



Report immediately

Smallpox

Disease plan

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Last updated: October 18, 2023 by Jade Murray-Thompson

Questions about this disease plan?

Contact the Utah Department of Health and Human Services Office of Communicable Diseases: 801-538-6191.

Smallpox critical clinician information

Smallpox is considered eradicated. All other diagnoses should be considered. If a true case is suspected this is of extreme concern and should be reported immediately.

Clinical evidence

Signs/symptoms

- **Ordinary smallpox²**
 - Prior to smallpox vaccine, ordinary smallpox was the most common form, accounting for over 85% of all cases
 - Severe prodromal illness with high fever (101°F-105°F)
 - Enanthem in mouth or on tongue
 - Rash which progresses through successive stages of macules, papules, vesicles, pustules, and then crusted scabs. The center of the vesicles will tend to dimple, a presentation called “umbilication.” The rash lasts around 14 days
- **Sequelae²**
 - Pockmarks and scarring are the most common complications.
 - They are a consequence of virus-mediated necrosis and destruction of sebaceous glands.
 - Scarring may occur all over the body but most scars are found on the face, which has the highest concentration of sebaceous glands.
 - Blindness happens rarely and is the result of corneal scarring following keratitis or corneal ulcerations. Generally, it occurs when malnutrition and/or an opportunistic infection are present.
 - Encephalitis
 - Osteomyelitis
 - Stillbirths and spontaneous abortions
 - Infertility (obstructive azoospermia) in males
- **Modified smallpox²**
 - Less severe prodromal illness
 - Rash with fewer, more superficial lesions than those seen in ordinary smallpox; rash lasts around 10 days
- **Flat (malignant) smallpox²**
 - Skin lesions develop slowly, merge together, and remain flat and soft (often described as “velvety” to the touch)
 - Toxemia
- **Hemorrhagic smallpox²**
 - More severe prodromal symptoms with high fever, severe headache, and abdominal pain
 - Development of a dusky erythema after illness onset, followed by petechiae and skin and mucosal hemorrhages
 - Toxemia or death

<ul style="list-style-type: none">● Variola minor²<ul style="list-style-type: none">● Less severe symptoms with shorter duration● Variola sine eruptione²<ul style="list-style-type: none">● Asymptomatic or brief rise in temperature, headache, and influenza-like symptoms
Period of communicability ² <ul style="list-style-type: none">● Generally contagious for 3 weeks, from the development of the earliest lesions in the mouth to the disappearance of all scabs; the first week of rash illness is the most infectious period
Incubation period ¹ <ul style="list-style-type: none">● Average 10–14 days; range 7–19 days
Mode of transmission <ul style="list-style-type: none">● Respiratory droplets● May occur through direct contact with an infected person or contact with an object soiled with infectious particles
Laboratory testing
Type of lab test <ul style="list-style-type: none">● PCR
Type of specimens <ul style="list-style-type: none">● Vesicular or pustular fluid
Treatment recommendations
Type of treatment <ul style="list-style-type: none">● Treatment for smallpox patients generally involves supportive care. There is no proven treatment for smallpox disease but the following can be used:<ul style="list-style-type: none">○ Vaccination with replication-competent smallpox vaccines (i.e., ACAM2000 and APSV) can prevent or lessen the severity of disease if given within 2 to 3 days of the initial exposure. They may decrease symptoms if given within the first week of exposure.²○ Antivirals for smallpox patients involve 3 primary antiviral therapies which have shown effectiveness against orthopoxviruses including variola (the virus that causes smallpox) in animals and <i>in vitro</i> studies.^{9,10}<ul style="list-style-type: none">■ Tecovirimat■ Brincidofovir■ Cidofovir
Prophylaxis <ul style="list-style-type: none">● Vaccination¹¹● ACAM2000® and JYNNEOS™ (also known as Imvamune or Imvanex) are the only 2 licensed smallpox vaccines in the United States.● Aventis Pasteur Smallpox Vaccine (APSV) is an investigational vaccine that may be used in a smallpox emergency under the appropriate regulatory mechanism (i.e., Investigational new drug application [IND] or Emergency use authorization [EUA]).

Isolation requirements

Isolation of case⁶

- Standard, contact, and airborne precautions, and use of appropriate personal protective equipment (PPE) until lesions have dried and crusts have separated.

Case contact management

- Contacts with symptoms should be placed under quarantine for 18 days from the time of the last contact or 14 days from successful vaccination (whichever comes first). See contact sections for more information.

Infection control procedures

- Personnel should wear personal protective equipment (PPE) and adhere to standard, contact, and airborne precautions.
 - Gloves and gown
 - Masking (fit-tested NIOSH-approved N95 or higher level respirator for healthcare personnel)
 - Face protection (goggles or face shield)

Why is smallpox important to public health?

