Welcome to Module 2 of this program on the laboratory approach to the diagnosis of smallpox.

This module comprises the poxvirus overview.

Module 2 of this series includes an overview of the poxvirus family, with a special focus on the poxviruses that infect humans. We will learn about smallpox epidemiology, transmission, and clinical diagnosis to differentiate smallpox from other vesicular rashes. Monkeypox, and the US outbreak in 2003 will be discussed. We will also learn about prevention of poxviruses through vaccination.

At the conclusion of this module, participants will be able to complete the following learning activities:

- Identify characteristics of members of the Poxviridae family.
- Differentiate between human and non-human poxvirus pathogens.
- Distinguish human pathogenic orthopoxviruses that cause systemic disease from those that typically cause localized infections.
- Demonstrate how similarities among orthopoxviruses allows vaccination with one orthopoxvirus to provide protection against infection with another species.
- Discuss laboratory testing for confirmation of adverse reaction to smallpox vaccination and orthopoxvirus disease.
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The first unit of module 2 describes numerous members of the poxvirus family. Poxviruses are a family (the Poxviridae family) of viruses currently recognized to naturally infect both vertebrates and arthropods. Variola, the virus that causes smallpox, and vaccinia, the virus used as the smallpox vaccine, are members of this family. The poxviruses are grouped into 2 subfamilies: Entomopoxvirinae and Chordopoxvirinae. Entomopoxvirinae infect arthropods and Chordopoxvirinae infect vertebrates. We will focus here only on the Chordopoxvirinae.

Listed here are the eight known vertebrate poxvirus genera. Species of four of the eight genera, Orthopoxviruses, Parapoxviruses, Molluscipoxviruses and Yatapoxviruses infect humans, but only Orthopox and Molluscipox viruses are reported to transmit between humans. Only variola, an orthopoxvirus, and Molluscum contagiosum, the only member of the molluscipox genera, are SOLE human pathogens. For the purpose of this training program we will primarily focus on those viruses that are orthopoxviruses, especially variola, the agent of smallpox, and vaccinia, the virus that is used for smallpox vaccination. For the next few minutes, however, we will briefly describe the other poxviruses as well.

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Members of the Poxviridae Family are large, complex double-stranded DNA viruses that replicate in the cytoplasm of their host’s cells. These viruses encode many of the proteins required for their replication and maturation; in general, these are essential genes. In addition, they encode a large number of proteins that are involved in evasion of their host’s immune defenses and in establishing host range. In in-vitro tissue culture experiments, these are non-essential genes, and they tend to exhibit a greater range of differences that differentiate species of virus. The presence of virus-specific DNA sequences is an important target for diagnostic testing (both species generic and species specific), as well as their characteristic large brick- or ovoid-shaped electron-microscopic appearance.

Molecular methods will be discussed in Module 5 and Electron Microscopy methods for detecting orthopoxviruses will be discussed in Module 6.
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The genus Orthopoxvirus comprises many species. The DNA of the brick-shaped orthopoxviruses ranges from 170 to 240 kilobase pairs and is composed of 36% guanine and cytosine.

Listed here are the members of the orthopoxvirus family. Camelpox is a sole camel pathogen. Ectromelia is known to infect only mice. Although cowpox is the species of orthopox originally used by Jenner as smallpox vaccine, vaccinia is the virus used today. Variola is the causative agent of smallpox; it along with Monkeypox will be covered in greater depth later in this program. These are all Eurasian or “Old World” orthopoxviruses. The last three orthopoxvirus species listed, Raccoonpox, Skunkpox, and Volepox, are found only in North America and are known as “New World orthopoxviruses”.

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This chart summarizes the geographic locations and hosts of orthopoxviruses. One interesting observation here is that some orthopoxviruses have limited host ranges while others have wider ranges. Variola infects only humans, and camelpox infects only camels. On the other hand, cowpox infects rodents, other carnivorous small mammals, and humans. The orthopoxviruses camelpox and ectromelia do not cause human infection. Reasons for these differences are not completely clear. You can often obtain clues as to the causative agent of an orthopoxvirus infection from the geographic area from which a case is reported.

Importantly, these viruses are genetically and antigenically very similar and provide cross-protective immunity from infection—hence the basis for vaccination with vaccinia to prevent smallpox. Serologically, there is much cross-reactivity among these viruses. We will cover this in more detail in Module 5, the Serology section.
Parapoxviruses are slightly smaller and somewhat narrower than the other poxviruses, and have ovoid ends as well as a characteristic criss-cross, spiral pattern seen on negative-stain electron microscopy. The linear, double-stranded DNA consists of about 140 kilobase pairs and is 64% guanine and cytosine.

Parapoxvirus infections are endemic in the United States in sheep, goats, and cattle. Human infections are a common occupational hazard for those in contact with infected animals. Farm workers, veterinarians, and others working with infected animals recognize infection and often tend not to seek medical attention. Re-infection is not uncommon. Parapox infection in sheep and goats is usually referred to as contagious pustular dermatitis or Orf, and the corresponding human infection as Orf. Parapox infection in dairy cattle is usually referred to as pseudocowpox, and the human equivalent as either pseudocowpox or paravaccinia. Parapoxvirus infection in beef cattle is referred to as bovine papular stomatitis virus. Sealpox is a less recognized occupational hazard of seal handlers.

The viruses that cause Orf and pseudocowpox are closely related. As stated previously, human infections are a common occupational hazard for those who come in contact with infected animals. Most of these viruses have a worldwide distribution, with the exception of the less common parapoxviruses that infect camels and red deer.

Molluscum contagiosum is regarded as a specific human infection and there is no evidence of transmission between humans and animals. The molluscipox virus genome is a double-stranded DNA of approximately 180 kilobase pairs and is 60% guanine and cytosine.

Molluscum is a benign skin lesion that occurs worldwide. The lesions can last for months and appear as pearly white pustules. Transmission of this brick-shaped virus is traditionally associated with mild trauma to the skin and skin-to-skin contact. There are usually 1 to 20 lesions, but occasionally there may be hundreds. In children, lesions occur mainly on the trunk and proximal extremities. In adults, they tend to occur on the trunk, pubic area, and thighs, but in all cases infection may be transmitted to other parts of the body by autoinoculation. In male HIV patients, lesions are often pronounced along the beard line.
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The fourth group of poxviruses that infect humans are the Yatapoxviruses. The brick-shaped virus has genomic DNA of about 145 kilobase pairs, and is 33% guanine and cytosine.

