

Background

The first case of human monkeypox was detected in 1970 in the Democratic Republic of Congo (DRC).¹ Monkeypox virus is a double stranded DNA virus that replicates in the cytoplasm of host cells. Monkeypox virus is a member of the Orthopoxvirus genus in the family Poxviridae. Other members of this viral genus include the viruses that cause smallpox (variola virus) and cowpox (vaccinia virus).²

Monkeypox has a similar but less severe clinical presentation compared to smallpox. Monkeypox is also considered less contagious than smallpox.³ Two distinct clades of monkeypox have been identified: the West African clade, which is typically associated with milder clinical presentation and a case fatality ratio ranging 0-6%, and the Congo Basin (Central African) clade, which is historically associated with greater human-to-human transmission and higher morbidity with a case fatality ratio ranging 8-13%.^{1,3-6}

Epidemiology

Monkeypox is considered a zoonotic disease with transmission primarily occurring from animals, such as rodents and primates, to humans. However, the full scope of animals that may carry or transmit monkeypox virus is not well understood.⁷ Human-to-human transmission also occurs with up to 6 to 9 generations of human-to-human transmission being previously identified in the longest chains of transmission. Secondary attack rates are often reported around 10%¹, although an outbreak in the DRC reported a median household attack rate of 50% (range 50%-100%).⁸

Transmission of the virus can occur through contact with bodily fluids, wounds on the skin or internal mucosal surfaces, respiratory droplets, or contaminated objects. Consumption of inadequately cooked meat or other products from infected animals may also pose increased risk of infection. Vertical transmission from mother to fetus via placenta or close contact during or after birth has been documented. The prevalence of asymptomatic transmission is currently unknown.⁷ These modes of transmission put health workers, household members, or other close contacts at increased risk of infection.³

Through 2021, 15 countries on 4 continents reported confirmed human monkeypox cases. The majority of cases are identified in countries where monkeypox is endemic, such as Nigeria, Central African Republic (CAR), Cameroon, and DRC.⁹ Until 2022, imported cases have been reported in the United States, the United Kingdom, Israel, Benin, South Sudan, and Singapore¹⁰, with importation events typically associated with contact with infected animals or recent travel to an endemic area.⁷

In recent years, monkeypox has been reevaluated as an emerging public health threat as the frequency and geographic distribution of cases have increased, particularly in West Africa, where contact between susceptible populations and infected animals is increasing due to factors such as deforestation and insecurity.⁵ Increased human-to-human monkeypox transmission may be partially attributed to the cessation of smallpox vaccination campaigns, as smallpox immunization

provides some cross-protection against monkeypox. Climate change and increased population mobility also are potential contributing factors to increased human-to-human transmission.⁷ Median age of cases also has increased in recent years from children to young adults.⁶

Clinical Characteristics and Diagnosis

The incubation period for monkeypox can range from 5-21 days but usually falls within 7-14 days. Clinical presentation of monkeypox can be similar to chickenpox, caused by varicella-zoster virus.¹¹ Symptoms usually begin within 5 days of infection with fever and chills, headache, muscle aches, back pain, fatigue, and swollen lymph nodes (lymphadenopathy), the latter symptom differentiating monkeypox from smallpox and chickenpox. About 1-3 days, sometimes longer, after the initial onset of symptoms, a rash or lesions can appear, usually beginning on the face and spreading throughout the body, often to the extremities rather than the trunk. Notably, monkeypox lesions can appear on the palms of the hands and soles of the feet (75% of cases). Most individuals with monkeypox experience rash with 1 to >100 skin lesions, but some do not experience these lesions.³

In most patients, symptoms of monkeypox are usually self-limiting and spontaneously resolve within 14-21 days. However, symptoms can be severe and require medical care.³ During a 2003 monkeypox outbreak in the US during which most patients appeared to contract the disease through direct or indirect contact with infected animals, 19 of 75 patients for which data were available were hospitalized. Of those, 2 developed severe disease, including a child with monkeypox-associated encephalitis.^{1,12}

Due to the similarity in clinical symptoms between monkeypox and chickenpox, healthcare providers often face difficulties in diagnosing cases based on clinical symptoms alone.¹³ Additionally, cross-protective antiviral immunity among adults who received childhood smallpox vaccination may lead to mild or no recognizable disease symptoms.¹⁴ Therefore, asymptomatic monkeypox infection and undetected circulation can occur.¹⁵

Diagnosis often is made presumptively based on clinical presentation and disease progression. The preferred laboratory test is polymerase chain reaction (PCR) detection of viral DNA, with the best specimens being skin, fluid, or crusts collected directly from skin lesions, or biopsy when possible. PCR blood serum tests are not recommended. Additionally, antigen and antibody detection methods are not recommended due to the serological cross-reactivity among orthopoxviruses and the potential for false positive results among people recently or previously vaccinated against smallpox.³ Viral isolation from a clinical specimen, electron microscopy, and immunohistochemistry also are acceptable techniques in addition to PCR. However, the expertise and equipment required for these tests limit their feasibility in rural or resource-poor areas without major laboratories.¹⁶

Prevention and Treatment

Monkeypox cases often are treated with medical countermeasures designed for the closely related smallpox virus. There are currently 3 smallpox vaccines that could be used in the US Strategic

National Stockpile (SNS), 2 of which are licensed for smallpox and the other could be used for smallpox under an investigational new drug (IND) protocol. The two licensed vaccines for smallpox are JYNNEOS™ (also known as Imvamune or Imvanex) and ACAM2000®. JYNNEOS™ also is licensed for monkeypox.