Thousands of years ago, variola virus (smallpox virus) emerged and began causing illness and death in human populations, with smallpox outbreaks occurring from time to time. Thanks to the success of vaccination, the last natural outbreak of smallpox in the United States occurred in 1949.⁴ In 1980, the World Health Assembly declared smallpox eradicated (eliminated), and no cases of naturally-acquired smallpox have happened since. Smallpox research in the United States continues and focuses on the development of vaccines, drugs, and diagnostic tests to protect people against smallpox in the event that it is used as an agent of bioterrorism, however only 2 WHO-designated sites have actual variola virus that can be used for research: the Centers for Disease Control and Prevention, Atlanta, Georgia, United States; and the Russian State Centre for Research on Virology and Biotechnology, Koltsovo, Novosibirsk Region, Russian Federation.⁴

The global eradication of smallpox has been one of the greatest achievements of modern public health.⁴ Although there have been no reported cases of naturally-occurring smallpox since 1977, public health is still interested in this virus because of the concern regarding smallpox as a potential agent of bioterrorism. A single confirmed case of smallpox today would likely be the result of an intentional act and would be considered a public health emergency.⁴

Disease and epidemiology

Clinical description

Smallpox infection typically begins with a prodromal illness characterized by a high fever (101–105°F), malaise, headache, backache, and abdominal pain.² This prodromal period typically lasts 2–5 days and often leaves the patient too sick to carry on with normal activities. A rash begins to develop after the prodromal period. The rash first appears as an enanthem, with tiny red spots developing inside the mouth or on the tongue that are often not noticeable.² These spots then change into sores that break open and spread large amounts of the virus into the mouth and throat. Once the sores in the mouth start breaking down, a rash appears on the skin, starting on the face and spreading to the arms and legs. The rash then spreads to the hands and feet. Usually, it spreads to all parts of the body within 24 hours.² The rash follows a characteristic “centrifugal” pattern, with the highest concentration of lesions on the face and distal extremities, including the palms of the hands and soles of the feet. This early rash period lasts about 4 days. Over the next 7–10 days the rash slowly progresses through successive stages of macules, papules, vesicles, pustules, and then crusted scabs.² The center of the vesicles will tend to dimple, a presentation called “umbilication.” Between day 7 and day 10 of the rash, the pustules reach their maximum size. The pustules are deeply embedded in the skin and give the feeling of small beads underneath

the skin. Three to 4 weeks after the rash onset, the scabs begin to fall off leaving depigmented, often pitted, scars.²

Before smallpox was eradicated, it was a serious infectious disease caused by the variola virus.

- **Variola major** is the more severe form of the disease and can have 4 very different clinical presentations:
 - o **Ordinary smallpox:** Ordinary smallpox is the most common form and accounted for more than 85% of all cases prior to smallpox eradication. This form follows the clinical presentation outlined above.²
 - o **Modified smallpox:** Modified-type smallpox occurs in previously vaccinated individuals. In this type, the prodrome stage may still consist of severe headache, backache, and fever, and may last as long as in ordinary smallpox. However, once the skin lesions appear, they generally evolve more quickly, and crusting completes within 10 days as opposed to 14 with ordinary smallpox. There may also be fewer, more superficial lesions than those seen in ordinary smallpox. Patients also do not tend to have a fever during the evolution of the rash.²
 - o **Flat (malignant) smallpox:** Flat-type—or malignant—smallpox is very rare, and is characterized by intense toxemia. It occurs more frequently in children. In contrast to ordinary smallpox, the skin lesions in this type develop slowly, merge together, and remain flat and soft (often described as “velvety” to the touch). They never progress to the pustular stage. The appearance of the lesions suggests a deficient cellular immune response to variola virus, and the majority of flat-type smallpox cases are fatal. If the patient survives, the lesions gradually disappear without forming scabs. Prior vaccination appears to protect against flat-type smallpox.²
 - o **Hemorrhagic smallpox:** Hemorrhagic-type smallpox can occur among all ages and in both sexes, but is more common in adults. Pregnant women appear to be more susceptible. The underlying biological reasons for this type are unclear. Prior vaccination is not protective. This type is differentiated from ordinary smallpox by:
 - Shorter incubation period
 - More severe prodromal symptoms with high fever, severe headache, and abdominal pain
 - Development of a dusky erythema after illness onset, followed by petechiae and skin and mucosal hemorrhages
 - Death usually occurs by day 5 or day 6 of the rash, often before characteristic smallpox lesions develop. Death results from a profound toxemia, leading to multi-organ failure.²

- **Variola minor** is a much less severe form of the disease with a shorter duration.²
- **Variola sine eruptione** or subclinical infection without a rash can occur among vaccinated contacts of a recent smallpox case or in infants with maternal antibodies. Affected persons are asymptomatic or have a brief rise in temperature, headache, and influenza-like symptoms; the transmission of clinical smallpox has not been documented with variola sine eruptione.²

Causative agent

Smallpox is caused by the variola virus, a DNA virus and a member of the *Poxviridae* family (genus *Orthopoxvirus*). The 2 clinical forms of the disease are caused by different strains of the virus, variola major and variola minor.

