Monkeypox

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INTRODUCTION

Monkeypox is a viral zoonotic infection that results in a rash similar to smallpox. However, the person-to-person spread and the mortality from a monkeypox infection are significantly lower than for smallpox. Clinically, these two viral infections are difficult to distinguish, raising concerns that monkeypox could be used for bioterrorism [1].

This topic will review the virology, epidemiology, clinical manifestations, diagnosis, and treatment of monkeypox. Topic reviews that discuss smallpox are presented separately. (See "Variola virus (smallpox)" and "Identifying and managing casualties of biological terrorism".)

VIROLOGY

Monkeypox, an orthopoxvirus, was first isolated in the late 1950s from a colony of sick monkeys. The virus is in the same genus as variola (causative agent of smallpox) and vaccinia viruses (the virus used in smallpox vaccine). Electron microscopy of cells infected with monkeypox virus shows a brick-like virion, indistinguishable from the virions of variola or vaccinia viruses (picture 1).

Two distinct strains of monkeypox exist in different geographic regions of Africa, as suggested by epidemiologic, animal, and molecular evidence [2]. In comparison to strains isolated from Central Africa, monkeypox from Western Africa is less virulent and lacks a number of genes present in the other viral strain [2,3].

EPIDEMIOLOGY

History — It is believed that monkeypox virus has infected humans for thousands of years in sub-Saharan Africa [1].

Monkeypox was first identified as a cause of disease in humans in the 1970s in the Democratic Republic of the Congo (formerly the Republic of Zaire) [1,4-7]. Following its recognition as a human pathogen, 59 cases of human monkeypox were reported between 1970 and 1980, with a mortality rate of 17 percent. All of these cases occurred in the rain forests of Western and Central Africa among individuals exposed to small forest animals (eg, rodents, squirrels, and monkeys).

The first outbreak of monkeypox in the Western Hemisphere occurred in the United States in 2003 [8-10]. (See 'United States' below and 'Other countries' below.)

Transmission

- **Animal-to-human transmission** – The virus is typically acquired through contact with an infected animal's bodily fluids or through a bite. In Africa, evidence of monkeypox virus infection has been found in many types of animals, including rope squirrels, tree squirrels, Gambian poached rats, dormice, and different species of monkeys [11].

  Monkeys and humans are incidental hosts; the reservoir remains unknown but is likely to be rodents. Infected rodents from Western Africa were accidentally imported into the United States; this led to the first human monkeypox infections in the Western Hemisphere.

  Based on findings during a 2003 United States outbreak, the route of infection and extent of exposure (eg, bite wound versus touching an infected animal) can influence the severity of clinical manifestations of monkeypox infection. For example, one study categorized exposures to a prairie dog as noninvasive (eg, the person touched an infected animal, cleaned an infected animal's cage) or "complex" (eg, invasive bite or scratch from an ill prairie dog) [12]. Patients with complex exposures were more likely than patients with noninvasive exposures to develop signs of systemic illness. (See 'United States' below.)

- **Human-to-human transmission** – Human-to-human transmission can occur through large respiratory droplets. Transmission can also occur through close contact with infectious skin lesions or from contact with lesion material.

  For droplet transmission, prolonged face-to-face contact may be required for transmission to occur (eg, within a six-foot radius for ≥3 hours in the absence of personal protection equipment [PPE]) [13].

In general, transmissibility from person-to-person is very low [14]. However, in May 2022 an outbreak of monkeypox in several non-endemic countries was reported with over 90 confirmed cases [15]. In this outbreak, close contact with infectious skin lesions during sexual contact may be the likely mode of transmission [15,16]. More detailed information will be available following further investigation. Additional information about this outbreak in specific geographic locations is found below. (See 'Geographic distribution' below.)

Geographic distribution — After the eradication of smallpox and the discontinuation of smallpox immunization (ie, vaccinia virus vaccine), the World Health Organization (WHO) monitored subsequent human monkeypox activity. The WHO was concerned that elimination of the vaccinia virus vaccine, which also protects against monkeypox, would lead to increased susceptibility of the population and the possibility of an increased incidence of monkeypox infection.

Since discontinuation of smallpox immunization, most cases have occurred in Central and West Africa. However, sporadic cases have been reported in several other countries, mostly related to travel. In the United States, there was an outbreak due to importation of exotic animals from Africa. (See 'United States' below.)

Africa — From 1996 to 1998, an outbreak of febrile illness with associated pustular lesions occurred among about 100 persons with reports of secondary attack rates of 80 percent [4,7]. A concurrent chickenpox outbreak may have resulted in misclassification of cases and likely explained the high secondary attack rates. Nevertheless, this outbreak created concern that monkeypox had mutated to become more like smallpox [4,7]. However, sequence analyses of monkeypox from persons with active cases indicated no significant genetic changes [14,17]. The overall low mortality during this outbreak of less than 5 percent was another indication that monkeypox had not mutated into a more lethal human pathogen [7,14].

A subsequent population-based surveillance study from 2005 to 2007 confirmed a 20-fold increase in incidence of monkeypox infection compared with that seen in the 1980s in the Democratic Republic of Congo [18]. From 2005 to 2007, 760 laboratory-confirmed human monkeypox cases were identified [18]. The study confirmed prior concerns of increased human cases of monkeypox due to the lack of prior smallpox vaccination; persons with a history of smallpox immunization had a fivefold lower risk of monkeypox infection than unvaccinated persons. Other factors associated with an increased risk of infection included living in forested areas, male sex, and age <15 years.

