

Monkeypox: Another emerging threat?

What do we know about this infection, and how do we treat it during pregnancy?

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CASE Pregnant woman's husband is ill after traveling

A 29-year-old primigravid woman at 18 weeks' gestation just returned from a 10-day trip to Nigeria with her husband. While in Nigeria, the couple went on safari. On several occasions during the safari, they consumed bushmeat prepared by their guides. Her husband now has severe malaise, fever, chills, myalgias, cough, and prominent submandibular, cervical, and inguinal adenopathy. In addition, he has developed a diffuse papular-vesicular rash on his trunk and extremities.

- What is the most likely diagnosis?
- Does this condition pose a danger to his wife?
- What treatment is indicated for his wife?

What we know

In recent weeks, the specter of another poorly understood biological threat has emerged in the medical literature and lay press: monkeypox. This article will first review the epidemiology, clinical manifestations, and diagnosis of this infection, followed by a discussion of how to prevent and treat the condition, with special emphasis on the risks that this infection poses in pregnant women.



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Virology

The monkeypox virus is a member of the orthopoxvirus genus. The variola (smallpox) virus and vaccinia virus are included in this genus. It is one of the largest of all viruses, measuring 200-250 nm. It is enveloped and contains double-stranded DNA. Its natural reservoir is probably African rodents. Two distinct strains of monkeypox exist in different geographical regions of Africa: the Central African clade and the West African clade. The Central African clade is significantly more virulent than the latter, with a mortality rate approaching 10%, versus 1% in the West African clade. The incubation period of the virus ranges from 4-20 days and averages 12 days.^{1,2}

Epidemiology

Monkeypox was first discovered in 1958 by Preben von Magnus in a colony of research monkeys in Copenhagen, Denmark. The first case of monkeypox in humans occurred in the Democratic Republic of Congo in 1970 in a 9-year-old boy. Subsequently, cases were reported in the Ivory Coast, Liberia, Nigeria, and Sierra Leone. The infection was limited to the rain forests of central and western Africa until 2003. At that time, the first cases in the United States were reported. The US cases occurred in the Midwest and were traced to exposure to pet prairie dogs. These animals all came from a single distributor, and they apparently were infected when they were housed in the same space with Gambian rats, which are well recognized reservoirs of monkeypox in their native habitat in Africa.¹⁻³

A limited outbreak of monkeypox occurred in the United Kingdom in 2018.

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Key points at a glance

- Monkeypox is a member of the orthopoxvirus genus and is closely related to the smallpox virus. It is a large, double-stranded, enveloped DNA virus.
- The virus is transmitted primarily by close contact with infected animals or other humans or by consumption of contaminated bushmeat.
- The infection evolves in 2 phases. The *pre-eruptive phase* is characterized by severe flu-like symptoms and signs. The *eruptive phase* is distinguished by a diffuse papular-vesicular rash.
- The most valuable test for confirming the diagnosis is a polymerase chain reaction test of a fresh skin lesion.
- In women who are pregnant, monkeypox has been associated with spontaneous abortion and fetal death.
- Three antiviral agents may be of value in treating infected patients: cidofovir, brincidofovir, and tecovirimat. Only the latter has an acceptable safety profile for women who are pregnant or lactating.
- The new nonreplicating smallpox vaccine Jynneos (Bavarian Nordic A/S) is of great value for pre- and post-exposure prophylaxis.

Seventy-one cases, with no fatalities, were reported. In 2021 another US case of monkeypox was reported in Dallas, Texas, in an individual who had recently traveled to the United States from Nigeria. A second US case was reported in November 2021 from a patient in Maryland who had returned from a visit to Nigeria. Those were the only 2 reported cases of monkeypox in the United States in 2021.¹⁻³

Then in early May 2022, the United Kingdom reported 9 cases of monkeypox. The first infected patient had recently traveled to Nigeria and, subsequently, infected 2

