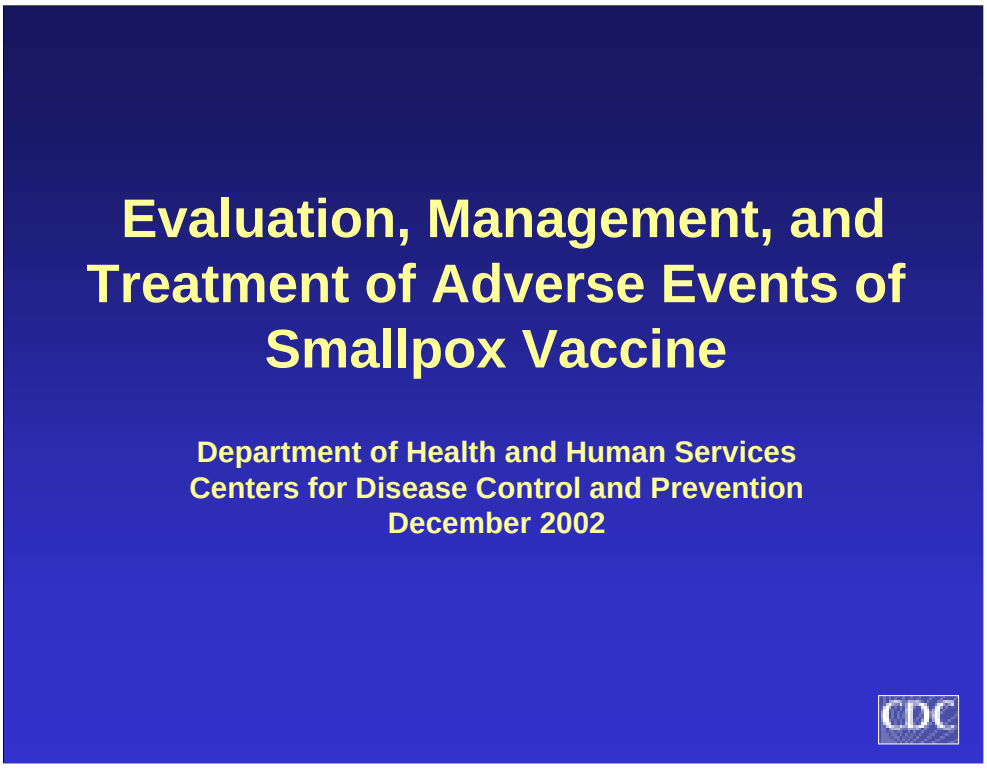
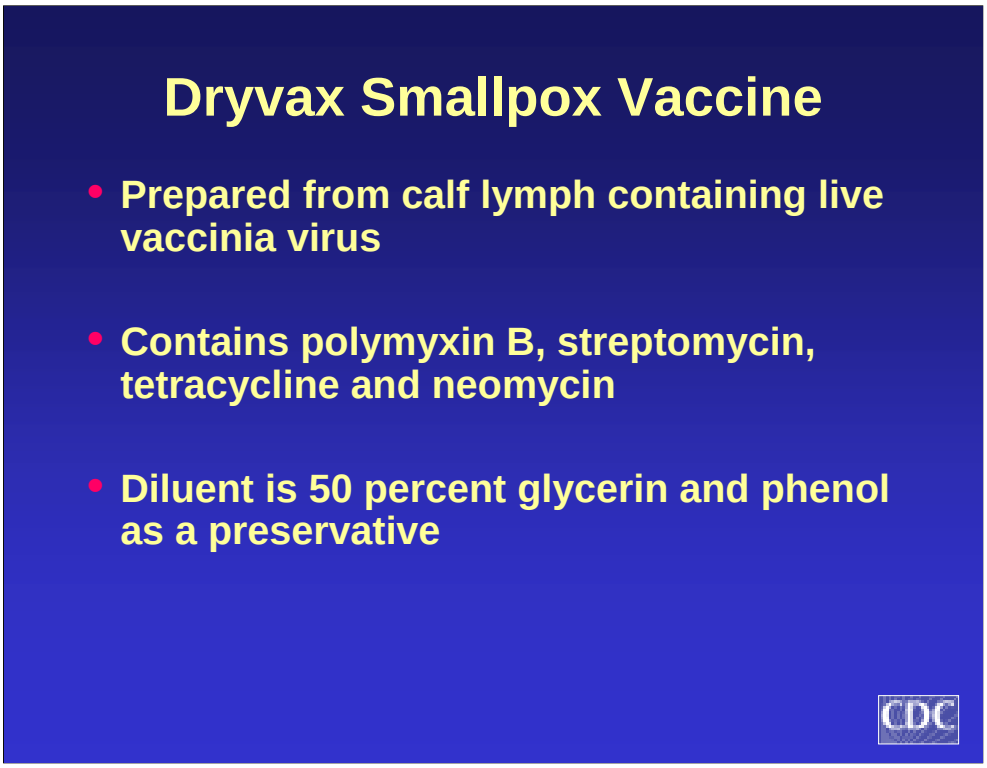


Presented by Dr. Lisa Rotz, BPRP, CDC.

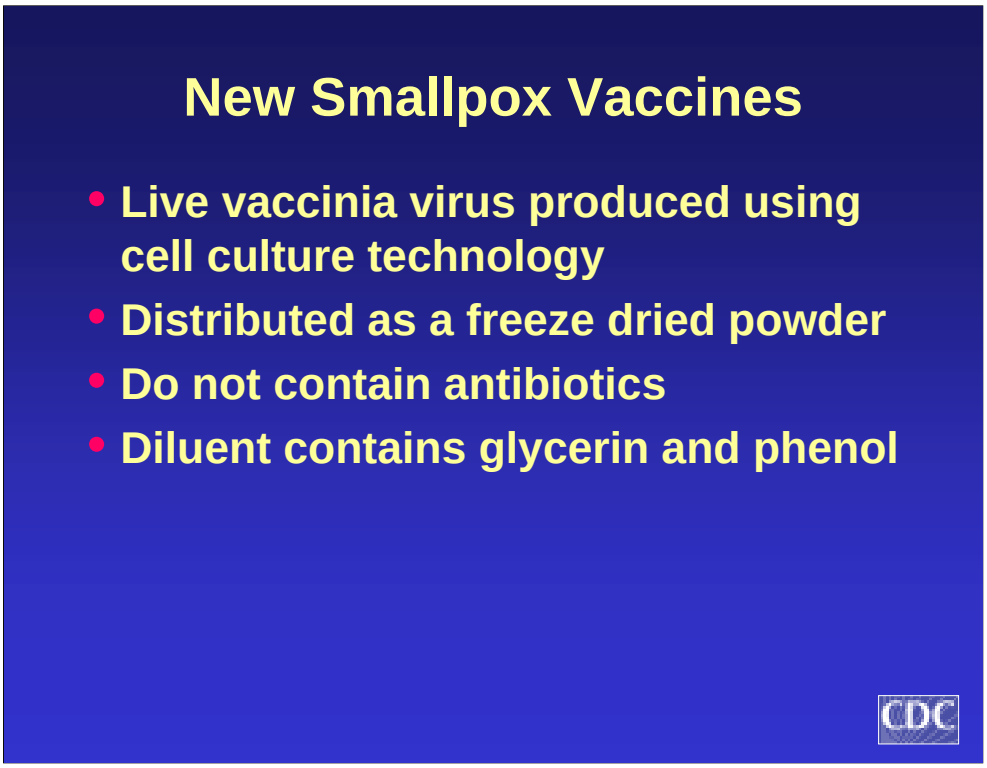
Evaluation, Management, and Treatment of Adverse Events of Smallpox Vaccine

- Learning Objectives:
  - Describe the common and serious adverse events expected after smallpox vaccination
  - Describe the treatment options available to clinicians when treating a patient with an adverse event to smallpox

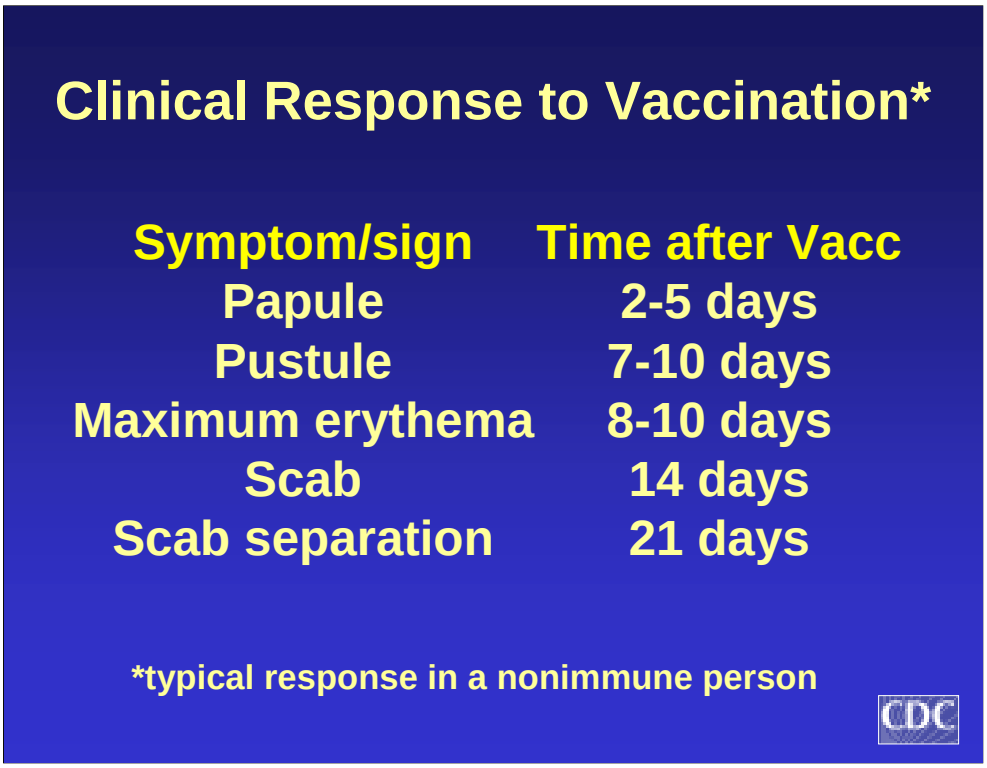
The vaccine currently used in the United States, Dryvax, is a lyophilized product that requires reconstitution before administration.



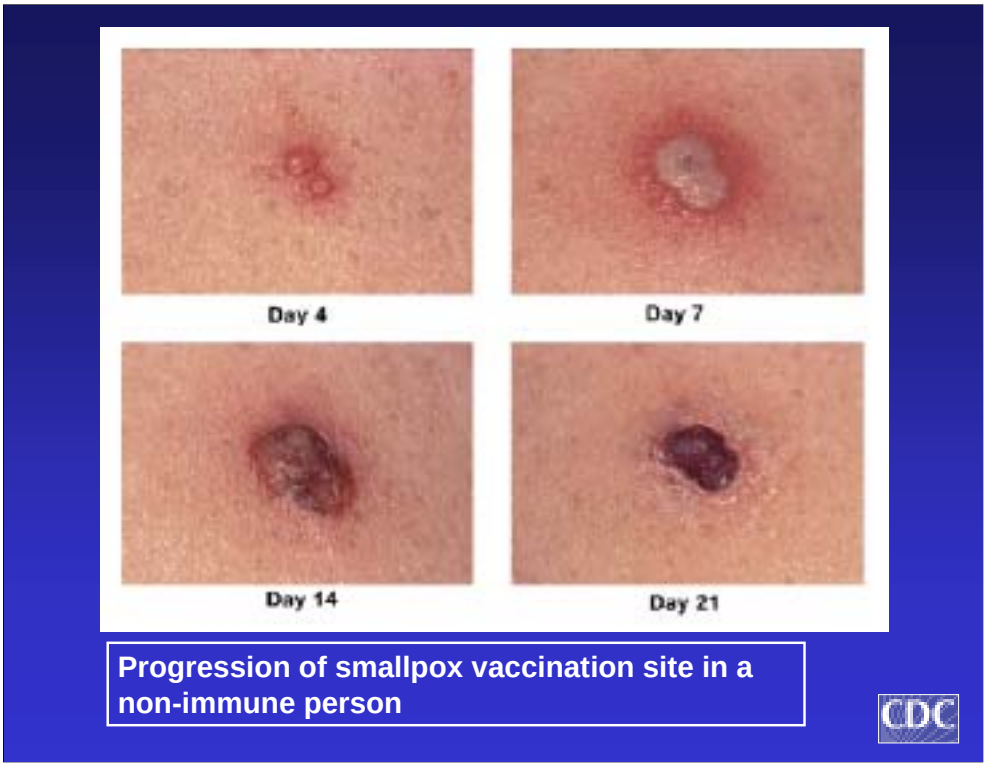
It was originally prepared from lymph harvested from the skin of calves that were infected with live vaccinia virus. Dryvax also contains the antibiotics polymyxin B, streptomycin, tetracycline, and neomycin and is reconstituted with a diluent that made up of 50% glycerin with a small amount of phenol as a preservative.



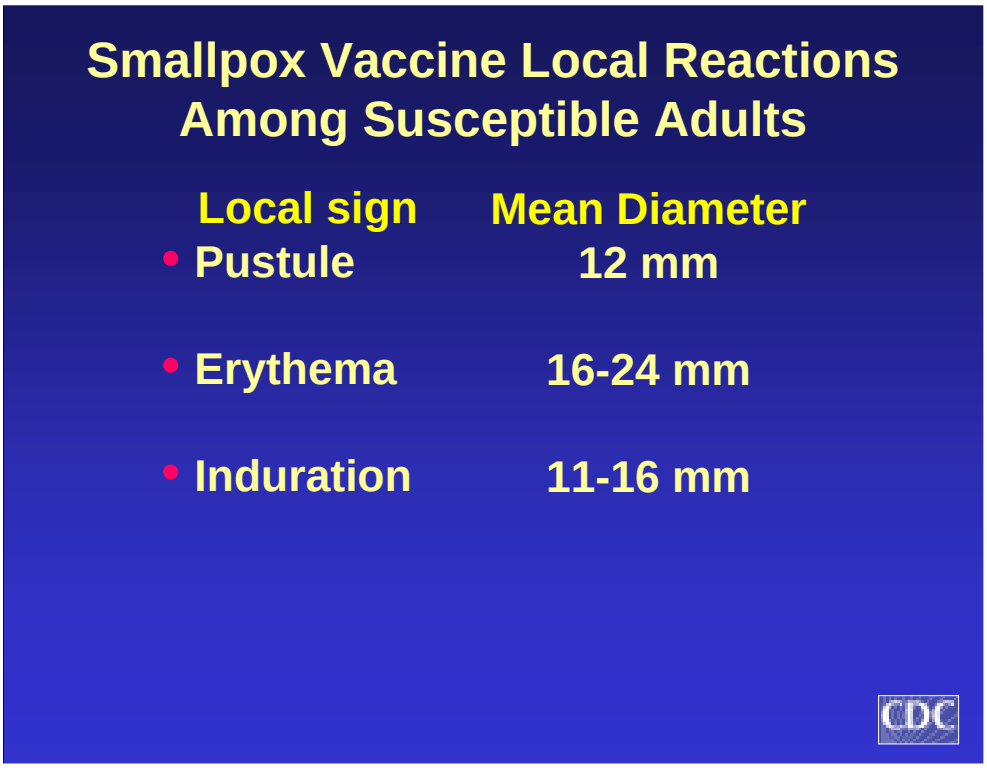
The newer vaccines being produced use more modern cell culture production techniques and won't contain antibiotics. However, they'll probably be distributed as a freeze dried powder and require reconstitution with a diluent before administration… similar to Dryvax.



The usual response to primary vaccination, or re-vaccination after a long period of time is called a “major”, or primary response. This involves the development of a papule at the vaccination site, 2-5 days following vaccination, that evolves into a pustule by days 7-10. The maximum 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. The site lesion then starts to dry up to form a scab at about day 14, with separation of the scab beginning around 21 days after vaccination.

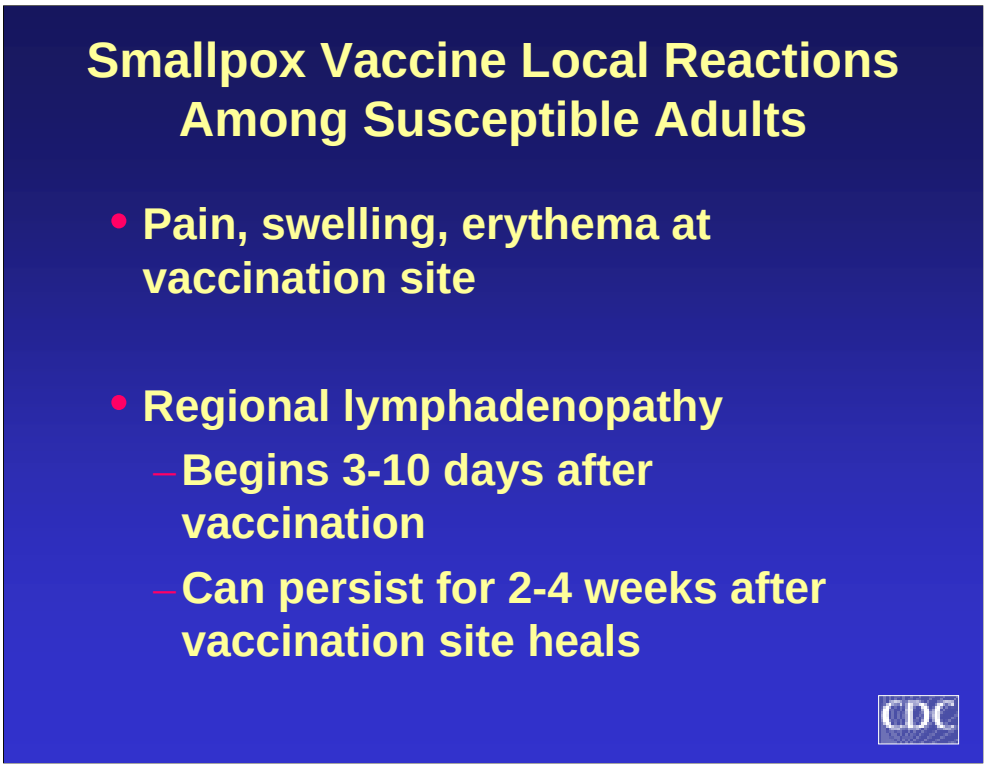


Vaccinees should have their vaccination site evaluated 7 to 8 days after vaccination to document that they have responded to the vaccine. A positive response to the vaccine is often called a "take." Here we see photos of the normal progression of the vaccination site. By day 4, vesicles have appeared. The lesion evolves into a pustule by day 7. The presence of a pustule at that time verifies that the vaccinee has responded to the vaccine and has a "positive take." By day 14, the pustule has dried and a scab has formed. By day 21, the scab has thickened and will soon separate, usually by 28 days post-vaccination. If the vaccinee has not responded to the first vaccination attempt, he should be vaccinated again, as soon as possible. This second vaccination may be placed on the same arm as the first attempt, although if possible, at least a centimeter from the first vaccination site.



