

# Monkeypox

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## Importance

Monkeypox is a viral disease that resembles smallpox, but unlike smallpox, is acquired from animals. Monkeypox virus is endemic in western and central Africa, where it circulates in unknown animal hosts and emerges periodically to affect humans. The consequences range from asymptomatic infections to severe, fatal illness. This virus also causes illness in nonhuman primates, and outbreaks have been seen occasionally in primate facilities, in various parts of the world. The only outbreak of human monkeypox reported outside Africa occurred in the United States in 2003. The virus entered North America in exotic African rodents imported as pets, and spread to pet prairie dogs, which were highly susceptible to infection. This virus subsequently infected approximately 70 people who had been in contact with these animals. Prompt diagnosis of monkeypox is essential, to prevent this disease from becoming established outside Africa. In addition, it must be distinguished from smallpox, which has been eradicated from human populations but is a potential bioterrorist weapon.

## Etiology

Monkeypox results from infection by the monkeypox virus, a member of the genus *Orthopoxvirus* in the family Poxviridae (subfamily Chordopoxvirinae). Two clades of monkeypox viruses, the West African and Congo Basin viruses, have been identified. The Congo Basin viruses are more virulent. Monkeypox virus is closely related to some other orthopoxviruses such as variola (smallpox) virus, and it cannot be distinguished from these viruses in some laboratory tests.

Monkeypox should not be confused with benign epidermal monkeypox (BEMP), a poxviral disease of primates caused by tanapox virus, an antigenically unrelated virus in the genus *Yatapoxvirus* of the family Poxviridae.

## Species Affected

The monkeypox virus's full host range is unknown. Species known to be susceptible to infection include diverse Old and New World monkeys and apes, and a variety of rodents and other small mammals. Two genera of African squirrels, *Funisciurus* spp. (rope squirrels) and *Heliosciurus* spp. (sun squirrels), have high seroprevalence rates, and have been suggested as possible maintenance hosts or vectors in Africa. Sun squirrels did not seem to be susceptible in the U.S. outbreak, which was caused by a West African virus; however, it is possible that they are reservoir hosts only for the Congo Basin clade. Another possibility is that African squirrels are incidental hosts. A recent study in Ghana (West Africa) found evidence of intermittent orthopoxvirus exposure in rodents of the genera *Cricetomys*, *Graphiurus* and *Funisciurus*, as well as in African ground squirrels (*Xerus* spp.), but it did not implicate any single species as a monkeypox reservoir host.

During the U.S. outbreak, a number of species were exposed to a West African monkeypox virus, many at the exotic animal importer where the shipment of infected animals arrived. Infected animals included Gambian giant pouched rats (*Cricetomys* spp.), rope squirrels, dormice (*Graphiurus* sp.), a groundhog/ woodchuck (*Marmota monax*), an African hedgehog (*Atelerix* sp.), a jerboa (*Jaculus* sp.) and two opossums (*Didelphis marsupialis* and *Monodelphis domestica*). North American black-tailed prairie dogs (*Cynomys ludovicianus*) were readily infected by this virus. Chinchillas (*Chinchilla lanigera*) and coatimundis (*Nasua nasua*) developed antibodies after exposure, but viral DNA or infectious virus was not found. Two cusimanse (*Crossarchus obscurus*), a genet (*Genetta genetta*) and 27 sun squirrels (*Heliosciurus gambianus*) in the infected shipment had no evidence of infection. Experimental infections with monkeypox virus have been established in prairie dogs, dormice, ground squirrels (*Spermophilus tridecemlineatus*), the cotton rat (*Sigmodon hispidus*) and the multimammate mouse (*Mastomys natalensis*). Anteaters were thought to have been involved in an outbreak among primates at the Rotterdam Zoo, the Netherlands in 1964.

## Zoonotic potential

Both clades of monkeypox virus are zoonotic.



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## Geographic Distribution

Monkeypox is endemic in central Africa (the Congo Basin) and West Africa. An outbreak of human monkeypox occurred in the U.S. in 2003, but there is no evidence that the virus became established in North America.