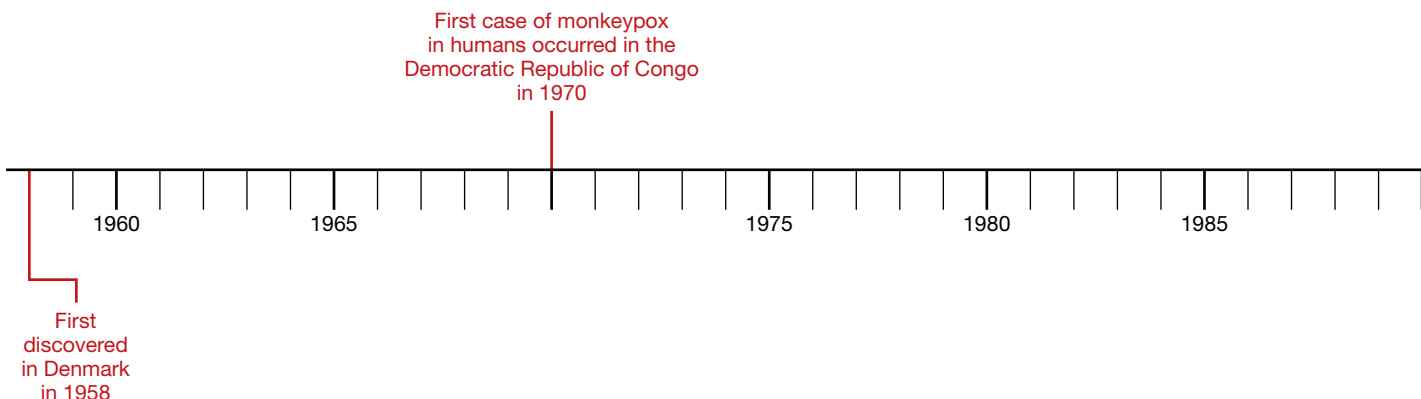
members of his family.⁴ On May 18, the Massachusetts Department of Public Health confirmed a case of monkeypox in an adult man who had recently traveled to Canada. As of July 7, 6,027 cases have been reported from at least 39 countries.⁵ Eight states in the United States reported cases. To date, 73 deaths have occurred in this recent outbreak of infections (case fatality rate, 4.5%).⁴⁻⁶

The current outbreak is unusual in that, previously, almost all cases occurred in western and central Africa in remote tropical rain forests. Infection usually resulted from close exposure to rats, rabbits, squirrels, monkeys, porcupines, and gazelles. Exposure occurred when persons captured, slaughtered, prepared, and then ate these animals for food without properly cooking the flesh.

The leading theory is that the present outbreak originated among men who had sex with men at 2 raves held in Spain and Belgium. The virus appears to have been spread by skin-to-skin contact, by respiratory droplets, by contact with contaminated bedding, and probably by sperm.^{2,4,6}

Clinical manifestations

Monkeypox evolves through 2 stages: a pre-eruptive stage and an eruptive stage. Prodromal symptoms include malaise, severe headache, myalgias, fever, drenching sweats, backache, fatigue, sore throat, dyspnea, and cough. Within 2-3 days, the characteristic skin eruption develops. The lesions usually begin on the face and then spread in a centrifugal



manner to the trunk and extremities, including the palms of the hands and soles of the feet. The lesions typically progress from macules to papules to vesicles to pustules. They then crust and scab over. An interesting additional finding is the presence of prominent lymphadenopathy behind the ear, beneath the mandible, in the neck, and in the groin.¹

Several different illnesses must be considered in the differential diagnosis of monkeypox infection. They include measles, scabies, secondary syphilis, and medication-associated allergic reactions. However, the 2 conditions most likely to be confused with monkeypox are chickenpox (varicella) and smallpox. Lymphadenopathy is much more prominent in monkeypox compared with chickenpox. Moreover, with monkeypox, all lesions tend to be at the same stage of evolution as opposed to appearing in crops as they do in chickenpox. Smallpox would be extremely unlikely in the absence of a recognized laboratory accident or a bioterrorism incident.⁷

Diagnosis

The presumptive diagnosis of monkeypox infection is made primarily based on clinical examination. However, laboratory testing is indicated to definitively differentiate monkeypox from other orthopoxvirus infections such as varicella and smallpox.

In specialized laboratories that employ highly trained personnel and maintain strict safety precautions, the virus can be isolated in mammalian cell cultures. Electron

microscopy is a valuable tool for identifying the characteristic brick-shaped poxvirus virions. Routine histologic examination of a lesion will show ballooning degeneration of keratinocytes, prominent spongiosis, dermal edema, and acute inflammation, although these findings are not unique to monkeypox.¹