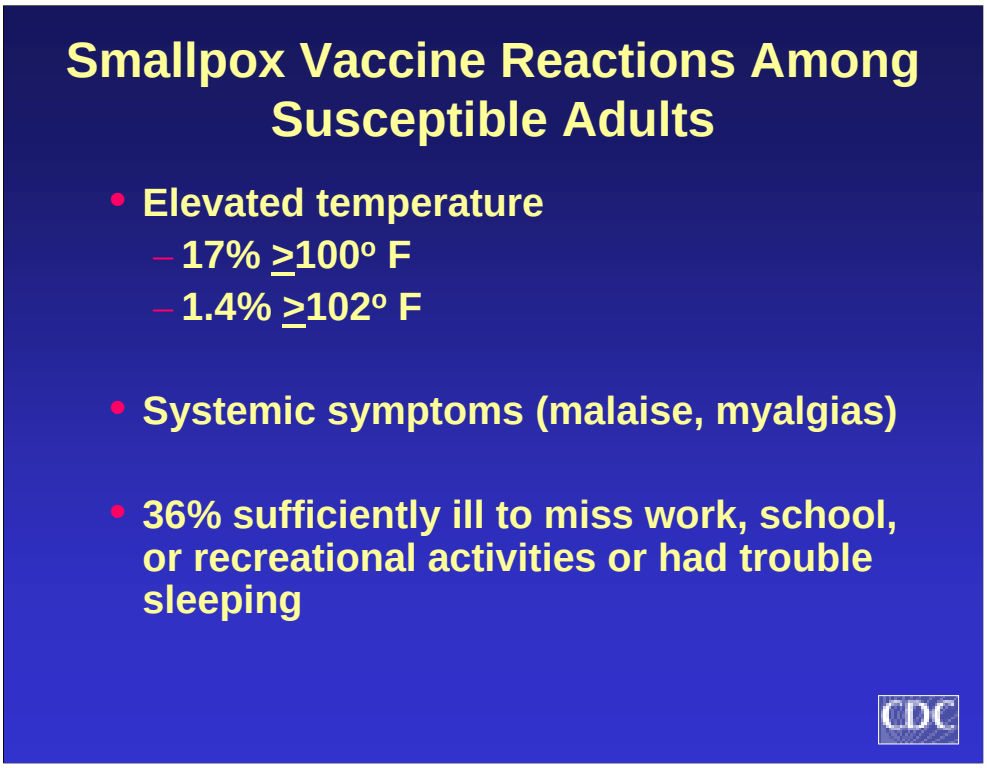
Data from the recent dilutional studies of smallpox vaccine showed that the pustule size was the same regardless of the dilution and was usually around 12 millimeters, or about a half an inch. The diameter of erythema was a little bigger in people getting undiluted vaccine.

Pustule size was the same regardless of dilution. Higher numbers in range were from undiluted vaccine. Only diameter of erythema was significantly different between undiluted (24 mm) and diluted vaccine (16-17 mm). Mild adenopathy was easily tolerated. Moderate was bothersome but did not preclude performance of routine activities. No subject had severe adenopathy.



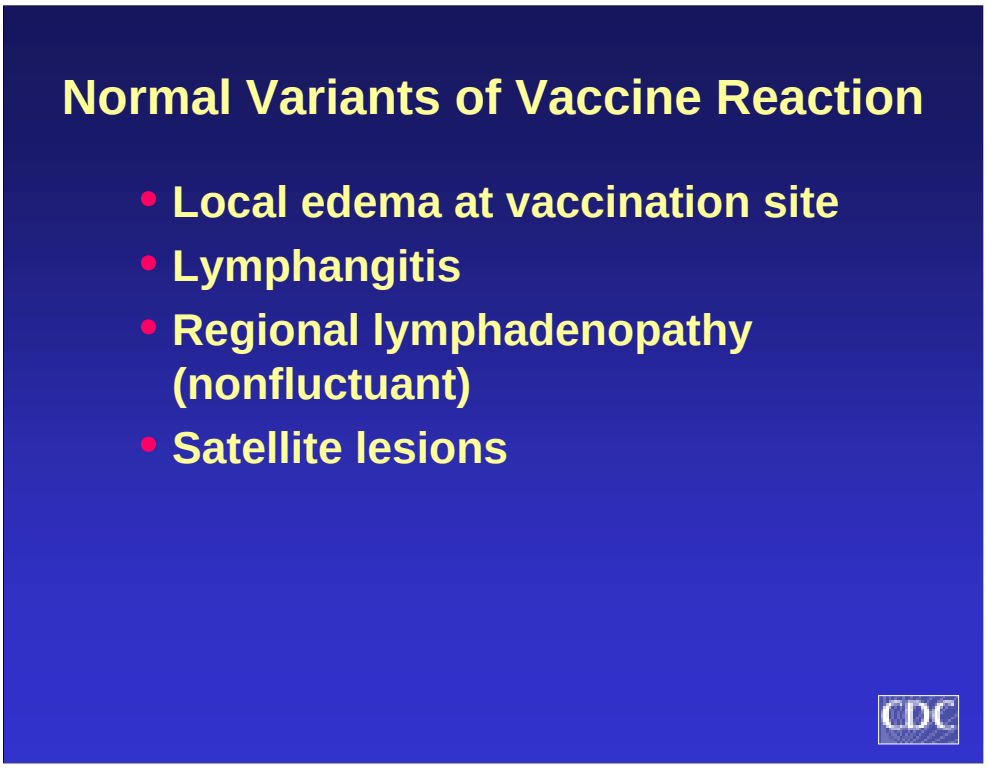
From cleared CDC Fact Sheet.

Most primary vaccinees or distant re-vaccinees can expect some amount of tenderness, swelling, and redness at the vaccination site. They can also expect to have swollen axillary lymph nodes that can sometimes persist for several weeks.

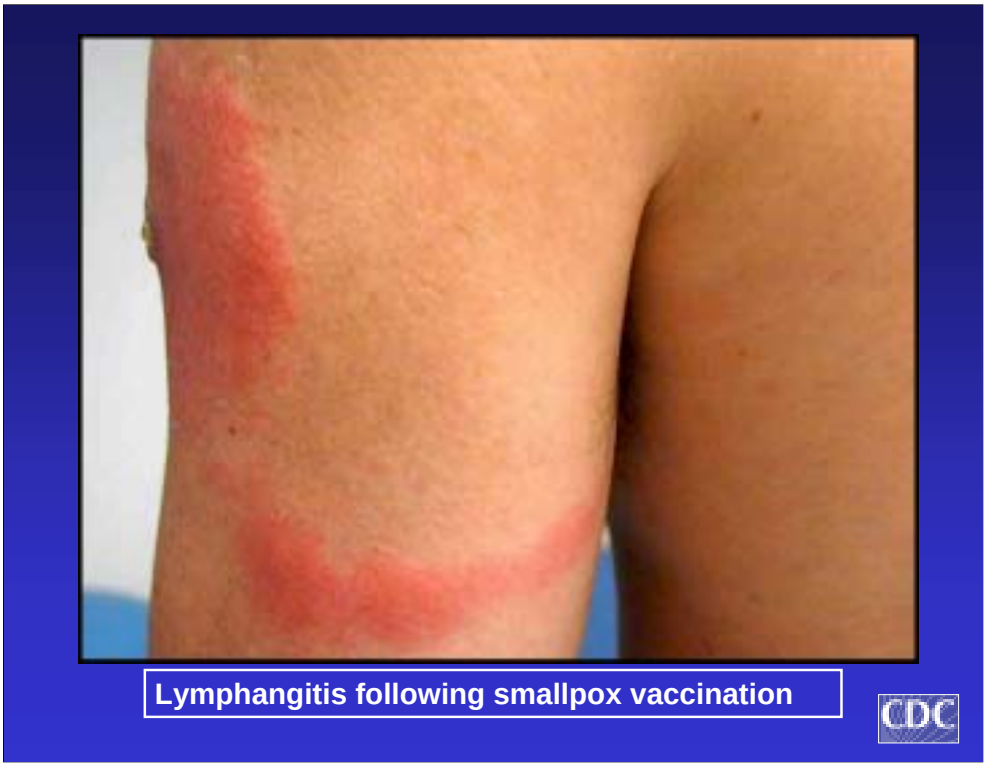


From cleared CDC fact sheet.

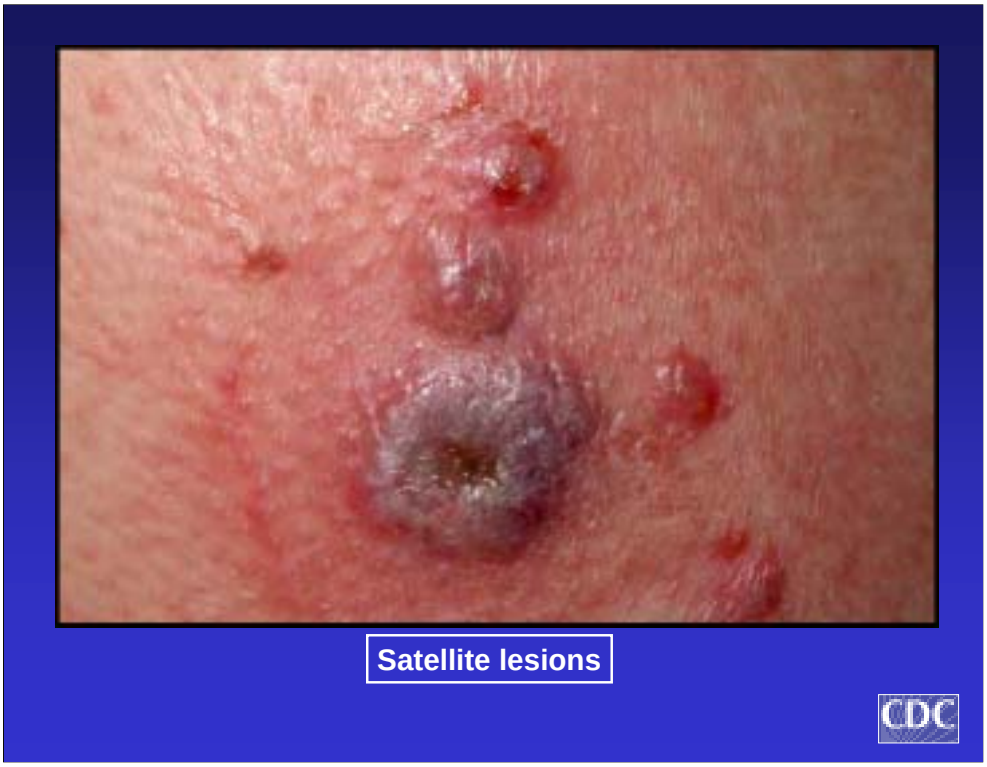
Fever most often occurs in people being vaccinated for the first time, and can be greater than 100 degrees Fahrenheit in more than 18% of vaccine recipients. Peak temperature elevation generally occurs about the time the vaccine site inflammatory reaction is at its greatest, on about days 8-10. General 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.



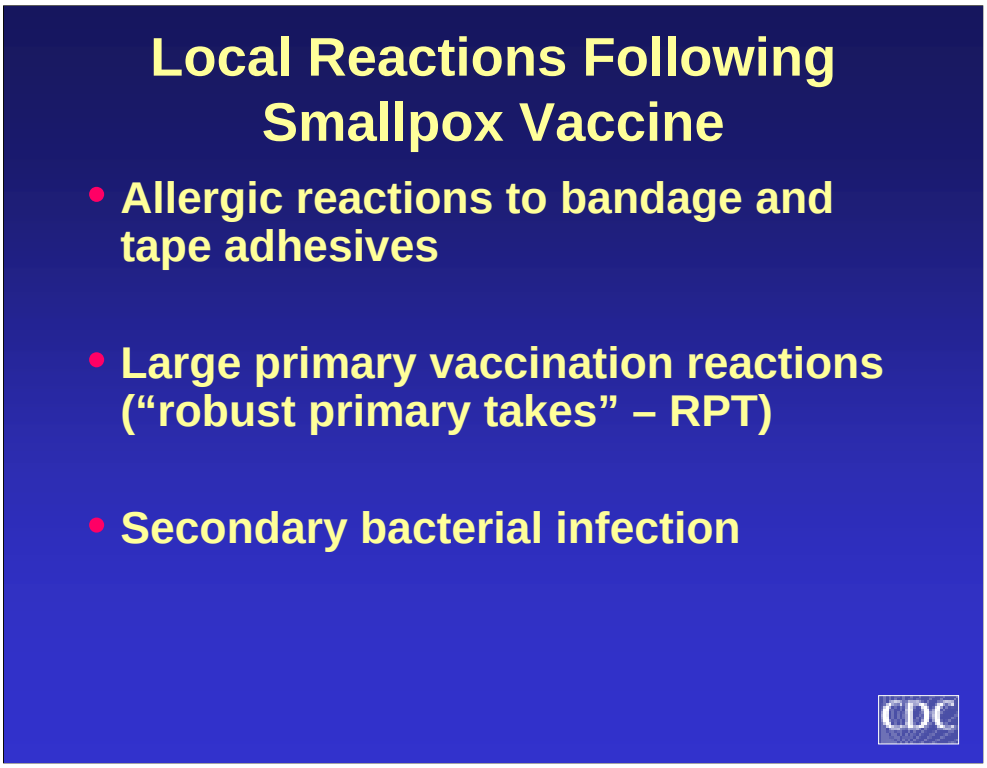
There is a range of expected reactions that can occur at the vaccine site. Some people may experience swelling, and some may develop lymphangitis or satellite lesions.



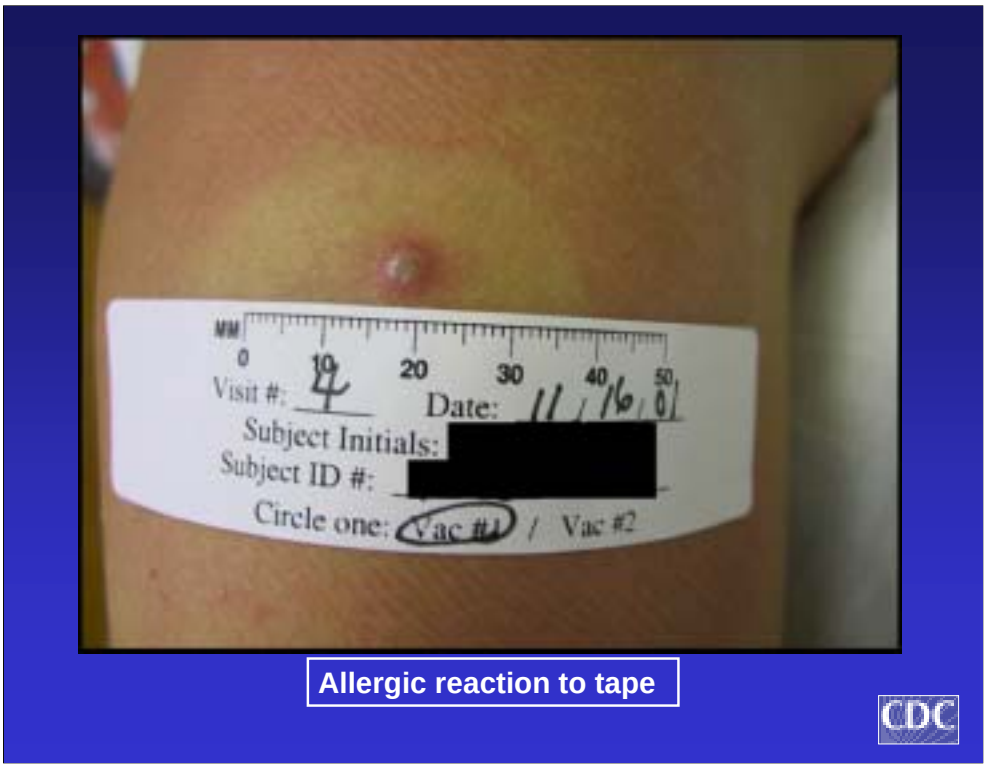
This image demonstrates the red streaking of lymphangitis. This is usually due to a normal robust reaction at the site but can be seen in secondary bacterial cellulitis. It can also be confused with allergic reactions to the dressing tape.



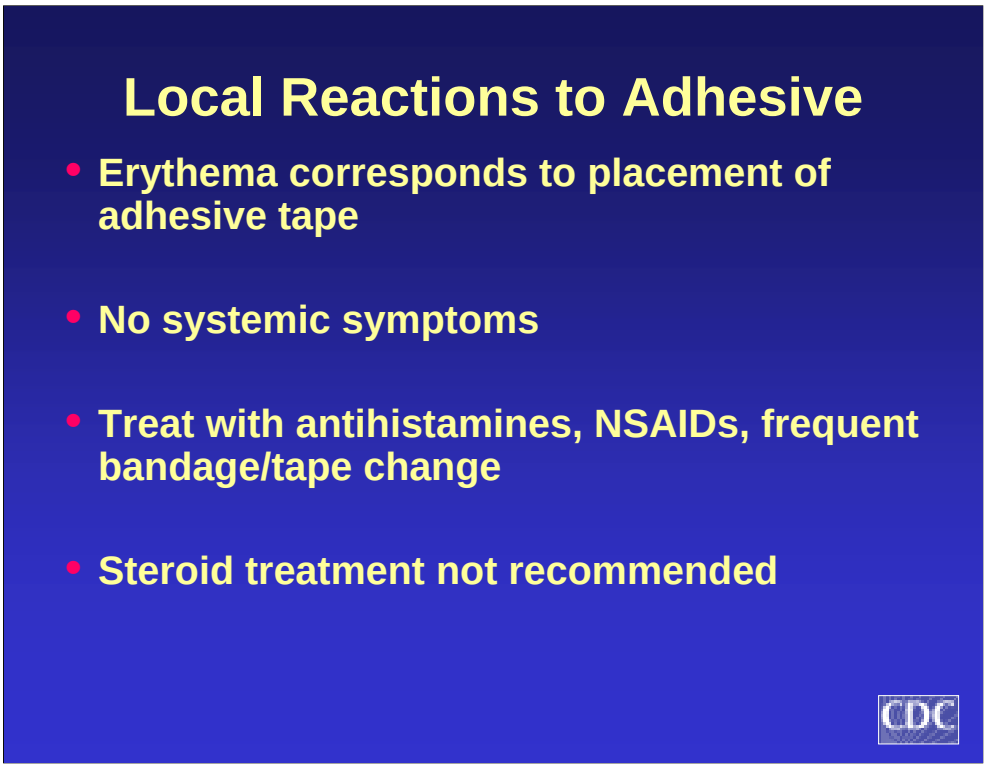
Here is an example of a satellite lesion near the vaccination site. These usually heal at the same rate as the primary vaccination site.



