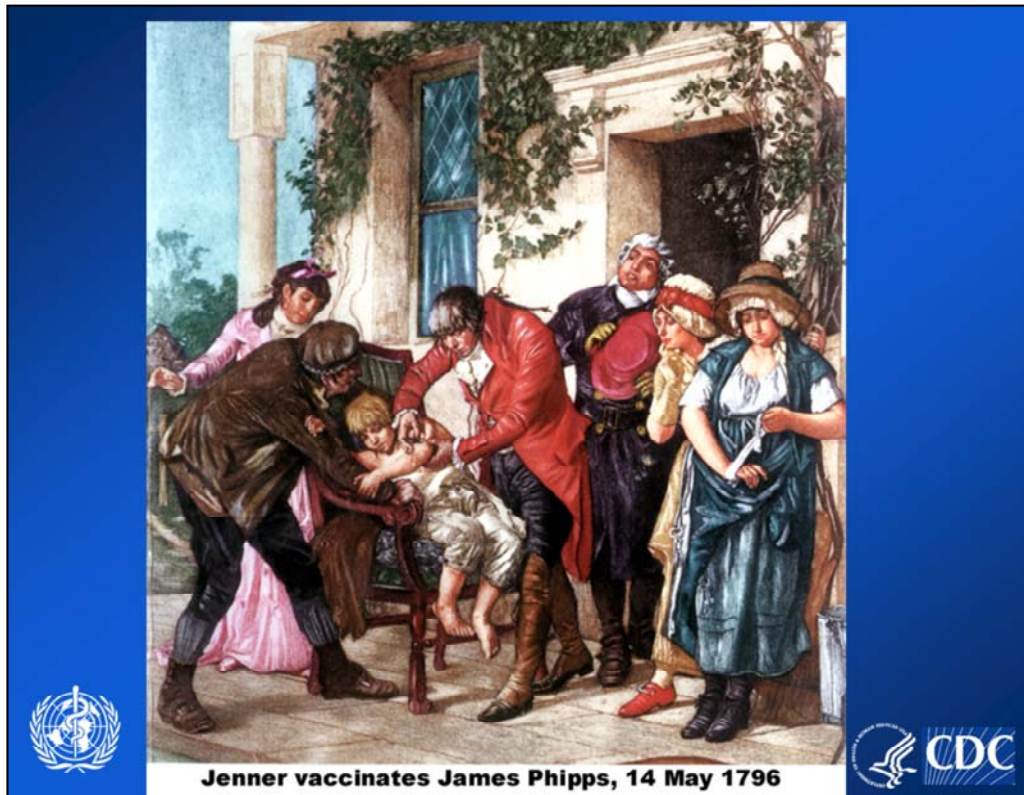


# Smallpox Vaccine Overview

Types of Vaccine  
Administration  
Contraindications  
Adverse Reactions





Smallpox has been a vaccine-preventable disease for more than 200 years. In 1796, Edward Jenner demonstrated that immunity to smallpox could be produced by inoculating a human with material from a lesion on the udder of a cow. Jenner called this infectious material vaccine, and the procedure came to be called vaccination.

## Smallpox Vaccine History

- Original material used by Jenner was probably cowpox.
- Cowpox to vaccinia in 19<sup>th</sup> Century.



The material Jenner used for his vaccine probably contained cowpox virus, a virus related to variola but not as virulent.

At some time during the nineteenth century, the virus used for smallpox vaccination ceased to be cowpox and changed to vaccinia. Vaccinia is in the same family as cowpox and variola, but is genetically distinct from both. The origin of vaccinia, and how it came to replace cowpox virus in the vaccine is not known.

# Vaccinia Virus

- Origin of vaccinia virus unknown.
- Genetically distinct from cowpox and variola.
- May be a virus now extinct in nature.



Neutralizing antibodies induced by vaccinia vaccine are cross protective for other Orthopoxviruses, such as monkeypox, cowpox, and variola viruses. That's why immunity produced by vaccinia virus protects against smallpox.

## Smallpox Vaccine

1796	Edward Jenner develops vaccine
1805	Use of cows to produce vaccine
1940's	Freeze-drying technology
1965	Licensure of bifurcated needle
1971	Routine vaccination stopped in US
1975	Attenuated strains - Japan
1983	Vaccine removed from civilian market



While there have been some technological advances that have made the eradication of smallpox possible, the vaccine is still basically the same concept pioneered by Edward Jenner in 1796.

An attempt to create an attenuated vaccine in Japan proved to have dramatic reductions in adverse reactions. However, it was never able to be challenged against naturally occurring disease, since eradication programs were so successful.

## Smallpox (Vaccinia) Vaccine Dryvax®

- Lyophilized vaccinia containing calf lymph.
- Original diluent in separate vial with attached needle (shaker tube)
- Trace amounts of antibiotics:
  - Polymyxin B.
  - Streptomycin.
  - Chlortetracycline.
  - Neomycin.



The vaccine is provided as a freeze dried powder in a 100 dose vial. The original diluent contains 50% glycerin, 0.25% phenol in sterile water for injection, 0.005% brilliant green.

The diluent used to reconstitute the vaccine contains the antibiotics polymyxin B, streptomycin, tetracycline, neomycin, and a small amount of phenol as a preservative.

# Vaccine Production

- Liquid vaccine – lost potency in tropical climates.
- 1909 – Freeze-drying technology.
- 1950's – Collier produced vaccine stable at 37°-45° C for 64 weeks.
- 1970's – Japanese produce attenuated virus vaccines that are less reactogenic



One of the key technological issues that had to be overcome was the fact that the liquid smallpox vaccine lost its potency in tropical climates. A freeze-drying technology developed in 1909 helped to improve this. However, it wasn't until Collier further worked with this process that the vaccine became stable for quite some time at higher temperatures.



## Vaccine Production

- Grown on skin of calves, sheep, water buffalo.
- Lesions harvested before crusting:
  - Maximizes viral titer.
- Pulp ground.
- Mixed with 40%-60% glycerol.
- Distributed in glass capillary tubes.



The virus for the vaccine is grown on the skin of calves, sheep, and water buffalo. Material from the lesions on these animals was harvested before the pustules formed scabs in order to obtain the highest viral load. This was then ground into a pulp and mixed with 40 to 60% glycerol.





## Dryvax® Vaccine Storage and Handling (Check Manufacturer's Instructions)

- Stable indefinitely at  $-20^{\circ}\text{C}$ .
- Unreconstituted – Stable >1 year at room temperature.
- Reconstituted – Stable 3 months\* at refrigerator temperature.



\* Recent FDA



The vaccine we're using now is stable indefinitely at  $-20^{\circ}\text{C}$ . If it's not reconstituted, it can remain stable for over a year at room temperature.

Once you reconstitute the vaccine, it can be kept for at least two months, possibly three, at refrigerator temperature. As its use continues in the United States, these storage times might change as more is learned about the vaccine using the new diluent.

## Dryvax Smallpox (Vaccinia) Vaccine Administration Schedule - Occupational

### Schedule:

- 1 Successful Dose >18 years of age.

### Revaccination:

- 10 Years - nonhighly-attenuated vaccinia and recombinants.
- 3 Years – highly attenuated orthopoxviruses.



The schedule for vaccinia vaccine for adults at occupational risk is to have one successful dose at 18 years of age or older. Those expecting exposure through the nonhighly attenuated viruses should be revaccinated every ten years. However, those who deal with the more virulent orthopoxviruses should be revaccinated more often.

## Smallpox (Vaccinia) Vaccine Administration Schedule – Non-Emergency

### Schedule:

- 1 Successful Dose >18 years of age.

### Revaccination:

- Unknown.



In a non-emergency situation, the current recommendation is only for adults. The need for revaccination is unknown, at this time.