## Transmission

The transmission of monkeypox virus between prairie dogs is still incompletely understood. In these animals, the virus or its nucleic acids have been found in skin lesions, urine, feces, and oral, nasal and conjunctival exudates. In terminal cases, it appears to be widely distributed in the tissues. Experimental infections have been established in prairie dogs by intranasal inoculation or contact with fomites (bedding from an animal with lesions). Aerosol transmission might also be possible; however, this is still not entirely certain, as the experimental design did not rule out the possibility of nose-to-nose contact between cages. Experimentally infected prairie dogs can shed monkeypox viruses until 21 days after inoculation.

There is little published information on transmission routes in other small animal pets. Monkeypox virus has been found in most tissues of dormice, and limited evidence suggests that some small animals, such as dormice and Gambian giant pouched rats, might carry this virus for a few weeks or months. Viral DNA was detected in the tissues, urine and feces of one dormouse for at least 6 months, but no viral antigens were found when this animal was euthanized. Whether such animals shed infectious virus is not known.

Monkeypox virus can be transmitted to people in bites from animals, in aerosols during close contact, or by direct contact with lesions, blood or body fluids. In Africa, human outbreaks have often been linked to handling, preparing and eating wild animals. In the U.S., most cases occurred among people who had close direct contact with prairie dogs; some infections were apparently acquired in scratches and bites, or through open wounds. Person-to-person transmission can also occur. In people, monkeypox virus has been isolated for up to 18 days after the onset of the rash. Potential routes of transmission between people include contact with skin lesions or infectious body fluids, or aerosol transmission during prolonged face-to-face contact. Transmission between humans appears to be relatively inefficient, and sustained person-to-person spread has not been reported. Until 2005, the longest documented chain was four serial transmissions. More efficient person-to-person spread, with six serial transmissions, was later reported from an outbreak in the Republic of Congo. It is possible that the efficiency of transmission differs between viruses.

## Disinfection

The U.S. Centers for Disease Control and Prevention (CDC) recommends disinfection of contaminated surfaces

with 0.5% sodium hypochlorite or other EPA-approved high-level disinfectants. Incineration or autoclaving is appropriate for some contaminated materials. Burial without decontamination is not recommended.

## Infections in Animals

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### Incubation Period

Reported incubation periods are 4 to 13 days in experimentally infected black-tailed prairie dogs, 11 to 18 days in 3 prairie dogs infected by exposure to fomites, and 4 to 5 days in experimentally infected ground squirrels. In two studies, experimentally infected cynomolgus monkeys developed clinical signs 3 to 7 days after aerosol exposure.

### Clinical Signs

#### *Nonhuman primates*

In nonhuman primates, the predominant syndrome is a self-limiting rash. The initial clinical signs include fever and 1-4 mm cutaneous papules, which develop into pustules, then crust over. A typical monkeypox lesion has a red, necrotic, depressed center, surrounded by epidermal hyperplasia. These “pocks” can be seen over the entire body, but may be more common on the face, limbs, palms, soles and tail. The number of lesions varies from a few individual pocks to extensive, coalescing lesions. The crusts over the pustules eventually drop off, leaving small scars. Some animals have only skin lesions. In more severe cases, there may also be respiratory signs (coughing, nasal discharge, dyspnea), anorexia, facial edema, oral ulcers or lymphadenopathy. Disseminated disease with visceral lesions is uncommon in natural infections among nonhuman primates. Pneumonia is common only in monkeys infected experimentally via aerosols.

Most naturally infected animals recover; however, fatalities are sometimes seen, particularly in infant monkeys. Asymptomatic infections also occur.

#### *Prairie dogs*

In prairie dogs, the clinical signs may include fever, depression, anorexia, weight loss, nasal discharge, sneezing and/or coughing, respiratory distress, diarrhea, a nodular skin rash and oral ulcers. During the outbreak in the U.S., blepharoconjunctivitis was often the first sign. Lymphadenopathy has been reported in naturally infected prairie dogs, but did not occur in all experimentally infected animals. Elevated serum levels of liver enzymes have also been seen. In experimentally infected prairie dogs, skin lesions appeared first on the head or extremities, followed by the trunk. On the trunk and limbs, characteristic monkeypox lesions developed from macules through vesicles and pustules before forming scabs. Macules and vesicles also occurred on the face in this experiment, but pustules were not seen.