There are 2 species of African origin within the Yatapoxvirus genus: Tanapox and Yaba monkey tumor virus.

Tanapox virus was first recognized in the Tana River area of Kenya in 1957. Infection occurs via the skin. In monkeys, tanapox is designated Yaba-like disease virus. The relatively large lesions of tanapox develop more slowly than the smaller lesions of monkeypox, have a nodular nature, and usually break down to form ulcers that heal more rapidly than those of tropical ulcers such as Buruli ulcer caused by *Mycobacterium ulcerans*. Tanapox may be transmitted from monkeys to humans. Recent reports of human disease outside Africa have been published and illustrate the need to consider poxvirus etiologies of illness in immigrants and travelers returning from endemic areas.

Yaba monkey tumor virus (YMTV) was first discovered in subcutaneous tumors in captive monkeys in Nigeria, but has not been found to naturally infect humans. On rare occasions humans have been infected, usually via inadvertent inoculation or contact with infected monkeys.

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As the name suggests, Avipoxviruses infect poultry and other species of wild birds. They have demonstrated DNA and serologic cross-reactivity. The DNA is about 260 kilobase pairs and consists of 35% guanine and cytosine.

The names of the viruses are related to their hosts. Arthropods provide a mechanism for transmission of virus between the various species of birds. There are now several types of avipox vaccines for poultry. Avipoxviruses are not known to naturally infect humans.

Avipoxviruses are now used as human vaccine vectors in clinical trials.
The three viruses of the Capripoxvirus family are brick-shaped and consist of approximately 150 kilobase pairs with approximately 27% guanine and cytosine. All three viruses have a lot of serologic and DNA cross-reactivity.

The family of Capripoxviruses consists of goatpox, sheeppox, and lumpy skin-disease viruses. Goatpox and sheeppox diseases are endemic in southwest Asia and most of Africa, infecting goats and sheep respectively. Although these 2 viruses are considered host-specific, either virus may infect either animal. There have been no documented transmissions to humans. Lumpy-skin disease is usually found in cattle in the different regions of Africa. The virus is probably transmitted via biting insects. There have been no documented transmissions to humans. The virus causes febrile exanthem where lesions heal slowly, and affected cattle are often debilitated for several months. The mortality rate in the young animals can range between 50 and 100%.

The brick-shaped Leporipoxvirus has a genomic DNA of 160 kilobase pairs and is 40% guanine and cytosine.

There are 5 species of the Leporipoxvirus, but only myxoma virus is considered to have veterinary importance. The disease caused by the myxoma virus is myxomatosis. Although myxomatosis in wild rabbits (Sylvilagus species) in the Americas is usually a localized fibroma, it is a very fatal disease in the European rabbit (Oryctolagus cuniculus).

Swinepox is the only virus of the Suipoxvirus genus. The brick-shaped virus’s genomic DNA is 170 kilobase pairs, and approximately 27% of the genome consists of guanine and cytosine.

Swinepox has a narrow host range, affecting only swine, causing a mild skin disease that can transmitted by the pig louse and flies. Restriction mapping of swinepox-virus DNA shows some similarities to the unclassified Brazilian poxvirus, Cotia virus.
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In summary, poxviruses can cause infections in a wide range of hosts. As shown here, only a small number of these affect humans. Varicella and monkeypox typically cause systemic febrile vesicular-pustular rash illnesses. Varicella is the only orthopoxvirus disease for which man is the only naturally occurring host. Although the orthopoxviruses are closely related at the genome and proteome level, the spectrum of disease caused in humans by different member species of the genus varies dramatically. This led to the historic use of those viruses causing localized disease (such as cowpox and vaccinia) as vaccines to protect against those causing more systemic and serious disease (such as varicella).
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Unit 2 of this module discusses smallpox. We will learn about the strategy that eradicated smallpox, see the various manifestations of the disease, and discuss concerns about bioterrorism.

Smallpox is a serious, highly contagious, and sometimes fatal infectious disease. There is no specific treatment for smallpox but it can be prevented by vaccination. The name *smallpox* is derived from the Latin word for “spotted” and refers to the raised bumps that appear on the face and body of an infected person.

Shown here is a transmission electron micrograph of variola, the virus that causes smallpox in humans.

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Prior to the mid 20th century, smallpox caused devastating disease throughout the world. This map shows the distribution of smallpox in countries that were endemic with the virus in 1945.

This map from 1955 reveals the distribution of the smallpox virus, and the many countries in which it was still endemic.

In 1967, some 10 to 15 million cases of smallpox still occurred annually in more than 30 countries. Of these some two million died and millions of survivors were left disfigured or even blind. On January 1, 1967, the World Health Organization launched the *Intensified Smallpox-Eradication Programme*, which was to rely entirely on an all-out attack or “mass vaccination” to contain smallpox outbreaks.
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After 1970 the smallpox campaign evolved to a new surveillance-containment strategy based on observations of local practices, customs, and conditions in western Nigeria and southern India. The surveillance-containment strategy, also called the “ring-vaccination” strategy, focused on containment and vaccination of each newly discovered case. Local campaigns adopted variations of their own surveillance-containment strategy to control outbreaks. The combined use of both strategies, mass vaccination and ring vaccination, resulted in the elimination of smallpox.

Because of new techniques and improvements of existing procedures, by the 1970s the incidence of smallpox in endemic areas was reduced. Each national program developed its own operating procedures.

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In this 1971 map of the smallpox virus distribution, the reduced number of endemic countries is evident.

As a result of improved compliance by all countries in the world; the rules and standards regarding detection, containment, and vaccination; and creative, problem-solving experimentation in the field, smallpox outbreaks could no longer spread.

This 1977 map shows Somalia, the last country in which smallpox was found.

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The last naturally occurring cases in Bangladesh in 1975 and Somalia in 1977 marked the successful completion of the WHO-sponsored eradication campaign. Subsequently, in 1980, the WHO’s Global Commission for the Certification of Smallpox Eradication formally certified that the world was smallpox-free and recommended that all countries cease vaccination.