# Vaccine Administration

- Surgical needle.
- Vaccinostyle.
- Rotary lancet.
- Jet injector.
- Bifurcated needle\*.

\*Only administration technique currently in use.



There have been several different ways of administering smallpox vaccine over the years. Those who immunize older adults might hear of some of these methods. However, the only administration technique currently in use today is the bifurcated needle.

## The Bifurcated Needle



Invented by Dr. Benjamin A. Rubin of Wyeth Laboratories, patented in July 1965. Developed in conjunction with Reading Textile Machine Company. Bifurcation holds exactly 1 mg of water, slightly more vaccine because of increased viscosity. WHO procured about 50 million bifurcated needles between 1967 and 1976. The 1970 price was about US\$5 per 1000.



## Smallpox Eradication Strategy The Bifurcated Needle



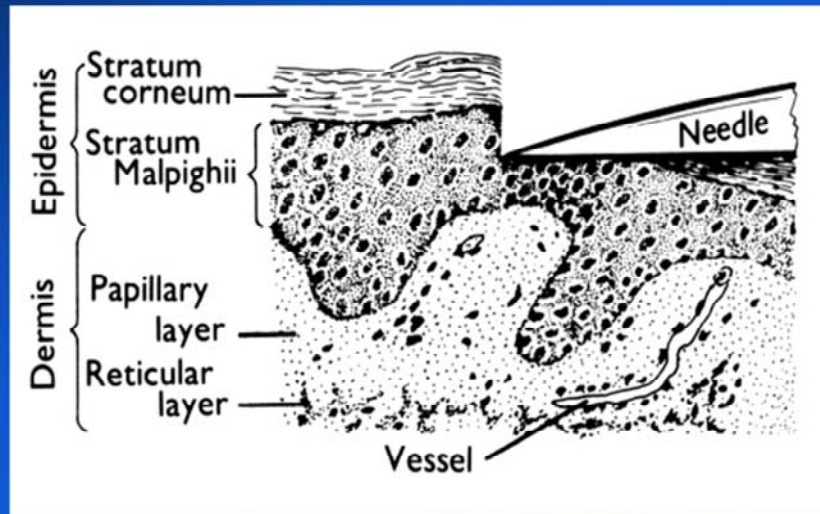
Fenner F et al.  
Smallpox and its  
Eradication, pp  
570



Smallpox vaccine is unique in that it is not administered by injection. It's administered with a two pronged, or bifurcated, needle like this one into the superficial layer of the skin.



## Vaccine Administration



Smallpox vaccine is unique in that it is not administered by injection. It's administered into the superficial layer of the skin with a two pronged, or bifurcated, needle. Bifurcated needles will be supplied to you in individual sterile packages.

## New Smallpox Vaccines, 2003

- Live vaccinia virus produced using cell culture technology.
- Distributed as a freeze-dried powder.
- Do not contain antibiotics.
- Diluent contains glycerin and phenol.



The new smallpox vaccines:

- Live vaccinia virus produced using cell culture technology
- Distributed as a freeze-dried powder
- Do not contain antibiotics
- Diluent contains glycerin and phenol

## Contraindications and Screening



Contraindications and screening are considerations for smallpox vaccinations.

## Smallpox Vaccine

- Vaccine contains live vaccinia virus.
- Vaccine virus can be transmitted to household and other close contacts.
- Candidates for vaccination must be carefully screened for contraindications.
- Certain medical conditions in the person's household contacts must also be considered as contraindications for vaccination.



Skin lesion contains vaccine virus for up to 3 weeks.

## Smallpox Vaccine Contraindications and Precautions Non-emergency Situations

- Serious allergic reaction to a prior dose of vaccine or vaccine component.



As with all vaccines, smallpox vaccine is contraindicated for persons who have experienced a serious allergic reaction to a prior dose of vaccine, or to a vaccine component. By serious allergic reaction, we mean anaphylaxis or symptoms of an anaphylaxis-like reaction, such as generalized urticaria, wheezing, or difficulty breathing

## Smallpox Vaccine Components

- Dryvax:
  - polymyxin B.
  - streptomycin.
  - tetracycline.
  - neomycin.
  - phenol.
- New vaccines do not contain antibiotics.



In addition to live vaccinia virus, The reconstituted Dryvax vaccine contains trace amounts of the antibiotics polymyxin B, streptomycin, tetracycline, and neomycin. It also contains phenol as a preservative. People with serious allergy to any of these products should not be vaccinated. The newer cell culture vaccines do not contain antibiotics. No smallpox vaccine available in the United States contains sulfa-type antibiotics or penicillin.

## Smallpox Vaccine Contraindications and Precautions Non-emergency Situations

- Serious allergic reaction to a prior dose of vaccine or vaccine component.
- Immunosuppression in the recipient or household contact.



People with significant immunosuppression should not receive smallpox vaccine. Replication of vaccinia virus can be enhanced among people with immunodeficiency diseases and immunosuppression, and result in serious adverse reactions. Also, because the recent vaccination site contains live virus that can be accidentally transmitted to other individuals, people with household contacts who are immunosuppressed should also not be vaccinated in non-emergency situations.



## Causes of Immunosuppression Diseases

- Leukemia.
- Lymphoma.
- Generalized malignancy.
- Solid organ or stem cell transplantation.
- Humoral or cellular immunity disorders.
- HIV infection.



Significant immunosuppression can be caused by many diseases, including leukemia, lymphoma, generalized malignancy; solid organ or stem cell transplantation; and humoral or cellular immunity disorders, including HIV infection. Certain autoimmune diseases and/or treatment for autoimmune diseases may also be immunosuppressive.

## Causes of Immunosuppression Therapies

- Alkylating agents.
- Antimetabolites.
- Radiation.
- High dose corticosteroid therapy:
  - $\geq 2$  mg/kg/day, OR
  - $\geq 20$  mg/day for  $\geq 14$  days.



Therapies that can cause immunosuppression include alkylating agents, antimetabolites, radiation, or high dose corticosteroid therapy. Prednisone doses of 2 milligrams per kilogram of body weight per day or higher or 20 milligrams per day or higher for 14 days or more should be considered immunosuppressive. As with other live vaccines, those on high levels of these drugs should not be immunized for three months after their last dose.

## Screening for HIV Infection

- Mandatory HIV testing not recommended, but:
  - Recommended for persons who have history of risk factor and do not know status.
  - Should be readily available for anyone concerned who wishes testing.



Persons with HIV infection or AIDS are at increased risk of progressive vaccinia (vaccinia necrosum) following vaccinia vaccination. Therefore, vaccinia vaccine should not be administered to persons with HIV infection or AIDS. Before vaccination, potential vaccinees should be educated about the risk of severe vaccinial complications among persons with HIV infection or other immunosuppressive conditions; persons who think they may have one of these conditions should not be vaccinated.

The ACIP does not recommend mandatory HIV testing prior to smallpox vaccination, but recommends that HIV testing should be readily available to all persons considering smallpox vaccination. HIV testing is recommended for persons who have any history of a risk factor for HIV infection and who are not sure of their HIV infection status. Because known risk factors cannot be identified for some persons with HIV infection, anyone who is concerned that they could have HIV infection also should be tested. HIV testing should be available in a confidential or, where permitted by law, anonymous setting with results communicated to the potential vaccinee before the planned date of vaccination. Persons with a positive test result should be told not to present to the vaccination site for immunization. Information about local testing options should be provided to all potential vaccinees, including sites where

testing is performed at no cost.

