

# SMALLPOX

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**Immediately report** any suspected or confirmed cases of smallpox to:  
**SFDPH Communicable Disease Control**  
**(24/7 Tel: 415-554-2830)**

- By law, health care providers must report suspected or confirmed cases of smallpox to their local health department immediately [within 1 hr].
- SFDPH Communicable Disease Control can facilitate specialized testing and will initiate the public health response as needed.

**Also notify your:**

- Infection Control Professional
- Clinical Laboratory

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## INTRODUCTION

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Smallpox is caused by variola viruses, which are large, enveloped, single-stranded DNA viruses of the Poxvirus family and the *Orthopoxvirus* genus. Variola major strains cause three forms of disease (ordinary, flat type, and hemorrhagic), whereas variola minor strains cause a less severe form of smallpox. Vaccination with vaccinia virus, another member of the *Orthopoxvirus* genus, protects humans against smallpox because of the high antibody cross-neutralization between orthopoxviruses.<sup>1-4</sup>

The Working Group for Civilian Biodefense considers smallpox to be a dangerous potential biological weapon because of "its case-fatality-rate of 30% or more among unvaccinated persons and the absence of specific therapy." Of the potential ways in which smallpox could be used as a biological weapon, an aerosol release is expected to have the most severe medical and public health outcomes because of the virus' stability in aerosol form, low infectious dose, and high rate of secondary transmission. A single case of smallpox would be a public health emergency.<sup>2</sup>

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## EPIDEMIOLOGY

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### **Smallpox as a Biological Weapon**

Smallpox has been used as a biological weapon in the distant past. More recently it has been a focus of bioweapons research. In the 18<sup>th</sup> century, British troops in North America gave smallpox-infected blankets to their enemies, who went on to suffer severe outbreaks of smallpox. Defecting Russian scientists describe covert Russian operations during the 1970s and 1980s that focused on

bioweapons research and development including creation of more virulent smallpox strains and development of missiles and bombs that could release smallpox.<sup>2, 4, 5</sup>

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).<sup>2, 5</sup>

Smallpox is of concern as a biological weapon because:<sup>2</sup>

- 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
- a vaccine that lacks significant side effects is not yet available for general use
- experience has shown that introduction of the virus creates havoc and panic

**An intentional release of smallpox would have the following characteristics:**<sup>6</sup>

- Clustering in time: Multiple similarly presenting cases of fever and rash in mouth and on face, arms, and legs generally 4 days after release

## **Naturally Occurring Smallpox**

### **Reservoirs**

The natural reservoir for smallpox was humans with disease; there was no chronic carrier state. In 1980, the World Health Organization (WHO) declared smallpox eradicated from the world and recommended destruction or transfer all remaining stocks to one of two WHO reference labs, the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, and the former Institute of Virus Preparations (later transferred to the Vector Institute) in Russia. Since eradication, there is no natural reservoir for smallpox. Presently, smallpox is only officially found in these designated WHO reference laboratories.<sup>2, 5, 6</sup>

### **Mode of Transmission**

Historically, humans were able to be infected in a number of ways:<sup>1, 2, 6</sup>

- Inhalation of droplet nuclei or aerosols originating from the mouth of smallpox-infected humans
- Direct contact with skin lesions or infected body fluids of smallpox-infected humans
- Direct contact with contaminated clothing or bed linens

### **Worldwide occurrence**

In 1967, a WHO-led international campaign of mass vaccination, surveillance and outbreak containment was started in order to eradicate smallpox globally. In 1977, the last community-acquired smallpox case was reported in Somalia, and in 1978, a laboratory accident in England caused the last human case.<sup>3</sup>

### **Occurrence in the United States**

The last case of smallpox in the United States occurred in the Rio Grande Valley of Texas in 1949. The risk of disease was low enough to end routine vaccination of the US population in 1971.<sup>3</sup>

Vaccination is currently required for most military personnel and is recommended for select health care and emergency workers, described below. Because of the relative frequency and seriousness of vaccine-related complications and the low risk of smallpox outbreak in the United States, routine vaccination is not recommended for the vast majority of healthcare workers or for the general U.S. population.<sup>7</sup>

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, 39,608 healthcare workers and first responders had been vaccinated nationally.<sup>6</sup>

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## CLINICAL FEATURES

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Historically, smallpox has been divided into variola major and variola minor based on severity of clinical disease. Variola major was more common and caused more severe disease relative to variola minor. The case mortality was 15 to 45% for variola major and 1% for variola minor.

