevents gas exchange, e.g., carbon dioxide vapors from dry ice, which can acidify samples). Scabs can be removed with forceps and also placed in a gasketed vial. The vial should not contain any transport medium. In addition, a droplet of vesicular fluid can be placed on a clean microscopic slide and allowed to air dry in a safe location. The slides should be placed in an airtight container. Specimens from different patients should not be mixed together. All specimens should

be safely secured for shipping. Specimens will be tested at the CDC's Biosafety Level 4 reference laboratory using the following tests:

- **Light or Electronic Microscopy**
Scrapings of vesicular lesions can be examined by electron microscopy for characteristic brick-shaped virions. This method does not distinguish variola from vaccinia, monkeypox or cowpox.
- **Viral cultures**
Requires isolation of virus and characterization of its growth on chorioallantoic membrane or cell culture.
- **Other Testing**
Polymerase chain reaction and restriction fragment length polymorphisms (RFLP) diagnostic techniques promise a more accurate and less cumbersome method of identifying variola virus. These techniques are currently only available at national reference laboratories, such as the CDC.

VI. **Handling Laboratory Specimens**

All other laboratory tests should be performed in Biological Safety Level 2 cabinets and blood cultures should be maintained in a closed system. Laboratory staff handling specimens from persons who might have smallpox must wear surgical gloves, protective gowns and shoe covers. Every effort should be made to avoid splashing or creating an aerosol, and protective eye wear and masks should be worn if work cannot be done in a Biological Safety Level 2 cabinet. A full-face mask respirator with a HEPA (high efficiency particulate air) filter is an acceptable, but cumbersome, alternative to masks and protective eye wear. Laboratories working with a large amount of viral organisms should use Biological Safety Level 3 cabinets.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (1% sodium hypochlorite or sodium hydroxide (0.1N)). All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, 1% peracetic acid, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. Treatment

Supportive care is the mainstay of therapy.

Currently, there are no anti-viral drugs of proven efficacy. Although, adefovir, dipivoxil, cidofovir and ribavirin have significant in vitro antiviral activity against poxviruses, their efficacy as therapeutic agents for smallpox is currently uncertain. Cidofovir is FDA-licensed and shows the most promise in animal models.

VIII. Isolation of Patients

Smallpox is transmissible from person-to-person by exposure to respiratory secretions (particularly from coughing patients), contact with pox lesions and by fomites (although not efficiently). All staff should observe **both Airborne and Contact Precautions**, in addition to Standard Precautions, when caring for patients with suspected or confirmed smallpox.

Patients should be placed in a closed-door, negative pressure room with 6 to 12 air exchanges per hour and HEPA filtration of exhausted air. Patients with smallpox should be placed on strict isolation from the onset of eruptive exanthem until all pox scabs have separated (generally 14-28 days). Healthcare workers and others entering the room should wear appropriate respiratory protection; respiratory masks should meet the minimal NIOSH standard for particulate respirators (N95). Healthcare providers should wear clean gloves and gowns for all patient contact.

In the event of a large-scale smallpox outbreak due to a bioterrorist attack, there may be massive numbers of victims. In this case, there may be a need to cohort patients due to limited availability of respiratory isolation rooms. If this is done, then all patients should receive smallpox vaccine or vaccine immune globulin within 3 days of exposure, if available, in the event that some of these patients are misdiagnosed with smallpox.

All healthcare workers providing direct patient care to persons with smallpox should be vaccinated. If vaccine is unavailable, then only staff who previously

received smallpox vaccine (*e.g., persons born before 1972 or persons who were in the military before 1989*) should be caring for patients with smallpox.

IX. **Disposal of Infectious Waste**

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. **Autopsy and Handling of Corpses**

All postmortem procedures are to be performed using Universal Precautions. In addition, due to concerns about aerosolization of the virus, personnel should use particulate respirators as recommended under **Strict Isolation** precautions.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.
- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

XI. **Management of Exposed Persons**

An exposed person is defined as a person who has been in close personal contact with a patient with suspect or confirmed smallpox. **Close personal contact** includes persons residing in the same household with the case-patient or persons with face-to-face contact with the case AFTER the case developed febrile illness. (During outbreaks in Europe in the 1960's, up to 10-20 secondary cases occurred after exposure to a single case-patient, if vaccination efforts were delayed.)