## Smallpox Vaccine Contraindications and Precautions Non-emergency Situations

- Serious allergic reaction to a prior dose of vaccine or vaccine component.
- Immunosuppression in the recipient or household contact.
- **Pregnancy in the recipient or household contact.**



Live viral vaccines are contra indicated during pregnancy. So smallpox vaccine should not be administered to pregnant women or people with pregnant household contacts for non-emergency indications. Pregnancy should also be avoided for at least 4 weeks after vaccination. Pregnancy is a contraindication because of the risk of fetal vaccinia, a very rare complication of smallpox vaccination.

## Screening for Pregnancy

- In pre-event setting, should NOT be given to:
  - pregnant women.
  - women trying to become pregnant.
- Educate women of child-bearing age about fetal vaccinia.
- Advise avoidance of pregnancy for 4 weeks following vaccination.



Fetal vaccinia is a very rare, but serious, complication of smallpox vaccination during pregnancy or shortly before conception. Therefore, vaccinia vaccine should not be administered in a pre-event setting to pregnant women or to women who are trying to become pregnant. Before vaccination, women of child-bearing age should be asked if they are pregnant or intend to become pregnant in the next 4 weeks; women who respond positively should not be vaccinated. In addition, the potential risk to the fetus should be explained and women who are vaccinated counseled not to become pregnant during the 4 weeks after vaccination. Routine pregnancy testing of women of child-bearing age is not recommended.

## Screening for Pregnancy

- If concerned, administer home test for pregnancy.
- Establish pregnancy registry for women inadvertently vaccinated.



To further reduce the risk of inadvertently vaccinating a woman who is pregnant, at the time of pre-screening, women of child-bearing age should be educated about fetal vaccinia, and abstinence or contraception to reduce the risk of pregnancy before or within four weeks after vaccination. Any woman who thinks she could be pregnant or who wants additional assurance that she is not pregnant should perform a urine pregnancy test with a “first morning” void urine on the day scheduled for vaccination. Such tests could be made available at the pre-screening and vaccination sites to avoid cost or access barriers to testing.

If a pregnant woman is inadvertently vaccinated or if she becomes pregnant within 4 weeks after vaccinia vaccination, she should be counseled regarding the basis of concern for the fetus. However, vaccination during pregnancy should not ordinarily be a reason to terminate pregnancy. To expand understanding of the risk of fetal vaccinia and to document whether adverse pregnancy outcome may be associated with vaccination, a pregnancy registry should be maintained and any adverse outcomes carefully investigated.



## Smallpox Vaccine Contraindications and Precautions Non-emergency Situations

- Serious allergic reaction to a prior dose of vaccine or vaccine component.
- Immunosuppression in the recipient or household contact.
- Pregnancy in the recipient or household contact.
- **Breastfeeding.**



Breastfeeding is a contraindication because of the close contact and risk of contact transmission to the infant.

## Smallpox Vaccine Contraindications and Precautions Non-emergency Situations

- Eczema or atopic dermatitis (current or past history) in the recipient or household contact.
- Acute, chronic, or exfoliative skin conditions (until improved or resolved) in the recipient or household contact.



Because of the increased risk for eczema vaccinatum, smallpox vaccine should not be administered to people with eczema or atopic dermatitis or a past history of these conditions. People who have a **HOUSEHOLD CONTACT** with eczema or atopic dermatitis or a history of these conditions should also not be vaccinated. People with other types of acute, chronic, or exfoliative skin conditions, such as psoriasis, contact dermatitis, burns, impetigo, or herpes zoster (shingles) might be at higher risk for inadvertent inoculation from the vaccine. People with exfoliative skin conditions, or whose household contact has this condition, should not be vaccinated until the condition resolves or is under good control or resolves.

## Screening for Eczema and Atopic Dermatitis

### Questions and Information:

- Have you or member of your household been diagnosed with eczema or atopic dermatitis?
- Have you had an itchy, red, scaly rash that lasts more than 2 weeks and comes and goes?
- If you or household member **EVER** had a rash like this, you should **NOT** receive smallpox vaccine.



To assist providers in identifying persons that should defer smallpox (vaccinia) vaccination, the ACIP offers the following two screening questions: 1) Have you, or a member of your household ever been diagnosed with eczema or atopic dermatitis—if you answered “yes,” you may NOT receive the smallpox (vaccinia) vaccine due to the risk that you or your household contact might develop a severe and potentially life-threatening illness called eczema vaccinatum; and 2) Eczema/atopic dermatitis usually is an itchy red, scaly rash that lasts more than 2 weeks and often comes and goes. If you or a member of your household have **ever** had a rash like this—you should NOT receive the smallpox (vaccinia) vaccine at this time unless you and a healthcare provider are sure that this rash is not atopic dermatitis or eczema. In cases where the dermatological risk factor or diagnosis is uncertain, some organizations, such as the military or CDC, may elect to develop more precise screening tools. These secondary screening tools should weigh the individual’s risk of developing an adverse event with the requirement of occupational readiness through safe smallpox vaccination to ensure national security.

## Smallpox Vaccine Contraindications and Precautions Non-emergency Situations

- Eczema or atopic dermatitis (current or past history) in the recipient or household contact.
- Acute, chronic, or exfoliative skin conditions (until improved or resolved).
- **Children <12 months of age.**



Children less than 12 months of age should not be vaccinated. All vaccinated people should take precautions to prevent virus transmission to young children and other household contacts. Infants are at risk of post-vaccinal encephalitis if infected.

## Smallpox Vaccine Contraindications and Precautions Non-emergency Situations

- Eczema or atopic dermatitis (current or past history) in the recipient or household contact.
- Acute, chronic, or exfoliative skin conditions (until improved or resolved).
- Children <12 months of age.
- **Moderate or severe acute illness.**



As with all vaccines, vaccination should be deferred for people with moderate or severe acute illnesses.



## Smallpox Vaccine Contraindications and Precautions Non-emergency Situations

- Serious allergic reaction to a prior dose of vaccine or vaccine component.
- Immunosuppression in the recipient or household contact.
- Pregnancy in the recipient or household contact.
- Breastfeeding.



In summary, the contraindications and precautions to smallpox vaccine are:

- A serious allergic reaction to a prior dose of vaccine or a vaccine component
- Immunosuppression in the recipient or a household contact
- Pregnancy in the recipient or a household contact
- Breastfeeding

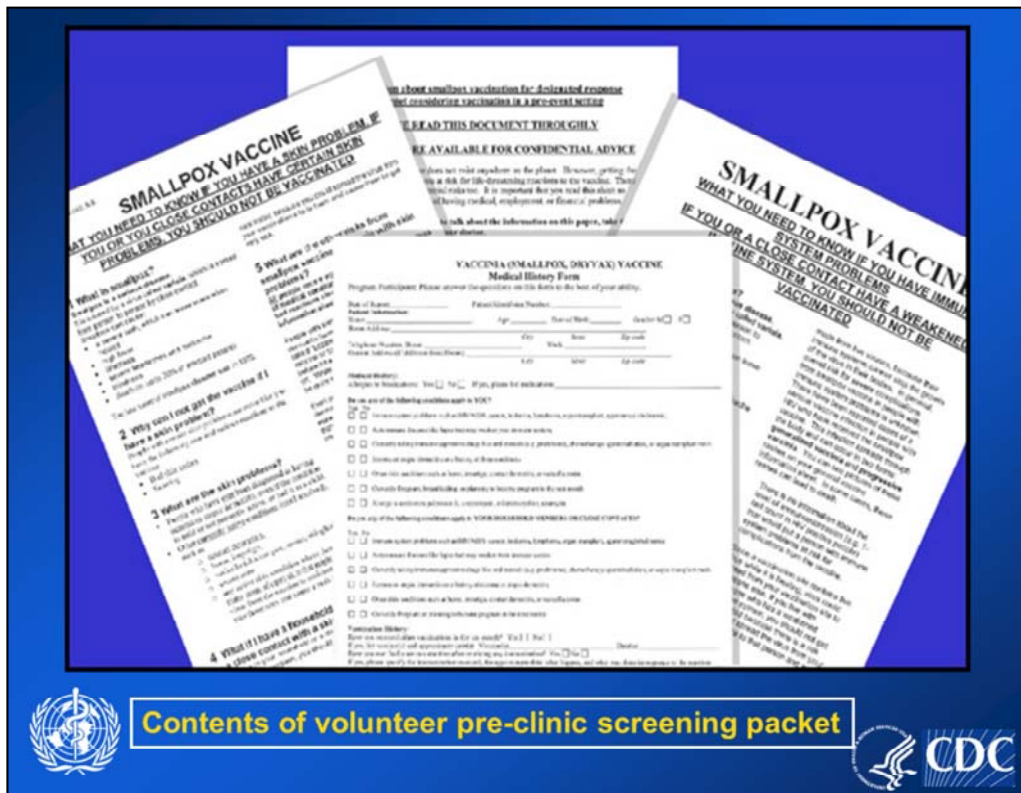
## Smallpox Vaccine Contraindications and Precautions Non-emergency Situations