Since 2017, there has been an increase in monkeypox cases in Nigeria; this occurred after almost 40 years with no reported cases [19]. These increased cases in Nigeria have resulted in

monkeypox cases occurring in travelers. In one study evaluating the 2017 outbreak of cases outside of Africa, a small pool of related isolates was the likely source for the exported infections [20]. (See 'United States' below and 'Other countries' below.)

In 2022, the WHO reported that monkeypox was endemic in several African countries, including Benin, Cameroon, the Central African Republic, the Democratic Republic of the Congo, Gabon, Ghana (identified in animals only), Ivory Coast, Liberia, Nigeria, the Republic of the Congo, Sierra Leone, and South Sudan. From January to May 2022, most cases occurred in the Democratic Republic of the Congo, with 1238 cases reported and 57 deaths [15].

United States

- **Outbreak in 2003** – Between May 15 and June 2003, an outbreak of 71 cases of human monkeypox in six states was investigated by the Centers for Disease Control and Prevention (CDC); 35 cases were laboratory confirmed [8-10]. Prior to this cluster of cases, monkeypox had not been previously found in the Western hemisphere.

  The investigation demonstrated that the onset of a febrile illness, with subsequent appearance of a pustular rash, had developed in patients who had recently purchased pet prairie dogs. The prairie dogs appeared to have acquired the virus from African rodents when the two species were housed at a distribution center in Illinois.

  Monkeypox infection was confirmed by DNA sequences obtained from skin lesions from 9 of 10 patients from Illinois, Indiana, and Wisconsin and in lymph node tissue of one pet prairie dog that died [8]. Most of the human cases had direct exposure to animals [21], although person-to-person transmission could not be excluded. Of the cases reported in Wisconsin, the veterinary staff who were exposed to an outbreak-associated prairie dog were at particularly high risk, with an attack rate of 23 percent [22].

  During this outbreak, monkeypox appeared to have a very low rate of person-to-person transmission. In one study of 57 health care workers who were exposed to patients with monkeypox, none reported signs and symptoms of disease [23]. Only one had laboratory evidence of recent orthopoxvirus infection, which was probably secondary to prior smallpox vaccination. By contrast, secondary attack rates for smallpox can be as high as 70 percent [5,24].

  Because of this outbreak, the transportation, sale, or release into the wild of prairie dogs and animals from Africa (including tree squirrels, rope squirrels, dormice, brush-tailed porcupines, and striped mice in addition to Gambian giant rats) was subsequently

prohibited by the CDC and the United States Food and Drug Administration (FDA) [10]. There have been no other United States outbreaks since the time of this prohibition.

- **Subsequent cases** – In July 2021, a patient was diagnosed with monkeypox in Dallas, Texas [13]. This patient developed symptoms during his return trip from Nigeria.

  On May 18, 2022, a case was reported in Massachusetts [16]. This patient had recently travelled to Canada by private transportation and had not traveled to Africa. Cases in other states have also been reported. As of June 1, 19 confirmed cases have been identified across the United States [25]. Given clusters of cases are also occurring in Europe, these cases are likely related to this multi-country outbreak of monkeypox (see 'Europe' below). Updated information on case counts in the United States can be found on the CDC website.

Europe — In May 2022, multiple clusters of monkeypox were reported in Europe, including Portugal, Spain, and the United Kingdom (UK) [26]. Most cases were identified in men who have sex with men (MSM). While at this time it is not known if there are direct connections between the cases in this outbreak, one hypothesis is that there may be spread within certain communities due to close contact during sexual activity. While a significant number of cases have been seen in MSM, this could be detection bias and cases in other patient populations are likely to be seen.

The first case, which occurred on May 7 in the UK, was identified in a person with recent travel to Nigeria. A week later, six additional cases were identified in the UK, but these were not associated with recent travel to an endemic area or close contact with a person known to have monkeypox.

Multiple other cases have been reported outside the UK. As an example, in Portugal, 5 confirmed cases and more than 20 suspected cases of monkeypox were reported on May 18. All cases were in young men in Lisbon and the Tagus Valley. Spain also reported cases. Updated information on case counts in Europe can be found on the WHO website.

Prior to the outbreak in May 2022, there had been seven cases of monkeypox reported in the UK since 2018, most associated with travel to endemic countries. In 2018, two cases of monkeypox were reported in patients who had recently traveled to the UK from southern Nigeria, where cases of monkeypox had recently been reported [27]. One of these patients appears to have spread monkeypox to a health care worker [28].

Other countries — Sporadic cases related to travel from Nigeria have been reported in Israel [29] and Singapore [30].

In May 2022, cases were reported in Canada [31] and Australia [32]. These cases were not related to travel to endemic areas and appear to be related to the outbreak in Europe, described above (see 'Europe' above). Additional cases are being reported in many countries [15].

