

ADVERSE EVENTS FOLLOWING SMALLPOX VACCINATION AND VACCINIA INFECTION

✓ DISEASE AND EPIDEMIOLOGY

Clinical description:

Vaccinia infection:

A vaccinia virus infection is very mild and is typically asymptomatic in healthy individuals, although it may cause a mild rash and fever. However, complications from the vaccinia virus can be severe in:

- Persons with atopic dermatitis or eczema (regardless of whether disease is active or quiescent).
- Persons with acute, active, or exfoliative skin conditions.
- Persons with altered immune states (e.g., HIV, AIDS, leukemia, lymphoma, immunosuppressive drugs) or their household contacts.
- Persons with physician-diagnosed heart disease or three of the five heart disease risk factors (hypertension, hyperlipidemia, current smoker, diabetes or a first degree relative with a heart condition before the age of 50).
- Pregnant women.
- Children younger than 12 months of age.

Adverse events following smallpox vaccination:

A normal reaction to the smallpox vaccine consists of a lesion developing at the vaccination site, ultimately healing to reveal a scar roughly 3 weeks after.

Normal Reaction Time Following Smallpox Vaccination	
Day	Description
0	Vaccination
3-4	Papule
5-6	Vesicle with surrounding erythema becomes vesicle with depressed center
8-9	Well-formed pustule
12+	Pustule crusts over and scab
17-21	Scab detaches revealing scar

*From CDC

Although smallpox vaccine is considered safe when used as indicated, post-vaccination adverse events can occur. The following table describes these adverse events.

Event	Description
Pain	Reported in 40-47% of vaccines; usually mild, but reports of severe pain have been received
Fever	Common adverse event, especially in children; most common 7-10 days after vaccination
Lymphadenopathy	Reported in ~30% of recipients; almost always mild

Event	Description
Constitutional symptoms (headache, myalgias, chills, nausea, fatigue)	Often reported in adults on or about the 8 th or 9 th day after vaccination
Inadvertent inoculation	Vaccine virus infection at a site other than the vaccination site; most common complication; reported in ~50% of recipients
Bacterial superinfection	Usually caused by staphylococci or streptococci; usually caused by using occlusive dressings.
Erythematous or urticarial rashes	Usually occurs within 10 days after vaccination; recovery in 2-4 days; require only symptomatic therapy
Generalized vaccinia	Relatively mild, disseminated disease caused by the vaccine virus; requires little to no therapy
Eczema vaccinatum	Superinfection by vaccine virus in persons with eczema or atopic dermatitis or vaccinee contacts with eczema or atopic dermatitis; usually mild and self-limited, can be severe and fatal
Vaccinia keratitis	Lesions of the cornea secondary to implantation of vaccinia are potentially threatening to eyesight.
Post-vaccinial encephalitis	Rare; most cases believed to result from autoimmune or allergic reactions rather than direct viral invasion of the nervous system; case fatality rate of 15-20%
Myopericarditis	Inflammation of heart muscle or membrane surrounding heart; may be serious
Fetal vaccinia	Rare; infection in the fetus in the last trimester. results in stillbirth or death of the infant soon after delivery
Progressive vaccinia	Also known as vaccinia necrosum; progressive necrosis in the area of vaccination; occurs almost exclusively in persons with cellular immunodeficiency
Death	Rare; most often the result of postvaccinial encephalitis or progressive vaccinia

Causative agent:

The vaccinia virus is an orthopoxvirus. Other orthopoxviruses are smallpox (variola), monkeypox, and cowpox. Vaccinia is used to vaccinate persons against smallpox since it is serologically similar to the smallpox virus.

Differential diagnosis:

The following table describes diseases and syndromes most commonly confused with smallpox and vaccinia.

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 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

Condition	Clinical Clues
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-grey, 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

Laboratory identification:

Vaccinia 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.

NOTE: UPHL is capable of testing specimens for vaccinia. Testing must be coordinated with UDOH, who will work with UPHL and CDC to determine the best course of action.

Treatment:

Vaccinia immune globulin intravenous (VIGIV) is used in the treatment or modification of eczema vaccinatum, progressive vaccinia, and severe generalized vaccinia. It should also be used for vaccinia infections in persons who have skin conditions such as burns, impetigo, varicella zoster, or poison ivy; or for persons who have eczematous skin lesions when it is warranted because of either the activity or extensiveness of such lesions. It is also indicated for aberrant infections induced by vaccinia virus, which include its accidental implantation in eyes (except in cases of isolated keratitis), mouth, or other areas where vaccinia infection would constitute a special hazard. Since postvaccinial encephalitis is not due to virus multiplication, VIGIV is not likely to be effective in treating this adverse reaction. Immune globulin products have no role in the treatment of smallpox. VIGIV is only available through CDC. The CDC Vaccinia Clinical Consultation Team should be contacted through the CDC Emergency Response Hotline at (770) 488-7100 for VIG. The antiviral cidofovir has also been shown to be effective at treating certain serious smallpox vaccine reactions.