Differential diagnosis

Table 1. Diseases and syndromes most commonly confused with smallpox⁵

Condition	Clinical clues
Varicella (Chickenpox)	Most common in children < 10 years; children usually do not have a viral prodrome
Disseminated herpes zoster	Immunocompromised or elderly persons; rash looks like varicella and usually begins in dermatomal distribution
Impetigo (caused by <i>Streptococcus pyogenes</i> or <i>Staphylococcus aureus</i>)	Honey-colored crusted plaques with bullae are classic but may begin as vesicles; regional not disseminated rash; patients usually not ill
Drug eruptions	Exposure to medications; rash often generalized
Contact dermatitis	Itching; contact with possible allergens; rash often localized in pattern suggesting external contact
Erythema multiforme minor	Target, “bull’s eye”, or iris lesions; often follows recurrent herpes simplex virus infections; may involve hands and feet
Erythema multiforme major (Stevens-Johnson syndrome)	Major form involves mucous membranes and conjunctivae; may be target lesions or vesicles
Enterovirus infection (particularly hand, foot, and mouth disease)	Summer and fall; fever and mild pharyngitis 1–2 days before rash onset; lesions initially maculopapular but evolve into whitish-gray, tender, flat, often oval vesicles; peripheral distribution
Disseminated herpes simplex	Lesions indistinguishable from varicella; immunocompromised host
Scabies; insect bites	Itching is a major symptom; patient is not febrile and is otherwise well
Molluscum contagiosum	May disseminate in immunosuppressed persons; can occur anywhere on the body; presents as small, raised, and usually white, pink, or flesh-colored lesions with a dimple or pit in the center

Mpox (previously known as monkeypox)	The main difference between mpox and smallpox is that mpox causes swelling in the lymph nodes (lymphadenopathy) while smallpox does not. Swelling of the lymph nodes may be generalized (involving many different locations on the body) or localized to several areas (e.g., neck and armpit).
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CDC has developed criteria that can be used to evaluate suspected smallpox cases and to categorize patients into high, moderate, or low risk for smallpox. There are 3 major and 5 minor smallpox criteria:

Major criteria

1. Febrile prodrome occurring 1 to 4 days before rash onset:
 - a. Fever $\geq 101^{\circ}\text{F}$ (38.3°C) **AND** at least 1 of the following:
 - i. prostration
 - ii. headache
 - iii. backache
 - iv. chills
 - v. vomiting
 - vi. severe abdominal pain
2. Classic smallpox lesions: deep-seated, firm/hard, round, well-circumscribed vesicles or pustules. As they evolve, lesions may become umbilicated or confluent.
3. Lesions in the same stage of development (e.g., all are vesicles or all are pustules) on any **1** part of the body (e.g., the face, arms).⁵

Minor criteria

1. Centrifugal distribution of rash: greatest concentration of lesions on face and distal extremities
2. First lesions on the oral mucosa/palate, face, or forearms
3. Severity: Patient appears toxic or moribund
4. Slow rash evolution: lesions evolved from macules to papules to pustules over days (each stage lasts 1 to 2 days)
5. Lesions on the palms and/or soles⁵

A person is considered at **high risk** for smallpox if they meet all 3 major criteria. Take immediate action to make sure contact precautions and respiratory isolation are implemented. These patients should be reported to local and/or state health authorities immediately. If possible, take photographs and consult with dermatology and/or infectious disease experts.⁵ If the patient is still considered to be at high risk after the consultation, the Utah Department of Health and Human Services will immediately report the case to CDC and arrangements will be made for laboratory

testing for smallpox virus. Do not proceed with laboratory testing for other diagnoses until smallpox has been ruled out.⁵

A person considered at **moderate risk** for smallpox must have a febrile prodrome and either 1 other major criterion or 4 or more minor criteria. These patients should be isolated and quickly evaluated to determine the cause of the illness. Persons classified as high or moderate risk should be seen in consultation with a specialist in infectious diseases and/or dermatology as soon as possible.⁵

Any person who did not have a febrile prodrome is considered at **low risk**, as are persons who had a febrile prodrome and fewer than 4 minor criteria. These patients should be managed as clinically indicated.⁵

Figure 1. Risk of smallpox⁵

High risk of smallpox Report immediately

1. Febrile prodrome (defined above) **AND**
2. Classic smallpox lesion (defined above) **AND**
3. Lesions in same stage of development (defined above)

Moderate risk of smallpox Urgent evaluation

1. Febrile prodrome **AND**
 2. One other **MAJOR** smallpox criterion (defined above)
- OR**
1. Febrile prodrome **AND**
 2. ≥ 4 **MINOR** smallpox criteria (defined above)