INCUBATION PERIOD

The classic incubation period of monkeypox virus infection is usually from 6 to 13 days but can range from 5 to 21 days [15]. The 2003 United States outbreak described above allowed estimation of time from exposure to onset of symptoms. Approximately half of the patients reported a scratch, bite, or petting of an infected animal [33]. For 29 patients, the estimated incubation time from exposure to illness was 12 days. Persons with a history of an animal bite or scratch may have a shorter incubation period than those with tactile exposures (9 versus 13 days, respectively) [12].

CLINICAL MANIFESTATIONS

Based largely on seroepidemiological studies in Africa, the majority of monkeypox infections are mild or asymptomatic.

In symptomatic individuals, monkeypox causes a systemic illness including fevers, chills, and myalgias, with a characteristic rash that is important to differentiate from that of smallpox. The clinical illness can also differ by viral strain.

Detailed information on the clinical manifestations of monkeypox can be found on the World Health Organization (WHO) and United States Centers for Disease Control (CDC) websites.

Outbreaks in Africa — In Africa, the monkeypox rash starts on the trunk and then spreads peripherally to involve the palms and soles of the feet. Lesions can also involve the mucous membranes and usually range from 0.5 to 1 centimeter in size. The rash usually begins as macules and papules; the rash then progresses over a two- to four-week period to vesicles, pustules, followed by umbilication, scabbing, and desquamation. Some patients develop only a localized rash on their hands associated with direct contact with the infected animal.

United States outbreaks — Although comprehensive clinical information is limited on monkeypox in Africa, the 2003 United States outbreak allowed further characterization of the illness in 34 of 37 subjects for whom medical records were available [33]. The predominant signs and symptoms were:

- Rash (97 percent)

- Fever (85 percent)
- Chills (71 percent)
- Lymphadenopathy (71 percent)
- Headache (65 percent)
- Myalgias (56 percent)

The onset of fever preceded the rash by approximately two days, but the median duration of fever was shorter than the rash (8 and 12 days, respectively). The following clinical pictures of the initial case identified in the United States were taken at the Marshfield Clinic in Wisconsin (picture 2A-D). The rash in this United States outbreak was described as maculopapular in nature on initial presentation; the rash subsequently evolved into vesicles, then pustules, which eventually crusted within a two- to three-week period [33].

Nine of the 34 patients were hospitalized for a variety of reasons, including nausea, vomiting, and dysphagia. The discharge diagnoses of two of the most seriously ill patients were encephalopathy and a retropharyngeal abscess. All of the patients in this case series survived with supportive therapy; no antiviral therapy was administered. Multiple nonspecific laboratory findings were also noted including abnormal aminotransferases, leukocytosis, mild thrombocytopenia, and hypoalbuminemia.

In the cluster of cases reported in May 2022, it was noted that some patients may present with proctitis or with lesions located on the genital or perianal area alone [16,34].

DIAGNOSIS

Clinical features are helpful in making the diagnosis; however, laboratory confirmation of monkeypox virus is necessary to differentiate this disease from those caused by other potential etiologies. The World Health Organization (WHO) and the United States Centers for Disease Control (CDC) have put forth case definitions for monkeypox during the 2022 outbreak that combine clinical, epidemiologic, and laboratory data.

Diagnostic assays include virus isolation (in mammalian cell cultures only in specialized laboratories), electron microscopy, real-time polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), and immunofluorescent antibody assay [1,35]. Characteristic brick-shaped poxvirus virions are found on electron microscopy. Histopathologic analysis may demonstrate ballooning degeneration of keratinocytes, prominent spongiosis, dermal edema, and acute inflammation; however these findings can also be seen in other viral infections [36].

Using sera from patients obtained during the 2003 United States outbreak, the Centers for Disease Control and Prevention (CDC) developed an immunoglobulin M-capture and an IgG ELISA that demonstrated recent monkeypox virus infection. Serum IgM and IgG antibodies were detected five and eight days after onset of rash, respectively [37]. Other experimental antibody and cellular based assays are under development, which may be useful for the prospective and retrospective diagnosis of monkeypox [24].

If the diagnosis of monkeypox is being considered, local and state public health officials, along with the CDC, should be notified so that the samples are quickly processed. Information on specimen collection is available on the CDC website.

DIFFERENTIAL DIAGNOSIS

Several infections need to be considered in the differential diagnosis of monkeypox; these include varicella, herpes simplex virus, smallpox, and other poxviruses.

Given the worldwide eradication of smallpox, the most likely diagnostic consideration is varicella (chickenpox). Unlike varicella where vesicular lesions are characteristically in different stages of development and healing when the patient is examined, monkeypox lesions are all generally at the same stage. (See "Clinical features of varicella-zoster virus infection: Chickenpox".)

Because of concerns regarding bioterrorism, it is also important to consider the possibility of smallpox in the differential diagnosis of a patient who has not been in the rain forests of Africa or exposed to potentially infected animals [6]. Lymphadenopathy, which has been observed in the majority of unvaccinated patients, is a key distinguishing feature of monkeypox [10]. Lymphadenopathy can occur in the submandibular, cervical, or inguinal regions. (See "Identifying and managing casualties of biological terrorism" and "Variola virus (smallpox)".)

Also in the differential diagnosis is tanapox, another African poxvirus that causes a febrile prodrome and skin lesions that resolve over several weeks without sequelae. A case of tanapox infection was diagnosed using electron microscopy and DNA analysis (polymerase chain reaction testing) of a biopsied skin lesion in an American college student who had worked in the Republic of Congo for eight weeks caring for chimpanzees; none of the others working with these animals developed the infection [38].