Case fatality:

Vaccinia virus infection is not considered fatal in healthy persons. Approximately one in one million persons will develop a fatal response to smallpox vaccination.

Reservoir:

Vaccinia viruses are considered to have no natural reservoir, and are propagated simply through smallpox vaccination programs.

Transmission:

Vaccinia virus is transmitted by direct contact with an active lesion or by direct contact with a contaminated fomite.

Susceptibility:

Routine vaccination in the US for smallpox using vaccinia virus 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.

Incubation period:

Based on two outbreaks of vaccinia virus, the incubation period appears to be 8-18 days.

Period of communicability:

An infected person is contagious for three weeks, from the development of the earliest lesions to the disappearance of all scabs.

Epidemiology:

Currently, there are 2 foci of naturally-occurring vaccinia-like viruses worldwide; one in southern Brazil, one on the Indian sub-continent. Both involve human-bovid cycles of transmission, and both have been hypothesized to be consequences of an “escaped” vaccine, although this has not yet been proven.

PUBLIC HEALTH CONTROL MEASURES

Public health responsibility:

- Conduct rash surveillance.
- Identify all cases.
- Assure that appropriate testing protocols are followed.

Prevention:

General principles for the care of vaccinees and the protection of healthcare system employees and susceptible patients follow.

Vaccinees

Vaccinees and/or guardians should be advised to take the following precautions until the vaccine site has healed (scab has completely separated):

- Keep the vaccination site covered. Clean or sterile gauze (loosely taped) is recommended. Healthcare workers involved in patient care should use gauze covered by a semi-permeable dressing.
- Do not touch, scratch or rub the vaccination site. This is particularly a problem because the site is usually itchy.
- Make sure the vaccine site is appropriately covered and good hand hygiene practices are followed whenever close physical contact with others is possible.
- Avoid touching, rubbing or otherwise performing any maneuvers that might transfer vaccinia virus to the eye or surrounding skin
- Discard the vaccination site covering carefully. The covering contains viable virus and can spread the infection to others. Carefully enclose the gauze in a plastic bag that can be sealed prior to placing it in a trash receptacle.
- After handling the vaccination site covering, thoroughly wash hands with soap and running water or other hand disinfectant

All vaccine recipients should be educated. DoD Smallpox Vaccination Program
<http://www.smallpox.army.mil/education/toolkit.asp?ste=milvax>

Healthcare Systems

The Advisory Committee for Immunization Practices (ACIP) has recommended that recently vaccinated healthcare workers who follow the appropriate guidelines for vaccine site dressing and hand hygiene do not need to be placed on leave as these precautions greatly minimize the risk to patients or other healthcare workers.

Environmental Measures

Disinfecting agents should be performed after materials have come into contact with the site to prevent transmission to other parts of the body or to unvaccinated persons. Clothing and linens that touch the site should be washed in hot water with detergent or bleach. Common disinfectants can be used to clean any surface that touches a dirty bandage or the vaccination site.

Chemoprophylaxis:

None

Vaccination:

The smallpox vaccine is made from a related orthopox virus – the vaccinia virus. The vaccine is highly effective at inducing immunity against smallpox when administered effectively prior to exposure. Smallpox vaccine production ceased in the early 1980s, and current supplies of smallpox vaccine are limited. However, recent studies have demonstrated that vaccines stored in the 1960s and 1970s still have excellent potency, even when diluted. New cell-culture-grown smallpox vaccines will become available soon.

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 vaccinee.

Currently, smallpox vaccine is recommended for **routine, non-emergency use** in the following groups:

- Laboratory workers who directly handle cultures or animals contaminated or infected with non–highly attenuated vaccinia viruses.
- Public health, hospital, and other personnel who may need to respond to a smallpox case or outbreak, and for persons who administer the vaccine to others.

Vaccination may also be considered for other healthcare workers who come into contact with materials such as dressings that may be contaminated with vaccinia or recombinant vaccinia.

In the event of an **intentional release** of variola virus, vaccination would be recommended for:

- Those exposed to the initial release
- Contacts of persons with smallpox
- Others at risk of exposure, ie
 - Those involved in direct medical or public health evaluation, care or transportation of confirmed or suspected smallpox patients.
 - Laboratory personnel who collect or process clinical specimens from confirmed or suspected smallpox patients.
 - Persons who may have contact with infectious materials, such as those responsible for medical waste disposal, linen disposal or disinfection, and room disinfection in a facility where smallpox patients are present.
 - Other groups (e.g., medical, law enforcement, emergency response, or military personnel) as recommended by public health authorities.