Low risk of smallpox Manage as clinically indicated

1. No febrile prodrome
- OR**
1. Febrile prodrome **AND**
 2. < 4 **MINOR** smallpox criteria (defined above)
-

Laboratory identification

Variola virus can be detected in vesicular or pustular fluid by culture or PCR. The diagnosis of an *Orthopoxvirus* infection can be made rapidly by electron microscopic examination of dried vesicular fluid on a microscope slide, but does not distinguish between vaccinia, variola and other poxvirus infections. PCR and culture testing will confirm the diagnosis.^{6a}

Laboratory testing for smallpox is warranted only once a case is classified as high risk. For cases that meet the moderate risk classification, the most important laboratory procedure is varicella-zoster virus testing.⁸

NOTE: The Utah Public Health Laboratory (UPHL) is capable of testing low, moderate, and high-risk specimens to rule out smallpox. Testing for smallpox must be coordinated with the Utah Department of Health and Human Services (DHHS), who will work with UPHL and CDC to determine the best course of action.

Treatment

There is no proven treatment for smallpox disease. Prevention is achieved through vaccination. Smallpox vaccines and antivirals can be used for purposes of controlling a smallpox outbreak.^{9,10}

Case fatality

- **Variola major** has a case fatality rate of 30–50% in unvaccinated persons.
- **Hemorrhagic** and **flat type smallpox** are usually fatal.
- **Variola minor** has an overall case fatality rate of less than 1%.

Reservoir

Humans are the only known reservoir for the variola virus.

Transmission

Transmission occurs primarily through the spread of respiratory droplets. However, transmission could also occur through direct contact with an infected person or contact with an object soiled with infectious particles.

Susceptibility

Routine vaccination in the United States for smallpox stopped in 1972. Those who have previously been vaccinated are most likely still immune; however, susceptibility among the unvaccinated is universal. Selected military, research, and medical personnel are immune to the disease because of vaccination.

Mpox (formerly known as monkeypox) is caused by a virus that is related to the virus that causes smallpox. JYNNEOS is a 2-dose vaccine developed to protect against mpox and smallpox infections. People who have received both doses of the vaccine during the 2022 mpox outbreak may have immunity against smallpox.

Incubation period

The incubation period ranges from 7–19 days; commonly 10–14 days to onset of illness and 2–4 days more to onset of rash.¹

Period of communicability

An infected person is generally contagious for 3 weeks, from the time the earliest lesions develop in the mouth to when all scabs disappear. The first week of rash illness is the most infectious period.

Epidemiology

The last case of naturally-acquired smallpox in Utah, the United States, and the world occurred in 1945, 1949, and 1977 (in Somalia), respectively. The last 2 laboratory-associated cases of smallpox in the world occurred in 1978 in England and were associated with a breach in laboratory safety. In 1980, global eradication of smallpox was certified by the World Health Organization. Currently, 2 WHO reference laboratories (the CDC and the Institute of Virus Preparations in Moscow, Russia) hold variola virus stocks under strict security. All laboratory work with the smallpox virus is done under strict biosafety level 4 procedures.

Public health control measures

Public health responsibility

- Immediately notify the DHHS epidemiologist on call or the state epidemiologist to discuss the situation and assess risk of smallpox.
- Rapidly investigate all suspect cases of disease and fill out and submit appropriate disease investigation forms.
- Make sure appropriate testing protocols are followed.
- Rapidly investigate all potentially exposed persons.
- Identify sources of exposure and stop further transmission.
- Identify cases and clusters of human illness that may be associated with a bioterrorism incident.

Prevention

Environmental measures

If a patient presents to an emergency department, clinic, or doctor's office with an acute generalized vesicular or pustular rash illness and there is concern for smallpox, take care to decrease the risk of disease transmission. Patients should not be left in common waiting areas. The patient should be assessed to determine whether there is a high, medium, or low risk of smallpox.^{3,7}

1. In a doctor's office or clinic, the patient should be placed immediately in a private room with the door kept shut.
2. When admitted or while being held for observation, the facility should institute appropriate airborne isolation and contact precautions and should alert the infection prevention/control department. The patient should be placed in a private room at negative pressure to the rest of the facility (airborne infection isolation). Keep the door closed at all times, except when staff or the patient must enter or exit.
3. Staff and visitors, regardless of vaccination status, should wear properly fitted respirators (N95 or higher level of protection), gloves, and gowns.
4. The patient should wear a surgical mask whenever they must be outside of the negative pressure isolation room and must be gowned or wrapped in a sheet so the rash is fully covered.⁷

Chemoprophylaxis

Vaccination after exposure to smallpox has reduced the rate of secondary cases in households by up to 91% when compared to unvaccinated household members. Secondary attack rates were lowest among contacts who were vaccinated within 7 days of their exposure. Contacts who did develop disease usually had much milder symptoms.^{3,7}