The infectious dose for smallpox is a few virions. The virus typically enters the body via respiratory or oral mucosa and is carried by macrophages to regional lymph nodes from which a primary asymptomatic viremia develops on the 3<sup>rd</sup> or 4<sup>th</sup> day after infection. The reticuloendothelial organs are invaded and overwhelmed leading to a secondary viremia around the 8<sup>th</sup> to 12<sup>th</sup> day after infection. Toxemia and fever onset follow. Seven to 17 days following infection, fever, malaise, and extreme exhaustion begin. A maculopapular rash first presents on the face, mouth, pharynx, and forearms and spreads to the trunks and legs. The rash progresses to a vesicular and pustular stage (round and deeply embedded). Scabs form on the 8<sup>th</sup> day of the rash. Scars are formed from sebaceous gland destruction and granulation tissue shrinking and fibrosis.<sup>1-4, 6</sup>

Although most data supports communicability with rash onset, some low level of communicability is present prior to rash onset because viral shedding from oral lesions occurs during the 1 to 2 days of fever preceding rash onset. However, secondary transmission peaks 3 to 6 days after fever onset (1<sup>st</sup> week after rash onset), and 91.1% of secondary cases occurred by the 9<sup>th</sup> day after fever onset.<sup>8</sup> The period of communicability ends when all the scabs have fallen off. Scabs are not very infectious because the tight binding of the fibrin matrix retains the virions; however secondary cases have been documented through transmission from direct contact with contaminated clothing and bedding.<sup>1-4, 6</sup>

Secondary bacterial infection and other organ involvement are uncommon. Encephalitis is a possible complication. Mortality is most commonly associated with toxemia of circulating immune complexes and soluble variola antigens and is seen in the second week of illness. Approximately 30 to 80% of unvaccinated close contacts will develop the disease. In addition, 3.5 to 6 transmissions per smallpox case are estimated.<sup>6</sup>

## Variola Major

Variola major is associated with the most severe disease, and presents as:

- ordinary (80% or more of cases: mortality is 30% in unvaccinated and 3% in vaccinated patients)
- flat (4 to 6% of cases: mortality is 95% in unvaccinated and 66% in vaccinated patients)
- hemorrhagic (2 to 3% of cases: mortality is 99% in unvaccinated and 94% in vaccinated patients)
- modified (13% of cases and low risk of death)
- variola sine eruptione (30 to 50% of vaccinated contacts of smallpox and low risk of death)