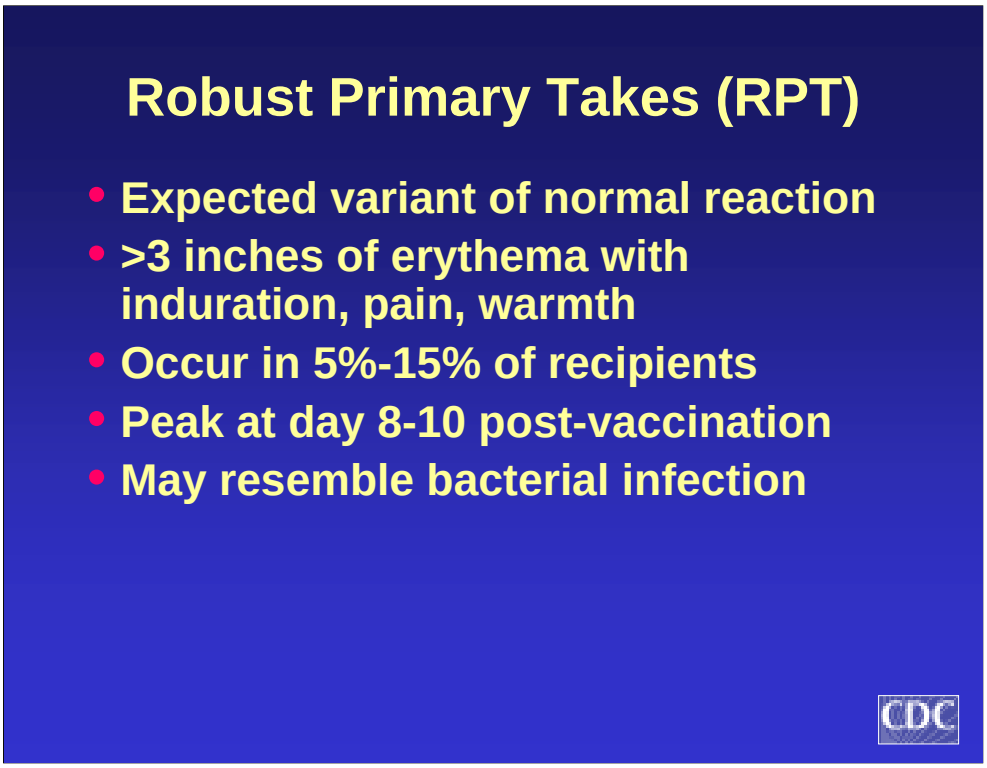
There are several other local reactions that can occur at the vaccination site, in addition to the expected reactions; an allergic reaction to the tape used to hold on the site bandage, a larger, more robust site reaction, or a secondary bacterial infection.



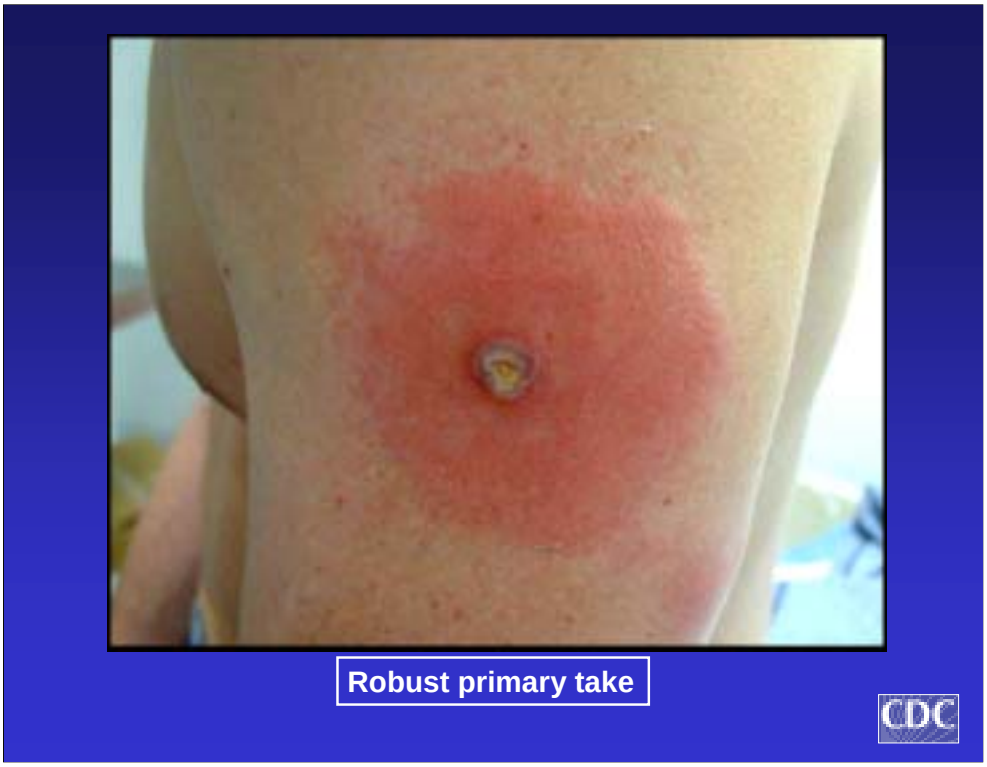
This picture demonstrates a local reaction due to a tape allergy. This can usually be distinguished from lymphangitis by observing that the reaction only occurs in the distribution of the tape.



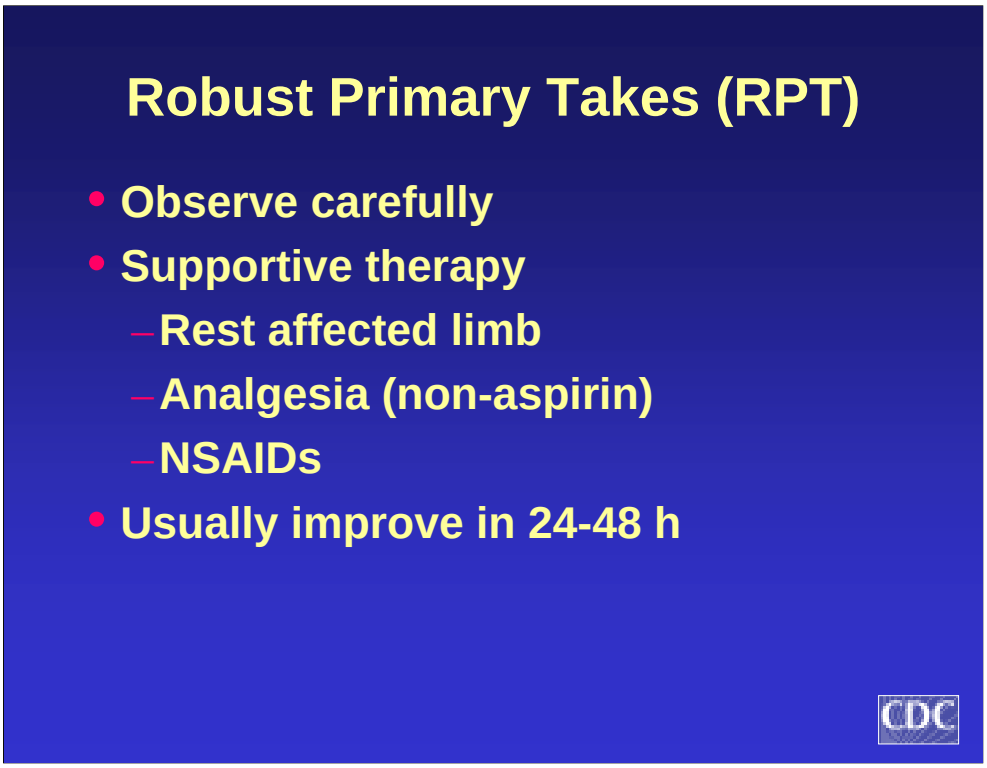
Usually, individuals with reactions to tape have no other systemic symptoms and can be treated by changing the type of tape or increasing the frequency of dressing changes. Antihistamines or non steroidal anti-inflammatory medications can be used if the local reaction is severe enough to cause discomfort. Steroid treatment is generally not needed or recommended.



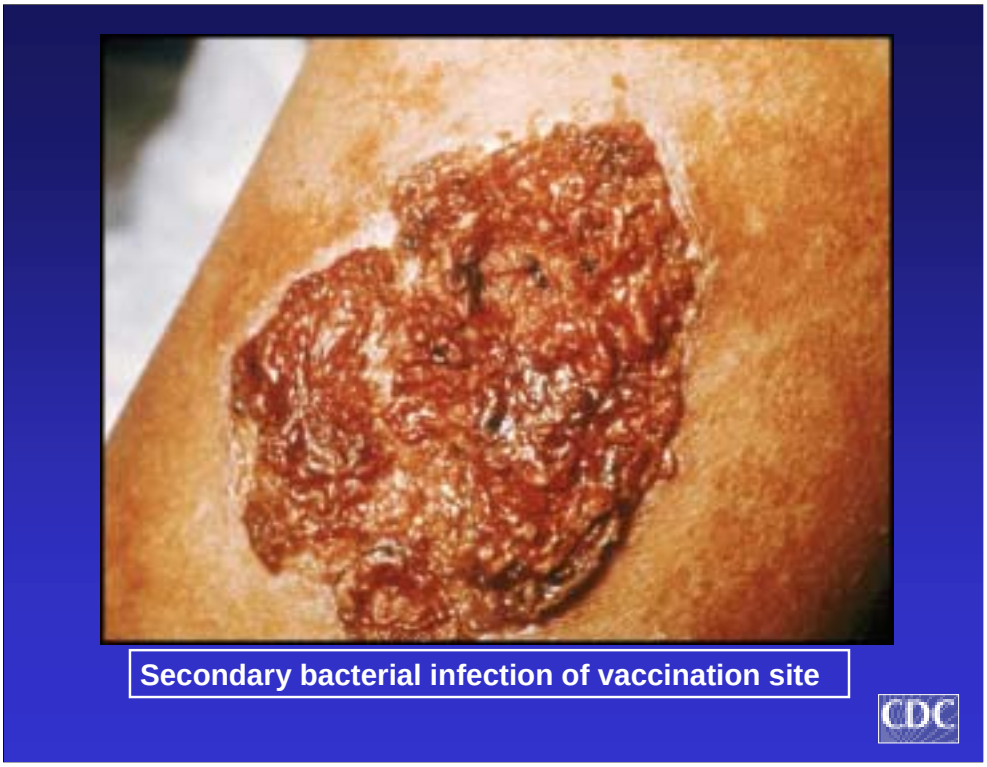
Some individuals can have a robust primary reaction that presents with a large amount of erythema, swelling, pain, and warmth at the vaccine site. The redness and swelling can sometimes be greater than 3 inches or even involve the entire upper arm. This peak reaction is seen on days 8-10, corresponding to the same time when the peak vaccine inflammatory reaction usually occurs. Unlike bacterial cellulitis, the clinical course usually isn't progressive, and the symptoms improve over a couple of days without specific therapy. In recent studies, this robust 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.



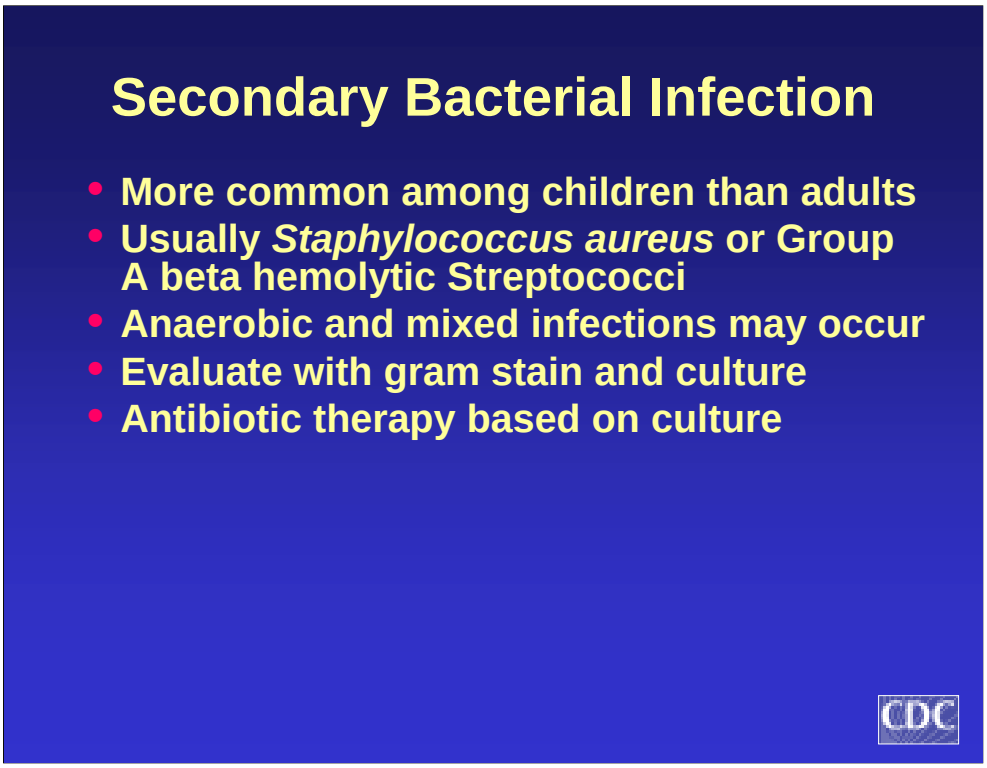
Here we see an example of a robust take. Note the large area of erythema and swelling, and the lymphangitic streaking. Swollen axillary lymph nodes are also often present and can be painful.



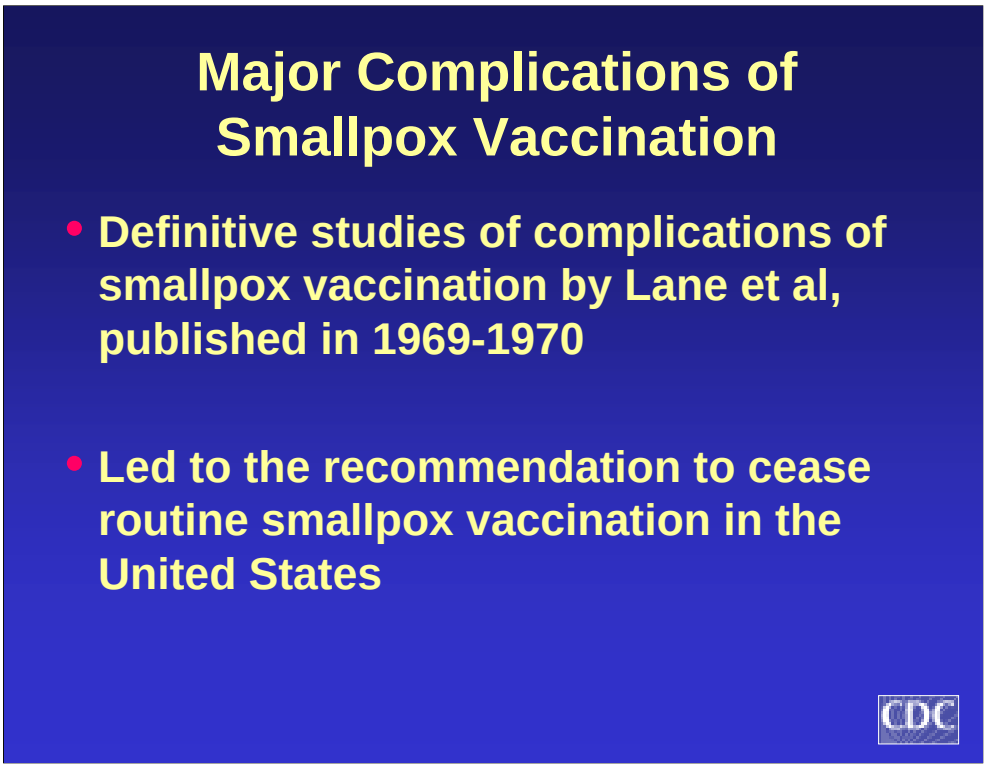
Persons with robust takes should be followed carefully. Some can have fever but most don’t usually experience high fevers or other severe systemic symptoms. This robust reaction generally improves in 1 to 2 days with only symptomatic treatment.



This is an example of a secondary bacterial infection of the vaccination site. Note the increased size and raised borders of the lesion.



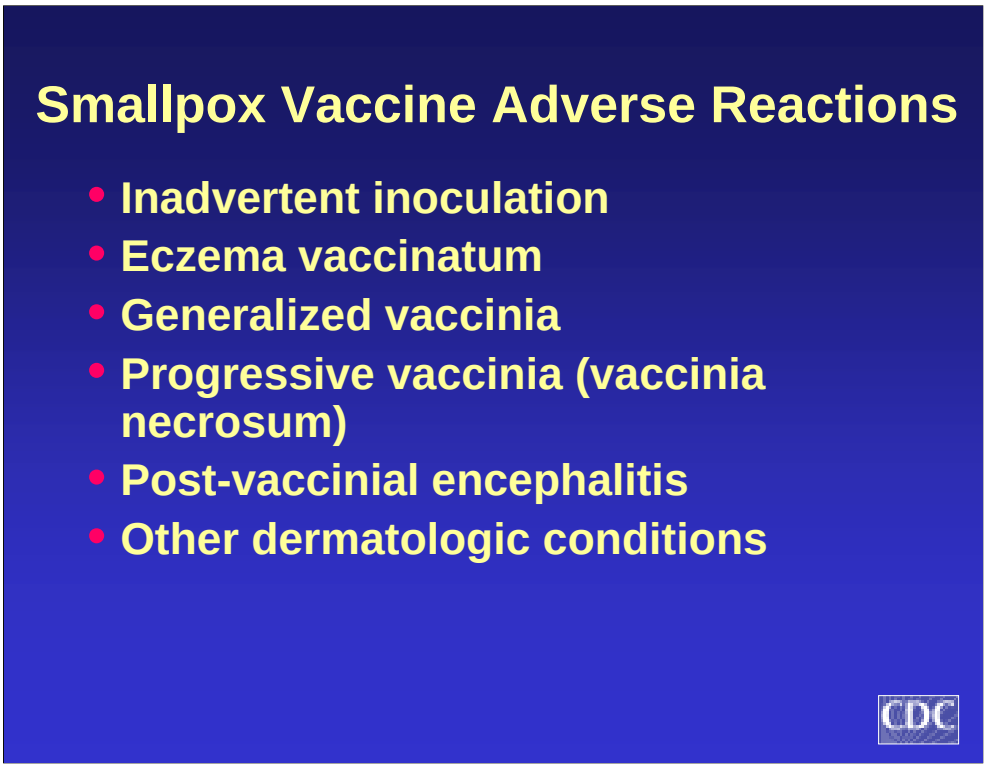
Individuals suspected of having bacterial cellulitis at the site should be evaluated with gram stain and culture of the lesion, and blood cultures if systemic symptoms like high fever and malaise are present. An elevated peripheral white blood cell count may also be more consistent with a bacterial infection. 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. Antibiotic therapy should be guided by culture and sensitivities.