Vaccine

The smallpox vaccine is made from a related *Orthopox* virus—the vaccinia virus.¹¹ The vaccine is highly effective at producing immunity against smallpox when administered effectively prior to exposure. Smallpox vaccine production stopped in the early 1980s and current supplies of smallpox vaccine are limited. However, recent studies show that vaccines stored in the 1960s and 1970s still have excellent potency, even when diluted. Imvamune is another vaccine formulation of a modified vaccinia that is under study as a future generation smallpox vaccine. It is a highly attenuated vaccinia virus with an excellent safety profile, even in immunocompromised people.³

Because the smallpox vaccine is a live-virus vaccine, vaccinia virus is present at the site of vaccination beginning about 4 days after vaccination. Viral shedding from the vaccination site usually occurs 4–14 days after vaccination, but vaccinia can be recovered from the site until the crust separates from the skin. Therefore, appropriate hand hygiene and/or keeping the vaccination site covered with a bandage is necessary to prevent transmission of the virus to contacts of the vaccine.³

- ACAM2000® and JYNNEOS™ (also known as Imvamune or Imvanex) are the only 2 licensed smallpox vaccines in the United States.¹¹
- Aventis Pasteur Smallpox Vaccine (APSV) is an investigational vaccine that may be used in a smallpox emergency under the appropriate regulatory mechanism (i.e., Investigational new drug application [IND] or Emergency use authorization [EUA]).¹¹

Individuals who were vaccinated with JYNNEOS as part of the mpox response (2022-2023) are expected to be protected against smallpox. JYNNEOS is a 2-dose vaccine developed to protect against mpox and smallpox infections. People need to get both doses of the vaccine for the best protection against mpox and smallpox infections. The second dose should be given 4 weeks after the first dose. Additional information can be found here:

<https://www.cdc.gov/poxvirus/mpox/vaccines/index.html>

Isolation and quarantine requirements

Isolation: Cases should be placed on standard, contact, and airborne isolation until lesions are dry and crusts separate.⁶

Healthcare settings: Cases should be placed on standard, contact, and airborne isolation. The patient should be placed in a private, airborne infection isolation room with negative pressure ventilation with high-efficiency particulate air filtration. Cases should remain isolated until lesions are dry and crusts separate.^{6,7}

Quarantine: Start contact tracing activities as soon as possible after a patient has been diagnosed with smallpox.

- Interview the patient—review the patient’s travel history for the previous 2 to 3 weeks. If more people are diagnosed with smallpox, this information will help determine a common source of exposure. If you can identify the source of exposure it will help to estimate the number of people who may be at risk for illness. Also identify other people the patient was in close contact with since the time their symptoms began (when the patient became infectious).
- Identify contacts of the patient and their own close household contacts—interview and assess contacts for symptoms. If any show symptoms of smallpox, arrange for their

transportation to the healthcare facility in the community designated to care for suspected smallpox cases.

- Vaccinate contacts and their household contacts—give all contacts and their respective close household contacts information about where and when they can get the smallpox vaccination. Arrange for transportation to the place to receive the vaccination, if necessary. Provide a time and place for a [vaccine “take” reading 6 to 8 days](#) after vaccination. Also provide vaccinated contacts with a way to report their temperatures to designated public health officials.
- Monitor vaccinated contacts for 14 to 18 days—establish a dedicated phone line or other method for vaccinated contacts to report their temperature readings each day (fever surveillance). Contacts who do not have symptoms should take their temperatures twice every day (every 12 hours) for 18 days after their last contact with the smallpox patient, or 14 days after being vaccinated, whichever comes first. Contacts should report their temperatures to the designated public health official daily. If the contact develops a fever $\geq 101^{\circ}\text{F}$ (38.3°C) for 2 successive readings, they should notify health department personnel and remain at home until transportation to the healthcare facility in the community designated to care for suspected smallpox cases can be arranged. Designate personnel to follow up with contacts who do not report regularly. Provide contacts with information about how to seek care for and report adverse events to vaccination.
- Monitor unvaccinated contacts for 18 days—any contact or other person deemed as high risk for developing smallpox who refuses vaccination should undergo fever surveillance and remain at home for 18 days after their last known exposure to the smallpox virus.⁶

Case investigation

Reporting

If smallpox were to recur in the United States, or elsewhere, the most likely circumstances of reintroduction are generally accepted to be:

- An unintentional infection in a laboratory. Currently there are only 2 WHO-approved smallpox virus research and repository laboratories. However, there is speculation that stockpiles of variola virus may exist elsewhere.
- A bioterrorist attack involving deliberate infection of a person.
- A bioterrorist attack involving intentional release of smallpox virus into the environment.

Any suspected or confirmed case of smallpox, or of any potential exposure to an agent which could cause smallpox, must be reported to the DHHS Office of Communicable Diseases immediately at 1-888-EPI-UTAH. Adverse events following smallpox vaccination are also reportable.