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In 1978, the unclear etiology of a researcher’s acquisition of smallpox in Birmingham, England, led to increased levels of biosafety and containment in working with the virus.

Although since 1977 no naturally acquired cases of smallpox have occurred anywhere in the world, there are serious concerns about the use of smallpox as a bioterrorist agent.
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In the event of an intentional release of the virus that causes smallpox, an effective public-health control strategy requires early recognition of smallpox. Most clinicians have never seen a case of smallpox and therefore lack experience in making its diagnosis. The Centers for Disease Control and Prevention has developed the Smallpox Response Plan and Guidelines, describing strategies to guide the public-health response and actions that must be carried out by federal, state, and local public-health agencies in the event of a smallpox outbreak.

The Smallpox Response Plan and Guidelines can be found on the CDC website; use this link to access the latest information.

Guide A of the plan specifically summarizes pre-event surveillance activities, as well as post-event activities necessary for smallpox surveillance and case reporting; contact identification, tracing, vaccination, and surveillance; and epidemiologic investigation at the local, state, and federal levels. Periodically, this material is updated, so check the website every so often.

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The modes of transmission shown here were observed during the Smallpox Eradication Era. Commonly, smallpox had spread amongst close contacts of a diseased person – often occurring in the family household. Epidemiology and laboratory studies suggested that those at highest risk for contagion were within 6 to 7 feet of a diseased person. The disease is transmitted by virus-laden airborne droplets. If smallpox were to recur, use of a fitted respirator NIOSH N-95 or better should be able to prevent transmission. The virus was rarely transmitted from fomites and was not known to be transmitted by food or water.
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The World Health Organization (WHO) established a classification system for smallpox case types based on disease presentation and rash burden.

Ordinary smallpox was the most common manifestation or category, making up approximately 90% of all clinical cases of smallpox.

The rash had a centrifugal base distribution, which will be further described in Unit 3. Lesions were present in greater numbers on the face and extremities, with fewer lesions on the trunk. The mortality rate of ordinary smallpox ranged from less than 10% to 75%, depending on the disease presentation and rash burden. Ordinary smallpox was sub-grouped into three categories which are depicted in the following slides.

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The 3 subgroups of ordinary smallpox: ordinary discrete, ordinary semi-confluent, and ordinary confluent, were based on the extent of rash on the face and the body. In ordinary discrete, patches of normal skin were visible between rash lesions on the extremities, trunk, and face. The mortality rate of ordinary discrete smallpox was less than 10%.

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In ordinary semi-confluent smallpox, areas of normal skin were visible between pustules on the extremities and trunk of the body, but the pustules on the face were confluent. The mortality rate for ordinary semi-confluent was higher than for ordinary discrete, but less than for ordinary confluent.
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The mortality rate for the third subgroup of ordinary smallpox, ordinary confluent smallpox, was much higher than for the other two ordinary types. Fifty to 75% of people hospitalized with this type of smallpox died, usually from toxemia or hemorrhage. People with ordinary confluent infection were also prone to develop thrombocytopenia.

A tertiary fever may have occurred with bacterial infection. In this subgroup of ordinary smallpox, almost no skin was visible; the rash was confluent on the trunk and face.

In ordinary confluent smallpox, the lesions are so dense that they form patches. This was a patient with confluent smallpox, a condition in which pustules become so numerous that they merge. Patients often remained febrile and toxic even after scabs had formed. In one case series, the case-fatality rate in confluent smallpox was 62%.

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The fourth category of smallpox is flat smallpox. Flat smallpox, which occurred in only about 5% of the cases, produced slowly developing focal lesions with generalized distribution and had an approximate 50% fatality rate. Edema produced the “flat” appearance of the lesions, which were either confluent or semi-confluent.

Flat smallpox was associated with intense toxemia and defects in the immune system. This type was rare and often fatal. The appearance of lesions was delayed and the evolution of the lesions was slow. The vesicles appeared flat, soft, and velvety.

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The fifth category of smallpox, hemorrhagic smallpox, comprised less than 1% of clinical cases. It is subdivided into early and late hemorrhagic smallpox.

The hemorrhagic types of smallpox, which were difficult to diagnose, are thought to have developed as a result of impaired immune response. They were associated with bleeding into the skin and mucous membranes and were invariably fatal. An individual with early hemorrhagic disease often died within the first week of illness before skin lesions developed.

People with late-stage hemorrhagic smallpox died later in the course of the disease, after eruption of lesions.
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The second category, the “modified” cases of smallpox, were rarely fatal and evolved more rapidly, comprising only 2% of cases in unvaccinated, and 25% in previously vaccinated, individuals. Its lesions were fewer, smaller, and more superficial than those of the “ordinary” cases.

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Finally, the first category of smallpox, *variola sine eruptione*, was the least severe manifestation often observed in previously vaccinated contacts as well as in infants with maternal antibodies. Affected individuals were either asymptomatic or had a slight increase in temperature with headache and generally mild flu-like symptoms. This type caused death in less than 1% of cases.

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Because smallpox is a disease eradicated for over 20 years, there is little recent clinical experience with diagnosis. The CDC and other organizations have put together materials and websites to aid in education efforts. Here we will describe what is contained in the links you are seeing; more information about diagnostic algorithms appears in Unit 3 of this module.
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The first link, the clinical febrile-vesicular rash algorithm is depicted in a poster (titled Evaluating Patients for Smallpox Poster) designed to assist clinicians in differentiating smallpox from other conditions often confused with smallpox by illustrating the differences between varicella and variola as well as listing criteria and risks for smallpox infection.

The second link is a worksheet titled, Evaluating Patients For Smallpox. It is for collecting information on cases of acute, generalized vesicular, or pustular rash illnesses and, using CDC criteria, to classify their risk of it being smallpox.

The third link titled, Evaluate a Rash Illness Suspicious for Smallpox, is an online form intended to instantly evaluate a rash illness suspicious for smallpox only when there is no release or circulation of smallpox.

The fourth link describes CDC’s experience with the clinical febrile-vesicular rash in a 2004 publication in the journal Clinical Infectious Diseases titled, “Development and Experience with an Algorithm to Evaluate Suspected Smallpox Cases in the United States, 2002–2004”.