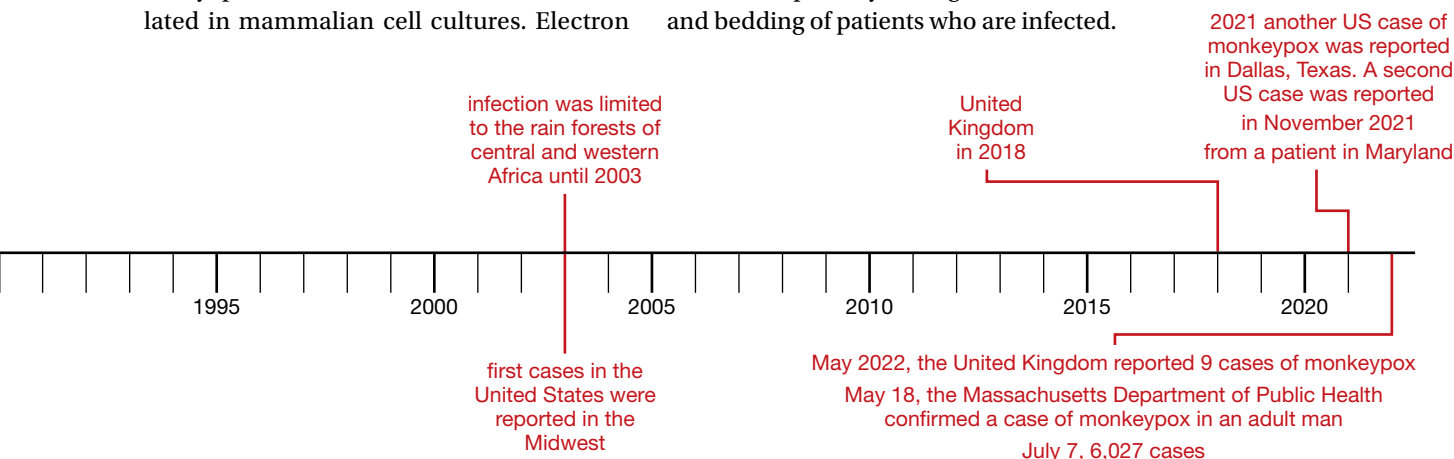
The Centers for Disease Control and Prevention (CDC) has developed serologic tests that detect immunoglobulin (Ig) M- and IgG-specific antibody. However, the most useful and practical diagnostic test is assessment of a skin scraping by polymerase chain reaction (PCR). This test is more sensitive than assessment of serum PCR.¹

When the diagnosis of monkeypox is being considered, the clinician should coordinate testing through the local and state public health departments and through the CDC. Effective communication with all agencies will ensure that laboratory specimens are processed in a timely and efficient manner. The CDC website presents information on specimen collection.⁸

How do we manage monkeypox?

Prevention

The first step in prevention of infection is to isolate infected individuals until all lesions have dried and crusted over. Susceptible people should avoid close contact with skin lesions, respiratory and genital secretions, and bedding of patients who are infected.



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TABLE Specific agents for treatment of orthopoxvirus infections such as smallpox and monkeypox¹²⁻¹⁶

Generic drug	Brand name of drug	Dosing regimen
Brincidofovir ^{13,a}	Tembexa (Chimerix, Inc.)	200 mg orally each week for 2 doses
Cidofovir ^{14,a}	Vistide (Gilead Sciences, Inc.)	5 mg/kg/dose IV weekly until lesions are healed
Tecovirimat ¹⁵	TPOXX (Catalent Pharma Solutions)	40-119 kg: 600 mg orally twice daily for 14 days >120 kg: 600 mg orally 3 times daily for 14 days No known risk of fetal harm based on animal data at 24 times the recommended human dose
Vaccinia immune globulin IV ¹⁶	VIGIV (Cangene Corporation)	6,000 units/kg 1 time Repeat as needed for severe infection Safe for use in pregnancy

^aThese 2 agents should not be used during pregnancy because of evidence of teratogenicity in animal studies.

FAST TRACK

For diffuse and more severe bacterial skin infections, systemic antibiotics may be necessary: amoxicillin-clavulanate 875 mg/125 mg orally every 12 hours or trimethoprim-sulfamethoxazole double strength 800 mg/160 mg orally every 12 hours (avoid in the first trimester)

The ultimate preventive measure, however, is vaccination of susceptible people either immediately before exposure (eg, military personnel, first responders, infection control investigators, health care workers) or immediately after exposure (general population). Older individuals who received the original smallpox vaccine likely have immunity to monkeypox infection. Unfortunately, very few women who currently are of reproductive age received this vaccine because its use was discontinued in the United States in the early 1970s. Therefore, the vast majority of our patients are uniquely susceptible to this infection and should be vaccinated if there is an outbreak of monkeypox in their locality.^{7,9}