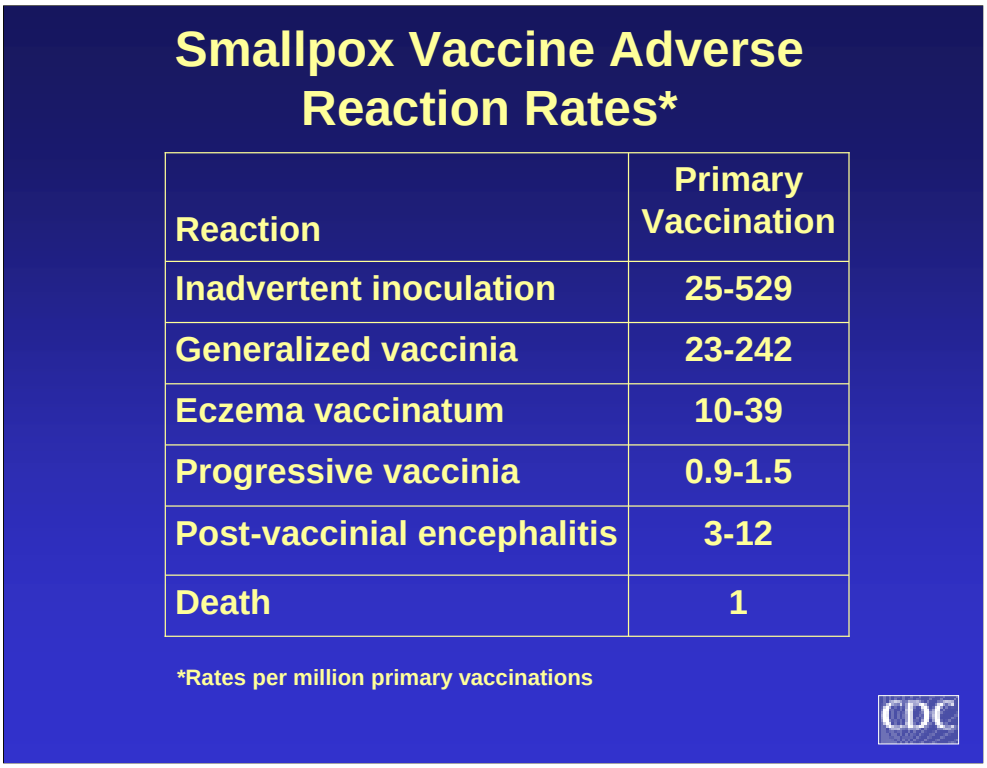
1969 National surveillance article in NEJM

1970 10-state survey in JID

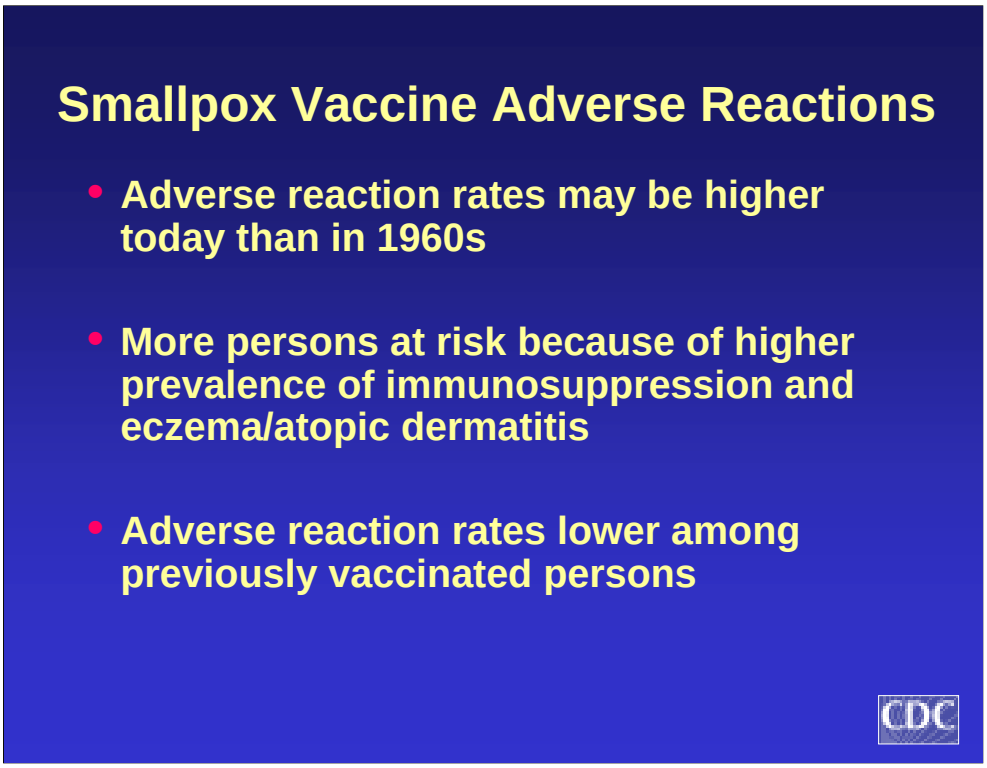
Two studies were done in the U.S. during the late 1960's that looked at adverse events associated with smallpox vaccination. These studies are most often quoted when discussing the rates of smallpox vaccine adverse events. One was a National surveillance study while the other was a survey of physicians in 10 states. The results of these studies prompted public health officials to re-evaluate the ongoing routine smallpox vaccination program in the United States, and ultimately led to the discontinuation of that program in 1972.



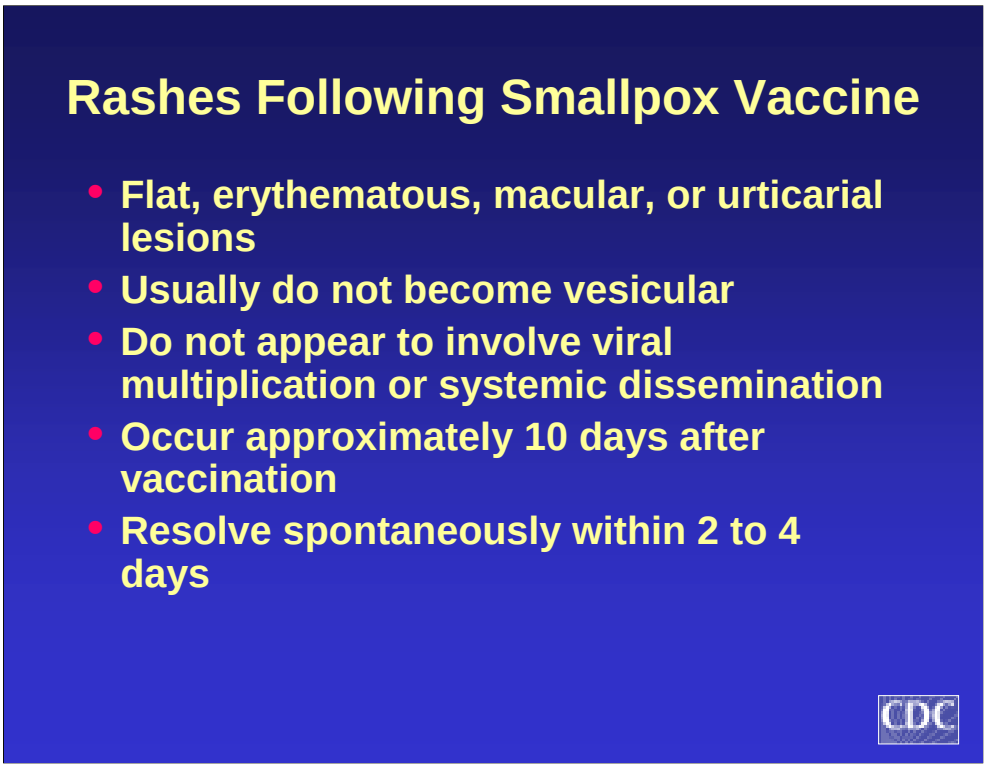
The most common adverse event associated with vaccination in these studies included: inadvertent inoculation; eczema vaccinatum; generalized vaccinia; progressive vaccinia, also called vaccinia necrosum; post-vaccinial encephalitis; and other dermatologic conditions or rashes. We'll discuss each of these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



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 is 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.

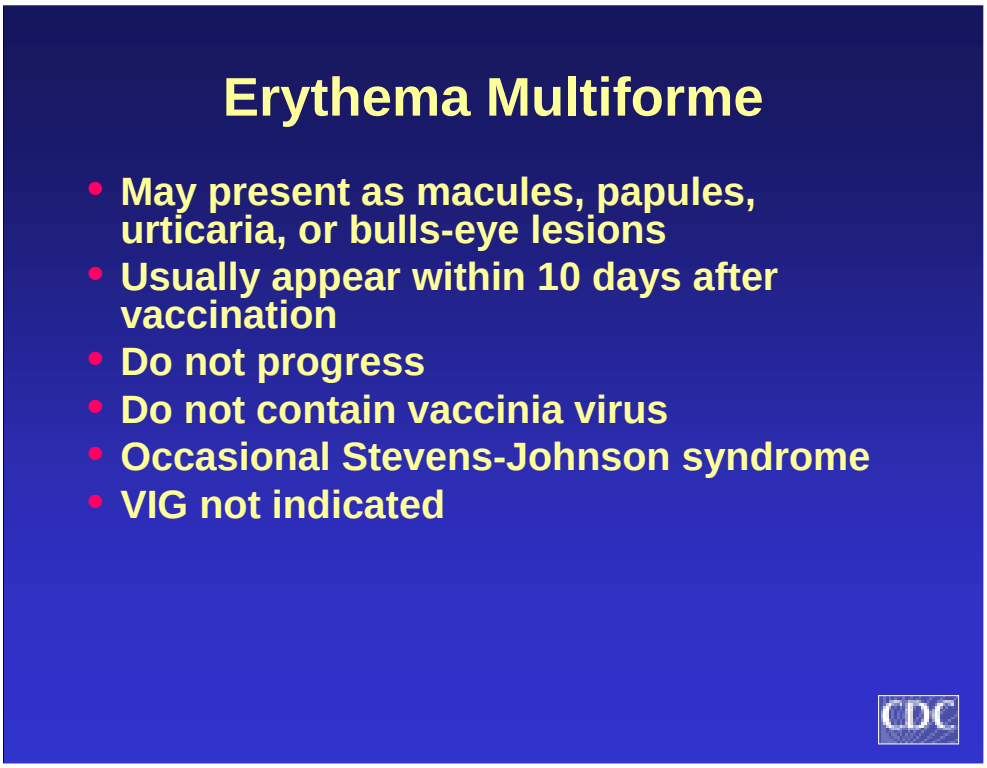


One of the biggest concerns regarding smallpox vaccination in today's society is that adverse events may be higher because of the greater number of immunosuppressed people. We may also have more people affected by eczema or atopic dermatitis. Both of these conditions have a higher risk for serious complications 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.

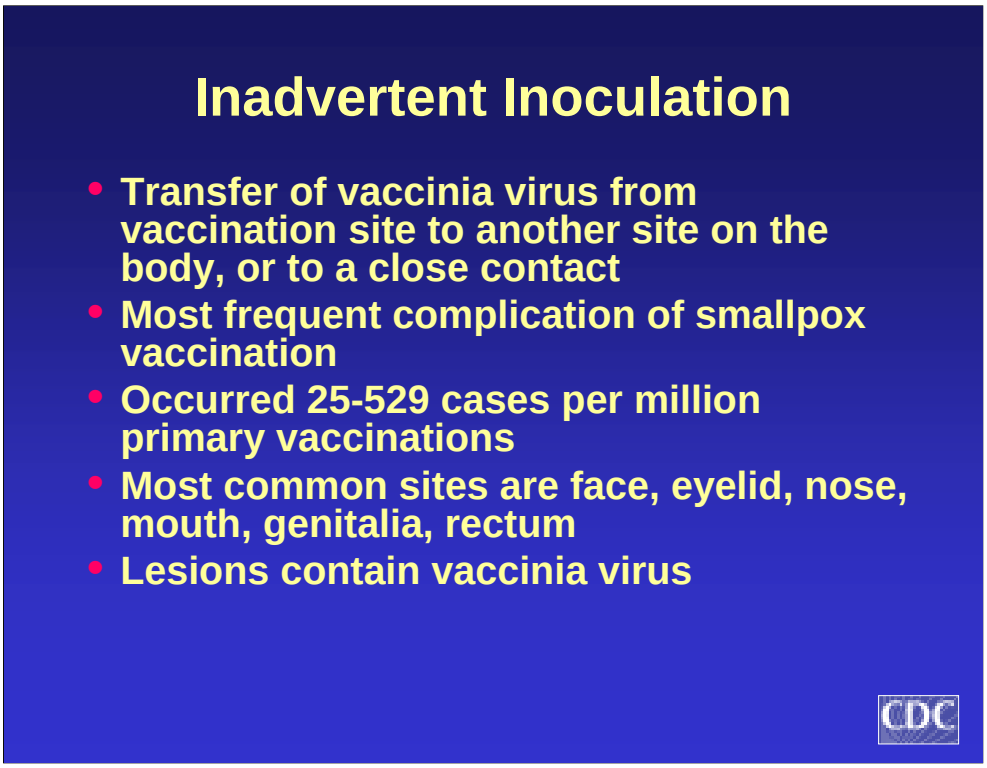


Some of the dermatologic manifestations that can follow vaccination include non-specific rashes. Most are mild, require no specific treatment, and last only a few days. These rashes generally occur about 10 days after vaccination, and can be only a few lesions or a generalized rash that is erythematous,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

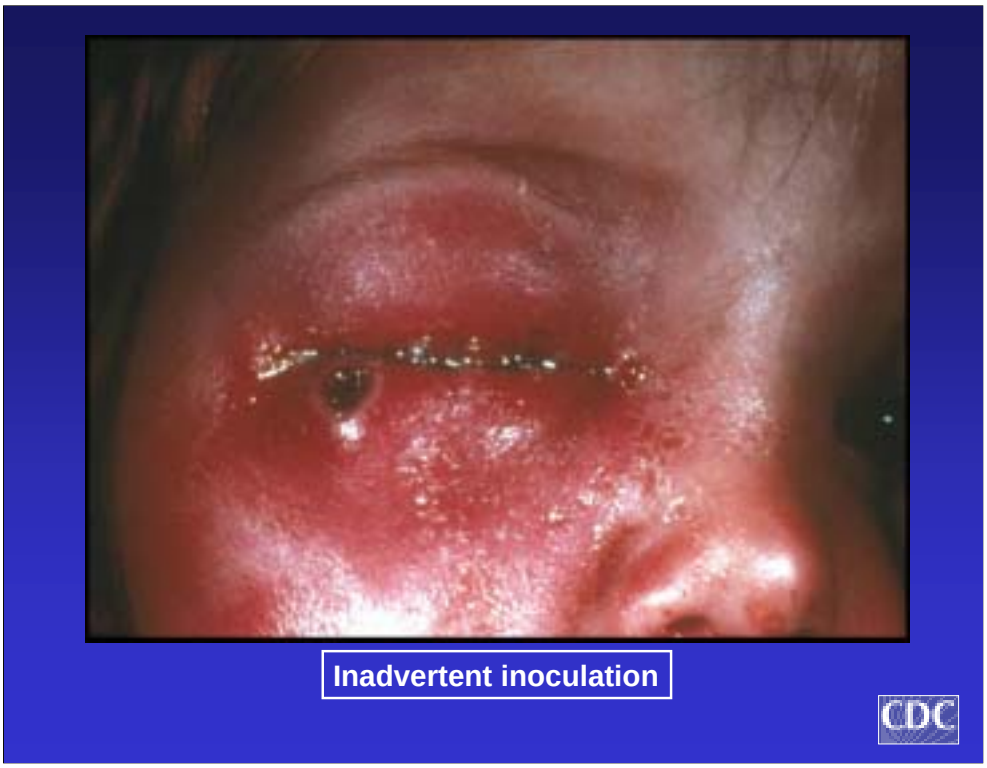
Occasionally, more severe non-specific immune reactions such as erythema multiforme or Stevens-Johnson syndrome can be seen following vaccination. This picture shows erythema multiforme following vaccination.



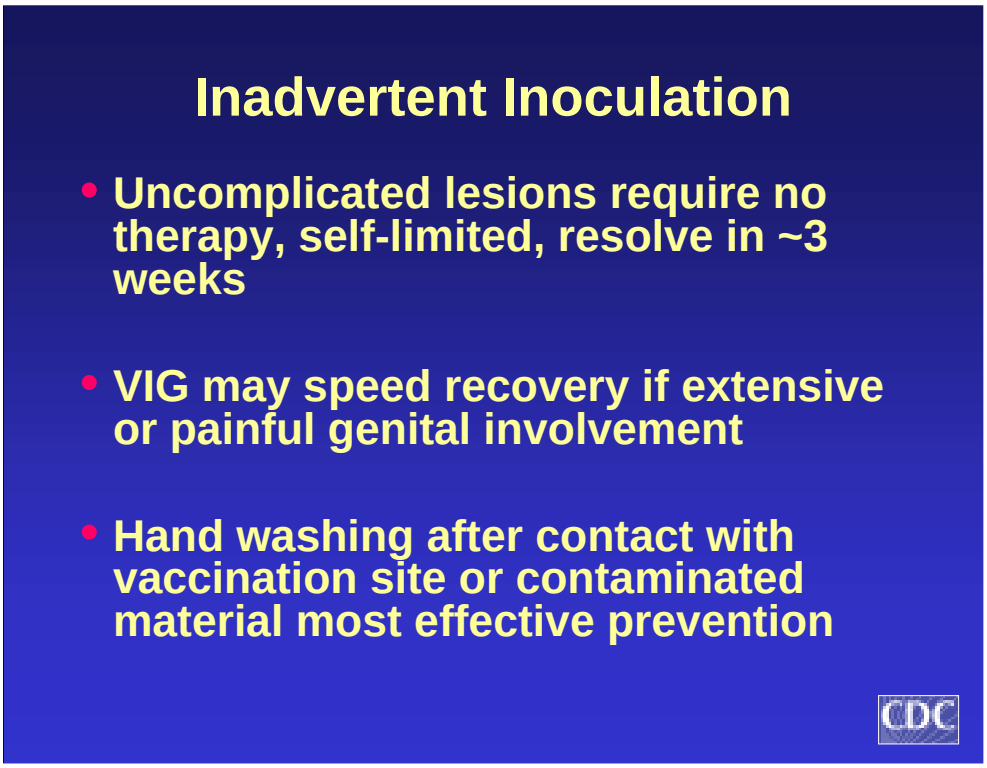
Erythema multiforme can present as macules, papules, urticarial lesions or the typical bulls eye lesions. The lesions usually do not progress to vesicles and don't contain live vaccinia virus because they are not a result of disseminated vaccinia virus. Vaccinia Immune Globulin, or VIG is not effective or indicated for the treatment of this complication.