Finally, the fifth link is an interactive training tool called Smallpox: What Every Clinician Should Know 2003. This tool provides clinicians with information on virology, epidemiology, clinical features, and diagnosis of smallpox; characteristics and use of smallpox vaccine; and proper management of smallpox-vaccine recipients. The program is based on a satellite broadcast that was produced by the Centers for Disease Control and Prevention (CDC).

After reviewing the links, click the “Next” button to continue.
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We come now to Unit 3 of this module, which concerns the differential diagnosis of smallpox—evaluating vesicular-rash disease for the risk of smallpox using the clinical rash algorithm.

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In the event of a bio-terrorist release of variola virus, effective public health-control strategies will require early recognition of any case of smallpox. Most clinicians have never seen a case of smallpox and therefore lack experience with making its diagnosis. Because other rash illnesses may be confused with smallpox, a diagnostic algorithm or a standard approach to evaluating rash illness cases is essential. The Clinical Febrile Vesicular Rash Algorithm, hereafter called the clinical-rash algorithm, developed by CDC, uses the clinical features of smallpox to establish major and minor diagnostic criteria. Based on these criteria, clinicians can classify cases of vesicular and pustular-rash illness into risk categories according to likelihood of being smallpox.

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The clinical-rash algorithm provides a strategy to triage cases of disease with varying degrees of similarity to smallpox and to couple appropriate public-health responses to each level of suspected disease. Based on the unique features of smallpox, this algorithm allows clinicians to triage a patient with fever and vesiculopustular rash to high, moderate, or low risk for smallpox.

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This algorithm also provides a framework for testing for orthopoxviruses in clinical samples. The algorithm was specifically designed to discriminate infection with variola virus (or smallpox) from other illnesses that may manifest with similar vesicular or pustular rashes. Combining differential diagnoses with appropriate laboratory testing will be critical for public health, as well as for differentiation of smallpox from other diseases that may be clinically confused with smallpox. Communication among clinical and epidemiology staff and laboratory personnel will be critical in enabling fast and appropriate laboratory tests to confirm the etiology of such rashes.
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The Clinical Febrile Vesicular-Rash Algorithm is further discussed in Module 3: Approach to Laboratory Diagnosis.

The poster of the algorithm can be downloaded and printed from the CDC smallpox web site. Copies of this poster are also available through state public health departments or ordered through the CDC online ordering system.

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The clinical-rash algorithm contains three major criteria.

The first is presence of a febrile prodrome occurring 1 to 4 days before rash onset, with a fever of greater than or equal to 101 degrees Fahrenheit, and at least one of the following: prostration, headache, backache, chills, vomiting, or severe abdominal pain.

The second major criterion for smallpox is classic smallpox lesions. Lesions are characteristically deep-seated, firm, round, circumscribed vesicles or pustules. The lesions may become umbilicated or confluent.

The third major criterion is that the lesions are in the same stage of development in any one area of the body. (Deep-seated vs. superficial rashes, and rashes being at the same stage of development, should help delineate the differential diagnosis.)

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Minor smallpox-diagnosis criteria have also been identified. These criteria describe other manifestations of smallpox and describe its rash distribution. The smallpox rash has a centrifugal distribution in which the greatest concentration of lesions is on the face and extremities (including the palms and soles), and fewer lesions are seen on the trunk. The first lesions appear on the oral mucosa of the palate and pharynx, and on the face or forearms. Evolution of the lesions is slow. Each stage from macules, papules, and vesicles to pustules may last 1 to 2 days. The patient may appear toxic or moribund; typically patients are so sick that they are bedridden.
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Depending on presence of the major and minor criteria, an individual risk for smallpox is classified as high (in red), moderate (in yellow), or low (in green). Public-health action is based on level of assessed risk.

Immediate actions for patients with generalized vesicular or pustular-rash illness are to institute airborne and contact precautions and to alert the infection-control team.

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Any patient presenting with all 3 major criteria is classified as at high risk for smallpox. The response to this type of case should be to request an infectious disease and/or dermatology consultation. If the high-risk status is confirmed, then immediately alert the local or state health department. It is helpful to obtain digital photos. After concurrence, the state health department will alert the CDC to arrange for specimen collection, chain-of-custody documentation, and appropriate testing at CDC and the Laboratory Response Network (or LRN).

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A patient classified with moderate risk for smallpox will most likely present with vesicular or pustular rash and report a prodrome and one other major criterion, or a prodrome and at least 4 minor smallpox criteria.

The response for a moderate-risk case is to request an infectious-disease or dermatology consultation to confirm the risk status. Expedient laboratory or pathology testing for varicella and other rash diseases should be conducted as appropriate at the hospital, local or state health laboratory or through a reference laboratory. Personnel should obtain digital photos and reevaluate at least daily to determine if risk level has changed.

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A patient at low risk for smallpox presents with a vesicular or pustular rash and reports no febrile prodrome prior to rash eruption, or reports a prodrome and fewer than 4 minor smallpox criteria. The response for a low-risk patient is management and laboratory testing as clinically indicated.

The smallpox algorithms will be discussed again in the next module (3), Approach to Laboratory Diagnosis.
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Other rash illnesses to consider as a part of the differential diagnosis in a patient with fever and a vesicular or pustular rash are varicella, disseminated herpes zoster, impetigo, drug eruptions, and erythema multiforme (particularly Stevens-Johnson Syndrome).

Clinicians should also consider enteroviral infections, especially Hand-Foot-Mouth Disease, as well as disseminated herpes simplex viral infections, scabies and insect bites, *Molluscum contagiosum*, and generalized vaccinia.

Other dermatological conditions, often rare, that might be confused with smallpox include acne; secondary syphilis; rickettsial diseases such as Rocky Mountain Spotted Fever, and disseminated-rash diseases such as monkeypox.

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Questions regarding presence of a febrile prodrome, characteristic appearance of the lesions (that is, deep-seated vs. superficial), and the same stage of lesion development will help delineate the differential diagnosis. Always consider varicella (chickenpox) and other disseminated-rash illnesses. In the absence of a confirmed case of smallpox in the world, in the presence of vaccination, or with a history of contact with a vaccinee, consideration should be given to one of the generalized rashes associated with vaccinia. Travel history or exposure to unusual animals brings the suspicion of monkeypox to mind.