CLINICAL FEATURES: ORDINARY VARIOLA MAJOR. <sup>1-4, 6</sup>	
<b>Incubation Period</b>	10-13 days (range 7-19 days)
<b>Transmission</b>	<ul style="list-style-type: none"> <li>• Inhalation of droplet nuclei or aerosols originating from the mouths of smallpox-infected humans</li> <li>• Direct contact with skin lesions or infected body fluids of smallpox-infected humans</li> <li>• Direct contact with contaminated clothing or bed linens</li> </ul>
<b>Signs and Symptoms</b>	<p>Prodromal phase</p> <ul style="list-style-type: none"> <li>• 2-4 days of fever, chills, headache, backache, and often GI symptoms</li> </ul> <p>Rash phase</p> <ul style="list-style-type: none"> <li>• Enanthem (papules, vesicles, then ulcers) of oropharyngeal mucosa beginning 1 day before skin lesions appear</li> <li>• First skin lesions ("herald spots") are often on the face</li> <li>• Lesions spread centrifugally: trunk to proximal extremities to distal extremities</li> <li>• Palms and soles are usually involved, and truncal rash is usually sparse</li> <li>• Lesion progression: maculopapular (days 1-2), vesicular (days 3-5), pustular (days 7-14)</li> <li>• Vesicles and pustules are frequently umbilicated</li> <li>• Pustules can be like small, embedded hard balls or "shotty"</li> <li>• Lesions tend to progress at same rate</li> <li>• Lesions may be discrete, semiconfluent, or confluent</li> <li>• Lesions are typically painful and cause pitted scars as they heal</li> <li>• Lesions gradually scab over during days 13-18</li> </ul>
<b>Progression and Complications</b>	<ul style="list-style-type: none"> <li>• Viral bronchitis or pneumonitis</li> <li>• Third spacing of fluid with resulting electrolyte and renal abnormalities</li> <li>• Skin desquamation</li> <li>• Secondary bacterial infection, particularly skin and pulmonary</li> <li>• Spontaneous abortion, stillbirth</li> <li>• Rarely: blindness, keratitis, corneal ulceration, encephalitis, osteomyelitis or arthritis, orchitis</li> <li>• Death may occur during 2<sup>nd</sup> week of illness, from high-level viremia and circulating immune complexes</li> </ul>
<b>Laboratory Findings</b>	<ul style="list-style-type: none"> <li>• Lymphocytopenia and/or granulocytopenia</li> </ul>
GI, gastrointestinal	

Other forms of smallpox caused by variola major infection include:

**Flat-type smallpox** (also known as **malignant smallpox**) occurred in about 4 to 6% of cases and more frequently in children. It is associated with a late, deficient cellular immune response. It is characterized by a short incubation period, prostrating prodromal illness, severe systemic toxicity and high mortality (90-97%). The lesions do not progress to the pustular stage, instead remaining soft, velvety and flattened. If the patient survives, the lesions will resolve by desquamation without scabs or scarring.

**Hemorrhagic smallpox** occurred in about 2 to 3% of cases. Pregnant women are highly susceptible. Similar to flat-type smallpox, it is associated with a defective immune response. It is characterized by a short incubation period, prostrating prodromal illness, severe systemic toxicity, and high mortality (96%). 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.

**Modified smallpox** occurred in about 13% of cases. It occurred in persons with some immunity. The pre-eruptive illness is typical in duration and severity as ordinary smallpox; however, during the eruption, fever is absent and the skin lesions are superficial, pleomorphic, fewer in number, and evolve rapidly.

**Variola sine eruption** occurred in about 30 to 50% of vaccinated contacts of smallpox cases. It is characterized by a sudden onset of fever, headache, occasional backache which resolves within 48 hours, influenza-like symptoms and no rash.

### **Variola Minor**

Variola minor, caused by different strains of variola, is a milder form of smallpox. Compared with variola major, there are milder constitutional symptoms, discrete lesions that evolve a bit more rapidly, lower rates of hemorrhagic disease, and only rare fatal outcomes (<1%). The illness may be difficult to distinguish clinically from modified smallpox and variola without eruption. In the 1890s, variola minor spread from South Africa to Florida. In the early 1900s, variola minor became prevalent in the United States, Latin America, and Europe.

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## DIFFERENTIAL DIAGNOSIS

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The characteristic features of smallpox need to be differentiated from other illnesses that present with vesicular or pustular rash. One disease that could be confused with smallpox is chickenpox. These may be differentiated clinically, as follows:

CLINICAL DIFFERENTIATION OF VARIOLA VS. VARICELLA <sup>9</sup>		
Feature	Variola	Varicella
<b>Prodrome</b>	<ul style="list-style-type: none"> <li>Duration: 2-4 days</li> <li>Fever, chills, headache, backache, often GI symptoms</li> </ul>	<ul style="list-style-type: none"> <li>Commonly does not occur</li> <li>If present, mild symptoms and duration of 1 day</li> </ul>
<b>Rash Distribution</b>	<ul style="list-style-type: none"> <li>Centrifugal: more dense on face and distal extremities</li> <li>Frequently involves palms and soles</li> <li>More involvement of back than abdomen</li> </ul>	<ul style="list-style-type: none"> <li>Centripetal: more dense on trunk</li> <li>Spare palms and soles</li> <li>Back and abdomen equally involved</li> </ul>
<b>Lesion Evolution</b>	<ul style="list-style-type: none"> <li>Usually appear on oropharyngeal mucosa first, then all over within 1-2 days</li> <li>Progress at same rate; at any point in time, lesions are at same stage of evolution</li> <li>Lesions progress slowly (7-14 days) from macules to papules to vesicles to pustules to scabs</li> </ul>	<ul style="list-style-type: none"> <li>Lesions appear in crops</li> <li>At any point in time, crops of lesions are at different stages of evolution</li> <li>Lesions progress quickly (1-2 days) from macules to papules to vesicles to scabs</li> </ul>
<b>Lesion Attributes</b>	<ul style="list-style-type: none"> <li>May be semiconfluent or confluent</li> <li>Deep</li> <li>May be umbilicated</li> <li>Often painful; pruritic only as scabs</li> </ul>	<ul style="list-style-type: none"> <li>Usually discrete</li> <li>Superficial</li> <li>Rarely found on palms and soles</li> <li>Do not umbilicate or dimple</li> <li>Typically painless; intensely pruritic</li> </ul>
GI, gastrointestinal		

Monkeypox is another disease that could be confused with smallpox. In 2003, an outbreak of monkeypox, associated with prairie dog contact, took place in the midwestern United States. Monkeypox in humans presents similarly to ordinary smallpox. However, monkeypox is milder and has prominent lymphadenopathy and a shorter duration of rash.

The CDC has outlined criteria for determining the risk of smallpox when evaluating patients with generalized vesicular or pustular rash:<sup>9, 10</sup>

Risk of Smallpox in Patients with Generalized Vesicular or Pustular Rash	
<b>High</b>	<p>All three major criteria present:</p> <p>a) <u>Febrile prodrome</u> 1-4 days before rash onset, with fever &gt;101°F, plus <u>1 or more</u> of the following: prostration, headache, backache, chills, vomiting, severe abdominal pain</p> <p>b) <u>Classic smallpox lesions</u> 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)</p> <p>c) Lesions on any one part of the body are in the <u>same stage of development</u></p>
<b>Moderate</b>	Febrile prodrome as in (a) above, plus <u>either</u> (b) or (c) above

	<p><u>OR</u></p> <p>Febrile prodrome as in (a) above, plus <u>at least four</u> of the following minor criteria:</p> <ul style="list-style-type: none"> <li>• Centrifugal distribution</li> <li>• First lesions appeared on the oral mucosa/palate, face, or forearms</li> <li>• Patient appears toxic or moribund</li> <li>• Slow evolution of lesions from macules to papules to pustules over several days</li> <li>• Lesions on the palms and soles</li> </ul>
<b>Low</b>	<p>No viral prodrome</p> <p><u>OR</u></p> <p>Febrile prodrome as in (a) above, plus &lt; 4 minor criteria above</p>

Additional considerations in the differential diagnosis of smallpox include:

Macular/papular stage

- measles
- scarlet fever
- rubella

Vesicular/pustular stage:

- disseminated herpes zoster
- disseminated herpes simplex
- Molluscum contagiosum
- bullous pemphigoid
- impetigo (*Streptococcus*, *Staphylococcus*)
- human monkey pox

Either stage:

- erythema multiforme major  
- (Stevens-Johnson syndrome)
- miscellaneous drug eruptions
- secondary syphilis
- enteroviral infection (hand, foot & mouth disease)
- chickenpox
- contact dermatitis
- generalized vaccinia
- acne
- scabies/insect bites

Hemorrhagic smallpox may resemble:

- meningococemia
- rickettsial infections
- Gram-negative septicemia

Flat-type smallpox may resemble:

- hemorrhagic chickenpox

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## LABORATORY DIAGNOSIS

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The diagnosis of smallpox requires a high index of suspicion because the disease has been eradicated and its clinical presentation is similar to other pox viruses. Routine laboratory findings for specific clinical presentations of smallpox are listed in the clinical features table. Radiographic findings do not assist in identification of smallpox.

