

Recognition of Adverse Reactions following Smallpox Vaccination

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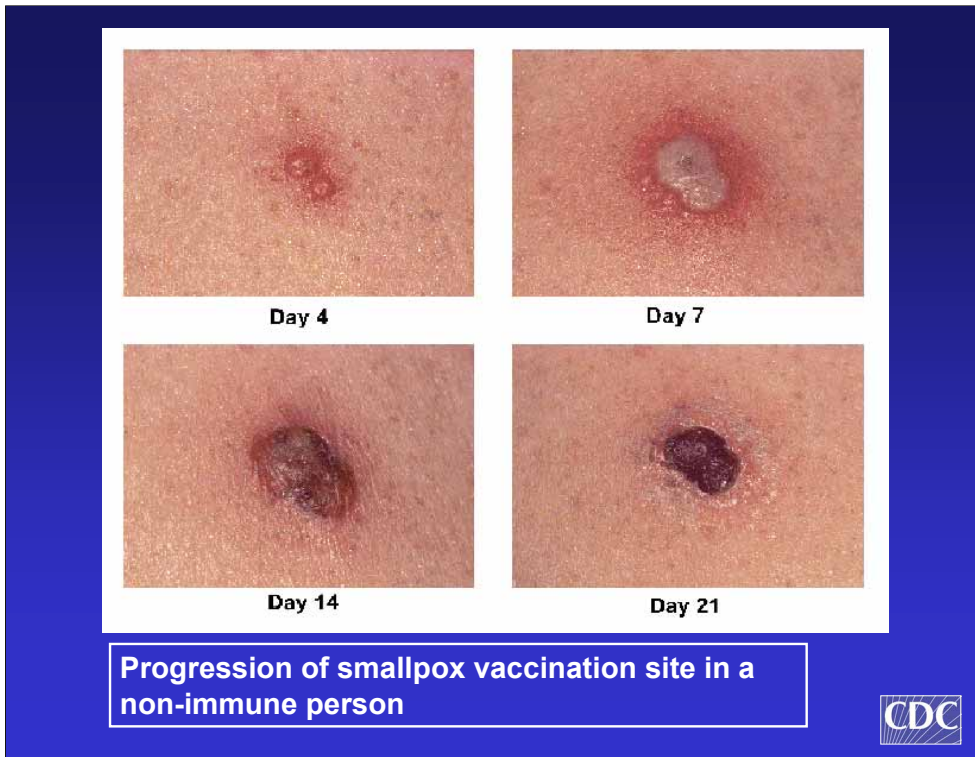
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Evaluation, Management, and Treatment of Adverse Events of Smallpox Vaccine

- Learning Objectives:
 - Recognize the common and serious adverse events expected after smallpox vaccination
 - Distinguish between common and serious adverse events



In this segment we will discuss how to recognize the common and serious adverse events expected after a smallpox vaccination. We will also discuss how to distinguish between common and serious adverse events.



Before we begin, let's talk about the clinical response to the smallpox vaccination. The usual response to a "first-time" or primary vaccination, or to a repeat vaccination after a long period of time is called a "major" response.

This involves the development of a papule at the vaccination site about 3-5 days following vaccination. It then evolves into a pustule by days 5-8. The peak site response occurs around days 8 to 10, and is when the greatest amount of erythema or swelling is seen.

Axillary lymph nodes may also be more swollen at this time and the vaccinee may experience fever for a couple of days. The site lesion then starts to dry up to form a scab at about day 14, with separation of the scab beginning about 14-21 days after vaccination.

Common Symptoms

- Fatigue (50%)
- Headache (40%)
- Muscle aches and Chills (20%)
- Nausea (20%)
- Fever 37.7 °C or 100 °F (10%)



Previous studies indicated that 21% of complications experienced by recent vaccinees required physician consult. The most common symptoms experienced by vaccinees in a recent vaccine trial were:

- fatigue in 50%
- headache in 40%
- muscle aches and chills or nausea in 20% and
- fever in 10%

Clinical Response to Vaccination*

| Symptom/sign | Time after Vacc |
|------------------|-----------------|
| Papule | 3-5 days |
| Pustule | 5-8 days |
| Maximum erythema | 8-10 days |
| Scab | 14 days |
| Scab separation | 14-21 days |

*typical response in a nonimmune person



Data from recent dilutional studies of smallpox vaccine showed that the pustule size was the same regardless of the dilution and was usually around 12 millimeters, or about a half an inch. The diameter of erythema was a little bigger in people getting undiluted vaccine.