Table 2. Criteria for reporting a case of smallpox to public health authorities

Criterion	Reporting		
<i>Clinical evidence</i>			
Fever ≥101°F (38.3°C)	N	N	N
Fever occurs 1–4 days before rash onset		N	N
Prostration	O	O	O
Headache	O	O	O
Backache	O	O	O
Chills	O	O	O
Vomiting	O	O	O
Severe abdominal pain	O	O	O
Generalized vesicular rash		N	
Generalized pustular rash			N
Identifiable cause of clinical findings		A	A
Death certificate lists smallpox as a cause of death or a significant condition contributing to death	S		
<i>Laboratory evidence</i>			
Polymerase chain reaction (PCR) identification of variola DNA in a clinical specimen	S*		
Isolation of smallpox (variola) virus from a clinical specimen	S*		
Polymerase chain reaction (PCR) identification of variola DNA in an isolate from a clinical specimen	S*		
<i>Epidemiological evidence</i>			
Contact (≤ 2 meters) for (≥ 3 hours) with a laboratory confirmed case of smallpox	N		

Notes:

S = This criterion alone is sufficient to report a case

N = This criterion in conjunction with all other “N” and any “O” criteria in the same column is required to report a case. A number following an “N” indicates that this criterion is only required for a specific clinical presentation (see below).

O = At least one of these “O” criteria in each category in the same column (e.g., clinical presentation and laboratory findings)—in conjunction with all other “N” criteria in the same column—is required to report a case. A number following an “O” indicates that this criterion is only required for a specific clinical presentation (see below).

A = This criterion must be absent (i.e., NOT present) for the case to meet the case definition.

*A requisition for any of the “S” or “N” laboratory tests is sufficient to meet the reporting criteria

1 = flat type smallpox

2 = hemorrhagic smallpox

3 = variola sine eruptione

Case definition

Smallpox (pre-event definition): **This definition is to be used for pre-event surveillance. It is more sensitive and less specific than the definition developed by CSTE, which is to be used only for post-event surveillance.*

Clinical case definition

An illness with acute onset of fever $\geq 101^{\circ}\text{F}$ (38.3°C) followed by a rash characterized by firm, deep seated vesicles or pustules in the same stage of development without another apparent cause.¹²

Laboratory criteria

- Polymerase chain reaction (PCR) identification of variola DNA in a clinical specimen, OR
- Isolation of smallpox (variola) virus from a clinical specimen *with* variola PCR confirmation

NOTE: Laboratory diagnostic testing for variola virus should be conducted in a CDC Laboratory Response Network (LRN) laboratory using LRN-approved PCR tests and protocols for variola virus. Initial confirmation of a smallpox outbreak requires additional testing at CDC.

NOTE: The importance of case confirmation using laboratory diagnostic tests differs depending on the epidemiological situation. Because of the low predictive value of a positive lab test result in the absence of a known smallpox outbreak, in the pre-outbreak (pre-event) setting, laboratory testing should be reserved for cases that meet the clinical case definition and are thus classified as being a potential high risk for smallpox according to the rash algorithm poster (<https://www.cdc.gov/smallpox/pdfs/smallpox-diagnostic-algorithm-poster-2-pages.pdf>).

Case classification

Suspect: A case with a febrile rash illness, with fever preceding development of rash by 1–4 days.

Probable: A case that meets the clinical case definition, or a case that does not meet the clinical case definition but is clinically consistent with smallpox and has an epidemiological link to a confirmed case of smallpox. Examples of clinical presentations of smallpox that would not meet the ordinary type (pre-event) clinical case definition are: a) hemorrhagic type, b) flat type, and c) variola sine eruptione.¹²

Confirmed: A case of smallpox that is laboratory confirmed, or a case that meets the clinical case definition that is epidemiologically linked to a laboratory confirmed case.¹²

Smallpox (2010) Post-event definition: **This definition is to be used ONLY during post-event surveillance.*

Clinical case definition

An illness with acute onset of fever $\geq 101^{\circ}\text{F}$ (38.3°C) followed by a rash characterized by firm, deep seated vesicles or pustules in the same stage of development without another apparent cause.¹²

Clinically consistent cases are those presentations of smallpox that do not meet this classical clinical case definition: a) hemorrhagic type, b) flat type, and c) *variola sine eruptione*. A detailed clinical description is available on the CDC website

(<https://www.cdc.gov/smallpox/clinicians/clinical-disease.html>).

Laboratory criteria for diagnosis

- Polymerase chain reaction (PCR) identification of variola DNA in a clinical specimen, OR
- Isolation of smallpox (variola) virus from a clinical specimen (Level D laboratory only; confirmed by variola PCR).

NOTE: Indications for laboratory testing of patients with suspected smallpox should be followed as described in detail in the CDC Smallpox Response Plan

(<https://www.cdc.gov/smallpox/lab-personnel/index.html>).

Case classification

Suspect: A case with a generalized, acute vesicular or pustular rash illness with fever preceding development of rash by 1–4 days.