Infected prairie dogs may either recover or become fatally ill. Some experimentally infected prairie dogs died 1-2 weeks after infection without developing lesions on the skin or mucous membranes.

## Other rodents

Little is known about the effects of monkeypox virus on most rodent species. In dormice inoculated intranasally, the clinical signs were limited to lethargy, an unkempt hair coat, a hunched posture, conjunctivitis and dehydration. Many infections were fatal. Experimentally infected cotton rats developed an acute illness with rhinitis, conjunctivitis, dyspnea, coughing and progressive emaciation, often ending in death. In ground squirrels, the first signs were anorexia and lethargy. Nasal hemorrhages and dyspnea were common with a Congo Basin isolate, but most ground squirrels inoculated with a West African strain did not have nasal hemorrhages, and respiratory distress occurred only terminally. Both strains were uniformly fatal at the dose used.

Fatal infections were reported among rope squirrels and one Gambian giant pouched rat in the shipment of exotic African rodents to the U.S. Mild clinical signs, with no respiratory signs and limited skin lesions, were seen in another Gambian giant pouched rat in the shipment. Some pouched rats that appeared healthy were seropositive.

## Post Mortem Lesions [Click to view images](#)

**Recommended biological safety guidelines for the necropsy of infected animals have been published by the CDC (see Internet Resources).**

At necropsy, the skin may contain papules, umbilicated pustules (“pocks”) with central necrosis, or crusts over healing lesions. The skin lesions may vary from barely detectable, single small papules to extensive lesions. Ulcers, erosions or lesions with necrotic centers may be found in the mouths of some animals. Lesions (e.g., white plaques, or small, white, firm, deeply embedded foci with umbilicated necrotic centers) have sometimes been found on internal organs. Additional visceral lesions including (but not limited to) multifocal necrotizing pneumonitis, orchitis and peripheral lymphadenopathy may be seen. Blepharoconjunctivitis is a common finding in prairie dogs.

In intranasally inoculated dormice, the gross lesions at necropsy included hepatomegaly, lymphadenopathy and hemorrhages in the upper gastrointestinal tract, nasal cavity, gall bladder and brain. Pulmonary edema and hemorrhages were reported in experimentally infected ground squirrels.

## Diagnostic Tests

The characteristic skin lesions are suggestive of monkeypox, and histopathology provides supportive evidence. The diagnosis can be confirmed by virus isolation or polymerase chain reaction assay (PCR). Monkeypox

virus can be recovered in mammalian cell cultures, and may be identified using PCR followed by restriction fragment–length polymorphism (RFLP) analysis or sequencing. Monkeypox-specific PCR assays are available in some laboratories, and a DNA oligonucleotide microarray can identify this virus rapidly and specifically. PCR can also be performed directly on clinical samples.

If the animal has not been exposed to other orthopoxviruses, monkeypox can be tentatively diagnosed by detecting orthopoxvirus virions with electron microscopy or orthopoxvirus antigens by immunohistochemistry. However, the specific virus cannot be identified with these techniques.

Serum, samples of skin lesions and conjunctival swabs may be collected from live animals. Monkeypox virus has also been detected in blood, and sometimes in oral and nasal secretions (e.g., oropharyngeal swabs), urine and feces. At necropsy, tissues should be collected from all organs that have lesions. In prairie dogs, monkeypox viruses, viral DNA or antigens have been detected in skin lesions, eyelid and tongue samples, and in many internal organs including the lung, liver, spleen and lymph nodes. In dormice, monkeypox viruses have been found in most organs and tissues. One study suggested that the liver contained particularly large amounts of virus in this species.