Smallpox Vaccine Reactions Among Susceptible Adults

- About 10% with temperature \geq 100F
- Systemic symptoms (malaise, myalgias)
- 36% sufficiently ill to miss work, school, or recreational activities or had trouble sleeping



Fever occurs most often in people being vaccinated for the first time. In recent vaccine trials fever of 100 degrees Fahrenheit or more occurred in about 10% of vaccine recipients. Peak temperature elevation generally occurs about the time the vaccine site inflammatory reaction is at its greatest, on about days 8-10. General malaise and muscle aches may also occur and may be severe enough in some people to alter their normal activities for a couple of days.

There is a range of other reactions that can occur at the vaccine site. Some people may experience significant swelling, and some may develop lymphangitis or satellite lesions. Let's look at some of these reactions.



Lymphangitis following smallpox vaccination



This image demonstrates the red streaking of lymphangitis. This is usually due to a normal robust reaction at the site that peaks around days 8-10, but can be seen in secondary bacterial cellulitis. It can also be confused with allergic reactions to the dressing tape.



Satellite lesions



Here is an example of a satellite lesion near the vaccination site. These usually heal at the same rate as the primary vaccination site.



Allergic reaction to tape

This picture demonstrates a local reaction due to a tape allergy. This can usually be distinguished from lymphangitis by observing that the reaction only occurs in the distribution of the tape. Usually, individuals with reactions to tape have no other systemic symptoms.

Large Vaccination Reactions and Robust Takes



Robust take with lymphangitis



Some individuals can have a robust primary reaction that presents with a large amount of erythema, swelling, pain, and warmth at the vaccine site. The redness and swelling can sometimes be greater than 3 inches or may even involve the entire upper arm. This large reaction is usually seen on days 8-10, corresponding to the same time when the peak vaccine inflammatory reaction usually occurs. In recent studies, this robust reaction or take occurred in 5%-15% of vaccine recipients. Both people getting vaccinated for the first time and people getting revaccinated after a long period since their last vaccination can have these robust takes. These robust reactions are expected variants of the evolution of the vaccination site and generally improve on their own within 24-72 hours.

However, sometimes these large vaccination reactions have been reported as adverse events and misinterpreted as a "bacterial cellulitis," prompting antibiotic treatment.



Secondary bacterial infection of vaccination site



This slide shows a secondary bacterial infection. Note the increased size and raised borders of the lesion.

Individuals suspected of having bacterial cellulitis at the site should be evaluated with gram stain and culture of the lesion, and blood cultures if systemic symptoms like high fever and malaise are present. An elevated peripheral white blood cell count may also be more indicative of a bacterial infection than a robust vaccine take. The most common organisms causing secondary infections are *Staphylococcus aureus* and Group A streptococci. Some anaerobic or mixed infections can be seen, and may occur if occlusive dressings are used for prolonged periods that prevent aeration of the site and promote an anaerobic environment.

Smallpox Vaccine Adverse Reaction Rates*

| Reaction | Primary Vaccination |
|-----------------------------|---------------------|
| Inadvertent inoculation | 25-529 |
| Generalized vaccinia | 23-242 |
| Eczema vaccinatum | 10-39 |
| Progressive vaccinia | 0.9-1.5 |
| Post-vaccinial encephalitis | 3-12 |
| Death | 1 |

*Rates per million primary vaccinations



Two studies were done in the US during the late 1960's that looked at adverse events associated with smallpox vaccination. These studies are most often quoted when discussing the rates of smallpox vaccine adverse events. One was a national surveillance study, while the other was a survey of physicians in 10 states.

The most common adverse events associated with vaccination in these studies included: Inadvertent inoculation, eczema vaccinatum; generalized vaccinia; progressive vaccinia, also called vaccinia necrosum; post-vaccinial encephalitis; and other dermatologic conditions or rashes. We'

This table shows the range of adverse event rates reported from both of these studies. The differences seen in the rates between the two studies are due to different data collection methods. The 10 state survey probably more accurately reflects the rates for the less serious complications that were frequently unreported, while the national study captured the rates of the more serious adverse events through national reporting and VIG distribution mechanisms.