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Varicella or chickenpox is the most likely condition to be confused with smallpox. Chickenpox is caused by the varicella-zoster virus, resulting in an itchy blister-like rash, fatigue, and fever. The rash appears first on the trunk and face, but can spread over the entire body, causing between 250 to 500 itchy blisters. During the smallpox-eradication era, varicella cases among adults, especially those with infected lesions, were the most difficult to differentiate from smallpox. These pictures demonstrate the similarity between varicella and smallpox rashes.
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Several characteristics can be used to help differentiate varicella and smallpox. Varicella lesions are typically in different stages of development and concentrated on the trunk but may involve the face. Thus, on any one part of the body, there may be macules, papules, vesicles, and crusted lesions at the same time. The superficial lesions evolve more rapidly than smallpox lesions; typically they progress from macule to vesicle and even crust within 24 hours.

In contrast, deep-seated smallpox lesions are distributed in a centrifugal pattern; in other words, the lesions are concentrated distally on the head and the extremities. These lesions are typically in the same stage of development on any one part of the body and develop more slowly. Evolution of the smallpox lesions may take up to 2 or 3 weeks.

This list is taken from the Evaluating Patients for Smallpox poster.

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Unlike smallpox, chickenpox lesions are superficial, and on any one part of the body there are lesions in different stages; that is, papules, vesicles, and crusts. In chickenpox, lesions tend to be concentrated on the trunk and face, with a few on arms and legs, while smallpox lesions tend to concentrate on the extremities and face. Chickenpox rarely shows lesions on the palms and soles. In smallpox, however, lesions often appear on the palms of the hands and soles of the feet. In this chickenpox patient, many lesions are present on the back, but only a few on his arms.

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To demonstrate comparative morphology, we have a chickenpox scab on the left and smallpox scab on the right, viewed from above.

A chickenpox scab is on the left and smallpox scab on the right, viewed in profile. These pictures demonstrate that scab morphology is not useful to differentiate varicella from variola. Though one can differentiate between chickenpox and smallpox during the early stage of infection when active lesions are present, once lesions have advanced to crusts, they are nearly indistinguishable.
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After chickenpox scabs have come off, pinkish areas on the skin may be seen like those after smallpox. Usually, the chickenpox patient has lost most of the scabs by the eighth day of the rash.

The most common complications from varicella are bacterial infections of the skin and soft tissues in children and pneumonia in adults. Prior to the availability of varicella vaccine there were approximately 4 million cases of varicella each year in the U.S.

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This plantar foot rash was initially suspected to be smallpox-related, but was finally determined to be caused by herpes zoster virus.

This infection is caused by the same virus as chickenpox, which normally occurs as a childhood disease, and which may later recur as a zoster, skin rash.

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A number of other rash illnesses may be confused with smallpox. Impetigo is usually caused by Group A *Streptococcus* sp. or *Staphylococcus aureus* bacteria. This patient presented with these gluteal lesions, which proved to be impetigo.

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Drug eruptions are sudden and often associated with fever and other systemic symptoms. They can include pustular and vesicular lesions and result in rapid mortality. This is a photo showing a phototoxic drug eruption.

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Erythema multiforme major, also known as Stevens-Johnson syndrome, is a toxic or allergic rash that can develop in response to the smallpox vaccine. This rash can take various forms, ranging from moderate to severe. After receiving a smallpox vaccination, this 1-year-old child developed erythema multiforme.
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The scabies rash appears as pimple-like eruptions, especially in the webbing between the fingers, the skin folds on wrist, elbow or knee, and on the penis, breast, or shoulder blades. This patient’s hand reveals a scabies infestation of the mite species *Sarcoptes scabiei*.

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The poxvirus *Molluscum contagiosum*, can be associated with widespread lesions, especially in the setting of atopic dermatitis. The presentation is more dramatic when associated with HIV disease. Diagnosis is based on biopsy, clinical spread, and lack of severe systemic symptoms.

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Rickettsialpox is an urban zoonosis. The causative agent, *Rickettsia akari*, has been identified on several continents. It is a relatively mild disease that has not been associated with fatalities. Rickettsialpox shares features with illnesses caused by high-profile biothreat agents", such as smallpox. "The initial recognition was traced to an epidemic of febrile rash illness in New York City in 1946. The name derives from the clinical similarities to varicella and rickettsial diseases.

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To review, there are several common conditions that might be confused with smallpox. The *Evaluating Patients for Smallpox* poster referred to earlier in this unit describes the common clinical features of these diseases.

After reviewing the link, click the “Next” button to continue.
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We have now arrived at Unit 4 of this Module 2 presentation, which will cover Monkeypox, its various hosts and disease manifestations.

Slide 3 of 11:
Monkeypox was first detected in captive Asiatic monkeys; however, the virus has been found naturally only in Africa, and evidence points to squirrels as important reservoir hosts. Particular attention was focused on monkeypox infection from 1970 when smallpox surveillance activities in Africa revealed cases clinically indistinguishable from smallpox, particularly in Zaire (now known as the Democratic Republic of Congo or DRC). The main differences between the two are that monkeypox shows a greater degree of lymphadenopathy and a lower capacity for case-to-case transmission than does smallpox. Between 1981 and 1986 in Zaire (now the DRC) most cases occurred in children who had not received smallpox vaccine. The overall mortality rate was approximately 10%, and all deaths occurred in unvaccinated children. 74% of confirmed cases were detected by electron microscopy and virus isolation. Laboratory workers should be vaccinated with vaccinia to prevent monkeypox infection.

Slide 4 of 11:
In general, the clinical features of monkeypox as seen in central Africa are the same as those of an ordinary or modified case of smallpox, including rash and fever. Clinically, lymphadenopathy is more pronounced in monkeypox than in smallpox.

This picture from Liberia, West Africa, shows lesions on the arm and leg of a 4-year-old girl with monkeypox virus infection.