- **Quarantine**: All exposed persons should be placed in strict quarantine with respiratory isolation for 17 days after last contact with suspect or confirmed smallpox case(s). In the setting of a large outbreak due to bioterrorism, this may not be possible - in which case, quarantine of exposed persons in their home with a daily fever watch may be an alternative public health measure.

- **Vaccination:**

Vaccine: In the United States, the smallpox vaccine supply is overseen by the CDC. The Wyeth vaccine (using the New York Board of Health vaccinia strain) is freeze-dried in multidose vials (50 doses per vial) at 20 °C.

Vaccine Indications: All exposed persons, including all household and face-to-face contacts of patients, should be vaccinated immediately, if vaccine is available. Additionally, all health care workers that might care for smallpox patients, emergency personnel who might transport patients, and mortuary staff should be vaccinated, if vaccine is available. **Vaccination is most effective at protecting against smallpox if given within 3 days of exposure.**

Methodology: A bifurcated needle is inserted into an ampule of reconstituted vaccine and, on withdrawal, a droplet of vaccine is held by capillarity between the two tines. The needle is held at right angles to the skin, the wrist of the vaccinator rests against the arm. Fifteen up and down (perpendicular) strokes of the needle are rapidly made in an area of 5-mm diameter. The strokes should be sufficiently vigorous so that a trace of blood appears at the vaccination site after 15-30 seconds. Excess vaccine should be wiped from the site with gauze (gauze should be discarded into a hazardous waste receptacle) and the site covered with a loose, non-occlusive bandage.

Evaluation of vaccine response:

(1) Primary vaccine response (never previously vaccinated):

Day 3: A red papule appears at the vaccination site

Day 5: Papule becomes vesicular

Day 7: A whitish, umbilicated, multilocular pustule develops, containing turbid lymph and surrounded by an erythematous areola which may expand further for 3 days. Fever during days 4-14, particularly for children, is common. The pustule dries and falls off after about 3 weeks.

(2) Re-immunization response (those previously vaccinated): May react as described above, or may have a papule surrounded by erythema that peaks between 3 and 7 days. A response that peaks within 48 hours is a hypersensitivity reaction; patients with this reaction should be revaccinated.

- **Contraindications to Vaccination:**

- Eczema or other exfoliative skin condition (*e.g., atopic dermatitis, burns, impetigo*)
- Leukemia, lymphoma, generalized malignancy or chemotherapy with alkylating agents, antimetabolites, radiation or high dose corticosteroids
- HIV infection or AIDS
- Hereditary immune deficiency disorders
- Pregnant women
- Life-threatening allergy to polymyxin B, streptomycin, tetracycline or neomycin.

In the setting of a large bioterrorist attack, the risk of vaccination must be weighed against the likelihood of acquiring infection. If VIG (vaccinia immune globulin) is available, those in close personal contact with a smallpox case AND with a clear contraindication to vaccine may receive vaccine PLUS VIG (0.3 ml/kg of body weight) simultaneously within the first week following exposure.

- **Potential Side-Effects of Vaccination:**

Side effects include: low grade fever, lymphadenopathy, autoinoculation, secondary inoculation, ocular vaccinia, urticarial rash, Stevens-Johnson syndrome, generalized vaccinia (3 per 10,000 vaccinations occurring from 6-9 days after vaccination), eczema vaccinatum, progressive vaccinia (1 per million vaccinations) and postvaccinial encephalitis (3 per million primary vaccinations occurring from 8-15 days after vaccination).

Severe vaccine complications should be treated with VIG (0.6 ml/kg body weight). The dose should be administered intramuscularly in 2 divided doses over a 24 to 36 hour period. The dose can be repeated in 2-3 days, if needed.

XII. Reporting to the Health Department

Smallpox is an international emergency and even an isolated suspect case must be reported immediately to the Humboldt County Public Health Department.

All suspect cases should be immediately reported **by telephone** to:

- **During business hours**

Humboldt County Public Health at 707-445-6200

- **After business hours**

Sheriff's Dispatch, (ask for the Health Officer), 707-445-7251

XIII. **References**

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October 2001

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