- Eczema or atopic dermatitis (current or past history) in the recipient or household contact.
- Acute, chronic, or exfoliative skin conditions (until improved or resolved) in the recipient or household contact.
- Children <12 months of age.
- Moderate or severe acute illness.



- Eczema or atopic dermatitis, either currently or in the past, in the vaccinee or a household contact
- Other acute, chronic or exfoliative skin conditions until they're improved or resolved
- Children less than 12 months of age (although no children are being vaccinated, right now)
- And moderate or severe acute illness





In the United States, a large packet of written materials will be provided to each volunteer. This packet contains a variety of material about smallpox vaccine, contraindications, and adverse events.

## Pre-Clinic Screening Materials

- Participant Advice Letter.
- Vaccine Information Sheet:
  - Smallpox Vaccine.
  - Immune System Problems.
  - Skin Conditions.
  - Pregnancy.
- Pre-Clinic Checklist.



A lengthy advice letter will be provided that outlines the risks and benefits of the vaccine, things to consider if the volunteer, or someone in their family, has possible contraindications, and possible risks involved with their employment should an adverse event occur. Other written materials will include a Vaccine Information Statement on the smallpox vaccine and further detailed information statements about various contraindications; including immune system problems, skin conditions and pregnancy. And finally, they will be given a checklist asking them to screen themselves for possible contraindications. They will not turn this form in, but can use it as a further aid to help them decide whether or not they can take the vaccine.

## Smallpox Vaccine Contraindications and Precautions Emergency (Post-Event) Situations

- Exposed Persons – NO Contraindications.
- Unexposed Persons – Same as in Non-Emergency.



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.

# World Health Organization Issues



## Watch Vaccine Administration Video



Now, let's watch a video developed by the US Department of Health and Human Services on the vaccine and the administration technique.

# Vaccine Administration Technique Review



Again, let's go over the key elements of smallpox vaccine administration.

## Smallpox Vaccine Reconstitution

- Diluent and instructions for reconstitution will be supplied with vaccine.
- Vaccine may be used for 30 days following reconstitution.



Only the diluent supplied with the vaccine should be used for reconstitution. Vaccine reconstituted with any other diluent should be discarded. Reconstituted vaccine should be kept at refrigerator temperature, 2-8 C. Once reconstituted, the vaccine may be used for 30 days if kept at the recommended storage temperature.

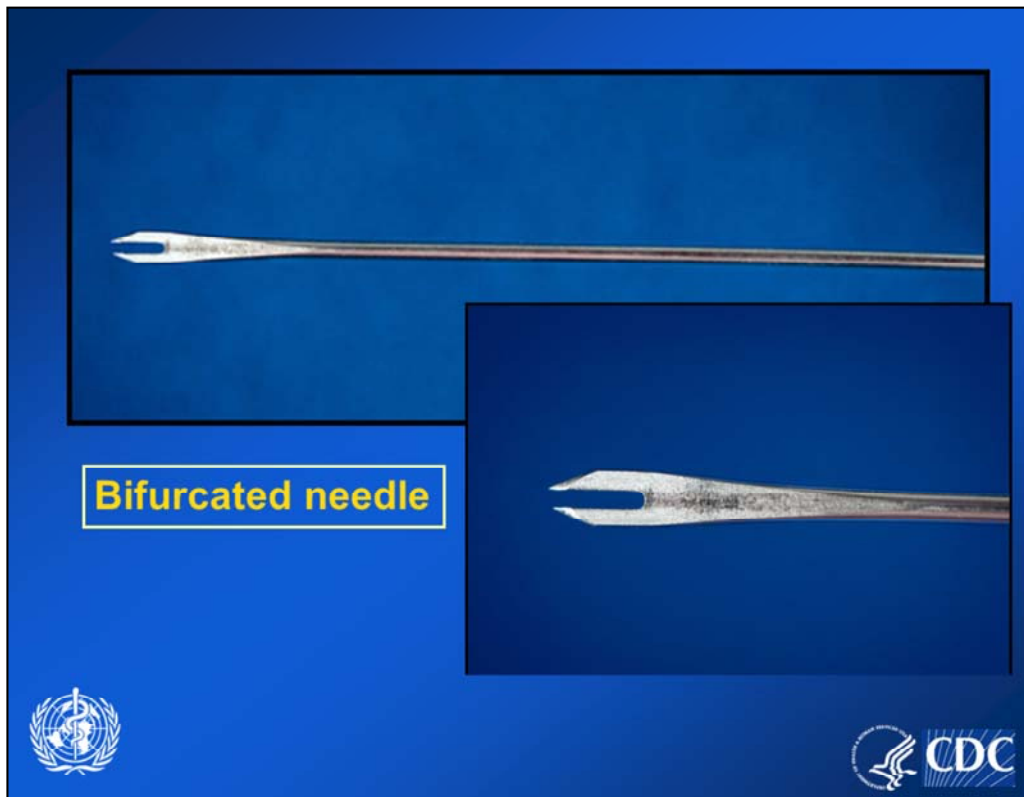


## Smallpox Vaccine Administration

- Use of gloves is recommended.
- Persons administering smallpox vaccine should be vaccinated.
- Healthcare workers with a contraindication to vaccination should not handle or administer the vaccine.



We recommend that you wear gloves when administering smallpox vaccines. Because of the risk of exposure to the vaccine virus, persons administering the vaccine should be vaccinated. Healthcare providers who have a contraindication to vaccination should not handle or administer the vaccine.