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As described in unit one, monkeypox is a member of the orthopoxvirus genus. Access to a virus diagnostic laboratory should permit detection of virus by electron microscopy (or EM) and molecular methods. Although EM will not be able to distinguish the viruses of variola and monkeypox, it will identify whether a poxvirus is present. Specifically, it can exclude or confirm varicella as a possible cause of a febrile-rash illness.
Slide 6 of 11:

Here a negative-stain electron micrograph demonstrates 2 forms of the brick-shaped monkeypox virus from a cell culture. Depending on the penetration of the stain, the surfaces of “M”, or “mulberry” virions, are covered with short, whorled filaments, while “C”, or “capsular”-form virions, when penetrated by stain, present as a sharply defined, dense core surrounded by several laminated zones of differing densities.

These two forms of the monkeypox virus, the “C” form and “M” form, can be seen in the intercellular mature virion (IMV). The “M” form is usually found in tissue-culture preparations, and the “C” form is usually found in lesions. See module 6 (Electron Microscopy) for more discussion of this process.

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In 2003, importation of infected exotic animals into the United States resulted in monkeypox infection of humans who were exposed to infected prairie dogs. The prairie dogs were likely infected after contact with infected West African small mammals imported as exotic pets. Disease in this outbreak appears to have been milder than human cases seen in Africa. Only two of the 37 cases had complications: one with keratitis and one with encephalitis.

The text in red demonstrates how EM can be used to diagnose a poxvirus quickly. 13 days after Patient 1 was seen by a physician on May 20, a poxvirus was identified by EM.

Exposure in the index case, Patient 1, a young child, was clearly linked to a prairie-dog bite. This outbreak illustrates the difficulties in recognizing and diagnosing orthopox infections in a real world context. Because monkeypox was not suspected, diagnosis of the initial cases were delayed. Electron microscopy was a useful tool to determine that a poxvirus was present in the lesions.

Illness in this country was generally mild with only two very severely ill patients; one with persistent keratitis and one with encephalitis as mentioned previously.

As to the rash, most patients had relatively few lesions although one had hundreds of lesions—in this case pustular lesions with focal hemorrhage.

As to transmission, all cases in the US were linked to prairie-dog exposure.
Epidemiologic criteria were useful in diagnosing infections during the 2003 US monkeypox outbreak.

The first criterion was exposure to an exotic or wild mammalian pet obtained on or after April 15, 2003, with clinical signs of illness such as conjunctivitis, respiratory symptoms, and/or rash.

The second criterion was exposure to an exotic or wild mammalian pet with or without clinical signs of illness that has been in contact with either a mammalian pet or a human with monkeypox.

Exposure to a suspect, probable, or a confirmed human case of monkeypox was another epidemiologic link used to facilitate diagnosis.

Because the monkeypox virus is related to the virus that causes smallpox, the smallpox vaccine can protect people from monkeypox as well as smallpox.

Smallpox vaccine is effective at protecting people against monkeypox when it is given before they are exposed to monkeypox. (Exposure includes very close contact with a person or animal that has monkeypox.)

Experts believe that vaccination after exposure to monkeypox may help prevent the disease or make it less severe.

Here is a link to a CDC Fact Sheet on Smallpox Vaccine and Monkeypox. Consult the fact sheet to see who should and should not receive the smallpox vaccine.

After reviewing the link, click the "Next" button to continue.

This chart presents a laboratory testing algorithm that should be used when a smallpox-vaccine adverse event or monkeypox infection is suspected. Because monkeypox can present with systemic and localized infections, this algorithm can be utilized to test for monkeypox. This algorithm will be discussed in more detail in Module 3: Approach to Laboratory Diagnosis.
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More information on monkeypox regarding transmission, pathogenesis, specimen collection, laboratory testing, vaccination, and infection control, can be found at these CDC websites.

After reviewing the links, click the “Next” button to continue.
Slide 2 of 24:
We have now arrived at our final unit in module 2, addressing smallpox vaccination.

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One of the interesting features of orthopoxviruses is their varied host range. Variola, or smallpox, infects only humans while vaccinia has a wider range, infecting cattle and rabbits as well as humans. We don’t know the reasons for these differences. Importantly, however, these viruses are genetically and antigenically very similar and provide cross-protective immunity in infection. This provides the basis for the use of vaccination with live vaccinia virus to prevent smallpox.

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The smallpox vaccine available in the United States since February 2008, continues to utilize a live-virus preparation of infectious vaccinia virus. The new formulation, ACAM2000, is a clonal derivative of the former vaccine, and is made by Sanofi Pasteur Biologics Co. It can be acquired from the CDC Drug Service. The ACAM2000 vaccine replaces the “Dryvax” produced by Wyeth. Smallpox vaccine does not contain smallpox (variola) virus.

In response to concerns about bioterrorism and the potential re-introduction of smallpox, the United States government has contracted for development of alternative, less reactogenic vaccines produced through cell culture. Some of these vaccines are currently being evaluated for effectiveness.
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ACAM2000, Smallpox (Vaccinia) Vaccine, is a live vaccinia virus derived from plaque purification cloning from Dryvax® (Wyeth Laboratories, calf lymph vaccine, New York City Board of Health Strain). ACAM2000 is provided as a lyophilized (or freeze-dried) powder in a 100-dose vial, containing the following non-active excipients: 6-8 mM HEPES (pH 6.5-7.5), 2% human serum albumin USP, 0.5-0.7% sodium chloride USP, 5% mannitol USP, and trace amounts of neomycin and polymyxin B. The diluent used to reconstitute the vaccine is 50 percent glycerin with a small amount of phenol as a preservative.

Vaccine continues to be delivered by the multiple puncture method.

The vaccine is supplied with diluent, transfer needle, and bifurcated needles. Its box contains the diluent and a vial of Acambis dried smallpox vaccine, and bifurcated needles.

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A normal primary vaccination appears as a papule in 3 to 4 days, and rapidly progresses to a vesicle with the surrounding erythema by the 5th to 6th day. The vesicle center becomes depressed and progresses to a well-formed pustule by the 8th or 9th day. By the twelfth day, or soon thereafter, the pustule crusts over forming a brown scab, which progresses from the center of the pustule to the periphery. After 2 1/2 to 3 weeks, the scab detaches and a well-formed scar remains.