Probable: A case that meets the clinical case definition, or a clinically consistent case that does not meet the clinical case definition and has an epidemiological link to a confirmed case of smallpox.

Confirmed: A case of smallpox that is laboratory confirmed, or a case that meets the clinical case definition that is epidemiologically linked to a laboratory confirmed case.

Exclusion criteria

A case may be excluded as a suspect or probable smallpox case if an alternative diagnosis fully explains the illness or appropriate clinical specimens are negative for laboratory criteria for smallpox.

Table 3. Criteria to determine whether a smallpox case is classified.

Criterion	Confirmed			Probable			Suspect	
<i>Clinical evidence</i>								
Fever ≥101°F (38.3°C)	N	N	N	N	N	N	N	N
Fever occurs 1–4 days before rash onset	N	N	N	N	N	N	N	N
Prostration	O	O	O	O	O	O	O	O
Headache	O	O	O	O	O	O	O	O
Backache	O	O	O	O	O	O	O	O
Chills	O	O	O	O	O	O	O	O
Vomiting	O	O	O	O	O	O	O	O
Severe abdominal pain	O	O	O	O	O	O	O	O
Rash with deep-seated, firm or hard, round, well-circumscribed vesicles or pustules; as they evolve, lesions may become umbilicated or confluent	N	N	N	N				
Rash with <i>flat, soft, focal</i> lesions; as they evolve, lesions may become confluent and portions of skin may slough					N1			
Lesions on any ONE part of the body (e.g., the face, arms) are all in the same stage of development (i.e., all are vesicles, or all are pustules)	N	N	N	N				
<i>Widespread hemorrhage</i> in skin and mucous membranes					N2			
Generalized vesicular rash						N		
Generalized pustular rash							N	
Identifiable cause of clinical findings			A	A	A	A	A	A
<i>Laboratory evidence</i>								
Polymerase chain reaction (PCR) identification of variola DNA in a clinical specimen	N			A		A	A	
Isolation of smallpox (variola) virus from a clinical specimen		N		A		A	A	
Polymerase chain reaction (PCR) identification of variola DNA in an isolate from a clinical specimen		N		A		A	A	
Detection of orthopox-reactive IgM antibodies, 3–56 days post symptom onset					N3			
<i>Epidemiological evidence</i>								
Contact (≤ 2 meters) for (≥ 3 hours) with a laboratory confirmed case of smallpox			N		N	N		
Contact (≤ 2 meters) with a confirmed, probable, or suspected case of smallpox								
Contact with smallpox infected bodily fluids or contaminated objects such as bedding or clothing								
Worker in a laboratory that contains smallpox virus								

Notes:

N = This criterion in conjunction with all other “N” and any “O” criteria in the same column is required to confirm a case. A number following an “N” indicates that this criterion is only required for a specific clinical presentation (see below).

O = At least one of these “O” criteria in each category in the same column (e.g., clinical presentation and laboratory findings)—in conjunction with all other “N” criteria in the same column—is required to confirm a case. A number following an “O” indicates that this criterion is only required for a specific clinical presentation (see below).

A = This criterion must be absent (i.e., NOT present) for the case to meet the case definition.

*A requisition for any of the “S” or “N” laboratory tests is sufficient to meet the reporting criteria

1 = flat type smallpox

2 = hemorrhagic smallpox

3 = *variola sine eruptione*

Case investigation process

1. The local health department (LHD) will be asked to investigate any case who lives within their community, including gathering the following information into UT-NEDSS/EpiTrax:
 - a. The case’s name, age, address, phone number, status (e.g., hospitalized, at home, deceased), and parent/guardian information, if applicable
 - b. The name and phone number of the hospital where the case is or was hospitalized
 - c. The name and phone number of the attending physician
 - d. The name and phone number of the infection control official at the hospital
 - e. If the patient was seen by a healthcare provider before hospitalization or seen at more than 1 hospital, these names and phone numbers.
 - f. Clinical information including symptoms and date of symptom onset
 - g. Any available diagnostic laboratory test information
2. Specimen collection, transport, testing, and submission for patients with suspected smallpox

Outbreaks

As smallpox no longer exists as a naturally-acquired disease, a single laboratory confirmed case of smallpox would be considered an outbreak and would warrant an extensive response involving many different federal, state, and local agencies.

Identifying case contacts

For the purposes of smallpox surveillance and case investigation, contacts are defined as follows:

Contact: A person who has been exposed to the risk of infection

- **Primary contact:** A person with contact to a confirmed, probable, or suspect case of smallpox during the infectious period. Primary contacts include both household and non-household contacts. Risks of smallpox transmission increase with longer duration of face-to-face contact of less than 2 meters (≤ 6.5 feet).
- **Secondary contact:** A household member of a primary contact, a non-household contact, and a person who works in the household of a primary contact.