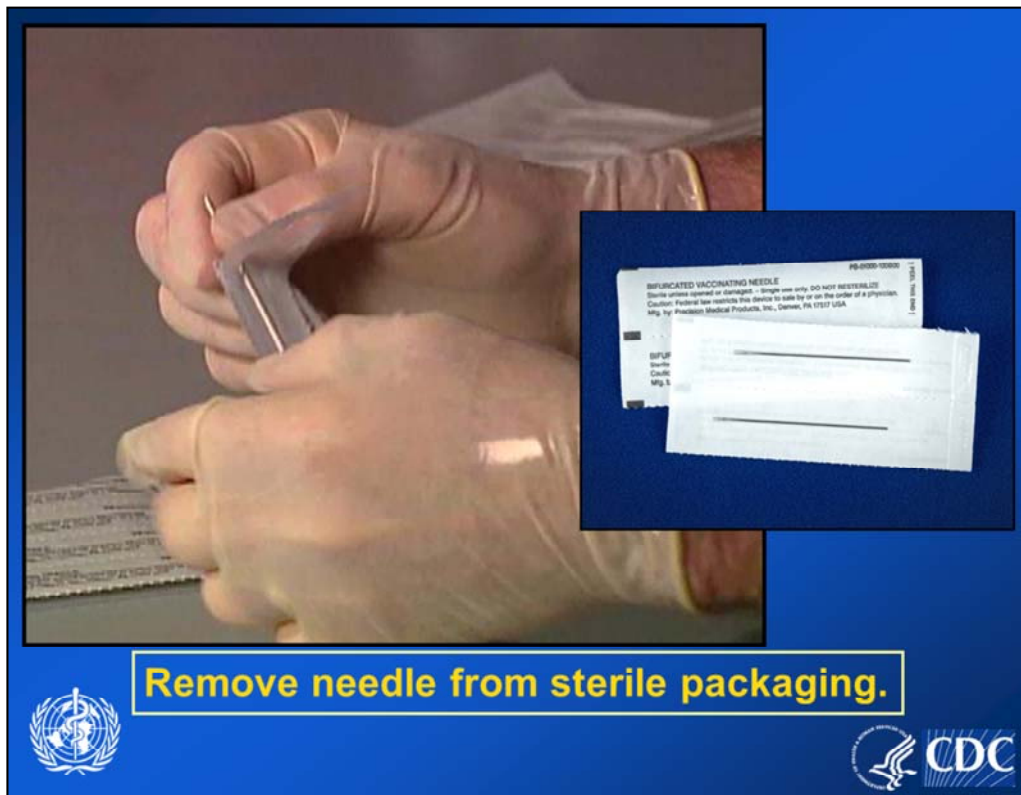
To administer the smallpox vaccine, a special bifurcated needle is used. No other vaccine uses this type of needle, and smallpox vaccine must never be administered by any other method. You should review the package insert or protocol that is provided with the vaccine for any additional instructions regarding vaccine administration.

## Vaccination Site Preparation

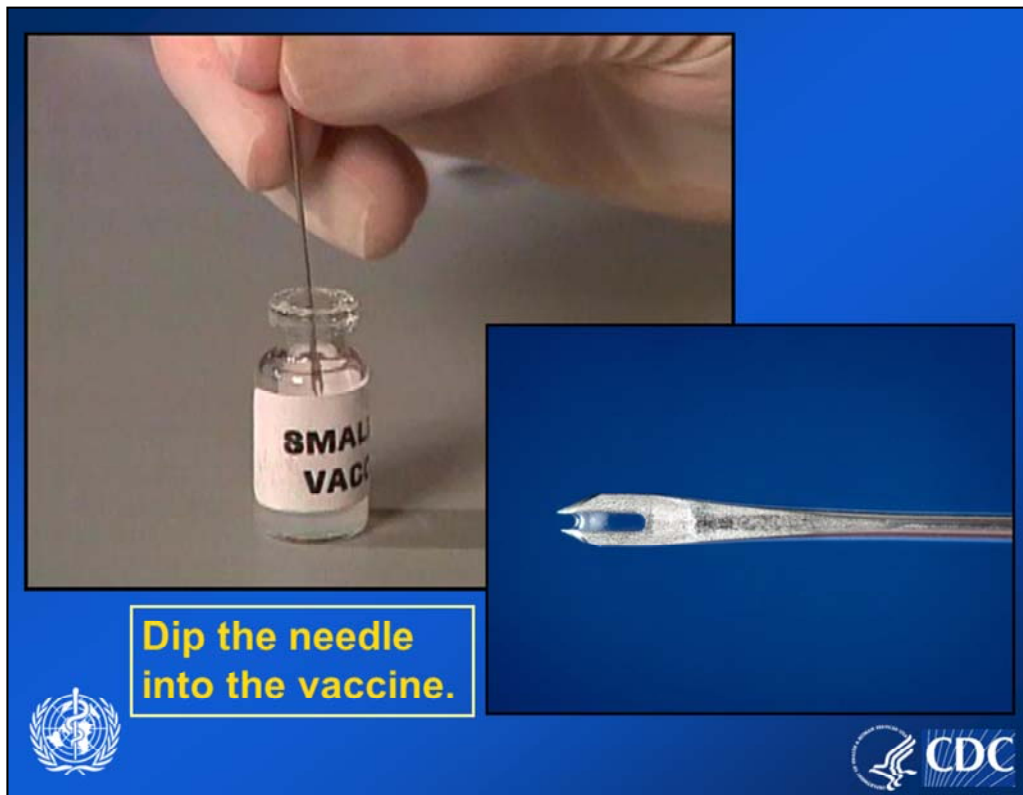
- Alcohol, soap and water, or chemical agents are not needed for preparation of the skin for vaccination unless grossly contaminated.
- If needed, soap and water are the preferred cleaning agents.
- Skin must be thoroughly dry in order to prevent inactivation of the vaccine.



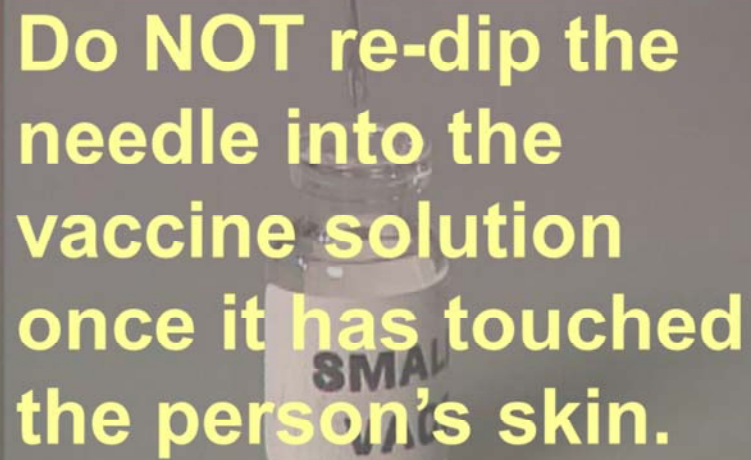
In general, alcohol, soap and water, or other chemical agents are not needed for preparation of the skin for vaccination unless the area is grossly contaminated. If needed, soap and water are the preferred cleaning agents. If any cleaning agent is used, the skin must be thoroughly dry in order to prevent inactivation of the vaccine.



Remove the bifurcated needle from its packaging. The needle is sterile, so be careful not to touch the bifurcated, pointed end.



Dip the bifurcated point of needle into the vaccine solution- so that the needle is perpendicular to the floor. The needle will pick up a drop of the vaccine in the space between the two prongs. Inspect the needle tip after dipping to assure that vaccine is present between the prongs. DO NOT shake the needle after it has been dipped into the vaccine vial. If no vaccine is between the prongs of the needle, and the needle has not touched the skin of the vaccinee (i.e., it is still sterile), it may be dipped again.



**Do NOT re-dip the  
needle into the  
vaccine solution  
once it has touched  
the person's skin.**



A single dip into the vaccine will prevent contamination of the vaccine vial.



Pull the skin on the arm taut, rest your wrist on the arm, and prick the skin the recommended number of times. This should be done rapidly, perpendicular to the skin, within an area 5 millimeters in diameter. The intention is to break the skin and introduce the vaccine into the skin. The wrist of the vaccinator should be resting on the arm while pricking the skin.



## Smallpox Vaccine Administration

- Prior to administration of smallpox vaccine, please refer to the package insert for number of bifurcated needle punctures to administer.