Erythema multiforme following smallpox vaccination



One of the biggest concerns regarding smallpox vaccination in today's society is that adverse events may be higher because of the greater number of immunosuppressed people. We may also have more people affected by eczema or atopic dermatitis. Both of these conditions have a higher risk for serious complications associated with vaccination. In addition, adverse event rates are higher among primary vaccinees, and currently there is a higher percentage of individuals who were not vaccinated as children because routine vaccinations were stopped in 1972. Now. Let's look at some of the dermatologic manifestations that can follow vaccination.

These manifestations include non-specific rashes. Most are mild, require no specific treatment, and last only a few days. These rashes generally occur about 10 days after vaccination, and can be only a few lesions or a generalized rash that is erythematous, macular, papular, or urticarial. These rashes usually don't become vesicular but can. They don't appear to be a result of systemic dissemination of the virus and may be due to a non-specific immune reaction following vaccination.



Source: V. Fulginiti MD

Erythema Multiforme



Occasionally, more severe, non-specific reactions such as erythema multiforme or Stevens-Johnson syndrome can be seen following vaccination.

Erythema multiforme can present as macules, papules, urticarial lesions or the typical bulls eye lesions. The lesions usually do not progress to vesicles and don't contain live vaccinia virus because they are not a result of virus dissemination.



Inadvertent inoculation



This picture shows inadvertent inoculation of the eyelid following vaccination. Inadvertent inoculation is the accidental transfer of vaccinia virus from the vaccine site to another area of the body or to another person. Self inadvertent inoculation is the most common adverse event seen following vaccination. Transfer to another body site results in a second, similar skin lesion that progresses through the same stages of resolution as the vaccination site. The most common body sites affected are the face, eyelid, nose, mouth, and other mucosal surfaces.

Inadvertent inoculation of the eyelid can lead to significant swelling and redness of the eyelid and periorbital area.

Vaccinia Specific Adverse Events



Palebral Autoinoculation



Transfer of vaccinia virus to another person can result in a lesion similar to a typical vaccine site lesion, or can lead to other more severe adverse reactions, especially in people with certain underlying medical conditions like eczema or, atopic dermatitis, or immune suppression.

Inadvertent inoculation of the eyelid can lead to significant swelling and redness of the eyelid and periorbital area.

Inoculation of the virus in the eye can result in several clinical manifestations including blepharitis or infection of the eyelid, conjunctivitis, keratitis or iritis, or a combination of these conditions.

Periocular and ocular implantation otherwise referred to as ocular vaccinia disease, account for the majority of inadvertent inoculations and were often noted within 7-10 days of vaccination in first-time vaccinees.

Because ocular vaccinia disease may occur in several forms when evaluating a patient with new onset of a red eye or periocular vesicles, vaccinia infection should be considered. The patient should be asked about recent vaccinia exposures including a smallpox vaccination or close contact with a vaccine recipient.



Generalized vaccinia



Generalized vaccinia usually presents as a rash that develops into vesicular or pustular lesions distal from the vaccination site. This vesicular rash may involve only a few, scattered lesions but can also be more extensive and generalized in nature. Fever and other systemic symptoms may be present but are usually not severe.

Here we see several pustular lesions of generalized vaccinia located on the lower legs.

Generalized Vaccinia

- Differential diagnosis
 - Erythema multiforme
 - Eczema vaccinatum
 - Inadvertent inoculation at multiple sites
 - Early progressive vaccinia
 - Disseminated herpes
 - Severe varicella



The differential diagnosis for this vaccine complication includes other non-specific immune rashes that can also occur following vaccination, eczema vaccinatum, metastatic lesions of early progressive vaccinia, or non-vaccinia related conditions such as disseminated herpes or severe varicella.



Eczema vaccinatum



Eczema vaccinatum is one of the more serious adverse events that can result from smallpox vaccination. This complication can occur in individuals with active eczema or atopic dermatitis, or in those with a history of these conditions even when the condition is not active. A less severe form of eczema vaccinatum can also occur in people with other skin disorders, like psoriasis or burns, that are currently active and effecting the integrity of the skin. Some of the most severe cases of eczema vaccinatum have occurred in people with eczema or atopic dermatitis who were contacts to recently vaccinated individuals.

The rash of eczema vaccinatum can occur anywhere on the body but has a predilection for areas effected by atopic dermatitis or eczema. The rash can be quite extensive and even become confluent with papular, vesicular, or pustular lesions. Patients with significant skin involvement can become severely ill.