In routine circumstances the vaccine should not be administered to persons younger than 18 years of age. In an emergency situation, there would be no age limit for vaccination of persons exposed to a person with confirmed smallpox.

The schedule for smallpox vaccine is one successful dose. A successful dose results in a major reaction at the vaccination site. A major reaction indicates a successful vaccine take and is characterized by a pustular lesion or an area of definite induration or congestion surrounding a central lesion, which can be a scab or an ulcer.

Several groups have been identified as being at higher risk for developing post-vaccination complications. These persons are advised not to receive smallpox vaccination unless they have been exposed or are at high risk of exposure to smallpox virus. These include:

- Persons with atopic dermatitis or eczema (regardless of whether disease is active or quiescent).
- Persons with acute, active, or exfoliative skin conditions.
- Persons with altered immune states (e.g., HIV, AIDS, leukemia, lymphoma, immunosuppressive drugs) or their household contacts.
- Persons with physician-diagnosed heart disease or three of the five heart disease risk factors (hypertension, hyperlipidemia, current smoker, diabetes or a first degree relative with a heart condition before the age of 50).
- Pregnant and breast-feeding women.
- Children younger than 12 months of age.
- Persons who have a serious allergy to any component of the vaccine.

In the event of an exposure to smallpox, there would be no contraindications to vaccination. In this situation, the benefit of vaccination would outweigh the risk of a complication from the vaccine.

Isolation and quarantine requirements:

Isolation: Cases should be placed on standard and contact isolation until lesions have dried and crusts have separated. Non-hospitalized patients should ideally be cared for by someone immune to the disease.

Hospital: Cases should be placed on standard and contact isolation until all lesions have dried and crusts have separated.

Quarantine: Contacts should be monitored for signs and symptoms of disease for 2 weeks after exposure.

✓ CASE INVESTIGATION

Reporting:

Adverse events following smallpox vaccination, including accidental inoculation of another person, should be reported to the local health department or the Utah Department of Health.

Reporting Swimlanes

Criterion	Reporting
Superinfection of the vaccination site or regional lymph nodes†	S
Inadvertent autoinoculation (nonocular)	S
Contact transmission (nonocular)	S
Ocular vaccinia	S
Generalized vaccinia	S
Eczema vaccinatum	S
Progressive vaccinia	S
Erythema multiforme major or Stevens-Johnson Syndrome§	S
Fetal vaccinia	S
Postvaccinial central nervous system disease	S
Myo/pericarditis	S

* Any adverse event that is of concern to the clinician or patient should be reported.

† Previously referred to as pyogenic infection of vaccination site.

§ Clinically defined.

Case Definition:

The Centers for Disease Control and Prevention have not defined a case definition for vaccinia infection. Please see the CDC's *Surveillance Guidelines for Smallpox Vaccine (Vaccinia) Adverse Reactions* (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5501a1.htm>) for case definitions of adverse events following smallpox vaccination.

Case investigation process:

- Local and state health departments and CDC should be immediately notified.
- The vaccinating agency should be notified of the adverse event.
- Appropriate laboratory samples and preliminary clinical and epidemiologic information should be obtained.
- Digital photographs of the lesions or rash should be taken.
- All lesions should be covered until they have dried and the crusts have separated.
- Assure that the case is closely followed by medical personnel throughout the course of illness.
- All case contacts should be identified and appropriately managed (explained in detail below).

- Ensure that appropriate environmental measures have been taken to disinfect contaminated materials.

Outbreaks:

Outbreaks of vaccinia virus are rare. Past outbreaks have been due to healthcare worker-mediated transmission or household transmission after mass vaccination campaigns.

Identify case contacts:

Case contacts are persons that have had sustained, intimate contact with the case.

Case contact management:

- Notify contacts of their exposure and recommend watching for signs or symptoms of disease for 2 weeks.
- Contacts that are at high risk for severe infection should be closely monitored by medical personnel for 2 weeks. The following are risk factors for severe infection:
 - Atopic dermatitis or eczema (regardless of whether disease is active or quiescent).
 - Acute, active, or exfoliative skin conditions.
 - Altered immune states (e.g., HIV, AIDS, leukemia, lymphoma, immunosuppressive drugs) or their household contacts.
 - Physician-diagnosed heart disease or three of the five heart disease risk factors (hypertension, hyperlipidemia, current smoker, diabetes or a first degree relative with a heart condition before the age of 50).
 - Pregnancy.
 - Children younger than 12 months of age.
- Contacts that develop symptoms should be treated as cases.

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