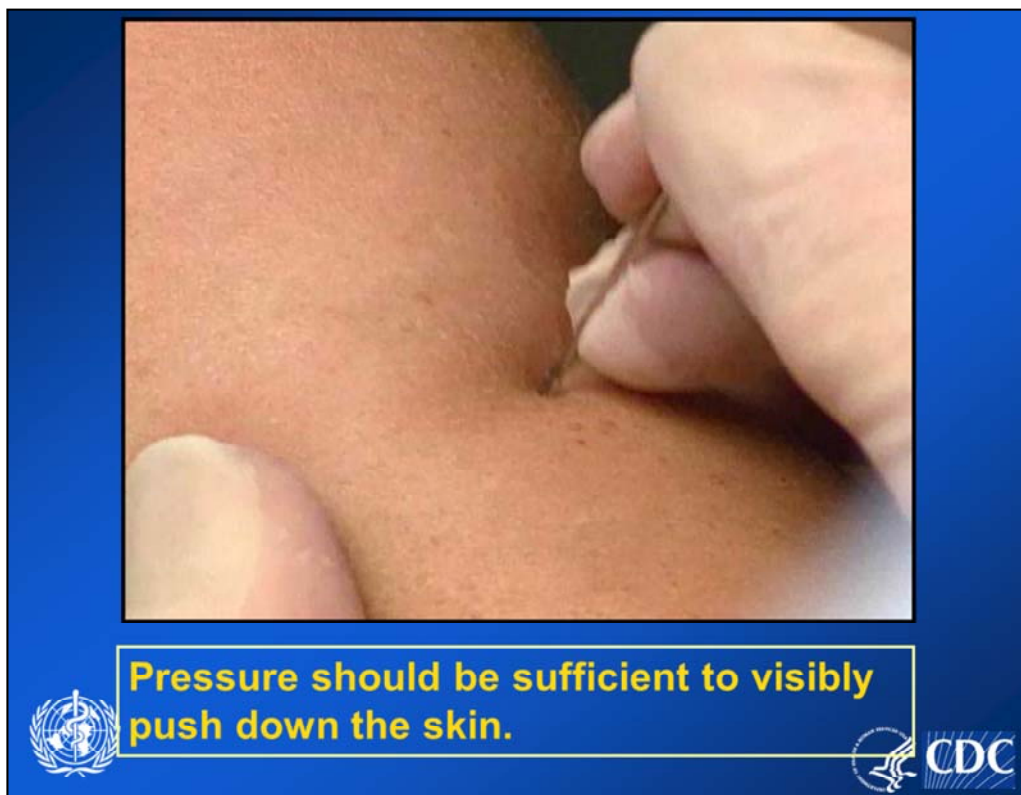
Prior to administration of smallpox vaccine, please refer to the package insert for number of bifurcated needle punctures to administer.

## Smallpox Vaccine Administration

- Apply strokes perpendicular to the skin.
- Prick the skin in about 3 seconds within an area of 5 millimeters.
- Apply sufficient pressure to visibly push down the skin.



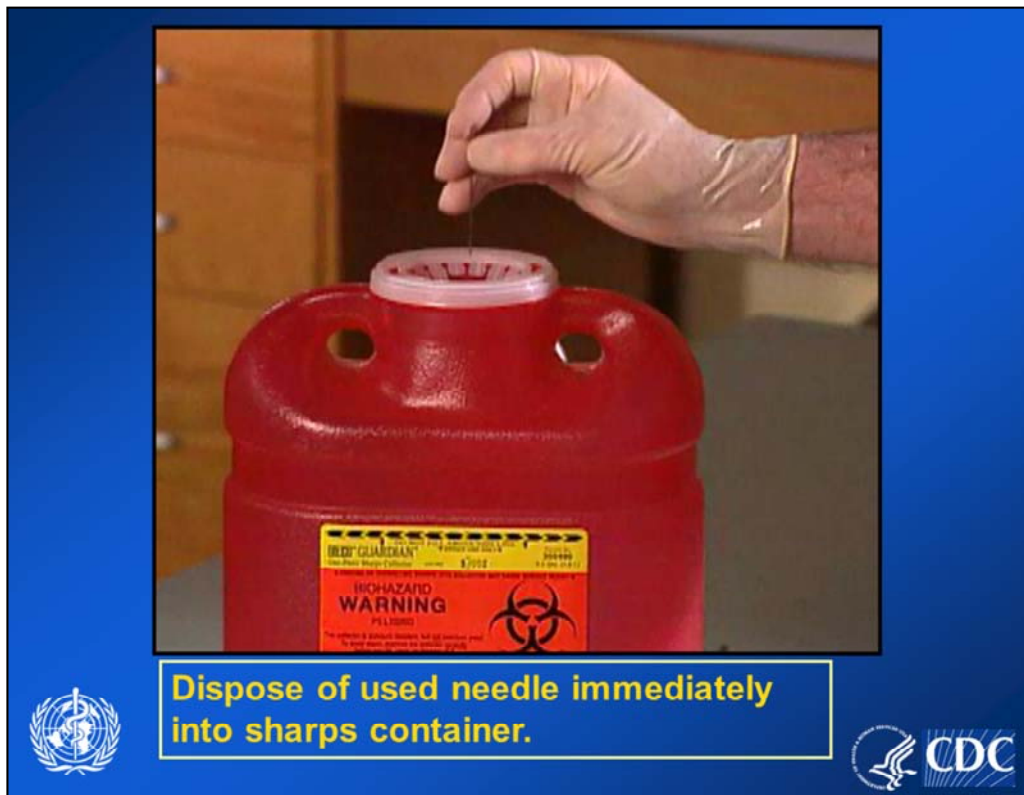
- Apply strokes perpendicular to the skin.
- Prick the skin in about 3 seconds within an area of 5 millimeters.
- Apply sufficient pressure to visibly push down the skin.



Administering the strokes rapidly, within about 3 seconds, also helps induce enough pressure by the needle to produce this small amount of bleeding and assure that the vaccine was administered appropriately. This method allows the live vaccinia virus to penetrate the superficial layers of the skin so that viral multiplication can occur and produce immunity.



A trace of blood should be present after 10-20 seconds.



Bifurcated needles should never be re-used.



Cover the vaccination site to prevent dissemination of the virus. The site should be covered by a gauze pad then tape applied over the gauze. For hospital personnel, the gauze should in turn be covered by a semi-permeable occlusive dressings. Semi-permeable dressing alone should not be used because it cause skin maceration and may increase the risk of secondary bacterial cellulitis.



## Smallpox Vaccine Administration

- Vaccinia virus may be cultured from the site of a primary vaccination from 2-3 days after vaccination until the scab separates.
- Care must be taken to prevent spread of the virus to other parts of the body or other persons.
- Hands must be washed after every contact with the vaccination site or any materials (clothing, dressing, etc.) that has come into contact with the vaccination site.



Vaccinees should be instructed that thorough hand washing with soap and water or disinfecting agents should be performed after any direct contact with the site or contact with materials that have come into contact with the site. Care must be taken to prevent contact of the site or contact with contaminated materials from the site by any other person. Keeping the site covered provides barrier protection against inadvertent inoculation or transmission.

## Clinical Response to Vaccination

- “Jennerian” vesicle at vaccination site.
- Swelling and tenderness of axillary lymph nodes, usually during 2<sup>nd</sup> week:
  - 15%-20% of primary vaccinees.
  - 0%-15% of revaccinees.
- Fever and malaise common.



Following vaccination, vaccinia virus replicates in the epidermis, resulting in the development of a lesion at the site of vaccination. As we described earlier in the program, individuals receiving their first dose of vaccine normally experience tenderness, redness, and swelling at the vaccination site. Primary vaccination may also be associated with fever for a few days and enlarged, tender lymph nodes in the axilla of the vaccinated arm.