Diagnosis of smallpox will be clinical initially, but followed by laboratory confirmation. 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 or to assist with law enforcement activities.

Clinicians should use the CDC-developed tools to assess the likelihood that patients with acute generalized vesicular or pustular rash illnesses have smallpox.<sup>9</sup> CDC has also developed algorithms for laboratory evaluation of suspect smallpox cases based on the likelihood of disease.<sup>10</sup> If a patient is determined to be at high risk for smallpox, clinicians should call their local public health authorities immediately and obtain photos of the patient. Public health will provide guidance on specimen collection and packaging and will facilitate transport of specimens to the appropriate public health laboratory.

Multiple tests will be used to evaluate for smallpox. Polymerase chain reaction (PCR) testing will be an important method; however, other methods will also be used including: electron microscopic examination of vesicular or pustular fluid or scabs, direct examination of vesicular or pustular material looking for inclusion bodies (Guarnieri's bodies), culture on egg chorioallantoic membrane, tissue culture, strain analysis with a restriction fragment length polymorphism assay, and serology. Definitive laboratory identification and characterization of the variola virus requires several days.

**If you are testing or considering testing for smallpox, you should:**

- **IMMEDIATELY notify SFDPH Communicable Disease Control (24/7 Tel: 415-554-2830).** SFDPH can authorize and facilitate testing, and will initiate the public health response as needed.
- **Inform your lab that smallpox is under suspicion.**

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## TREATMENT AND PROPHYLAXIS

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

### **Treatment**

The management of confirmed or suspected cases of smallpox 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.<sup>1-4, 6</sup>

Currently there are no FDA approved antiviral agents with proven activity against smallpox in humans.



Antiviral agents that have shown some activity in vitro against poxviruses may be available from the CDC under an investigational protocol. ST-246 is a novel agent that is currently undergoing safety and efficacy testing.<sup>6, 11</sup> Additionally, cidofovir, a nucleoside analogue DNA polymerase inhibitor, might be useful if administered within 1-2 days after exposure; however, there is no evidence that it would be more effective than vaccination, and it has to be administered intravenously and causes renal toxicity.

### **Immunity from prior vaccination**

Protection from smallpox is estimated to last between 11.7 to 28.4 years after primary vaccination and longer for variola minor than for variola major. Those who were previously vaccinated may retain some protection that could decrease the severity of the disease and allow for greater mobility thereby complicating public health response.<sup>12</sup>

### **Postexposure prophylaxis**

Postexposure prophylaxis for smallpox is the administration of vaccinia vaccine after suspected exposure to smallpox has occurred but before symptoms are present. Immunity generally develops within 8 to 11 days after vaccination with vaccinia virus. Because 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. Postexposure vaccination may be particularly important for those vaccinated in the past, provided that revaccination is able to boost the anamnestic immune response. In addition to vaccination, exposed persons should be monitored for symptoms. Temperature should be checked once a day, preferably in evening, for 17 days after exposure for fever (over 38°C).<sup>2-4, 6, 7</sup>

If a case or cases of smallpox occur, public health authorities will conduct surveillance and implement containment strategies. Ring vaccination will be important and includes identification of contacts of cases and provision of prophylaxis and guidance on monitoring for symptoms. Large-scale voluntary vaccination may be offered to low-risk populations to supplement and address public concerns.