## Treatment

Treatment is supportive, but may not be advisable or allowed in some situations. During the 2003 outbreak in the U.S., the CDC recommended that all animals with suspected monkeypox be euthanized to prevent zoonotic infections and reduce disease transmission to other animals. Nonhuman primates are not necessarily euthanized during outbreaks in facilities.

## Control

### Disease reporting

Veterinarians who encounter or suspect monkeypox should follow their national and/or local guidelines for disease reporting. In the U.S., state or federal authorities must be notified immediately.

### Prevention

As a result of the 2003 outbreak, the U.S. banned the importation of six types of African rodents – sun squirrels (*Heliosciurus* sp.), rope squirrels (*Funisciurus* sp.), dormice, Gambian giant pouched rats, brush-tailed porcupines (*Atherurus* sp.), and striped mice (*Hybomys* sp.). These animals can no longer be imported except for scientific purposes, education or exhibition under a permit from the government. This ban applies to these animals whether they were born in Africa or on another continent. In addition, prairie dogs cannot be captured from the wild for use as pets. Exceptions to the restrictions are allowed, by permit, for organizations such as zoos. Similarly, some other countries and governing bodies such as the E.U.

banned the import of prairie dogs from the U.S., and some rodents from Africa.

Good infection control measures, including the isolation of new animals, help prevent outbreaks in primate facilities. Care should be taken to avoid spreading the virus on fomites. Vaccination with vaccinia virus is protective. Because infections have been reported in Asian monkeys mixed with primates from Africa, these species should not be housed in the same area. Anyone who has been exposed to monkeypox should avoid contact with animals, particularly rodents and nonhuman primates, to avoid transmitting the virus to them.

## Morbidity and Mortality

The prevalence of infection in wild primates is unknown. In one study, 8% of nonhuman primates in Africa were seropositive. Few outbreaks have been reported among captive primates. The morbidity rate is usually high and the mortality rate low; most adult animals recover. More severe illness may be seen in infants, which may die, as well as in cynomolgus monkeys, orangutans, and primates of all ages infected experimentally via aerosols. Cynomolgus monkeys developed more severe clinical signs after inoculation with a Congo Basin virus than a West African strain.

Prairie dogs appear to be very susceptible to monkeypox. Mortality rates as high as 60% have been reported after experimental inoculation. During the U.S. outbreak, which was caused by a West African strain, some prairie dogs died rapidly, but others recovered. Little is known about the effects of monkeypox virus on other rodents, although fatal infections have been reported in some animals, including rope squirrels and dormice. Experimental infections in dormice, cotton rats and ground squirrels can result in mortality as high as 100%. Other rodents might be relatively resistant. During the outbreak in the U.S., monkeypox virus was found in one Gambian giant pouched rat that died soon after arrival. Another member of this species had a very mild illness, and orthopoxvirus antibodies were found in 12 of 18 healthy giant pouched rats after the outbreak.

## Infections in Humans

### Incubation Period

The incubation period is reported to be 7 to 17 days, with a mean of 12 days, in Africa. In the U.S. outbreak, the incubation period was 4 to 24 days, with a mean of 14.5 days.

### Clinical Signs

In humans, monkeypox resembles smallpox; however, the symptoms are generally milder, and unlike smallpox, the lymph nodes are usually enlarged. The initial symptoms are flu-like and may include malaise, fever, chills, headache, sore throat, myalgia, backache, fatigue and a nonproductive cough. Lymphadenopathy most often affects

the submandibular, postauricular, cervical and/or inguinal lymph nodes. Nausea, vomiting and conjunctivitis were reported from some cases in the U.S. A rash, initially characterized by macules and papules, develops one to several days after the prodromal signs; these lesions develop into vesicles and pustules (“pocks”), which umbilicate, form scabs and are eventually shed. The number of skin lesions varies from less than 25 to more than a hundred. They are usually concentrated on the extremities, but can also be seen on the head and torso. Lesions may develop on the mucous membranes, as well as on the palms, soles and genitalia. Confluent rashes and recurrent febrile periods can occur in severe cases. Corneal ulceration, coagulation disorders, respiratory complications including dyspnea, encephalitis (rarely) and multiorgan failure have also been reported. Although most patients survive, some cases end in death. In patients who recover, the illness generally lasts for 2 to 4 weeks, and the skin lesions usually resolve within 14 to 21 days. Residual varioliform scarring, with hypopigmented and/or hyperpigmented skin lesions, may be a sequela. Severe scarring, as seen in smallpox, is rare. Subclinical and very mild cases have also been reported.