The current preferred vaccine for prevention of both smallpox and monkeypox is the Jynneos (Bavarian Nordic A/S) vaccine.¹⁰ This agent incorporates a replication-deficient live virus and does not pose the same risk for adverse events as the original versions of the smallpox vaccine. Jynneos is administered subcutaneously rather than by scarification. Two 0.5-mL doses, delivered 28 days apart, are required for optimal effect. The vaccine must be obtained from local and state health departments, in consultation with the CDC.^{7,9}

There is very little published information on the safety of the Jynneos vaccine in pregnant or lactating women, although

animal data are reassuring. Moreover, the dangers of monkeypox infection are significant, and in the event of an outbreak, vaccination of susceptible individuals, including pregnant women, is indicated.

Treatment

Infected pregnant women should receive acetaminophen 1,000 mg orally every 8 hours, to control fever and provide analgesia. An antihistamine such as diphenhydramine 25 mg orally every 6-8 hours, may be used to control pruritus and provide mild sedation. Adequate fluid intake and optimal nutrition should be encouraged. Skin lesions should be inspected regularly to detect signs of superimposed bacterial infections. Small, localized bacterial skin infections can be treated with topical application of mupirocin ointment 2%, 3 times daily for 7-14 days. For diffuse and more severe bacterial skin infections, a systemic antibiotic may be necessary. Reasonable choices include amoxicillin-clavulanate 875 mg/125 mg orally every 12 hours, or trimethoprim-sulfamethoxazole double strength 800 mg/160 mg orally every 12 hours.¹¹ The latter agent should be avoided in the first trimester of pregnancy because of potential teratogenic effects.

Several specific agents are available through the CDC for treatment of orthopox-

virus infections such as smallpox and monkeypox. Information about these agents is summarized in the **TABLE**.¹²⁻¹⁶

Unique considerations in pregnancy

Because monkeypox is so rare, there is very little information about the effects of this infection in pregnant women. The report most commonly cited in the literature is that by Mbala et al, which was published in 2017.¹⁷ These authors described 4 pregnant patients in the Democratic Republic of Congo who contracted monkeypox infection over a 4-year period. All 4 women were hospitalized and treated with systemic antibiotics, antiparasitic medications, and analgesics. One patient delivered a healthy infant. Two women had spontaneous abortions in the first trimester. The fourth patient experienced a stillbirth at 22 weeks' gestation. At postmortem examination, the fetus had diffuse cutaneous lesions, prominent hepatomegaly, and hydrops. No structural malformations were noted. The placenta demonstrated numerous punctate hemorrhages, and high concentrations of virus were recovered from the placenta and from fetal tissue.

Although the information on pregnancy outcome is quite limited, it seems clear that the virus can cross the placenta and cause adverse effects such as spontaneous abortion and fetal death. Accordingly, I think the following guidelines are a reasonable approach to a pregnant patient who has been exposed to monkeypox or who has developed manifestations of infection.^{3,7,9}

- In the event of a community outbreak,

bioterrorism event, or exposure to a person with suspected or confirmed monkeypox infection, the pregnant patient should receive the Jynneos vaccine.

- The pregnant patient should be isolated from any individual with suspected or confirmed monkeypox.
- If infection develops despite these measures, the patient should be treated with either tecovirimat or vaccinia immune globulin IV. Hospitalization may be necessary for seriously ill individuals.
- Within 2 weeks of infection, a comprehensive ultrasound examination should be performed to assess for structural abnormalities in the fetus.
- Subsequently, serial ultrasound examinations should be performed at intervals of 4-6 weeks to assess fetal growth and re-evaluate fetal anatomy.
- Following delivery, a detailed neonatal examination should be performed to assess for evidence of viral injury. Neonatal skin lesions and neonatal serum can be assessed by PCR for monkeypox virus. The newborn should be isolated from the mother until all the mother's lesions have dried and crusted over.

CASE Resolved

Given the husband's recent travel to Nigeria and consumption of bushmeat, he most likely has monkeypox. The infection can be spread from person to person by close contact; thus, his wife is at risk. The couple should isolate until all of his lesions have dried and crusted over. The woman also should receive the Jynneos vaccine. If she becomes symptomatic, she should be treated with tecovirimat or vaccinia immune globulin IV. ●

FAST TRACK

The pregnancy outcome information is limited for monkeypox infection; however, severe adverse effects have been reported in the medical literature

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