### **Vaccine Supply, Administration, and Efficacy**

The smallpox vaccine used in the United States (formerly Dryvax, now ACAM2000) 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 ACAM2000 uses vaccinia virus derived from the Dryvax vaccine via plaque purification cloning. The virus is then grown in African green monkey (Vero) cells. The ACAM2000 preparation also contains HEPES, human serum albumin, mannitol and trace amounts of neomycin and polymyxin B. The diluent contains glycerin and a phenol preservative.<sup>13</sup>

Production of the Dryvax vaccine stopped in the 1980s. Acambis currently makes the ACAM2000 vaccine which received FDA approval in September 2007. By that time 192.5 million doses of ACAM2000 were already in the United States stockpile. All lots of Dryvax vaccine expired February 20, 2008, and were destroyed by March 31, 2008.<sup>6, 14</sup>

**Technique.** The Dryvax vaccine should be administered by trained, vaccinated personnel using a bifurcated needle that is stroked against the skin until blood appears. Vaccinees are 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. **Should smallpox vaccination be deemed necessary, it will be coordinated by local, state and federal health agencies.** For additional information on vaccine administration, see <http://www.bt.cdc.gov/agent/smallpox/vaccination>.<sup>7</sup>

### **Vaccine Contraindications and Complications**

The ACAM2000 and Dryvax vaccines have similar safety profiles.<sup>14</sup> Both have serious complications. Likelihood of adverse effects is 3 to 4-fold higher in infants and in primary recipients. Based on the U.S. Vaccine Adverse Events Reporting System of recently vaccinated people, there was a rate of 26.4 deaths per 10,000 vaccinees. Adverse events included the following: 33% cardiac, 25% nonspecific chest pain, 21% neurological, 14% infection, 3% malignancy, 3% pulmonary (noninfectious), and 1% normal vaccination response.<sup>13, 15, 16</sup>

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 public health authorities.** Current contraindications to vaccination are as follows (see [www.bt.cdc.gov/agent/smallpox/vaccination](http://www.bt.cdc.gov/agent/smallpox/vaccination) for further description):<sup>7, 13</sup>

- 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 (vaccination may offer partial protection for mother, but increases risk of fetal vaccinia)
- breastfeeding
- hypersensitivity to vaccine components
- under 18 years of age in nonemergency situations
- having a household contact who is immunodeficient, who has past or present eczema or atopic dermatitis, or who has an acute, chronic, or exfoliative skin condition
- physician-diagnosed cardiac disease, or 3 or more major risk factors for cardiac disease

Well-documented adverse reactions to vaccination are listed below:<sup>1, 2, 7, 13</sup>

- tenderness, erythema, or other localized reactions at the injection site
- systemic symptoms of fever, malaise, myalgias, local lymphadenopathy
- dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, urticaria, exanthems, contact dermatitis, and erythematous papules
- secondary bacterial infections at injection site
- focal and generalized suppurative folliculitis (without evidence of viral infection; may be mistaken for generalized vaccinia)
- inadvertent autoinoculation of another body site (most common sites are face, eyelid, nose, mouth, genitalia, rectum)
- generalized vaccinia: vesicles or pustules appearing distant from the vaccination site

- eczema vaccinatum: localized or dissemination of vaccinia virus; usually mild but may be severe and fatal
- vaccinia keratitis
- progressive vaccinia: progressive necrosis in vaccination area, often with metastatic sites; can be severe and fatal
- postvaccinial encephalitis
- fetal vaccinia: occurs when mother is vaccinated during pregnancy; usually results in premature birth or miscarriage
- myopericarditis, identified among military personnel vaccinated between December 2002 and December 2003
- death: 1.1 deaths per 1 million primary vaccine recipients
- contact vaccinia: transmission of vaccinia virus from newly vaccinated persons to susceptible unvaccinated contacts

The primary therapy for adverse reactions to smallpox vaccination is vaccinia immunoglobulin (VIG).<sup>7</sup> However VIG is contraindicated in vaccinia keratitis and provides no benefit in postvaccinial encephalitis. VIG is manufactured from the plasma of persons vaccinated with vaccinia vaccine. An intravenous preparation (VIGIV) was recently licensed by the FDA.<sup>17</sup> Cidofovir and topical ophthalmic antiviral agents are also recommended by some experts.<sup>7</sup> Cidofovir use requires an Investigational New Drug (IND) protocol, and topical ophthalmic agent use is off-label.