## Clinical Response to Vaccination

Symptom/Sign	Time after Vaccination
Papule	3 Days
Vesicle	5-6 Days
Pustule	7-11 Days
Maximum Erythema	8-12 Days
Scab	14 Days
Scab Separation	21 Days

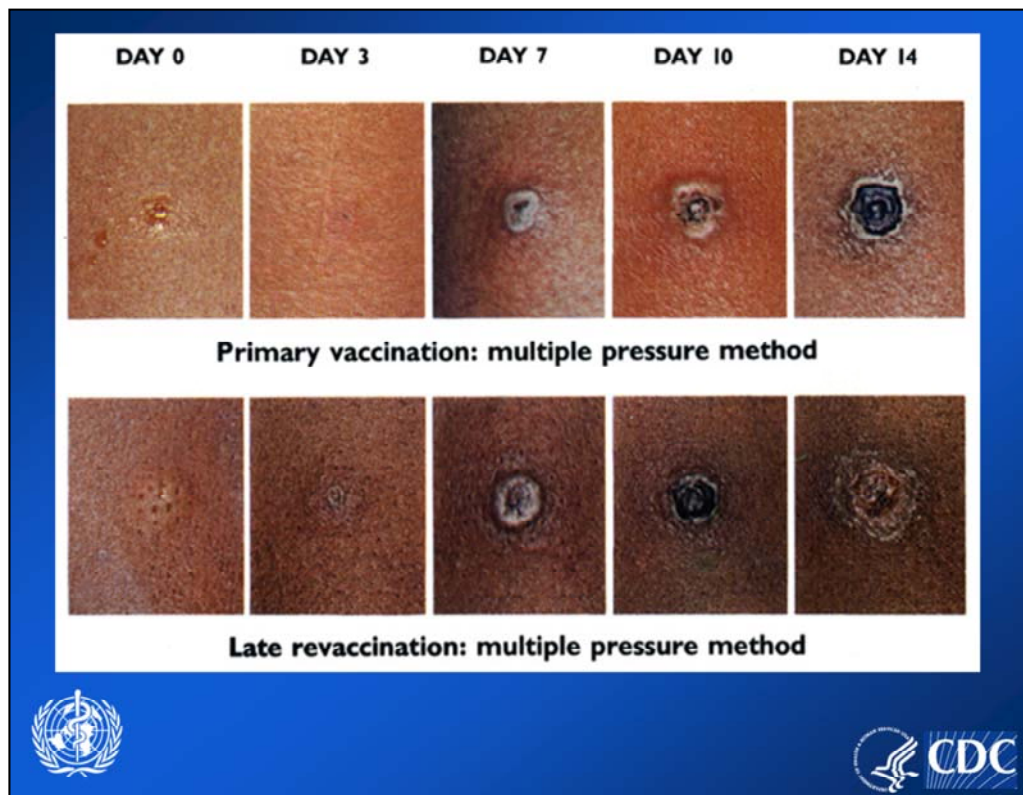


\*typical response in a nonimmune person



A papule develops at the inoculation site 3 to 5 days after primary vaccination. About 7 days following primary vaccination, a vesicle surrounded by erythema forms at the site. This is known as a "Jennerian vesicle". The vesicle usually becomes pustular by 11 days after vaccination. Maximum erythema occurs 8 to 12 after vaccination. The erythema then subsides, the pustule dries, and a crust develops 2 to 3 weeks after vaccination. By the end of the third week, the crust separates, leaving a permanent scar at the vaccination site.

This response to vaccination is called a major reaction. It indicates that virus replication has taken place, and that vaccination was successful. A person is considered immunized with the development of a major reaction at the vaccination site. A revaccinated person often develops a skin reaction similar to that after primary vaccination, but the lesion progresses faster than after primary vaccination.



Vaccine sites should be examined for the expected vesicle or pustule around day 7 following vaccination to confirm the vaccination was successful.

## Clinical Response to Vaccination

- Neutralizing antibody:
  - 10 days after primary vaccination.
  - 7 days after revaccination.
- Considered fully protected after a successful response demonstrated at vaccination site.



Vaccinia virus replicated in the basal cells of the epidermis, producing a papule surrounded by erythema 3 to 5 days after primary vaccination. A vesicle forms, which becomes pustular by 7 to 11 days after vaccination.

A person is considered protected with the development of a pustule like this at the vaccination site. Vaccinia virus is present at the vaccination site beginning 3 to 4 days after vaccination until the scab separates. Care must be taken to avoid transferring virus to other parts of the body, such as the eye, or to other people.



## Clinical Response to Vaccination

- Major (primary) reaction:
  - Indicates viral replication has occurred and vaccination was successful.
- Equivocal reaction:
  - Indicates immune suppression of viral replication or allergic reaction without production of immunity.
  - Poor vaccination technique.
  - Inactive vaccine.



Some people do not develop a typical skin lesion after vaccination. All responses other than major reactions are referred to as equivocal. There are several possible causes of equivocal reactions.

The person may be sufficiently immune to suppress viral replication. Unless the person was recently vaccinated or vaccinated multiple times in the past, they are probably not immune. The person may be allergic to a component of the vaccine, which leads to a hypersensitivity reaction at the site. An equivocal reaction could also be caused by insufficiently potent vaccine or incorrect administration technique. In general, a person who has an equivocal response to vaccination should be revaccinated using vaccine from another vial, if possible.



## Major Reaction 6-8 Days After Vaccination

- Primary vaccination:
  - Vesicular or pustular lesion.
  - Area of definite palpable induration surrounding a central crust or ulcer.
- Revaccination:
  - Less pronounced and more rapid progression.
  - Pustular lesion or induration surrounding a central crust or ulcer.



For those patients who are being revaccinated, there will be a less pronounced lesion with more rapid progression. A revaccinated patient is considered to have had a major reaction if they produce a pustular lesion or have an induration surrounding a central crust or ulcer.

## Equivocal Reaction

- All responses\* other than major reactions.
- Caused by immunity, insufficiently potent vaccine, vaccination technique failure.
- Vaccination should be repeated with another vial, if possible.

\*Includes accelerated, modified, vaccinoid, immediate, early, or immune reactions.



Equivocal reactions are all responses other than that described under the major reaction.

It's usually caused by immunity from previous doses, or could indicate that the vaccine was compromised or that the vaccination technique wasn't correct. These patients should receive another dose, preferably from another vial.

## Vaccine Efficacy

- Clinical efficacy estimated in household contact studies.
- 91%-97% reduction in cases among contacts with vaccination scar.
- Studies did not consider time since vaccination or potency of vaccine.



The efficacy of smallpox vaccine has never been measured precisely in controlled trials. However, protection has been determined in studies of people exposed to a smallpox patient in their household. There was a 90% reduction in smallpox among contacts with a vaccination scar compared to contacts without a scar.

Epidemiologic studies demonstrated that this high level of protection against smallpox persists for up to 5 years after primary vaccination and substantial but waning immunity can persist for ten years or more.

## Post-Exposure Vaccine Efficacy

- Clinical efficacy estimated in household contact studies.
- SAR 2%-75%, varied by time since exposure.
- Disease generally less severe (modified type) in those with post exposure vaccination.



Although vaccination 30 or more years ago many not protect against smallpox, vaccinated people appear to have less severe disease.