Orf and bovine stomatitis (also caused by parapoxviruses) can produce localized skin lesions similar to those of monkeypox, but can be differentiated by an experienced microscopist by morphologic features on electron microscopy. Parapoxvirions are slightly smaller than orthopoxvirus virions and have a more regular surface pattern than orthopoxviruses.

PATIENT MANAGEMENT

Supportive care — Most patients have mild disease and recover without medical intervention. Others who have risk factors for dehydration (eg, nausea, vomiting, dysphagia) may require a short hospital stay for intravenous hydration. For the seriously ill patient, supportive care is necessary until the patient recovers from the infection.

Antiviral therapy

Indications — For most patients monkeypox is a mild, self-limited disease; however, antiviral treatment may be reasonable for patients with severe disease and those at risk for severe disease (eg, immunocompromised patients, those younger than eight years of age, pregnant or breastfeeding women, patients with complications of the infection) [39]. Treatment can also be considered for monkeypox infection in traditionally atypical sites (eg, mouth, eyes, genital area) [39]. These decisions should be made in consultation with local departments of health and/or the Centers for Disease Control and Prevention (CDC).

Immunocompromised patients typically include those with advanced HIV-1 infection, leukemia, lymphoma, generalized malignancy, solid organ transplantation, therapy with alkylating agents, antimetabolites, radiation, tumor necrosis factor inhibitors, high-dose corticosteroids, being a recipient with hematopoietic stem cell transplant <24 months post-transplant or ≥24 months but with graft-versus-host disease or disease relapse, or having autoimmune disease with immunodeficiency as a clinical component [39].

Additional information regarding indications for treatment of monkeypox during an outbreak can be found at the CDC website.

Specific agents — Several antivirals may be useful for the treatment of monkeypox. Some of these drugs were approved for treatment of smallpox based on animal models and dose studies in healthy humans but are expected to have the same activity against human monkeypox. (See "Variola virus (smallpox)", section on 'Antiviral therapy'.)

In general, tecovirimat is the treatment of choice, although some experts may suggest dual therapy with tecovirimat and cidofovir in patients with severe disease. Regimen selection should be made in consultation with public health officials.

- Tecovirimat — Tecovirimat is a potent inhibitor of an orthopoxvirus protein required for the formation of an infectious virus particle that is essential for dissemination within an infected host. This drug protects nonhuman primates from lethal monkeypox virus infections [40-42], and is likely to be efficacious against this infection in humans as well. In

the United States, tecovirimat was approved for the treatment of smallpox in July 2018 [42], and is only available through the CDC [39].

Oral and intravenous preparations are available. The recommended dose of tecovirimat depends upon the patient's weight, as described in manufacturer labeling and the Lexicomp drug information topic within UpToDate. The duration of treatment is 14 days.

Tecovirimat appears to be well tolerated. The most frequently reported side effects are headache, nausea, and abdominal pain. It was administered to approximately 360 human volunteers in an expanded safety trial, which found an adverse effect profile similar to that of placebo [42]. In a small series of seven patients with monkeypox, the one patient treated with tecovirimat experienced no adverse effects, and had a shorter duration of viral shedding and illness compared with the others (including some that received brincidofovir) [43].

Additional information on this agent is found in a separate topic review. (See "Variola virus (smallpox)", section on 'Tecovirimat'.)

- Cidofovir/Brincidofovir — Cidofovir has in vitro activity against monkeypox and has been shown to be effective against lethal monkeypox challenge in animal models [44-46]. However, there are no clinical data regarding its efficacy against monkeypox infection in humans and its use can be associated with significant adverse events, including nephrotoxicity. (See "Cidofovir: An overview".)

  In June 2021, brincidofovir was approved for use in the United States for treatment of smallpox [47]. Brincidofovir is an analog of cidofovir that can be given orally; however, its clinical availability is uncertain at this time. (See "Variola virus (smallpox)", section on 'Brincidofovir'.)

  There are only limited published data with the use of brincidofovir for treatment of monkeypox. Animal models show that it is likely an effective treatment of orthopoxvirus infections [48-50]. However, in one case series, three patients with monkeypox were treated with brincidofovir (200 mg once a week orally), and all developed elevated liver enzymes resulting in discontinuation of therapy [43].

PREVENTION

Data suggest that prior immunization with smallpox vaccine prevents infection and ameliorates symptoms. The role of postexposure prophylaxis with smallpox vaccine or vaccinia

immunoglobulin is unclear, as discussed below.

Smallpox immunization — Prior smallpox vaccination with vaccinia virus has a significant protective effect against acquisition of monkeypox virus and may ameliorate the clinical manifestations of this infection [5,24]. In September 2019, a modified vaccinia Ankara (MVA) vaccine (sold under the trade names Imvamune and Jynneos) was approved for prevention of smallpox and monkeypox [51]. More detailed information on the use of this vaccine is presented elsewhere. (See "Vaccinia virus as the smallpox vaccine", section on 'Modified vaccinia Ankara vaccine'.)