The 2003 monkeypox outbreak in the U.S., which was caused by a West African strain of the virus, differed in some respects from the classical description of the disease in Africa. Most people in the U.S. had a relatively mild form of the disease, with less marked lymphadenopathy than reported in Africa, relatively few lesions and a self-limiting course. In many patients, the skin lesions were localized and confined to the extremities; generalized rash was rare. Some pustules had prominent erythematous flares; such flares have not been noted in African cases, possibly because most affected people have darker skin. In the U.S., skin lesions sometimes occurred at a bite or scratch, the apparent inoculation site, before systemic signs developed. The skin lesions usually healed without dyspigmented scars in this outbreak. Two severe cases were reported, both in children. One child developed encephalitis, a complication that had been reported only once before. The other child had generalized lesions including lesions in the oropharynx, and severe cervical and tonsillar lymphadenopathy, which caused difficulty in breathing and swallowing. An adult developed complications of keratitis and corneal ulceration, and received a corneal transplant. Patients with other symptoms of monkeypox and immunological evidence of exposure, but no skin lesions, were described in this outbreak. All patients recovered.

### Diagnostic Tests

Monkeypox can be tentatively diagnosed if the characteristic skin lesions are present and there is a history of exposure. Tests to isolate the virus, or identify its nucleic acids or antigens, are similar to those used in animals. In humans, monkeypox virus can be found in skin lesions (e.g., in scabs or material from vesicles) or throat and

nasopharyngeal swabs. Serology may also be helpful. Convalescent-phase serum can be tested for orthopoxvirus-specific IgM with an enzyme-linked immunosorbent assay (ELISA) if the lesions have resolved. Cross-reactions between orthopoxviruses, including smallpox and monkeypox viruses, can occur in serological tests. The possibility of exposure to undiscovered orthopoxviruses also complicates the interpretation of serology in endemic areas. Cross-adsorbed virus neutralization, immunofluorescence or hemagglutination inhibition assays, as well as immunoblotting (Western blotting), can be used to distinguish reactions between monkeypox virus and smallpox virus, although some of these assays are not always easy to interpret. A specific ELISA that may detect monkeypox antibodies in people vaccinated for smallpox has been reported in the literature.

## Treatment

Treatment of monkeypox is mainly supportive. The antiretroviral drug cidofovir has been promising *in vitro* and in animal studies, but its efficacy against monkeypox in humans is unknown. The toxic effects of this drug must also be considered. The efficacy of vaccinia immune globulin (which was used to treat smallpox) in cases of monkeypox is unknown.

## Prevention

Smallpox vaccination, particularly when recent, appears to provide some protection from monkeypox, and has been recommended for some groups at high risk of exposure. Post-exposure vaccination also seems to be helpful. The general population is not currently vaccinated in endemic areas of Africa. Any consideration of routine vaccination in healthy people must evaluate the risks and expense of the vaccine, as well as the benefits, in that population. Some people, including those with severe T cell immunodeficiencies, may not be able to receive the smallpox vaccine.

As a routine preventive measure, care should be taken to treat and cover breaks in the skin when working with nonhuman primates or other animals that may be hosts for monkeypox virus. Infection control procedures such as good hygiene, frequent hand washing, disinfection of surfaces and equipment, and the use of personal protective equipment (PPE) are important during contact with animals suspected to have monkeypox. Necropsies should be done in Biosafety Level 2 laboratories, using a certified Class II Biological Safety Cabinet. The person performing the necropsy should have a recent smallpox vaccination and wear PPE. Anyone who has been in contact with a monkeypox suspect should contact a health care provider immediately. Health authorities (e.g., the local or state health department) must also be informed.