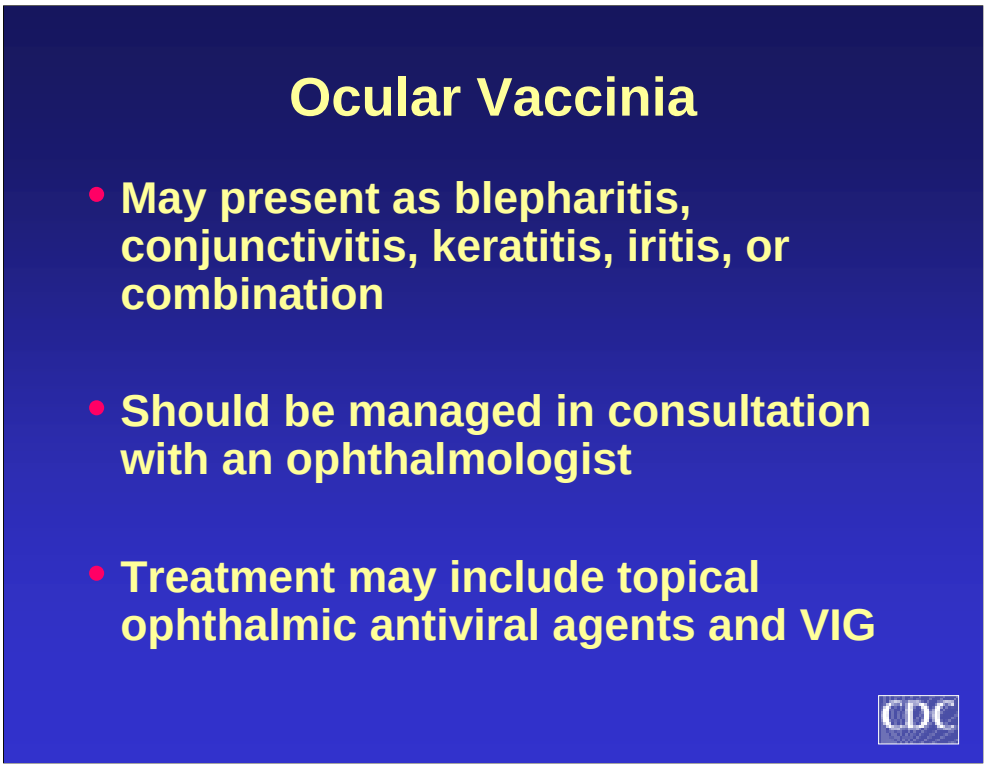
Inadvertent inoculation is the accidental transfer of vaccinia virus from the vaccine site to another area of the body or to another person. This is the most common adverse event seen following vaccination. Transfer to another body site results in a second, similar skin lesion that progresses through 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. 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, atopic dermatitis, or immune suppression.



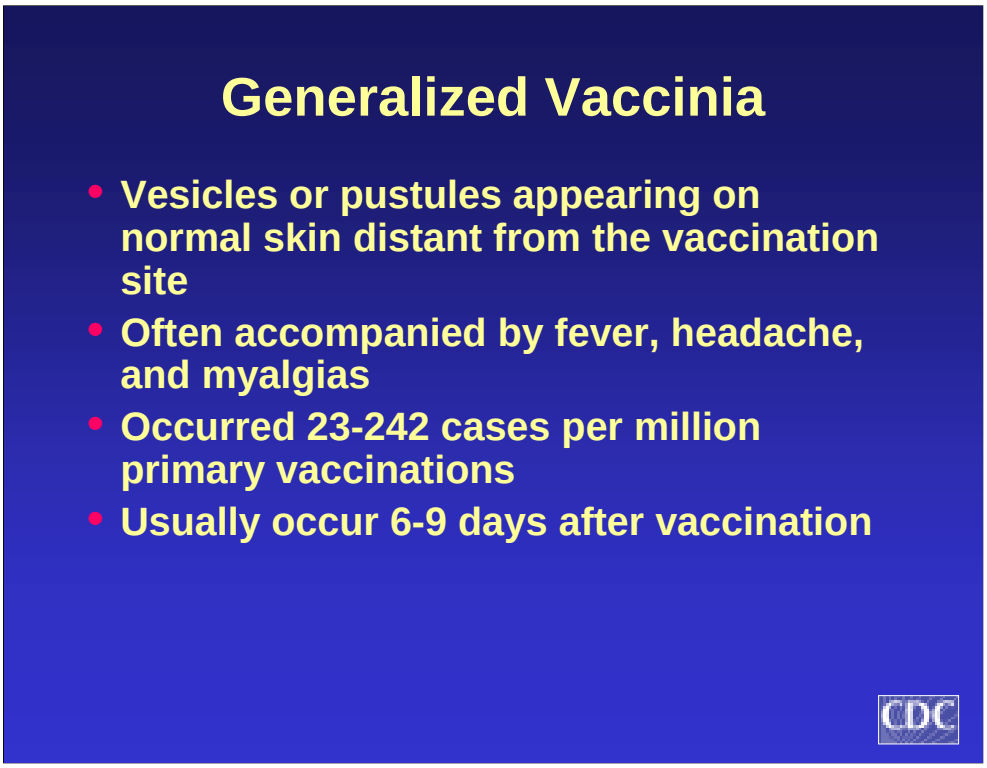
Inadvertent inoculation of the eyelid can lead to significant swelling and redness of the eyelid and periorbital area.



Usually, lesions resulting from inadvertent inoculation are uncomplicated and don't require specific therapy other than good site care. If there are multiple, clinically significant lesions, or lesions that cause the individual a great deal of discomfort, VIG may help speed the recovery if given early in the course before neutralizing antibodies appear on their own.

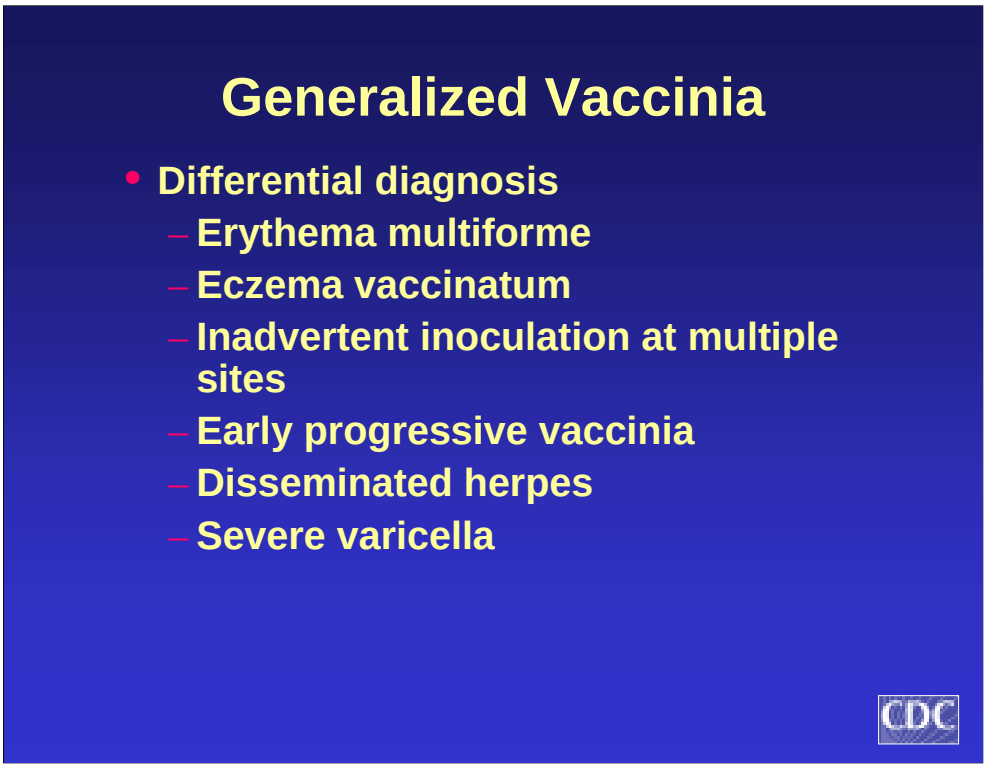


Inoculation of the virus in the eye can result in several clinical manifestations including blepharitis or infection of the eyelid, conjunctivitis, keratitis or iritis, or a combination of these conditions. Ocular vaccinia should be managed in consultation with an ophthalmologist as the treatment and monitoring of these eye complications can be complex and may involve the use of current ophthalmologic antiviral agents and possibly vaccinia immune globulin.

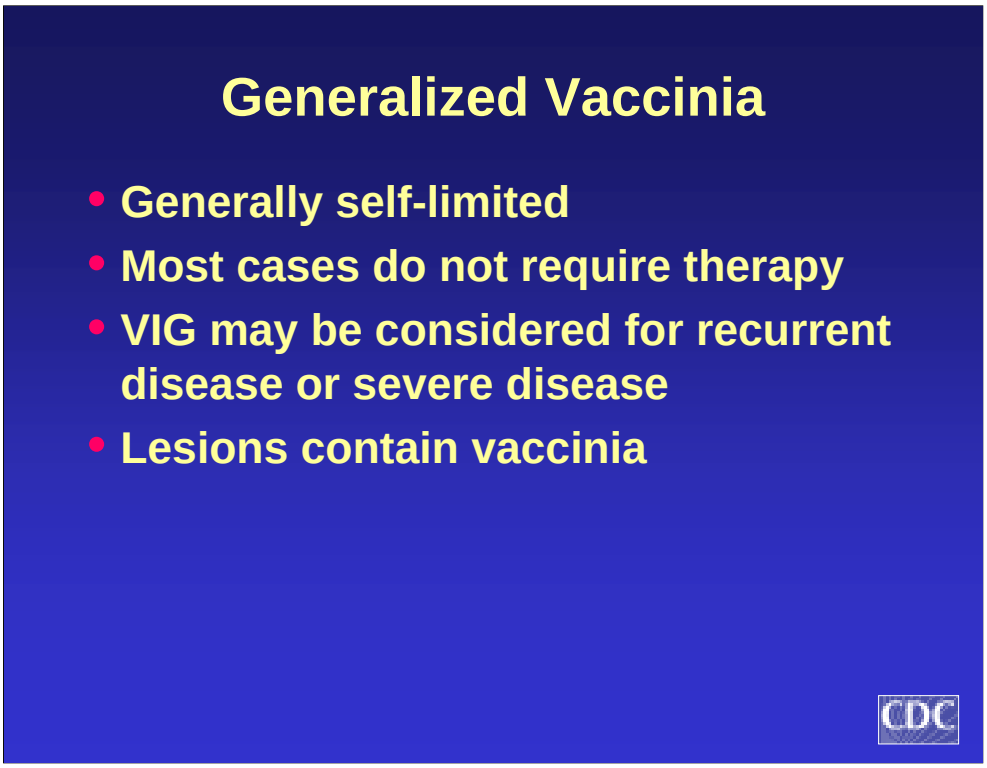


Generalized vaccinia usually presents as a rash that develops into vesicular or pustular lesions distal from the vaccination site. This vesicular rash may involve only a few, scattered lesions but can also be more extensive and generalized in nature. Fever and other systemic symptoms may be present but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

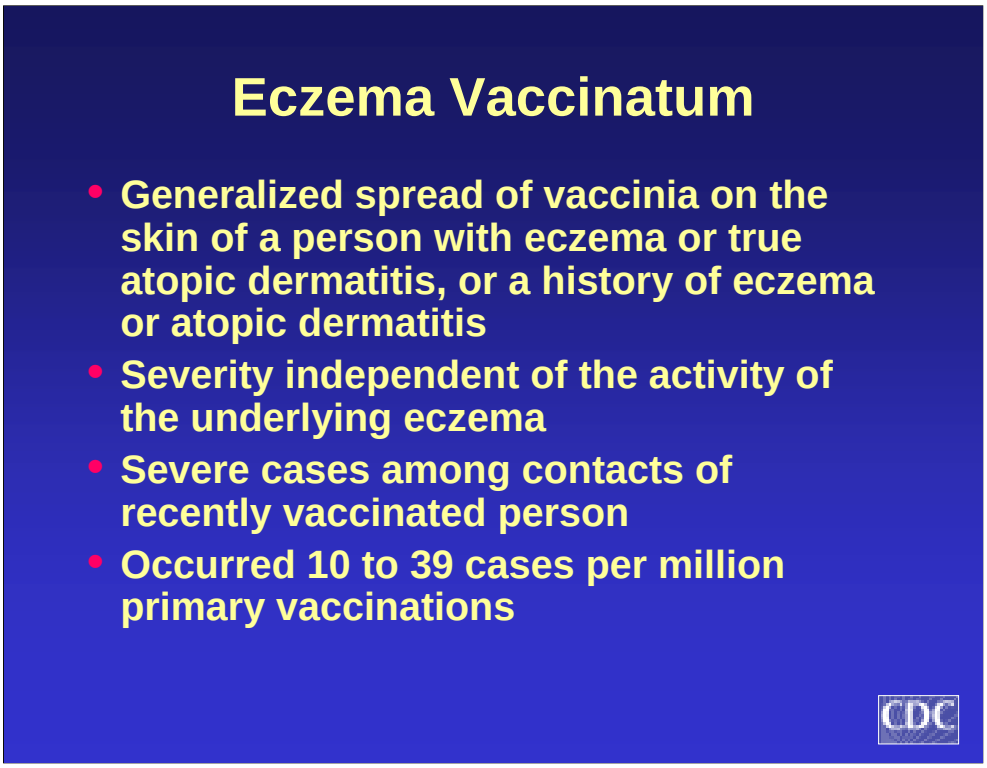
Here we see several pustular lesions of generalized vaccinia located on the lower legs.



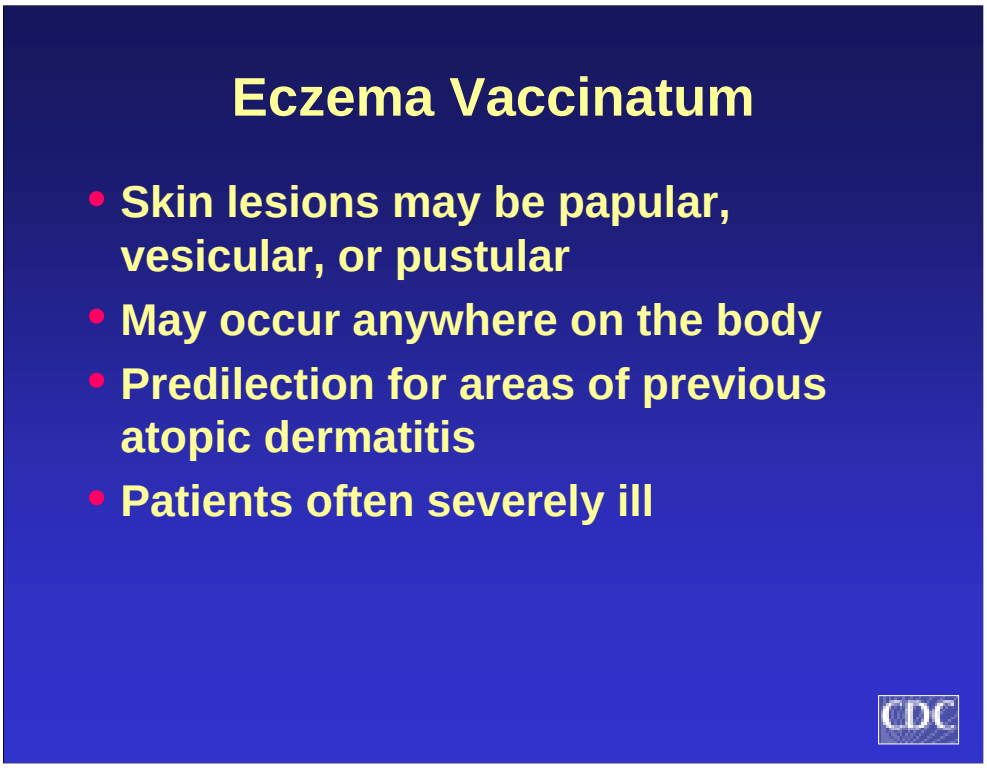
The differential diagnosis for this vaccine complication includes other non-specific immune rashes that can also occur following vaccination, eczema vaccinatum, metastatic lesions of early progressive vaccinia, or non–vaccinia related conditions such as disseminated herpes or severe varicella.



In a person with a normal immune system, generalized vaccinia is usually self-limited, and doesn't require specific therapy. VIG may be utilized in cases where the individual is more seriously ill or has an underlying immune problem. This complication is felt to result from hematogenous spread of the virus and the rash lesions do contain live vaccinia virus unlike the other non-specific rashes that can occur following vaccination.