The JYNNEOS™ vaccine is an attenuated live virus vaccine that is replication-deficient, meaning the virus cannot reproduce in humans. It is administered subcutaneously in 2 doses, given 4 weeks apart.¹⁷ Pre-exposure prophylaxis to monkeypox can be conferred by the smallpox vaccine JYNNEOS™. Data from Africa suggests that the JYNNEOS™ vaccine is at least 85% effective in preventing monkeypox. This conclusion is supported by studies assessing the immunogenicity of this vaccine in humans and efficacy data from animal challenge studies.¹⁸ Additionally, the JYNNEOS™ vaccine is considered to be a potential post-exposure prophylactic to minimize potential development and severity of disease. For post-exposure prophylaxis, the US CDC recommends that the first dose of the vaccine be given within 4 days from the date of exposure to prevent disease onset. If given between 4-14 days after the date of exposure, vaccination may reduce the symptoms of disease but may not prevent disease.¹⁹

The ACAM2000® vaccine is a replication-competent live vaccinia virus vaccine, meaning the vaccinia virus in the vaccine can be transmitted to contacts of the immunized individual. The vaccine historically has been given to individuals with high-risk of exposure to poxviruses, such as laboratory staff, and is available for use as post-exposure prophylaxis for monkeypox under an expanded access IND protocol (in 2021, the US CDC Advisory Committee on Immunization Practices recommended the JYNNEOS™ vaccine be used for personnel at high risk of occupational exposure instead of ACAM2000®).²⁰ ACAM2000® is given as a single dose via the multiple puncture technique for percutaneous administration.¹⁷ The vaccination schedule for post-exposure prophylaxis with ACAM2000® is the same as for the first dose of the JYNNEOS™ vaccine. A 2020 study administered the antiviral tecovirimat and ACAM2000® to evaluate tecovirimat's effect on ACAM2000® immunogenicity and efficacy. Tecovirimat is the active pharmaceutical ingredient in TPOXX, which is US FDA-approved to treat confirmed smallpox diagnosis. Clinical signs of disease were elevated in the tecovirimat-treated group of the monkeypox challenge trial, suggesting TPOXX may affect ACAM2000® immunogenicity if administered concomitantly.²¹

The third smallpox vaccine is the Aventis Pasteur Smallpox Vaccine (APSV). It is a replication-competent vaccinia virus vaccine that could be used under an IND or emergency use authorization (EUA). This vaccine would only be used for smallpox if the licensed vaccines are unavailable or contraindicated.¹⁷ It is unclear if this vaccine could be used for monkeypox.¹⁹ Other vaccines for monkeypox are in development, including VACΔ6 and LC16.²⁰

The FDA-approved antivirals cidofovir and brincidofovir could be used to treat monkeypox under IND or EUA, though there is insufficient data on their effectiveness for monkeypox treatment in humans. However, animal studies have demonstrated effectiveness against monkeypox in certain mammalian species.²² Brincidofovir is approved to treat smallpox under the FDA's Animal Rule. Brincidofovir and cidofovir work by inhibiting the viral DNA polymerase and have been used to treat other viral infections with varying levels of success.^{23,24}

The FDA approved the antiviral tecovirimat (ST-246; TPOXX) in 2018 to treat smallpox based on *in vitro* studies using variola virus and related orthopoxviruses. The antiviral, which is included in the US SNS, could be used to treat monkeypox under an IND, though there is no data on its effectiveness in humans.²² Studies using tecovirimat in animal species have demonstrated its effectiveness in treating a variety of poxvirus-caused infections. Tecovirimat is an inhibitor of the viral envelope protein p37 that blocks the ability of virus particles to be released from infected cells.²⁵

Another potential treatment for monkeypox is vaccinia immune globulin (VIG). However, use of VIG for monkeypox or smallpox has not been tested in humans and there is no data on its effectiveness against either virus. VIG for monkeypox treatment would need to be conducted under an IND. Research is ongoing to develop new immune globulin-based treatments for poxviruses. CDC and its partners have developed 4 new monoclonal antibody (mAb) mixes that appear to be effective against intracellular and enveloped virion forms of variola and monkeypox viruses in animals.²⁰

Recent Outbreaks in Europe & North America as of May 20, 2022*

Recent cases in the United Kingdom (20 confirmed),²⁶ Spain (30 confirmed),²⁷ Portugal (14 confirmed)²⁸, Australia (2 confirmed)²⁹, Belgium (2 confirmed)³⁰, Canada (2 confirmed)³¹, France (1 confirmed),³² Germany (1 confirmed),³³ Italy (3 confirmed)³⁴, Sweden (1 confirmed), and the United States (1 confirmed)³⁵ have renewed concern regarding the threat of monkeypox. To date, no deaths are reported. Contact tracing is underway, but it is likely that cases may have occurred through community transmission. Additionally, it has been noted that an unusual number of the new cases have arisen among gay, bisexual, or other men who has sex with men (MSM).^{4,36,37} However, MSM are not the only community at risk, as close contact historically is the primary mode of transmission. Sexual transmission has been hypothesized as a potential mode of transmission but has not been reported as a driver of transmission in past monkeypox outbreaks.⁷

*As of 1:30 pm ET

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