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## COMPLICATIONS AND ADMISSION CRITERIA

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Before smallpox was eradicated worldwide, viral bronchitis and pneumonitis were the most frequent complications of ordinary-type smallpox. Cutaneous complications included desquamation, massive subcutaneous fluid accumulation with electrolyte abnormalities and renal failure, or, less commonly, secondary bacterial infection of smallpox lesions. Infrequently, smallpox patients experienced encephalitis, osteomyelitis, corneal ulceration, or ocular keratitis. Ordinary-type smallpox with confluent lesions, rather than discrete lesions, carried a much higher risk of massive exfoliation, tissue destruction, bacterial sepsis, and death. Hemorrhagic-type and flat-type smallpox were nearly always fatal.<sup>1-4, 6</sup>

Many patients do not require hospitalization. Those with discrete lesions, nonhemorrhagic and non-flat-type, are less likely to become critically ill or require much supportive care and can be more easily managed outside the hospital. These people should be isolated and monitored at home or in a nonhospital facility, and smallpox vaccination should be provided to caregivers and household members. Patients with evidence of severe disease or presentations that suggest progression to severe disease is likely should be considered for admission to a negative-pressure environment with strict maintenance of Airborne Precautions.<sup>2, 6</sup>

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## INFECTION CONTROL

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

Clinicians should notify local public health authorities, their institution's infection control professional, and their laboratory of any suspected smallpox cases. Public health authorities may conduct epidemiological investigations and will implement disease control interventions to protect the public. Infection control professionals will implement infection control precautions within the healthcare setting. Laboratory personnel should take appropriate safety precautions.

Smallpox is transmissible from person to person by exposure to respiratory secretions and by direct contact with pox lesions and fomites. **Airborne and Contact Precautions** in addition to **Standard Precautions** should be implemented for patients with suspected smallpox and until all scabs have separated. Healthcare workers caring for patients with suspected smallpox should be vaccinated immediately.<sup>18, 19</sup>

### Decontamination

Survival of the virus in the environment is inversely proportional to temperature and humidity. All bedding and clothing of smallpox patients should be minimally handled to prevent re-aerosolization and autoclaved or laundered in hot water with bleach. Standard disinfection and sterilization methods are deemed to be adequate for medical equipment used with smallpox patients and cleaning surfaces and rooms potentially contaminated with the virus. Airspace decontamination (fumigation) is not required.<sup>2, 19</sup>

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## PEARLS AND PITFALLS

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1. The CDC has developed a number of clinical diagnostic tools to assist with the visual recognition, differential diagnosis, and initial management of suspected smallpox. These resources are available at: <http://www.bt.cdc.gov/agent/smallpox/index.asp>.<sup>20</sup>
2. Hemorrhagic smallpox is rare but can be confused with invasive meningococcal disease, rickettsial infections, or gram-negative sepsis because of the patient's ill appearance, petechial and purpuric lesions, and hemorrhagic manifestations.
3. Smallpox is most often transmitted through direct contact with respiratory droplets as a result of close (within 2 meters) or face-to-face contact. Viruses can also travel over greater distances as airborne particles, particularly in cases with coughing. Transmission has occasionally been linked to fomites carried on clothing or bedding that has been contaminated by dried respiratory secretions or draining skin lesions.

4. Since 2003, many health departments have established smallpox preparedness teams consisting of providers who have been pre-vaccinated against smallpox who can assist with the response to a suspected case of smallpox.