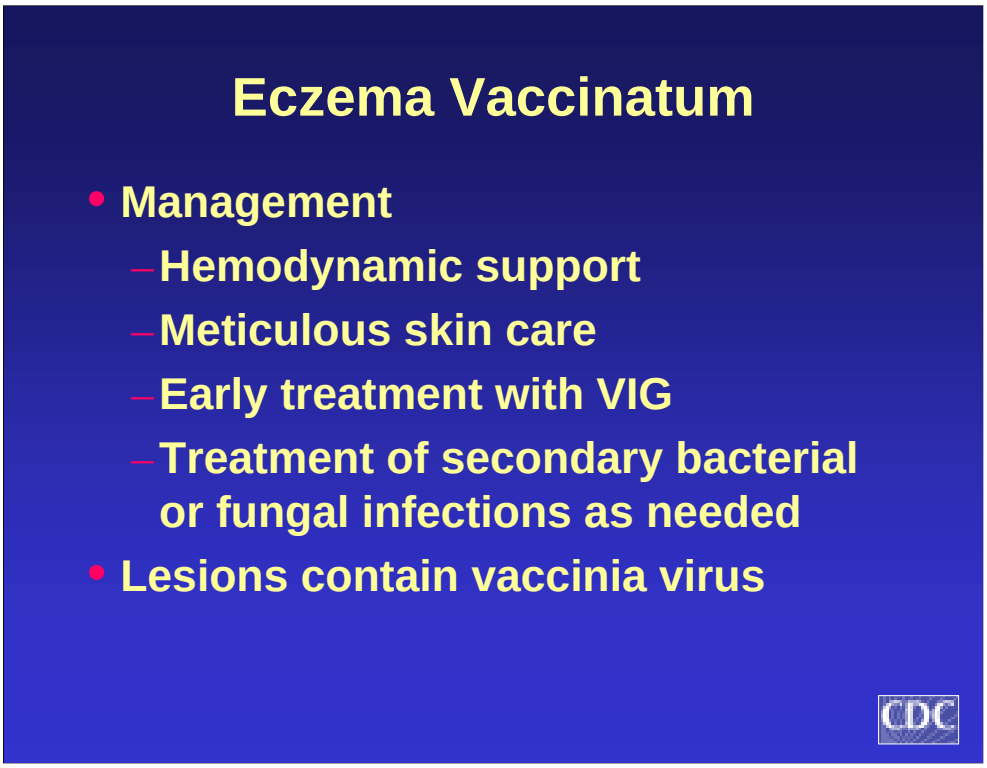


Eczema vaccinatum is one of the more serious adverse events that can result from smallpox vaccination. This complication can occur in individuals with active eczema or atopic dermatitis, or in those with a history of these conditions even when the condition is not active. A less severe form of eczema 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. Good medical history screening of potential vaccine recipients and their close contacts for the presence or a history of these conditions is the most important way to reduce the occurrence of this adverse event.

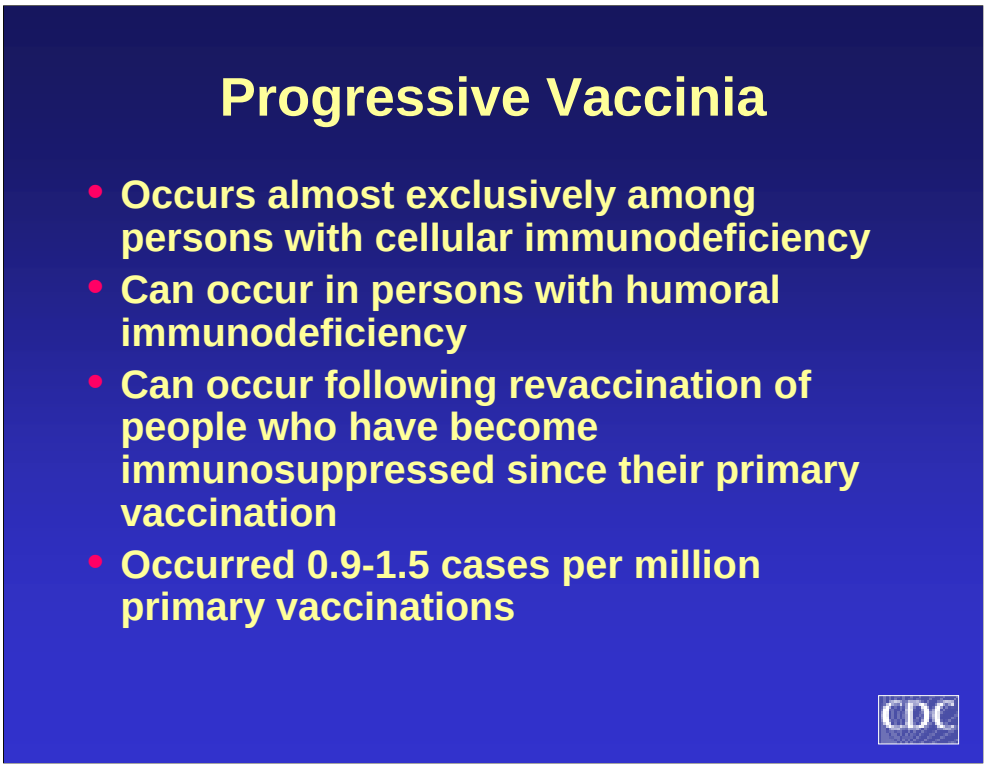


The rash of eczema vaccinatum can occur anywhere on the body but has a predilection for areas effected by atopic dermatitis or eczema. The rash can be quite extensive and even become confluent with papular, vesicular, or pustular lesions. Patients with significant skin involvement can become severely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

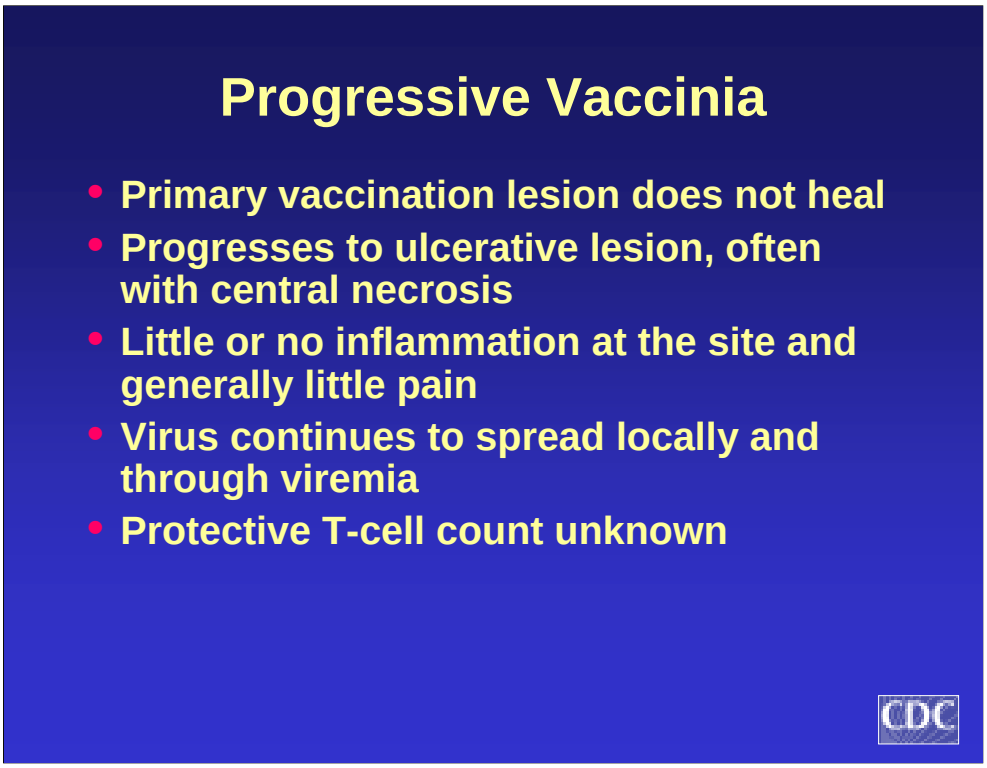
This picture demonstrates the extensive skin involvement of eczema vaccinatum in a close contact to a recently vaccinated person. Extensive skin involvement may result from inoculation of vaccinia virus in skin sites with compromised dermal integrity due to eczema or other skin conditions or may be the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



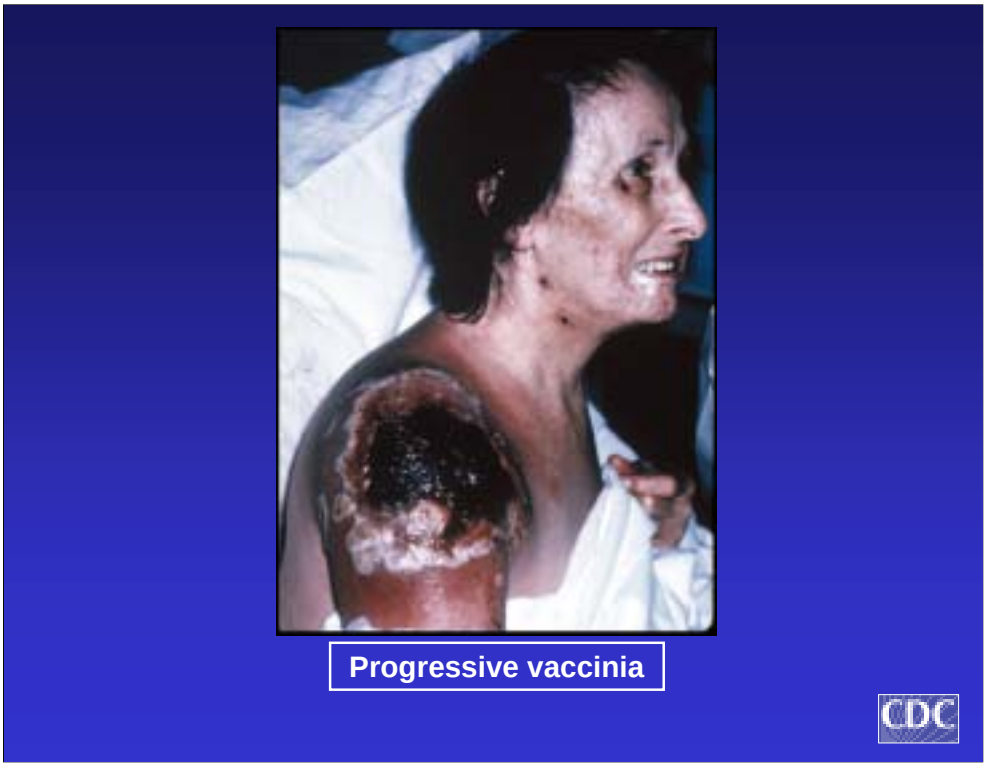
Eczema vaccinatum can be quite severe and even result in death. Management of this complication involves treatment with VIG and supportive care, including good fluid management and skin care as is done with other conditions like burns that effect large areas of the skin. It is also important to remember that the lesions contain vaccinia virus that can be shed into the patient's room environment. Strict contact precautions should be followed by care givers to prevent nosocomial transmission of virus from the lesions to themselves or to other patients. If extensive skin lesions are present there is a possibility for greater amounts of virus to be shed into the room environment from the lesion drainage. Additional precautions may be needed to prevent potential contamination of other areas outside of the room from air current transportation of virus. Healthcare personnel who are pregnant or who have eczema, atopic dermatitis, or immune system problems themselves, should not be utilized to care for EV patients.



Progressive vaccinia or vaccinia necrosum is a rare but serious adverse event that can occur in people with cellular immunodeficiencies or in individuals with humoral or immune globulin deficiencies.

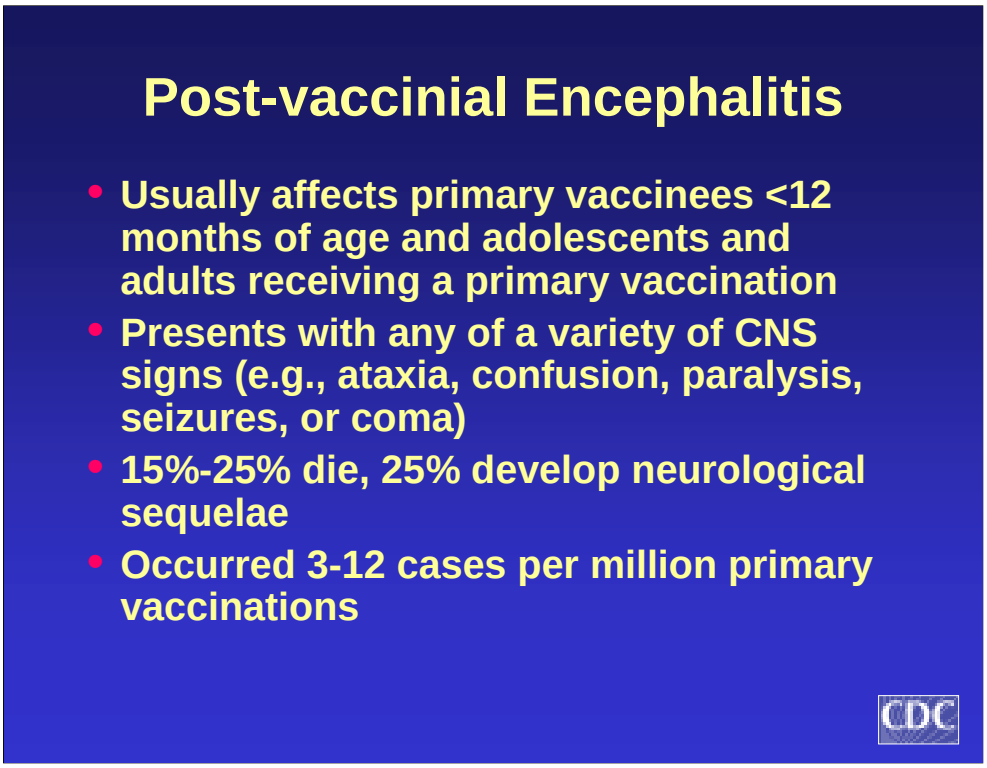


Persons with progressive vaccinia usually present with a non-healing, expanding vaccination site. The site often ulcerates and central necrosis, or necrosis of the surrounding skin can occur. There is generally little or no inflammation at the site initially, because of the poor local immune response 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. Therefore, careful medical history screening of potential vaccinees and their close contacts for conditions such as leukemia or HIV, or the use of medications like steroids or other immune suppressive drugs, is important in preventing this adverse event. It is currently unknown exactly what level of cellular or humoral immune depression would put a person at risk for this complication.

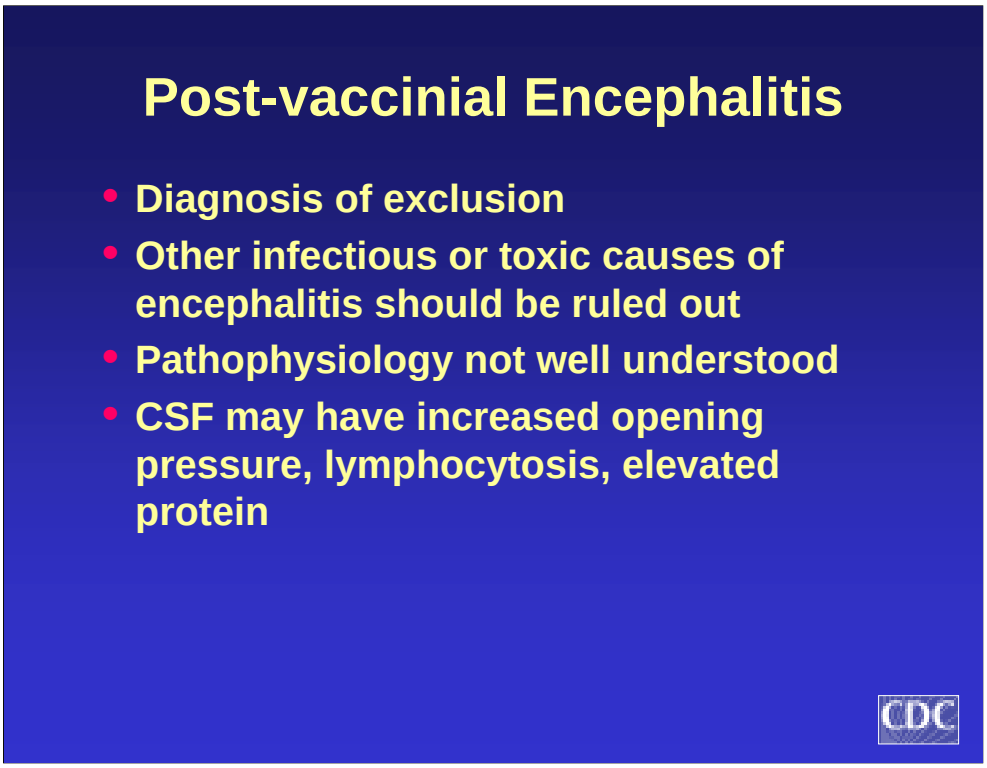


This woman had chronic lymphocytic leukemia. Notice how the infection from the vaccine site has spread to involve the surrounding skin and the necrotic appearance of the area. This woman also has metastatic lesions on her neck and other areas of her body presumably from hematogenous spread of the virus.

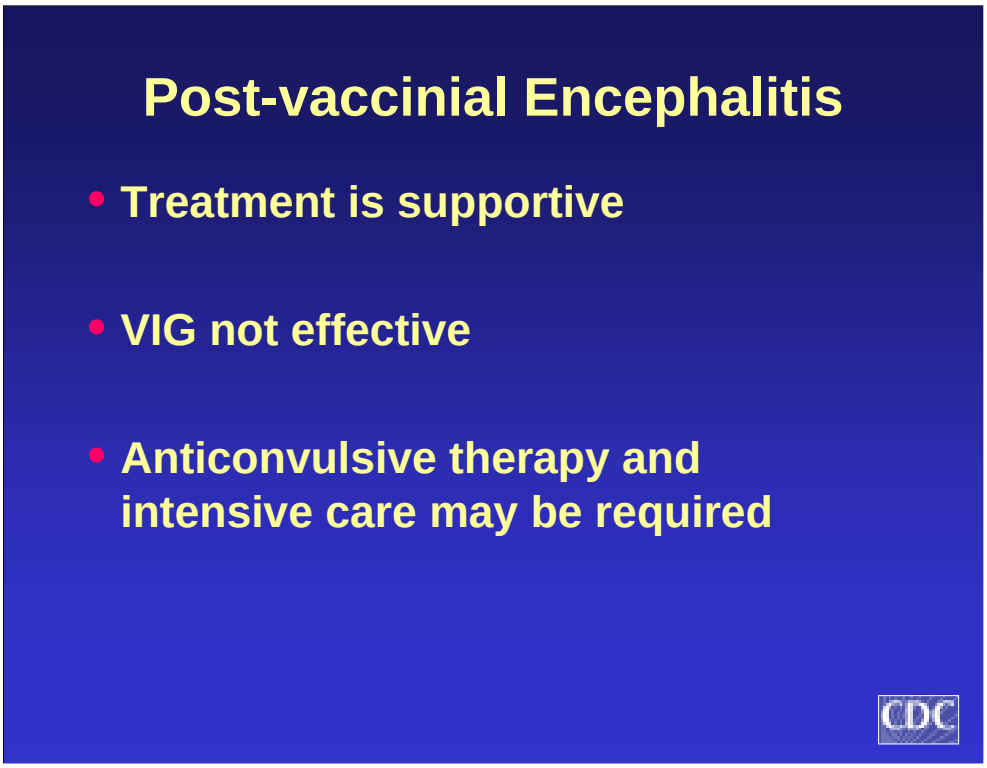
Progressive vaccinia was historically treated with aggressive VIG therapy, and sometimes with surgical debridement to remove necrotic tissue and reduce the overall viral burden on the immune system. Antiviral therapy was utilized at that time with varying degrees of success and it is unclear how effective newer antivirals today would be in the treatment of this complication. Progressive vaccinia lesions also contain vaccinia virus and appropriate precautions should be taken to prevent the contact transmission of virus.