Priority categories for contacts, from highest priority to lowest, are as follows:

1. Case's household family members and others who spend 3 or more hours in the household since the case's onset of fever.
2. Non-household members with contact of 2 meters or less (≤ 6.5 feet) with a case who has a rash for 3 or more hours.
3. Non-household members who spend less than 3 hours with a case who has a rash and are within 2 meters or less (< 6.5 feet) of the case.
4. Non-household members who have any contact with a case who has a rash for 3 or more hours.
5. Non-household members who have any contact with a case who has a rash for less than 3 hours.

Case contact management

The best way to protect those at greatest risk for contracting the disease is to vaccinate and monitor contacts of cases and family contacts of contacts. Those 2 things will also form a buffer of immune individuals to prevent the spread of disease. Large-scale vaccination in potentially exposed communities may be necessary, although it is crucial that cases be identified and isolated. Large-scale vaccination might also be applied to unaffected communities to protect against further spread of smallpox, any additional releases, and to build the public's confidence in protection and their ability to return to normal activities.

Contact tracing

Contact tracing should include the following steps:

1. Trace each contact whose name, address, and/or telephone number is known.

2. Use work and school contact numbers, telephone directories, voting lists, neighborhood interviews, site visits, "hangouts," etc., to trace contacts when contact information is unknown or incomplete. If contacts cannot be found through these mechanisms, other sources may need to be considered for notification of potential contacts (such as media announcements).
3. Locate and interview each primary contact to confirm contact with the suspect, probable, or confirmed smallpox case, the presence or absence of symptoms in the contact (fever and/or rash), and to identify additional contacts that may not have been listed by the case.
4. Identify household contacts of each primary contact of the smallpox case (secondary contacts).
5. Arrange for immediate vaccination of each primary contact and their household contacts (secondary contacts). Contacts in the household can either be vaccinated (if this is feasible given vaccine supply, security issues, and resources), or a vaccination ticket can be provided, with identifying information and a designated vaccination facility for the contact(s) to attend as soon as possible. It is extremely important for smallpox outbreak control to prioritize the vaccination of contacts. In the past, when vaccination was done in the household, the task was given priority over transportation of a case to an isolation facility.
6. If the primary contact is symptomatic with fever or rash, arrangements should be made for prompt vaccination and transportation to get the contact to a Type C facility (capable of isolating contagious individuals) or other designated evaluation site for medical evaluation to rule out smallpox. Contacts who have symptoms should be counseled, interviewed, and reported as suspect cases using the appropriate smallpox surveillance (case reporting) form, and their contacts should be identified, interviewed, and vaccinated as soon as possible.
7. If the primary contact does not have a fever or rash, vaccinate or arrange for prompt vaccination, and place the contact under surveillance (quarantine) so if or when the contact develops a fever or rash, the contact is immediately isolated and evaluated and does not expose other people to smallpox (see #8 below).
8. If a household member cannot be vaccinated because of contraindications, the household member should be instructed to avoid physical contact with the primary contact until the incubation period of the disease has passed (19 days) or all vaccinated people in the household are non-infectious for vaccinia virus (after the scab at the vaccine site has separated, 14–21 days after vaccination).
9. Each household contact should be given a vaccination ticket and instructed to attend a designated vaccination clinic site as soon as possible.
10. If any contacts have left the state, contact tracers should notify the supervisor responsible for out-of-state contacts. The supervisor will then notify the appropriate authorities.

Surveillance (monitoring) of health status and vaccine “take” of contacts

Surveillance of contacts of cases of smallpox will be conducted for early signs of smallpox disease (fever on 2 consecutive days and/or rash) and for vaccine “take.” Contacts will be provided with a health department phone number to call if they develop any of the severe vaccine adverse reactions shown on the Vaccine Information Statement.

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Version control

Update July 2017: Updated Format. Added Critical clinician information section. Updates to sections: Clinical description, Differential diagnosis, Public health responsibility.

Update October 2023: Updated to DHHS format. Added Critical clinician information section. Updates to sections: Clinical description, Differential diagnosis, Public health responsibility. Added Citations for EAG approval.

UT-NEDSS/EpiTrax minimum/required fields by tab

Demographic

- First name
- Last name
- Date of birth
- County
- Birth sex
- Race
- City
- Street name
- ZIP code
- Ethnicity
- Area code
- Phone number

Clinical

- Date diagnosed
- Date of death
- Died
- Disease
- Onset date
- Clinician name
- Clinician phone

Laboratory

- Organism
- Result value
- Test result
- Test type
- Lab test date
- Specimen sent to state lab
- Specimen source

Epidemiological

- Imported from
- Occupation

Investigation

- Contact (≤ 2 meters) for (≥ 3 hours) with a laboratory confirmed case of smallpox
- Contact (≤ 2 meters) with a confirmed, probable, or suspected case of smallpox
- Contact with smallpox infected bodily fluids or contaminated objects such as bedding or clothing
- Worker in a laboratory that contains smallpox virus

Reporting

- Date first reported to public health

Administrative

- State case status
- Outbreak associated