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In 1967, the WHO launched the worldwide smallpox-eradication program. Starting first with mass vaccination, then moving to a ring-vaccination strategy, the WHO was able to declare smallpox eradicated in 1980. Here we see a physician in a field checking the immunization reaction of a young man vaccinated during a 1972 smallpox epidemic in Kosovo, Yugoslavia.
Slide 8 of 24:
Smallpox vaccination provides high-level immunity for 3 to 5 years and decreasing immunity thereafter. If a person is vaccinated again later, immunity lasts even longer. Historically, the vaccine has been effective in preventing smallpox infection in 95% of those vaccinated. In addition, the vaccine was proven to prevent or substantially diminish infection when given within a few days of exposure to smallpox. It is important to note, however, that at the time when the smallpox vaccine was used to eradicate the disease, testing was not as advanced or precise as it is today, so there may still be things to learn about the vaccine and its effectiveness and length of protection.

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This chart demonstrates long-term protection from smallpox vaccination in different age groups. This study was performed from a smallpox outbreak in Liverpool, England, between 1902 and 1903. Note that the highest case-fatality rate in each age group occurred among groups that were not vaccinated.

In the first group, ages zero to four, 45% of this age group that were never vaccinated against smallpox died.

10.5% of the 5-to-14-age group that were not vaccinated died.

The previously unvaccinated 15-29-age group died at a rate of 13.9%.

For ages 30 to 49 and more than 50 years, 54.2% and 50%, respectively, died if they were never vaccinated, while only 5.5% of those vaccinated as infants died.

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Vaccination following exposure to smallpox can diminish the severity of the disease. As demonstrated in the studies shown here, the lowest disease rates occurred among persons vaccinated 7 days or fewer after exposure to smallpox. Studies have also shown that the disease was generally less severe in persons receiving post-exposure vaccination. It is difficult to define precisely the time of best protection, although, as with other post-exposure immunizations, it is probably safe to assume that 'earlier is better'.
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In October 2002, the Advisory Committee on Immunization Practices (known as ACIP) recommended that enhanced bioterrorism preparedness should include vaccination of Smallpox Public Health Response and Health Care Teams. These revised recommendations regarding vaccinia (smallpox) vaccine, published in the Morbidity and Mortality Weekly Report (MMWR), update the 1991 ACIP recommendations. These updated recommendations include current information regarding the non-emergency use of vaccinia vaccine among laboratory and health-care workers occupationally exposed to vaccinia virus, recombinant vaccinia viruses, and other orthopoxviruses that can infect humans. In addition, this report contains ACIP’s supplemental recommendations for use of vaccinia vaccine should smallpox (variola) virus be used as an agent of biological terrorism or should a smallpox outbreak occur for any reason. Visit the CDC MMWR website for more information.

CDC has developed a Fact Sheet on smallpox vaccine and monkeypox. Consult this fact sheet to see who should and should not receive the smallpox vaccine.

After reviewing the links, click the “Next” button to continue.

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Because smallpox vaccination was discontinued in the 1970s, many healthcare providers have never administered the vaccine. In response to heightened concerns about bioterrorism and the remote possibility of an intentional release of variola virus, in December of 2002 CDC clinicians began training state-licensed vaccine administrators in delivering smallpox vaccine safely and efficiently. Once their initial training was completed, they provided additional smallpox-vaccine administration training in their home states.

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Here, during the 2002 Smallpox Vaccinator Workshop, a CDC clinician demonstrates administration of the vaccine using the multiple-puncture technique with a bifurcated needle. This process penetrates the stratum corneum of skin and delivers a small, standardized amount of vaccine to the deep epidermis.
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Smallpox vaccination is not without complications. Dr. Vincent Fulginiti, Professor Emeritus of Pediatrics at the University of Arizona & the University of Colorado, who was active in the treatment of vaccine related adverse events, is quoted as saying “Because of the presence of live virus on the skin for up to 2 weeks, vaccination can result in unpleasant effects and adverse reactions. Some are serious, but treatable. These should not be cause for fear or panic but rather for prudence in screening and administration of the vaccine. A few are serious and life-threatening.”

And this is a reminder that because the smallpox vaccine is "live", it can be spread to other people, as well as to other parts of one's own body.

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Severe reactions to smallpox vaccine are rare. In the past, about 1,000 people for every 1 million people vaccinated for the first time experienced reactions that, while not life-threatening, were considered serious.

Two primary sources are available regarding the frequency of adverse events in the US from the NYCBOH smallpox vaccine: the U.S.1968 national survey and the 1968 10 state survey. Results of these surveys, showing rates of both serious but not life threatening reactions and life threatening reactions, are summarized in this table.

More details about these studies can be found in “Smallpox and its Eradication” published by WHO in 1988. Guidance for clinicians on Smallpox vaccination and adverse events is detailed in the 2003 MMWR Recommendations and Reports shown here.

After reviewing the links, click the “Next” button to continue.
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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. During the eradication era, there were no survivors of organ transplantation, or people living with HIV, and people often did not survive following different forms of chemotherapy. We may now also have more people affected by eczema or atopic dermatitis. All of these conditions convey higher risk of serious complications 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.

This CDC web page illustrates normal vaccination reactions, and contains evaluating tools for adverse reactions.

After reviewing the link, click the "Next" button to continue.

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Inadvertent inoculation is the accidental transfer of vaccinia virus from the vaccine site to another area of the body or to another person. It 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 does the vaccination site. The most common body sites affected are face, eyelid, nose, mouth, and other mucosal surfaces. Transfer to another person can produce 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.
Eczema vaccinatum is one example of the more serious adverse events that can result from smallpox vaccination. Shown here are eczema vaccinatum skin lesions on the torso of a smallpox-vaccine recipient. 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 affecting the integrity of the skin.

Some of the most severe cases of eczema vaccinatum have occurred in people with eczema or atopic dermatitis, who came into contact with recently vaccinated individuals. These are eczema vaccinatum lesions on the skin of a patient who had danced with a vaccinated partner. Eczema vaccinatum can be quite severe and even fatal. 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 adverse events.