## Post-Exposure Vaccine Efficacy

		% with smallpox
Madras	Post Exposure Vaccination	29.5
	Never Vaccinated	47.6
Pakistan	Vaccination < 10 days	75.0
	Never Vaccinated	96.3
Pakistan	Vaccination < 7 days	1.9
	Never Vaccinated	21.8



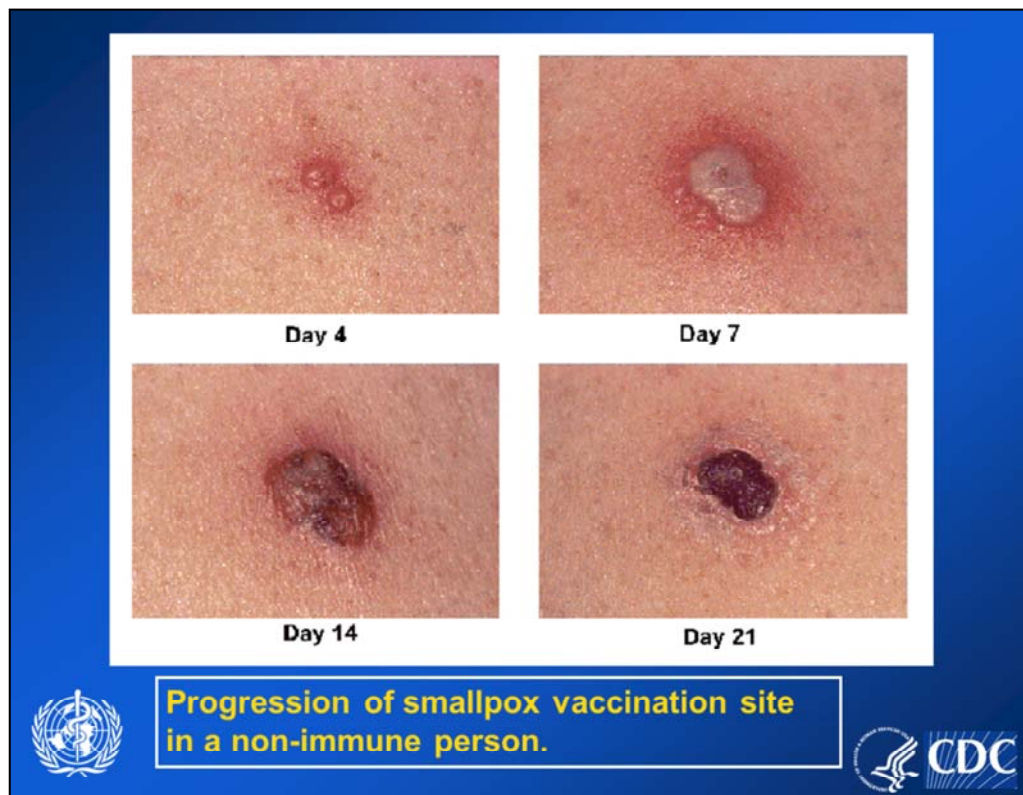
Smallpox vaccination also provides post-exposure protection. Administration of vaccine within the first days after initial exposure to smallpox virus can reduce symptoms or prevent disease. Studies in Pakistan and India showed that secondary cases in households were reduced up to 91% compared to unvaccinated people, if the vaccine was administered less than 7 days after exposure.

## Adverse Events following Smallpox Vaccination



Let's take a look at the adverse events that can occur following smallpox vaccination.





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.

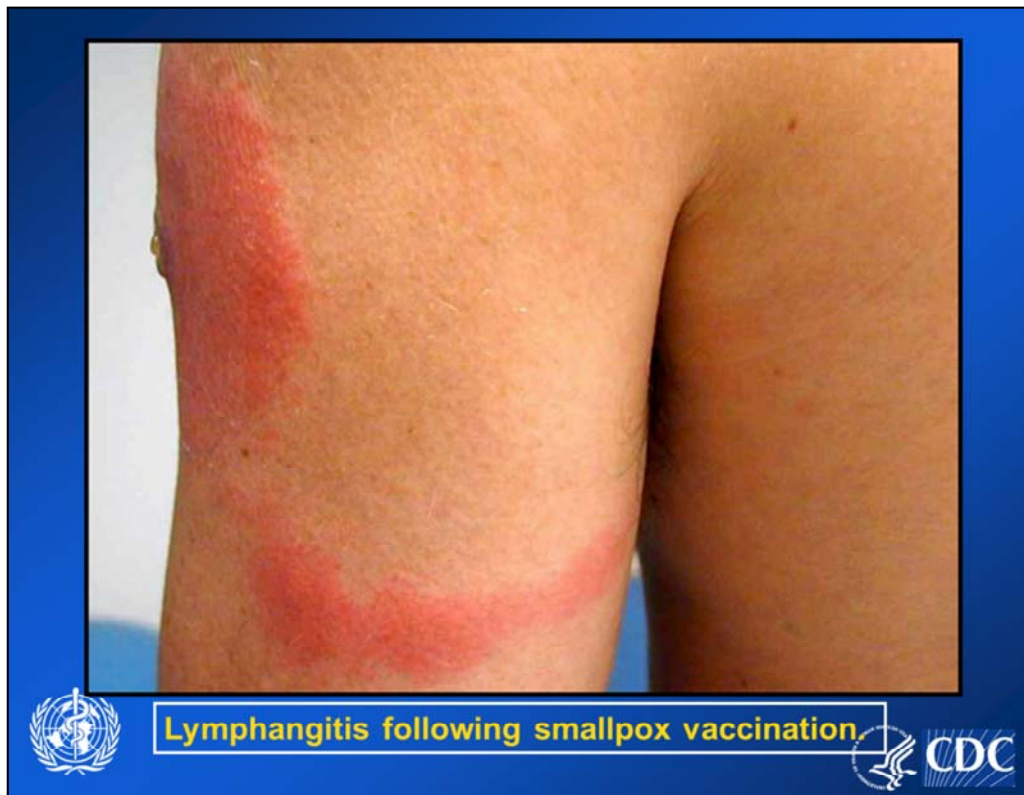
## Smallpox Vaccine Reactions Among Susceptible Adults

- 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.



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.



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



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.





**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.





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.

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.



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 Autoinoculation

- Transfer of vaccinia virus to sites other than the intended vaccination site
- Commonly on mucocutaneous borders (eye, mouth, rectum)
- Lesions heal spontaneously without specific treatment
- Highest risk in children 1-4 years
- Vaccinia Immune Globulin (VIG) may be useful







**Inadvertent autoinoculation**





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.





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.

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 vesicular skin lesions occurring in the absence of eczema or other preexisting skin diseases
- Believed to result from a viremia with implantations in the skin
- Fever and systemic signs vary widely but are generally mild
- VIG may attenuate severity if given early in course of illness





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

- Generalized spread of vaccinia on skin of patients with eczema or past history of eczema (atopic dermatitis)
- May result from blood dissemination of vaccinia virus or from direct skin inoculation of vaccinia on broken skin
- Vaccinia virus readily recoverable from lesions of the rash
- VIG helpful





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

- Also known as vaccinia necrosum and vaccinia gangrenosa
- Occurs only in patients with impaired immunologic function
- Characterized by spreading necrosis at site of vaccination, with or without metastatic necrotic lesions elsewhere on the body
- Painless, progressive, +/- systemic illness
- VIG is used to treat







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-vaccinal 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-vaccinal 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-vaccinal 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

- 47 fetal vaccinia cases reported in world literature (as of 1970)
- Most result from primary vaccination of mother early in pregnancy
- May results in stillbirth or death of infant soon after delivery
- VIG may benefit live born infant





**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.

# Vaccinia Immune Globulin

- Antibodies limit viral replication
- Cangene® intravenous
  - First-line therapy
  - Under IND
  - Available only through CDC
- Administer as soon as possible after onset
  - Inadvertent inoculation (severe, or underlying illness)
  - Generalized vaccinia (severe, or underlying illness)
  - Eczema vaccinatum
  - Progressive vaccinia
  - Consider for severe ocular complications



# Vistide®, cidofovir

- Antiviral therapy
- FDA approved for CMV retinitis in AIDS patients
- Second-line treatment
  - Not tested in humans against vaccinia
  - Nephrotoxic (probenecid, hydration)
  - Carcinogenic
- Investigational New Drug (IND)





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