In 2021, The Advisory Committee and Immunization Practices (ACIP) voted to recommend the use of this vaccine for certain workers at high risk for exposure to orthopoxvirus infection, such as research laboratory personnel and specialized clinical laboratory personnel performing diagnostic testing for orthopoxviruses (eg, labs that are part of the Laboratory Response Network), as well as designated response team members who are at risk for occupational exposure to orthopoxviruses. The ACIP also recommended vaccination for healthcare personnel who administer ACAM2000 (a live vaccine for active immunization against smallpox disease) or care for patients infected with replication competent orthopoxviruses, based on shared clinical decision-making [52]. The CDC approved the updated ACIP smallpox vaccine recommendations in 2022 [53].

The benefit of smallpox vaccination with vaccinia virus was demonstrated in a study of human-to-human transmission of monkeypox in Africa [23]. In this study, secondary attack rates varied greatly among 2278 household contacts depending on their prior smallpox vaccination status (7.5 compared with 1.3 percent in vaccinated and unvaccinated subjects). In another study that showed an increasing incidence of human monkeypox cases in Africa [18], vaccinated people had a fivefold lower risk of monkeypox as compared with unvaccinated persons (0.78 versus 4.05 per 10,000); vaccine efficacy was estimated to be approximately 81 percent in those with a distant history of smallpox vaccination.

In the 2003 United States outbreak, further investigation using experimental techniques identified three additional monkeypox exposures in individuals who had previously received smallpox vaccination 13, 29, and 48 years prior to exposure to monkeypox [24]. These individuals were unaware that they had been infected because they did not have any recognizable disease symptoms. These findings suggested that the United States monkeypox outbreak was larger than previously realized. Furthermore, cross-protective antiviral immunity against West African monkeypox can potentially be maintained for decades after smallpox vaccination.

Postexposure prophylaxis

Postexposure vaccination — In addition to monitoring and isolating close contacts, postexposure vaccination with MVA vaccine may be considered for certain patients after exposure to monkeypox (eg, direct contact with patient or materials from patient's room without personal protection equipment (PPE) [28]). This decision must be made in conjunction with public health authorities. Public Health England developed risk assessment and public health recommendations for persons potentially exposed that are summarized in the table (table 1) [28]. The CDC has also issued guidance on the use of post-exposure prophylaxis.

Since prior vaccination with vaccinia virus protects against monkeypox infection, the Centers for Disease Control and Prevention (CDC) recommended vaccination with vaccinia virus for the limited number of individuals exposed to monkeypox in the 2003 United States outbreak, including children and pregnant women. The CDC also recommended pre-exposure vaccination for those involved in the investigation of the outbreak and for health care workers caring for patients with monkeypox [8,10]. Twenty-eight adults and two children received the smallpox vaccine for this purpose and no cases of monkeypox were identified among these recipients [10]. Furthermore, no cases of monkeypox were identified during pregnancy during the 2003 outbreak; it is not known if the infection carries a different prognosis in pregnant women [54].

Based on historical data on postexposure vaccination for smallpox with vaccinia vaccine, the optimal time for monkeypox postexposure vaccination is within four days; however, vaccination can be considered for up to 14 days of a close contact exposure, according to the CDC [55]. Close contact is defined as direct exposure within six feet of a probable or confirmed monkeypox case in an animal with respiratory symptoms such as nasal discharge, cough, or conjunctivitis in a setting where the animal has been manipulated (eg, an exam room) [55]. (See "Vaccinia virus as the smallpox vaccine" and "Immunizations during pregnancy", section on 'Smallpox'.)

Vaccinia immune globulin — The use of vaccinia immune globulin may be considered in immunosuppressed patients with an exposure history, since immunization with vaccinia virus vaccine is contraindicated [1].

Infection control precautions — Use of standard, contact, droplet, and airborne precautions are recommended for any generalized vesicular rash of unknown etiology in which monkeypox and smallpox are included in the differential diagnosis [23]. (See 'Differential diagnosis' above.)

When a rash is present, persons with suspected monkeypox should be considered infectious and be isolated until all scabs separate and results of throat swab polymerase chain reaction (PCR) are negative [1].

Detailed information on infection control precautions to reduce transmission of monkeypox in the home and healthcare setting can be found on the CDC website [56].

Monitoring after an exposure — Individuals who have had close contact with an infected animal or person confirmed to have monkeypox should be monitored for symptoms for 21 days after their last exposure [57]. Detailed information on the approach to monitoring after an exposure can be found on the CDC website.

MORTALITY

In Central Africa, the fatality rate is approximately 10 percent and deaths generally occur in the second week of illness [1,58]. In contrast, there were no deaths in the outbreak in the United States. These more favorable outcomes in the United States may be related to a healthier patient population, greater availability of supportive medical care, and a less virulent strain of monkeypox, which was imported from the West African nation of Ghana [33].

SUMMARY AND RECOMMENDATIONS

- **Virology** – Monkeypox, an orthopoxvirus, was first isolated in the late 1950s from a colony of sick monkeys. The virus is in the same genus as variola (causative agent of smallpox) and vaccinia viruses (the virus used in smallpox vaccine). (See 'Virology' above.)

- **Transmission** – The virus is typically acquired through contact with an infected animal's bodily fluids or through a bite. Monkeys and humans are incidental hosts; the reservoir remains unknown but is likely to be certain rodents. (See 'Transmission' above.)