This 28-year-old with eczema vaccinatum contracted it from her vaccinated child. The woman had a history of atopic dermatitis, which was inactive when her child was vaccinated. She was treated with vaccinia immune globulin (VIG), idoxuridine eye drops, and methisazone, resulting in healed lesions, no scarring, and no lasting ocular damage.
Generalized vaccinia is the result of systemic spread of virus from the primary vaccination site, and is usually a benign complication in a primary vaccinee that is self-limited, except in some individuals dealing with immunosuppression.

This patient displayed a rash indicative of generalized vaccinia on day 10 following a smallpox vaccination. The next two slides show more examples of generalized vaccinia.

Another manifestation of generalized vaccinia is erythema multiforme major, also referred to as Stevens-Johnson syndrome. As seen in this image of a one-year old child, erythema multiforme is a toxic or allergic rash in response to the smallpox vaccine that can take various forms, and range from moderate to severe.

Generalized vaccinia can occur even in the absence of predisposing factors. This generalized-vaccinia reaction occurred in a 15-month-old child with no history of eczema or immunologic disorders.

Vaccinia necrosum or progressive vaccinia is a rare but serious adverse event that can occur in people with cellular immunodeficiencies or in individuals with humoral or immune-globulin deficiencies. People with progressive vaccinia usually present with a non-healing, expanding vaccination site. The site often ulcerates and central necrosis, or necrosis or death of the surrounding skin, can occur. Because local immune response is inadequate, the virus can spread locally and systemically. This condition is usually fatal.

Post-vaccinial encephalitis is a rare condition, occurring in 1 in 100,000-500,000 vaccinations. It was seen in infants younger than 1 year of age or in older adolescents and adults receiving their first vaccination. It is characterized by the sudden onset of headache and vomiting in the second week after vaccination. Patients present with the typical symptoms of encephalitis. The disease varies in severity and prognosis; it can be mild and self-limited or progressive and fatal. The pathophysiology of this complication is not well understood but thought to result from a post-vaccination immune response. Post-vaccinial encephalitis has not been causally linked to the presence of vaccinia virus in the central nervous system.
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CDC has provided standardized orthopox testing methods to reference level laboratories in the Laboratory Response Network. Specimens from individuals suspect for vaccinia adverse events that require identification of vaccinia should go to the nearest LRN laboratory. Contact your state public-health laboratory director to determine where the nearest LRN laboratory equipped to perform this testing is located. For vaccinia testing, standard shipping guidelines are appropriate.

For specimens with a high suspicion of smallpox, contact your state public health department who will contact CDC.

These guidelines are available at the lab issues section of the CDC website. For more information on Laboratory testing and specimen collection, visit Modules 3 and 4.

After reviewing the links, click the “Next” button to continue.

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This chart (Laboratory Testing for Suspected Smallpox Vaccine (Vaccinia) Adverse Events or Monkeypox in the United States) presents a testing algorithm that should be used when a smallpox-vaccine adverse event or monkeypox infection is suspected. More detail on the testing algorithms will be presented in Module 3.

To learn more about smallpox vaccination, CDC has available two webcasts. The first is “Smallpox and Vaccinia Laboratory Testing: A National Training Initiative” developed to help prepare the nation's laboratorians to respond effectively to vaccine adverse events and the intentional release of smallpox.

The second webcast of interest is "Clinical Management of Adverse Events Following Smallpox Vaccination: A National Training Initiative". The goals of this video include explaining the rationale for smallpox vaccination, defining risks, recognizing complications, diagnosing, managing, and treating patients with vaccine-adverse events, and explaining procedures for adverse-event reporting.

After reviewing the links, click the “Next” button to continue.
Prevention of adverse events requires careful and adequate screening to avoid vaccination of susceptible persons, and to prevent susceptible persons from having contact with vaccinees. Susceptible persons include those who are pregnant, immunodeficient, or immunosuppressed, and persons with eczema/atopic dermatitis, or disruptive skin diseases. Some important and helpful websites are listed here:

The first link, from CDC’s Smallpox Response Plan and Guidelines (Version 3.0), outlines many of the federal, state, and local public-health strategies relevant to a smallpox emergency. Annex 4 of this document describes the monitoring and reporting of adverse events following smallpox vaccination. Its training page reveals the right way to collect, package, store, and transport specimens.

The second link, the Smallpox Vaccine and Adverse-Events Training Module, provides up-to-date information for medical professionals on the vaccinia (smallpox) vaccine, the method of vaccination, and the spectrum of normal and adverse vaccination reactions.

The third link is the MMWR titled Smallpox Vaccination and Adverse-Reactions Guidance for Clinicians.

And the last link listed here is to the Vaccination Adverse-Events Reporting System (VAERS). You should know that this website receives all vaccine adverse event reports. It contains instructions and report forms for reporting same.

After reviewing the links, click the “Next” button to continue.
This chart shows the reporting of adverse events for any smallpox outbreak.

A Vaccine Adverse-Events Report (VAER) should be filed within 48 hours; all other VAERS should be reported within 7 days of VAE identification. CDC will monitor these reports and provide information to assist the states. Adverse events following smallpox vaccination that are judged to be serious, unexpected, or for which Vaccinia Immune Globulin (or VIG) or cidofovir (or CDV) are indicated, should be reported without delay to the state adverse-event coordinator.

Electronic reporting is preferred to other submission methods for VAERS reports.

Rapid and accurate laboratory documentation of infections with smallpox and smallpox look-alike diseases or conditions is critical for implementation of a public-health emergency response to bioterrorism.
The module that you have just finished is a comprehensive overview of the orthopoxvirus diseases, particularly smallpox. It presented information on the virology, epidemiology, clinical features and diagnosis of smallpox, protective measures for those persons working with or who may come in contact with someone with the virus, and the characteristics and use of the smallpox vaccine. The remaining modules will collectively provide an overview of diagnostic approaches and capacity, discuss development and validation of rapid diagnostic methods, and convey laboratory needs and requirements.

Please keep in mind that as knowledge and experience change, we highly recommend that you check the Centers for Disease Control and Prevention website for updates.

After completing this module, to obtain Continuing Medical Education credit or other continuing education credit, enroll online where shown, register as a new or returning user separately for each module, and complete a post-test and evaluation form for each module. For assistance, contact CDC CE Learner Support at 1-800-41TRAIN or email ce@cdc.gov.