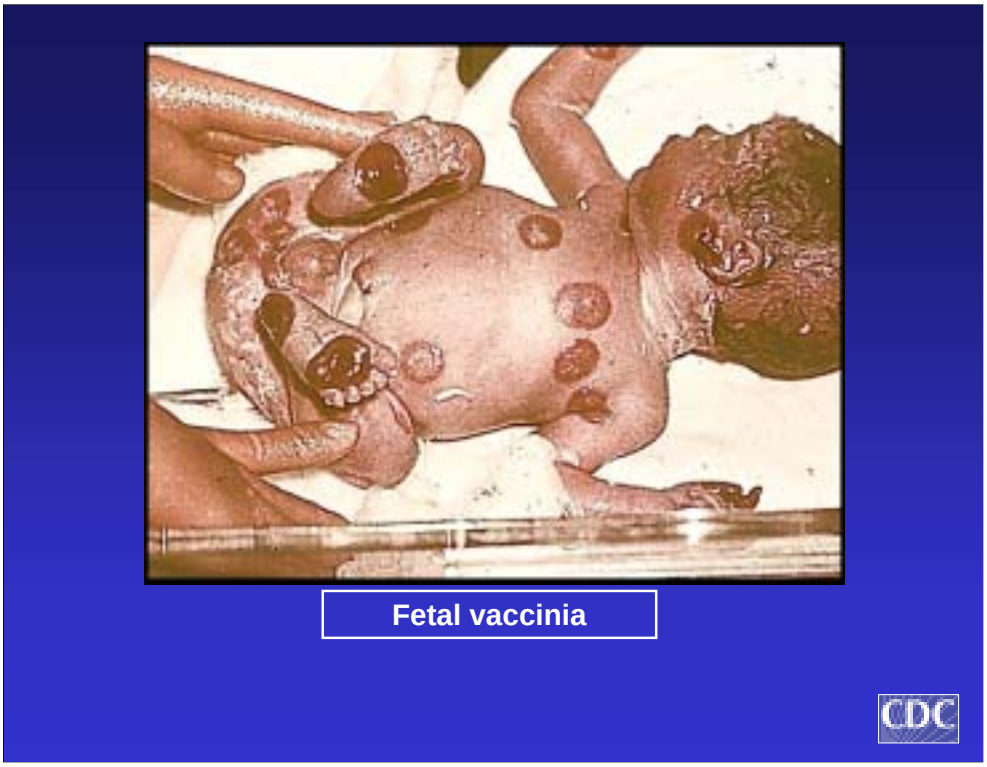
Post-vaccinial encephalitis is also a very rare but serious vaccine complication. It was more frequently seen in vaccinated infants less than 1 year old or in older adolescents or adults receiving their first vaccination. It can present with a variety of CNS manifestations from confusion to seizures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



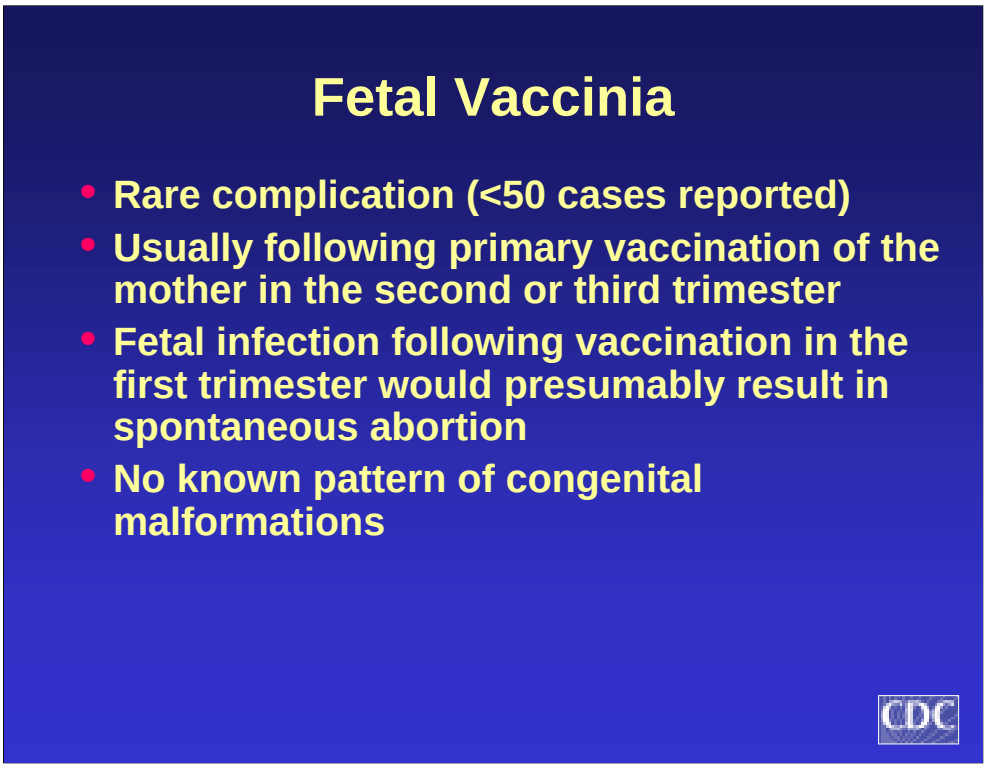
Symptoms of post-vaccinial encephalitis usually occurred between 9 and 14 days following vaccination and it's diagnosis involves excluding other potential causes for encephalitis. The pathophysiology of this complication is not well understood but it is thought to be a result of a post vaccination immune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



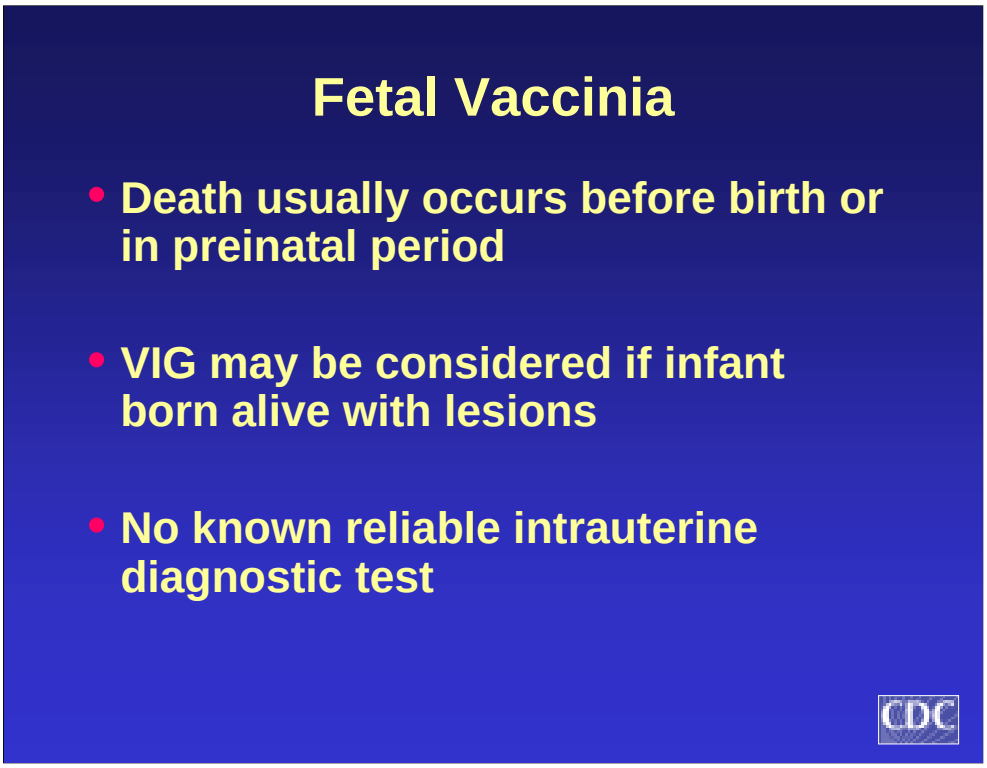
VIG was not effective in treating this complication and is therefore not indicated. Treatment is supportive and may require intensive care monitoring and anticonvulsive therapy.



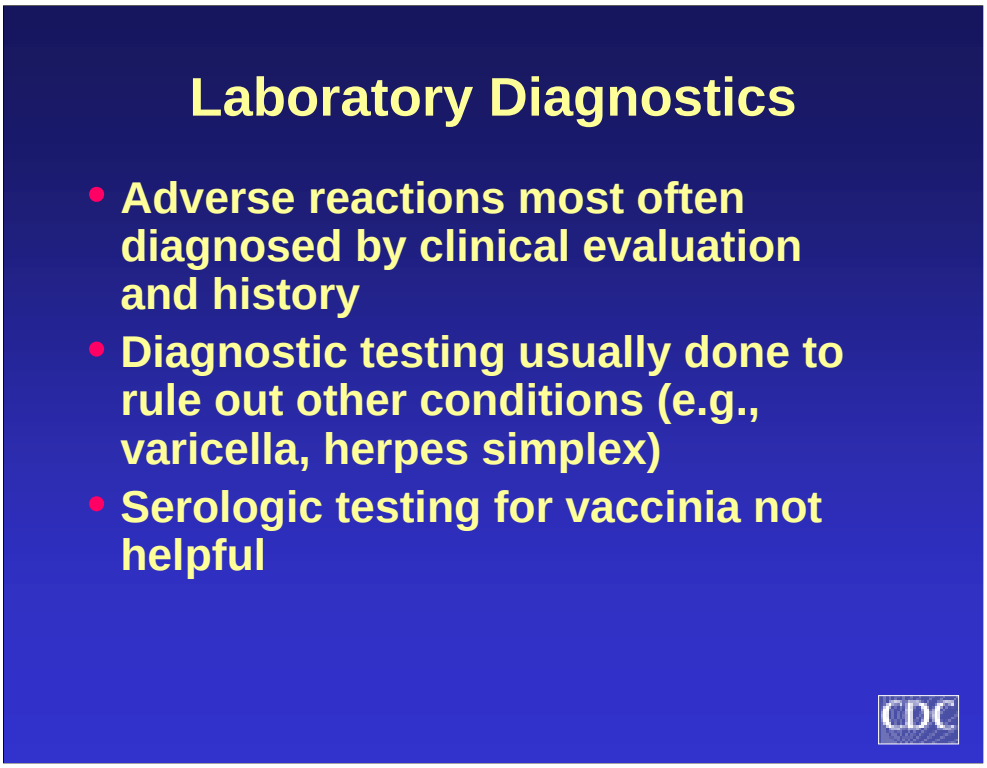
This is a picture of an infant infected with vaccinia virus in utero. Intrauterine infection of a fetus is referred to as fetal vaccinia.



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.

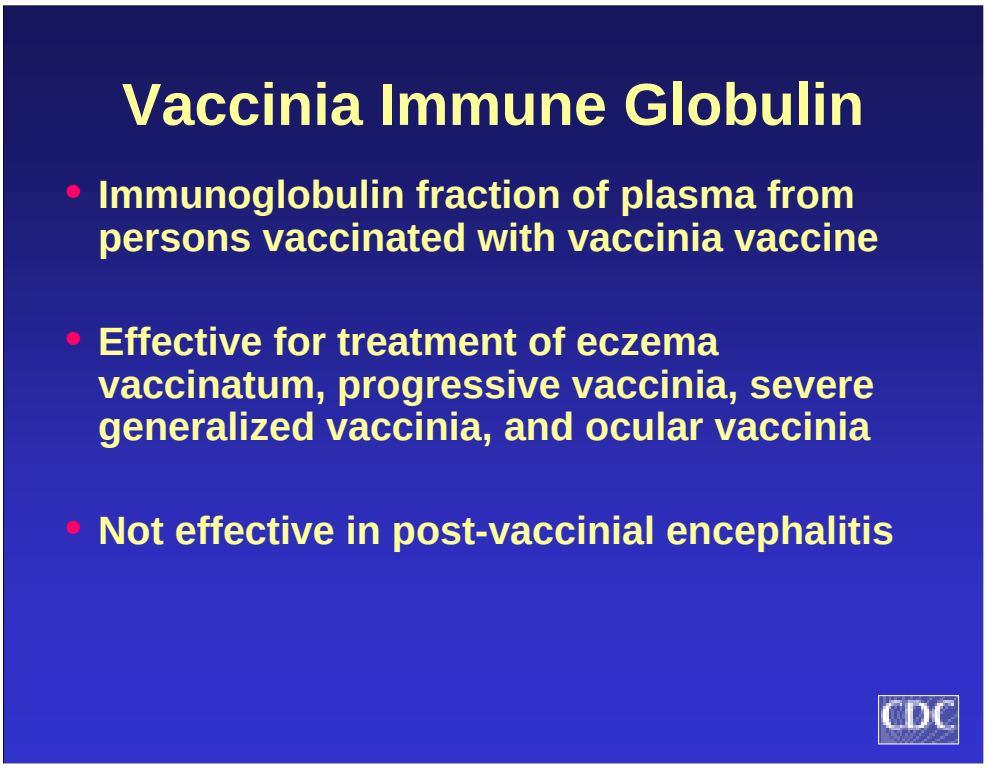


happened in-utero, or in the prenatal period. For infants born alive with vaccinia lesions, VIG may be considered, though no data exists regarding the dosage or efficacy of this treatment for fetal vaccinia. There is no known reliable intrauterine diagnostic test to confirm fetal infection.

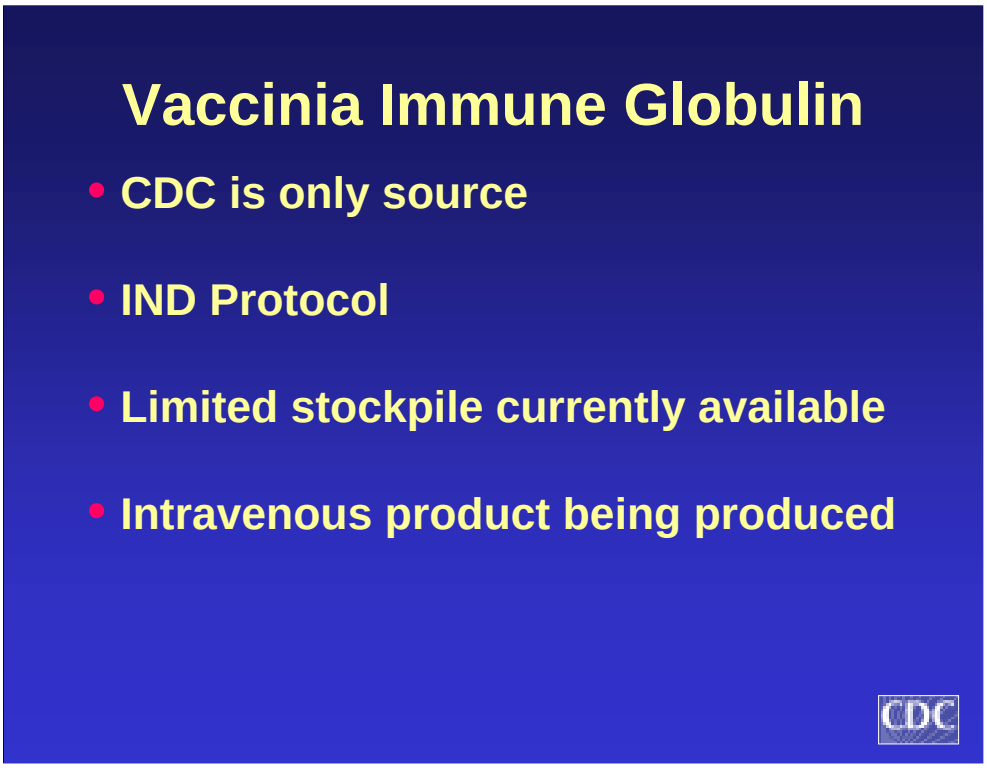


The diagnosis of smallpox vaccine adverse events is most often done with a thorough history and clinical evaluation. Viral isolation or PCR detection of vaccinia virus for adverse events that are associated with viral replication or dissemination is also helpful in confirming these vaccine complications. For individuals who are being evaluated for a possible complication that may have resulted from contact transmission of vaccinia, diagnostic testing to rule out other more common causes of vesicular rashes should also be done. On a separate note, serologic and cell mediated immunity testing following vaccination are currently research tools to assess the immune response to vaccination, and not tools to determine whether vaccination was successful. The level of these immune responses that correlates with protection against smallpox is unknown. That's why we look to the skin site reaction to determine if a vaccination was successful, because "major" or primary reactions following vaccination correlated well with immunity to smallpox during the eradication period.