  Human-to-human transmission can also occur. Transmission can occur through large respiratory droplets, and prolonged face-to-face contact may be required (eg, within a six-foot radius for ≥3 hours in the absence of personal protection equipment [PPE]). Transmission can also occur through close contact with infectious skin lesions. In May 2022, an outbreak in non-endemic countries appears to be associated with sexual activity, although the exact mechanism of transmission is not yet known.

- **Geographic distribution** – Since discontinuation of smallpox immunization, most cases have occurred in Central and West Africa. However, sporadic cases have been reported in several nonendemic countries, typically in returning travelers. In the United States, an outbreak of monkeypox due to infected prairie dogs exposed to imported animals from Africa occurred in 2003. In 2022, an ongoing outbreak of monkeypox has been reported in many countries outside of Africa and is under investigation. (See 'Geographic distribution' above.)

- **Clinical features** – In patients with monkeypox, the classic incubation period is usually from 6 to 13 days, but can range from 5 to 21 days. (See 'Incubation period' above.)

  Predominant symptoms of monkeypox include fever, rash (picture 2A-D), lymphadenopathy, myalgias, and chills. Most patients with monkeypox have a mild illness; those with nausea, vomiting, or dysphagia may need hospitalization for intravenous hydration. (See 'Clinical manifestations' above.)

- **Diagnosis** – The clinical features are helpful in making the diagnosis of monkeypox; however, laboratory confirmation is necessary to differentiate this disease from those caused by other potential etiologies. (See 'Diagnosis' above.)

  Diagnostic assays include virus isolation (in mammalian cell cultures in specialized laboratories), electron microscopy, real-time polymerase chain reaction (PCR), enzyme-linked immunosorbent assay (ELISA), and immunofluorescent antibody assay. If the diagnosis of monkeypox is being considered, local and state public health officials, along with the Centers for Disease Control and Prevention (CDC), should be notified.

  When evaluating a patient with suspected monkeypox, varicella, herpes simplex infection, smallpox, and other orthopoxvirus infections should be included in the differential diagnosis. (See 'Differential diagnosis' above.)

- **Patient management** – Most patients have mild disease and recover without medical intervention. For the seriously ill patient, supportive care is necessary until the patient recovers from the infection. (See 'Supportive care' above.)

  The antiviral agents, tecovirimat and brincidofovir, which have been approved for treatment of smallpox in the United States, also have activity against monkeypox in animal models and are likely to be efficacious against this infection in humans as well. Cidofovir also has in vitro activity against monkeypox and has been shown to be effective against lethal monkeypox challenge in animal models. Treatment decisions should be made in consultation with public health officials. (See 'Antiviral therapy' above.)

- **Prevention** – Standard, contact, droplet, and airborne precautions should be initiated in any hospitalized patients with generalized vesicular rash of unknown etiology in which monkeypox and smallpox are included in the differential diagnosis. In addition, close contacts should be monitored. (See 'Infection control precautions' above.)

  The use of smallpox vaccination for pre-exposure and post-exposure prophylaxis may also be reasonable in select settings, and should be considered in consultation with public

health authorities. (See 'Smallpox immunization' above and 'Postexposure prophylaxis' above.)

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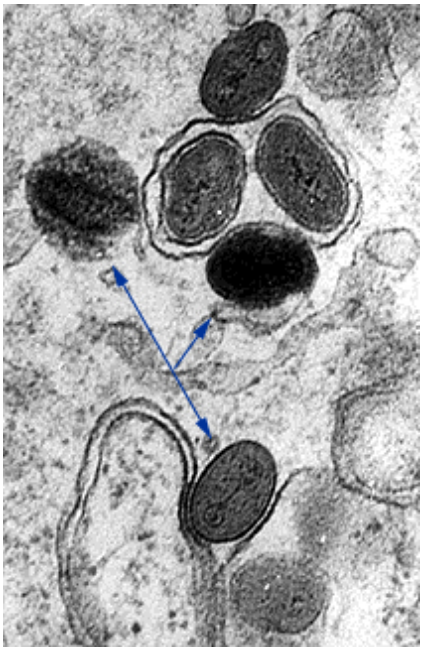
Topic 8295 Version 26.0