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## REFERENCES

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1. Damon I. Orthopoxviruses: Vaccinia (Smallpox Vaccine), Variola (Smallpox), Monkeypox, and Cowpox. In: Mandel GL, Bennett JE, Dolin R, eds. *Principles and practice of infectious diseases*. 6 ed. New York: Churchill Livingstone; 2005:1742-1751.
2. Henderson DA, Inglesby TV, Bartlett JG, et al. Smallpox as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *Jama*. Jun 9 1999;281(22):2127-2137.
3. Breman JG, Henderson DA. Diagnosis and management of smallpox. *N Engl J Med*. Apr 25 2002;346(17):1300-1308.
4. Moore ZS, Seward JF, Lane JM. Smallpox. *Lancet*. Feb 4 2006;367(9508):425-435.
5. Rotz LD, Cono J, Damon I. History of Smallpox and Bioterrorism. In: Mandel GL, Bennett JE, Dolin R, eds. *Principles and practice of infectious diseases*. 6 ed. New York: Churchill Livingstone; 2005:3612-3617.
6. CIDRAP. Smallpox: Current, comprehensive information on pathogenesis, microbiology, epidemiology, diagnosis, treatment, and prophylaxis. *Center for Infectious Disease Research and Policy, University of Minnesota*. Available at: <http://www.cidrap.umn.edu/cidrap/content/bt/smallpox/biofacts/smlpx-summary.html>.
7. CDC. Smallpox Vaccination, Information for Health Professionals. *Centers for Disease Control and Prevention*. Available at: [www.bt.cdc.gov/agent/smallpox/vaccination](http://www.bt.cdc.gov/agent/smallpox/vaccination).
8. Nishiura H, Eichner M. Infectiousness of smallpox relative to disease age: estimates based on transmission network and incubation period. *Epidemiol Infect*. Oct 2007;135(7):1145-1150.
9. CDC. Smallpox: Diagnosis/Evaluation. *Centers for Disease Control and Prevention*. Available at: <http://www.bt.cdc.gov/agent/smallpox/diagnosis/>.
10. CDC. Acute, Generalized Vesicular or Pustular Rash Illness Testing Protocol in the United States. *Centers for Disease Control and Prevention*. November 14. Available at: <http://emergency.cdc.gov/agent/smallpox/diagnosis/pdf/poxalgorithm11-14-07.pdf>.
11. Jordan R, Tien D, Bolken TC, et al. Single-dose safety and pharmacokinetics of ST-246, a novel orthopoxvirus egress inhibitor. *Antimicrob Agents Chemother*. May 2008;52(5):1721-1727.
12. Nishiura H, Schwehm M, Eichner M. Still protected against smallpox? Estimation of the duration of vaccine-induced immunity against smallpox. *Epidemiology*. Sep 2006;17(5):576-581.
13. FDA. Produce Approval Information: Smallpox (Vaccinia) vaccine. *U.S. Food and Drug Administration*. August 31. Available at: <http://www.fda.gov/cber/products/acam2000.htm>.
14. CDC. Notice to Readers: Newly Licensed Smallpox Vaccine to Replace Old Smallpox Vaccine. *MMWR*. February 29 2008;57(08):207-208.

15. Casey CG, Iskander JK, Roper MH, et al. Adverse events associated with smallpox vaccination in the United States, January-October 2003. *Jama*. Dec 7 2005;294(21):2734-2743.
16. Sejvar JJ, Labutta RJ, Chapman LE, Grabenstein JD, Iskander J, Lane JM. Neurologic adverse events associated with smallpox vaccination in the United States, 2002-2004. *Jama*. Dec 7 2005;294(21):2744-2750.
17. FDA. FDA approves new plasma-derived product to treat complications of smallpox vaccination. *U.S. Food and Drug Administration*. February 18. Available at: <http://www.fda.gov/bbs/topics/ANSWERS/2005/ANS01341.html>.
18. CDC. Guide F: Environmental Control of Smallpox Virus, Smallpox Response Plan. *Centers for Control and Prevention*. March 20. Available at: [www.bt.cdc.gov/agent/smallpox/response-plan/files/guide-f.doc](http://www.bt.cdc.gov/agent/smallpox/response-plan/files/guide-f.doc).
19. Siegel JD, Rhinehart E, Jackson M, Chiarello L, HICPAC. Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings, 2007. *Centers for Disease Control and Prevention*. Available at: [http://www.cdc.gov/ncidod/dhqp/gl\\_isolation.html](http://www.cdc.gov/ncidod/dhqp/gl_isolation.html).
20. CDC. Smallpox. *Centers for Disease Control and Preventino*. Available at: <http://www.bt.cdc.gov/agent/smallpox/index.asp>.