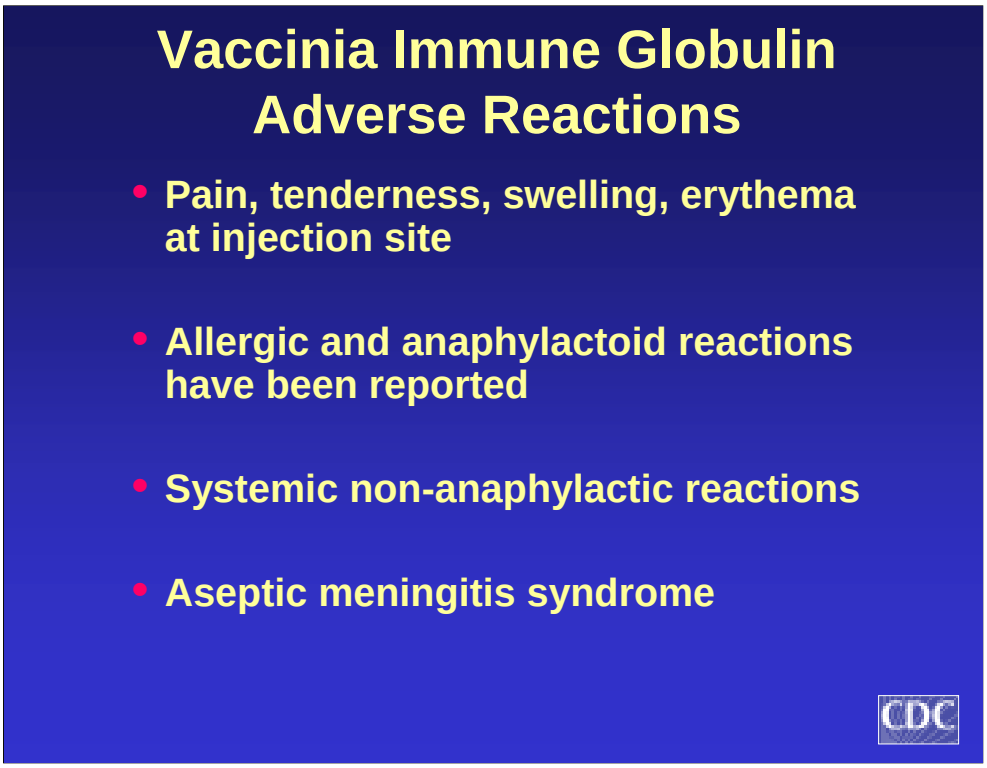
(for additional information, see Laboratory Support module)



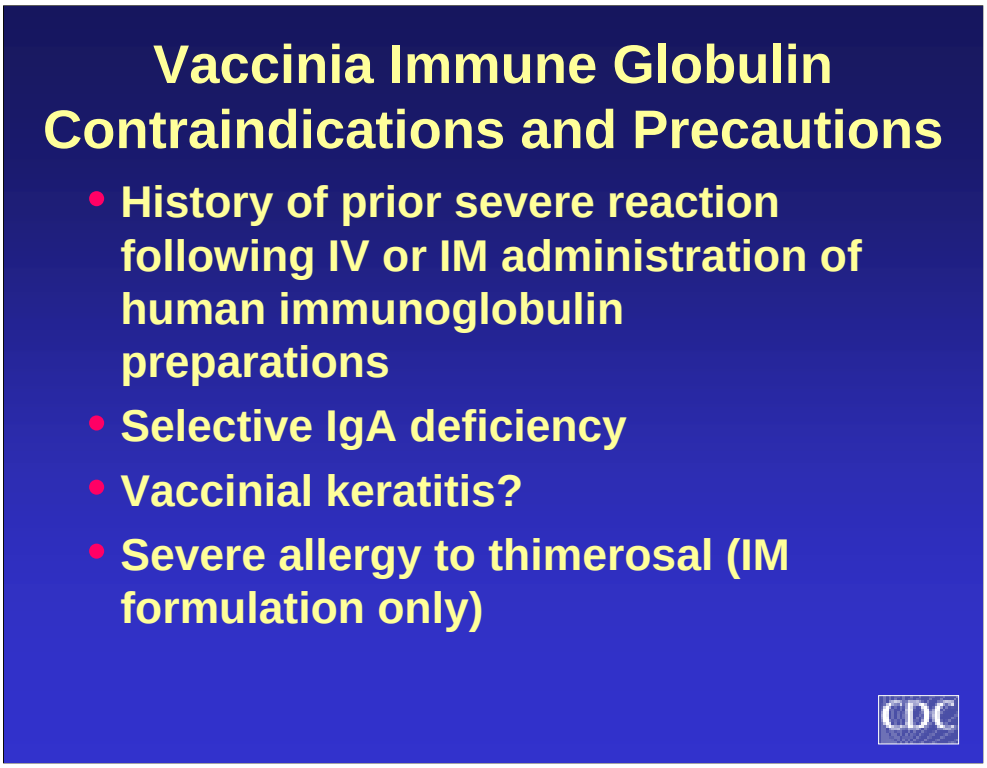
The primary treatment for adverse events involving uncontrolled replication or dissemination of vaccinia virus following vaccination is VIG. VIG is a human immune globulin product derived from the plasma of persons vaccinated with vaccinia vaccine. It is effective in the treatment of eczema vaccinatum, serious generalized vaccinia, and serious manifestations of inadvertent inoculation such as ocular vaccinia. VIG is also indicated for progressive vaccinia and has variable effectiveness in treating this complication. Since post vaccinial encephalitis is not due to virus multiplication, VIG is not effective in treating this adverse event.



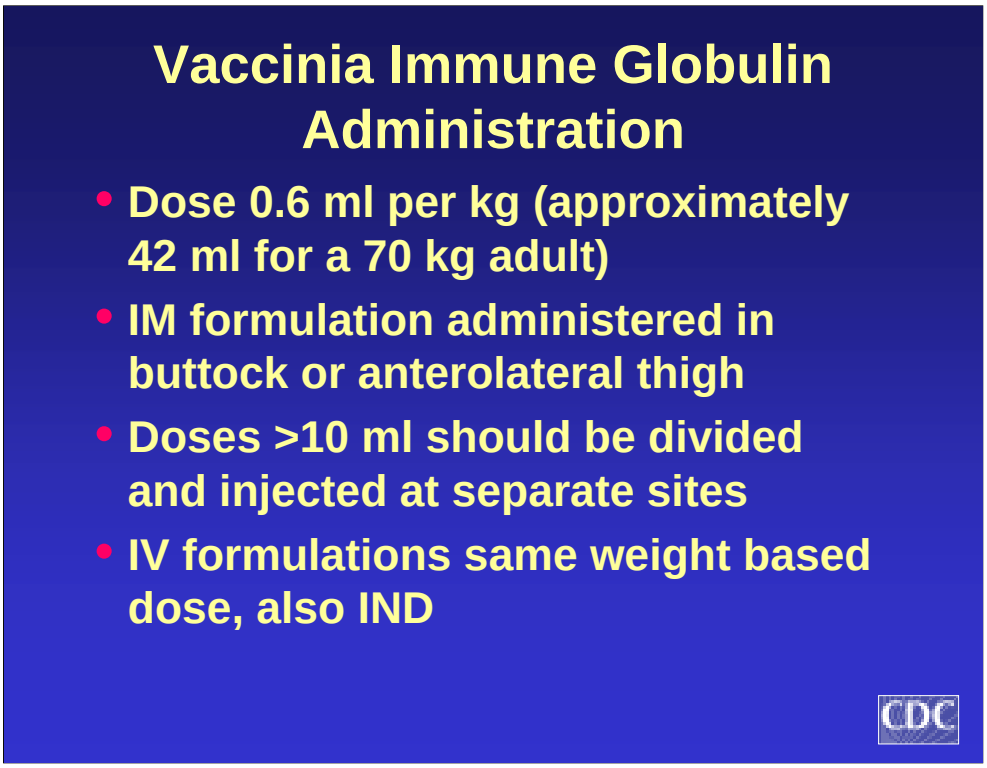
Currently, CDC is the only source of VIG for use in treating vaccine adverse events in the civilian population. It is not licensed at this time and must be utilized under an Investigational New Drug or IND Protocol. A new intravenous formulation of VIG is being produced and will be available for treatment of adverse events. But, stores of this and the previously produced intramuscular product are still limited and VIG should be reserved for use in the treatment of more serious vaccine complications.



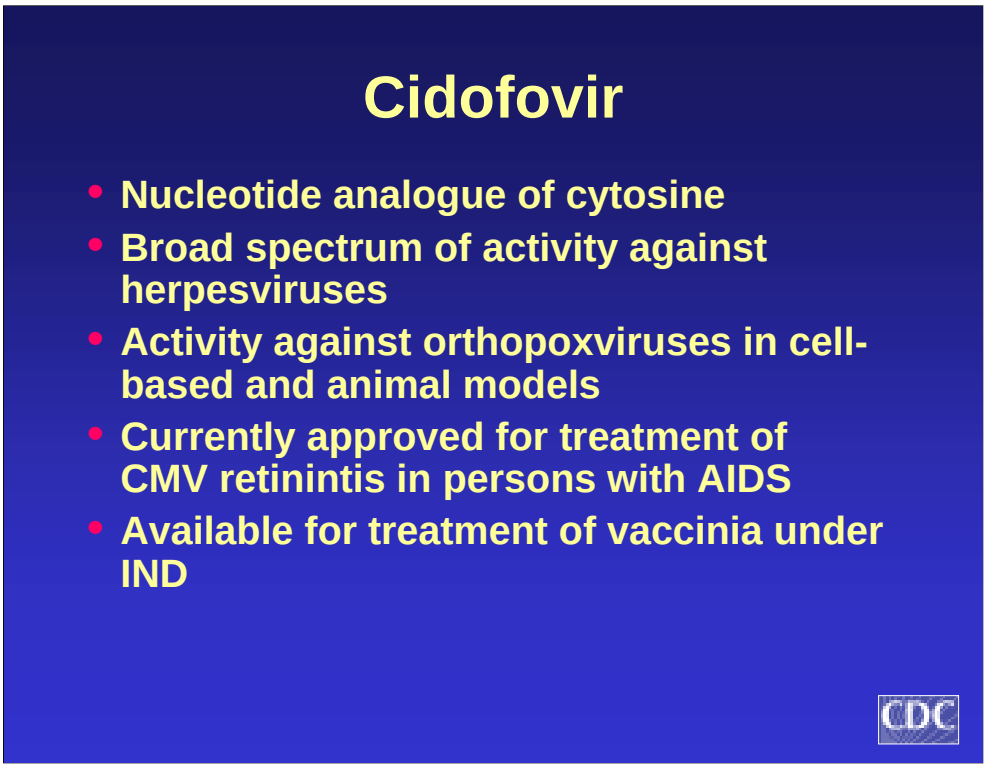
Side effects from VIG are rare and are similar to those seen with other human derived immune globulin products as listed here.



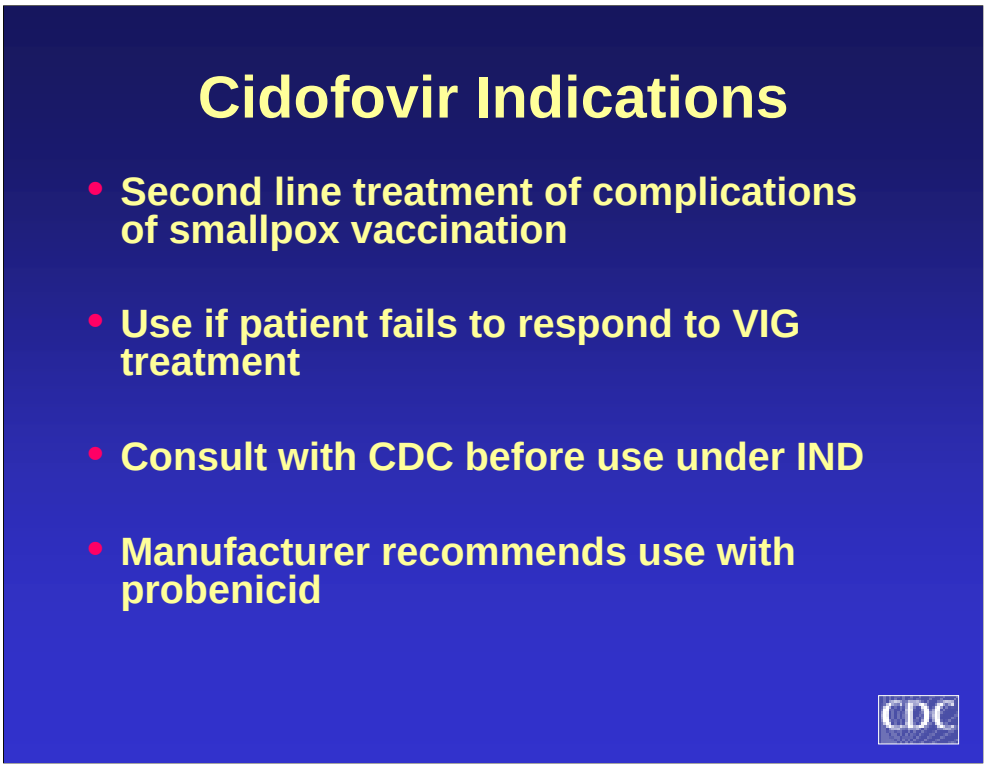
People with selective IgA deficiency or those who have had a severe allergic reaction to other immune globulin products can also experience a severe anaphylactic response to VIG. The intramuscular formulation of VIG contains thimerosal and people with a severe allergy to this component could also experience an allergic reaction to IM VIG. VIG use in the presence of vaccinial keratitis may increase the possibility of corneal scarring but might be considered if an ophthalmology specialist feels that more serious consequences of keratitis can be prevented with this treatment.



The initial treatment dose for VIG is 0.6 milliliters per kilogram, which is about 100 milligrams per kilogram. Because the total dose can be large, the IM VIG dose is often divided and given in multiple sites or with several injections over a 24 hour period. Administration of the IV product can usually be done during a single intravenous administration over an hour or so depending on the total dose.

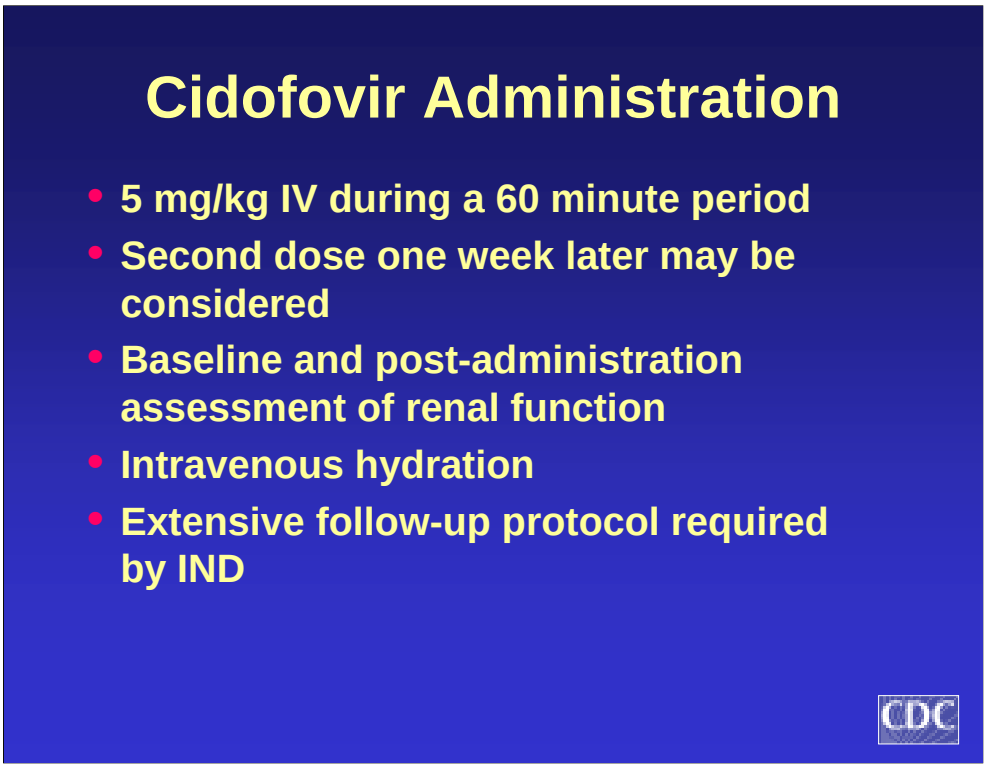


Cidofovir is an antiviral medication that is currently licensed for the treatment of CMV retinitis. In vitro and animal studies with this drug have shown some activity against vaccinia virus, but it is unclear how well it would work in treating vaccinia infections in humans. Because it is not licensed for this indication, use of cidofovir for treating vaccinia infections should be done under an investigational new drug protocol with careful monitoring.

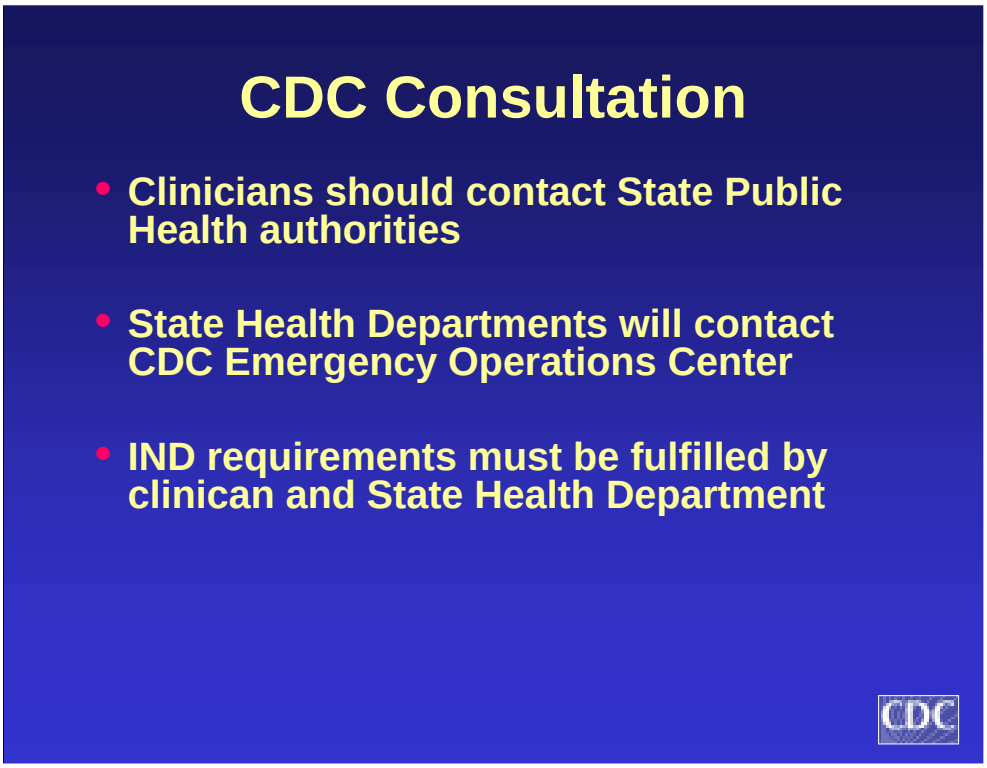


Cidofovir is a second line treatment for complications of smallpox vaccination as VIG is still considered the standard treatment. CDC is developing the investigative protocol for use of this medication. Probenicid and hydration should be used with cidofovir to help reduce the risk of renal toxicity.

Cidofovir has been associated with these side effects. The occurrence of renal toxicity can be decreased with careful pre- and post infusion hydration along with the use of probenicid.



Cidofovir has a long half live and therefore only requires once weekly administration. The dose of cidofovir for vaccinia infections not responsive to VIG is the same as the dose used for treatment of CMV retinitis. Renal function should be carefully monitored. If the patient is still experiencing serious symptoms of the vaccinia infection 1 week following the first dose of cidofovir, a second dose may be considered. Because cidofovir itself can have severe side effects, and we don't know how effective it will be in treating vaccinia adverse events, good clinical evaluation and follow-up is essential. There is little to no experience with the use or dosing of cidofovir in children and probenicid is not otherwise recommended for use in children under 2 years of age.



In summary: it is very important for public health and medical personnel to again become familiar with smallpox vaccine, the expected vaccine reactions, and the evaluation and management of vaccine adverse events. The CDC website has several educational resources that can help. CDC personnel are available to consult with public health officials and clinicians on the evaluation and management of smallpox vaccine adverse events and CDC will provide VIG and Cidofovir under an IND protocol, when indicated, to treat these complications. Thank you for your attention.

For More Information

- CDC Smallpox website
  www.cdc.gov/smallpox

- National Immunization Program website
  www.cdc.gov/nip

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