GRAPHICS

Poxvirus virions

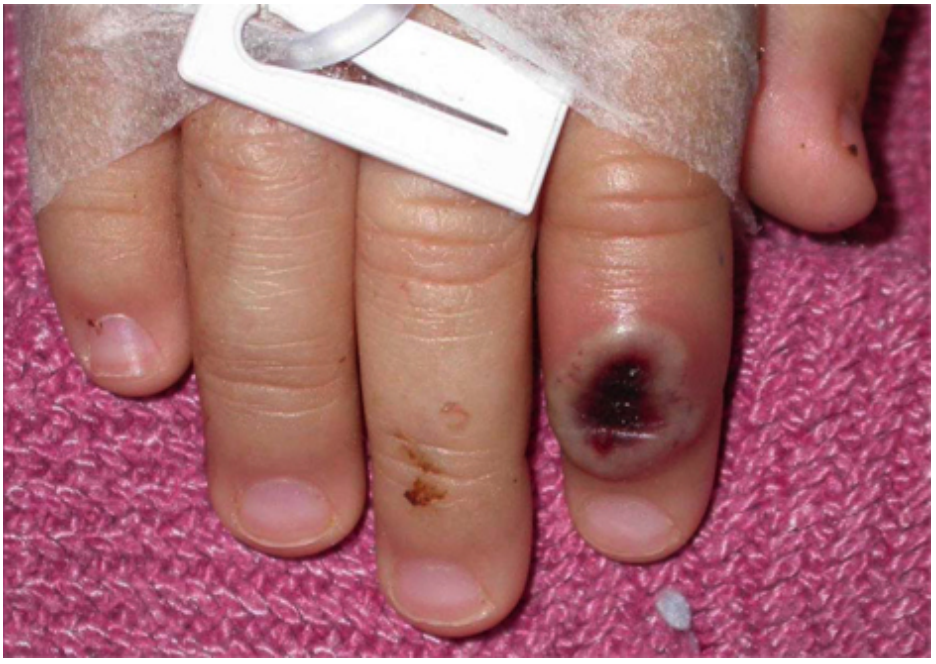


Electron micrograph shows intracellular brick-shaped vaccinia virions with dense central core and outer viral membranes (blue arrows). The electron microscopic image of variola virus would be identical to that seen here with vaccinia virus.

Reproduced with permission from Herrera E, del mar Lorenzo M, Blasco R, Isaacs SN. J Virol 1998; 72:294.

Graphic 56100 Version 3.0

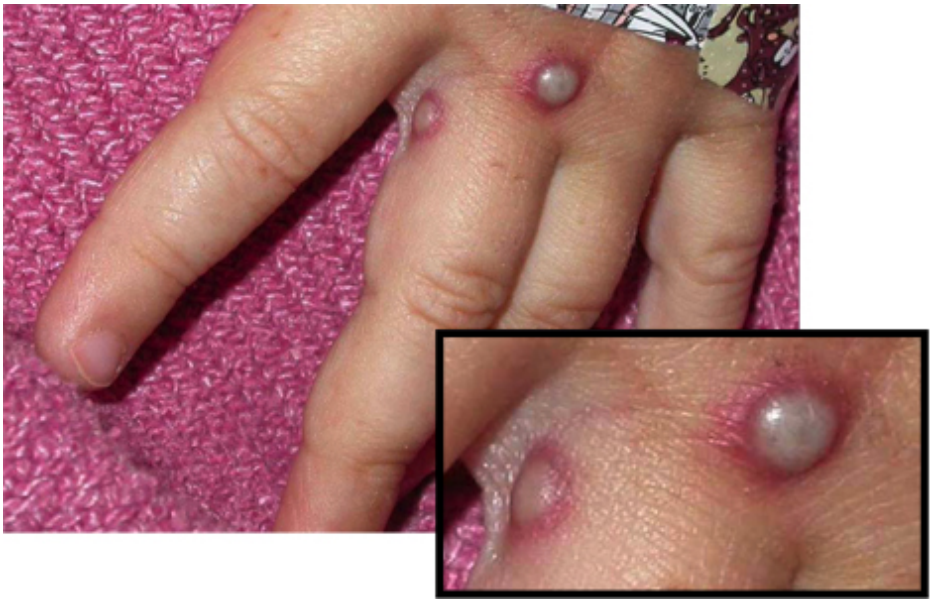
Child, marshfield index case



Primary inoculation site right index finger, 5/27/03. 14 days after prairie dog bites, 11 days after febrile illness, hospital day 5.

Graphic 71549 Version 2.0

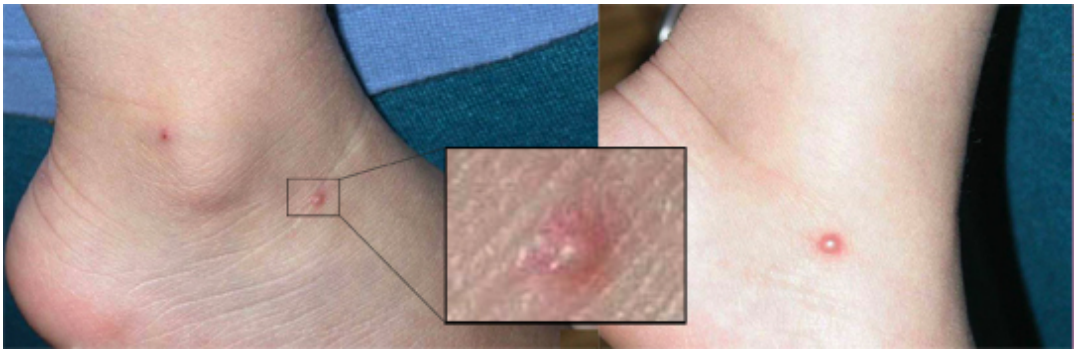
Child



Secondary lesions, 5/27/03, adjacent to primary inoculation site on left hand.