This picture demonstrates the extensive skin involvement of eczema vaccinatum in a close contact to a recently vaccinated person. Extensive skin involvement may result from inoculation of vaccinia virus in skin sites with compromised dermal integrity due to eczema or other skin conditions or may be the result of hematogenous spread following initial infection with the virus. Lesions of eczema vaccinatum can result in skin discoloration or scarring following resolution.



Progressive vaccinia



Progressive vaccinia or vaccinia necrosum is a rare but serious adverse event that can occur in people with deficiencies of the cell mediated or humoral immune system

People with progressive vaccinia usually present with a non-healing, expanding vaccination site. The site often ulcerates and central necrosis, or necrosis of the surrounding skin can occur. There is generally little or no inflammation at the site initially, because of the poor local immune response to the infection that is induced by vaccination. This lack of adequate local immune response presumably allows the virus to spread locally and systemically. Medical conditions or medications that suppress the immune system would put a person at risk for this complication. It is currently unknown exactly what level of immune suppression would put a person at risk for this complication.

This woman had chronic lymphocytic leukemia. Notice how the infection from the vaccine site has spread to involve the surrounding skin and the necrotic appearance of the area. This woman also has metastatic lesions on her neck and other areas of her body presumably from hematogenous spread of the virus.

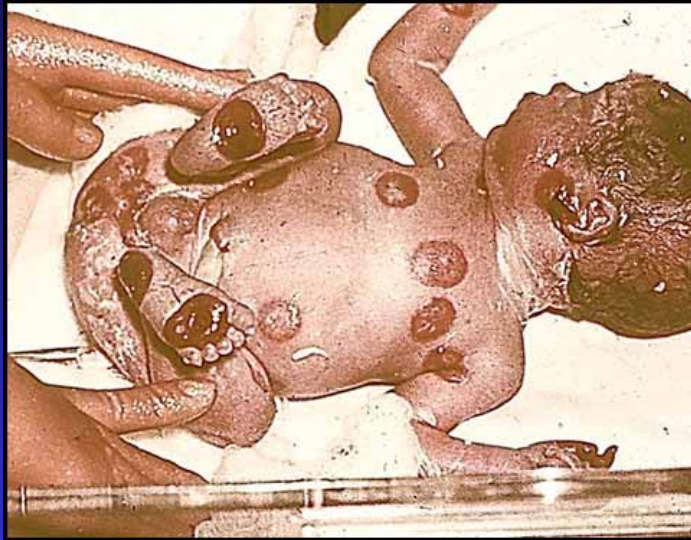
Post-vaccinial Encephalitis

- Diagnosis of exclusion
- Other infectious or toxic causes of encephalitis should be ruled out
- Pathophysiology not well understood
- CSF may have increased opening pressure, lymphocytosis, elevated protein



Post-vaccinial encephalitis is also a very rare but serious vaccine complication. It was more frequently seen in vaccinated infants less than 1 year old or in older adolescents or adults receiving their first vaccination. It can present with a variety of CNS manifestations from confusion to seizures or coma. Death results in about 15%-25% of the cases, while 25% had some degree of residual neurologic sequelae.

Symptoms of post-vaccinial encephalitis usually occurred between 9 and 14 days following vaccination and its diagnosis involves excluding other potential causes for encephalitis. The pathophysiology of this complication is not well understood but it is thought to be a result of a post vaccination immune response, similar to other post-infectious encephalitides. It has not been causally linked to the presence of vaccinia virus in the CNS.



Fetal vaccinia



Fetal vaccinia is a very rare complication that can occur following primary vaccination of a pregnant woman in the second or third trimester, from hematogenous spread of virus to the amniotic fluid or directly to the fetus. Only about 50 cases of this complication have been reported in the literature. Studies are contradictory as to whether spontaneous abortions were increased in pregnant women vaccinated during the first trimester. There is no known reliable intrauterine diagnostic test to detect the presence of vaccinia virus.

For More Information

- CDC Smallpox website
www.cdc.gov/smallpox
- National Immunization Program website
www.cdc.gov/nip



For more information on the recognition of adverse events please go to the CDC Smallpox website at www.cdc.gov/smallpox and the National Immunization Program website at www.cdc.gov/nip.

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