Isolation of infected patients, good infection control measures and ring vaccination are helpful in preventing person-to-person transmission. Infected individuals are

assumed to be contagious starting one day before the rash, and for up to 21 days after the initial symptoms (or until all scabs have separated and throat swabs are negative by PCR). Because the full host range of monkeypox virus is uncertain, infected individuals should also limit their contact with any pet, particularly species known to be susceptible.

## Morbidity and Mortality

Case fatality rates of 0% to 33% have been reported during outbreaks of monkeypox in Africa. Congo Basin (Central African) strains of the virus, such as those found in the Democratic Republic of Congo (DRC), seem to cause more severe disease than the West African clade. In recent surveillance from the DRC, the case fatality rate was approximately 10-17%. The highest risk of death is in young children. Monkeypox seems to be less severe in people who have been vaccinated for smallpox, although the protection might decrease with time.

In Africa, monkeypox is usually seen in rural populations, particularly in children. Most cases occur among people who live in or near heavily forested areas, where the virus is thought to be endemic in animals. Infections tend to occur after contact with wild small mammals, which are caught for food and other purposes. In the past, monkeypox was thought to be a rare disease; however, recent data from the Congo Basin may challenge that assumption. Active surveillance conducted in the DRC between 1981 and 1986 indicated an incidence of < 1 case per 10,000 population. In contrast, the average annual incidence in the central DRC was 5.5 cases per 10,000 population (760 cases) during active surveillance from 2005 to 2007. Passive surveillance programs reported 215 possible monkeypox cases to the DRC Ministry of Health between 1998 and 2002, and 88 were subsequently confirmed by laboratory testing. Sporadic cases and outbreaks have also been documented in neighboring countries. Because most of these cases occurred in young people born after smallpox vaccination ended, some authors suggest that waning immunity may be contributing to an increase in the prevalence rate. Other societal factors (e.g., changes resulting from poverty or war) that increase exposure to the reservoir hosts are also plausible.

Current information on monkeypox in residents of West Africa is limited. No outbreaks have been reported recently in endemic areas; however, these viruses are thought to cause milder illness than the Congo Basin clade, and cases might be underreported. In a recent survey from Ghana, antibodies to orthopoxviruses were found in 36% of young people who had not been vaccinated against smallpox and lived near a forest where monkeypox is endemic. These individuals frequently entered these forests, but reported no previous illness suggestive of this disease. Because it is difficult to distinguish antibodies to the various orthopoxviruses, the study could not exclude reactivity to other, unknown orthopoxviruses circulating in

the area. Another study reported serological evidence of recent exposure to orthopoxvirus(es) among young, unvaccinated individuals in Sierra Leone.

The monkeypox outbreak in the U.S. was caused by a West African strain of the virus. In this outbreak, all human cases were associated with direct contact with pet prairie dogs, and not African rodents, although some of the latter animals had high viral titers. The types of behavioral interactions with different types of pets might have contributed to this phenomenon. (One case was originally thought to have been acquired from a rabbit, but testing by the CDC determined that the rabbit was not infected.) Seventy-two human infections were reported in this outbreak, with 37 of these laboratory confirmed. Most clinical cases were relatively mild. Severe disease occurred in two children, as the result of encephalitis or generalized monkeypox, but no deaths were reported. The availability of advanced health care facilities and good supportive care, as well as the absence of poor nutrition and concurrent diseases, may have contributed to the survival rate. The route of inoculation might also contribute to differences in clinical signs or severity; some people in Africa might be infected by ingestion during food preparation.

## Internet Resources

Centers for Disease Control and Prevention (CDC).

Monkeypox

<http://www.cdc.gov/ncidod/monkeypox/index.htm>

CDC necropsy guidelines for animals

<http://www.cdc.gov/ncidod/monkeypox/necropsy.htm>\*

Wisconsin National Primate Research Center News and Outreach

<http://www.primates.wisc.edu/wprc/news.html>

World Health Organization. Monkeypox

<http://www.who.int/mediacentre/factsheets/fs161/en/>

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