Graphic 81821 Version 2.0

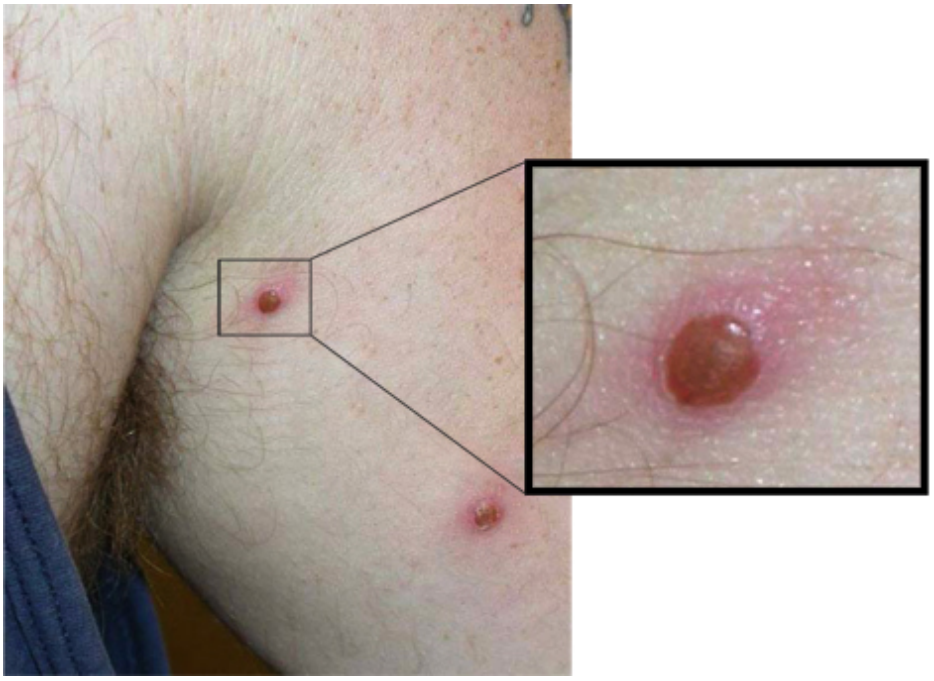
Child



Disseminated acral lesions 5/27/03.

Graphic 65425 Version 2.0

Father



Graphic 79666 Version 4.0

Public Health England risk assessment and public health recommendations for persons potentially exposed to 2 patients with monkeypox, United Kingdom, 2018*

Risk group	Description	Public health surveillance	Postexposure vaccination with Imvanex	Number of persons in risk group¶	Number (%) of persons in risk group who received postexposure vaccination¶
No risk	No known contact (direct or indirect) with a symptomatic monkeypox case-patient.Δ OR Laboratory staff handling specimens from a monkeypox case-patient, in a laboratory conforming to UK laboratory standards.◇	None	Not recommended	Not applicable	0
Low	HCW involved in care of monkeypox case-patient while wearing appropriate PPE (with no known breaches) for all contact episodes.	Passive§	Not recommended	158	0

	OR HCW involved in care of monkeypox case-patient while not wearing appropriate PPE for all contact episodes but not within 1 m of case-patient and with no direct contact with body fluids or potentially infectious material. OR Community contact not within 1 m of case-patient.				
Intermediate	Intact skin-only contact with a symptomatic (with rash) monkeypox case-patient, their body fluids, or potentially infectious material[¥] or contaminated fomite. OR No direct	Active[¥]	Vaccination may be considered	125	84 (67)

	contact but within 1 m of symptomatic monkeypox case-patient without wearing appropriate PPE (including disposable FFP3 respirator or equivalent).				
High	Direct exposure of broken skin or mucous membranes to monkeypox symptomatic case-patient, patient's body fluids, or potentially infectious material‡ (including clothing or bedding) without wearing appropriate PPE (including disposable FFP3 respiratory or equivalent). Exposure includes inhalation of respiratory droplets or material from scabs from cleaning rooms where	Active¥	Vaccination recommended	5	5 (100)

	a monkeypox case-patient has stayed, mucosal exposure to splashes, penetrating injury from used sharps, device or through contaminated gloves or clothing.				

FFP3: filtering facepiece 3; HCW: healthcare worker; PHE: Public Health England; PPE: personal protective equipment.

* Imvanex (modified vaccinia Ankara, Bavarian Nordic, http://www.bavarian-nordic.com) was approved by the European Medicines Agency in July 2013 for active immunization against smallpox in adults. Jynneos (modified vaccinia Ankara; Bavarian Nordic) was approved by the US Food and Drug Administration in September 2019 for the prevention of smallpox and monkeypox disease in adults ≥18 years of age determined to be at high risk for smallpox or monkeypox infection.

¶ For patients 2 and 3 combined.

Δ Case-patients are considered potentially infectious 24 hours before the onset of rash.

◇ Refer to http://www.hse.gov.uk/pubns/books/clinical-laboratories.htm.

§ A person requiring passive surveillance is given information about monkeypox and what to do if illness develops.

¥ A person requiring active surveillance is given information about monkeypox and instructed to report health status daily to PHE, regardless of symptoms, for 21 days from the date of most recent exposure, and to report any illness immediately. In addition, HCWs with high-risk exposures are to be excluded from work for 21 days after the most recent exposure (note this recommendation was introduced after diagnosis of the third case-patient).

‡ Potentially infectious biological material consists of skin lesions and detached scabs.

Reproduced from: Vaughan A, Aarons E, Astbury J, et al. Human-to-Human Transmission of Monkeypox Virus, United Kingdom, October 2018. Emerg Infect Dis 2020; 26:782.

Graphic 132286 Version 1.0

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