



Monkeypox 2022: Gearing Up for Another Potential Public Health Crisis

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Abstract

Monkeypox virus, a member of the *Orthopoxvirus* genus, was first identified as the etiology of monkeypox in 1970 in the Democratic Republic of Congo and remains endemic in regions of Central and West Africa. Following the most recent outbreak of monkeypox in multiple countries throughout Europe and North America, the infection has been declared a public health emergency by the Centers for Disease Control and Prevention. Within this report, we aim to provide clinicians with a focused overview of the epidemiology, clinical manifestation, diagnosis, and approaches to treat and prevent monkeypox infection amidst the global outbreak.

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As health care systems continue to adjust to the ongoing coronavirus disease 2019 (COVID-19) pandemic, multiple cases of monkeypox have been reported in nonendemic countries. Investigations are in progress to identify the source of infection and to characterize transmission routes and spread. With this report, we attempt to provide clinicians with a focused overview of monkeypox, emphasizing pearls needed while establishing preparedness strategies, and a summary of relevant epidemiologic and clinical considerations. Approaches and strategies will have to consider not only what is known about monkeypox, but also the system changes needed to cope with the ongoing COVID-19 pandemic.

VIROLOGY

Monkeypox virus is a member of the *Orthopoxvirus* genus within the Poxviridae family. Members of this family are large, enveloped viruses with a double-stranded DNA genome. The genus also includes variola virus, the causative agent of smallpox, and vaccinia virus, the foundation of the smallpox vaccine. The smallpox vaccine program was discontinued in the United States in 1972 and in Africa in 1977 after global eradication of the

disease. Smallpox vaccination confers immunity to other orthopoxviruses, including monkeypox virus. As it has been several decades since routine smallpox vaccination anywhere in the world, there has been concomitant decrease in population-wide immunity to monkeypox virus in endemic regions of Africa and elsewhere.^{1,2} This is, at least in part, a reason for the increasing number of human cases of monkeypox. There are 2 clades of the virus associated with human disease: the West African clade, which is associated with mortality of 1% to 4%; and the Congo Basin (Central African) clade, which is associated with higher mortality of 10%.³

As monkeypox possesses a DNA genome, it is less prone to high mutation rates compared with RNA viruses, such as SARS-CoV-2. However, the increased rate of human-to-human spread during the 2022 outbreak has raised questions about whether the currently circulating virus has acquired traits that enhance transmission. In May 2022, the first draft sequence of the circulating virus was generated and demonstrated that the 2022 virus belongs to the West African clade. Phylogenetic analysis revealed that the 2022 virus is most closely related to a strain exported from Nigeria in 2018,

which led to isolated cases in the United Kingdom, Israel, and Singapore. To date, sequencing has not revealed any significant genetic differences in the 2022 virus that may suggest increased transmissibility or disease severity.⁴

EPIDEMIOLOGY

Monkeypox has primary rodent reservoirs in Central and Western Africa. Human monkeypox was first identified in 1970 in Zaire (now the Democratic Republic of the Congo).^{1,5,6} Since then, outbreaks have been reported in countries in Central and Western Africa. Although monkeypox has only now come into the global forefront, this has been a prevalent concern in endemic regions in Africa; monkeypox cases have been reported in the Democratic Republic of the Congo (>1000 cases per year) and the Central African Republic (19 cases), and there is an active, ongoing outbreak in Nigeria (>80 cases).⁷ In the Western world, monkeypox has been associated with localized outbreaks in the United States in 2003, with the source being infected prairie dogs that became ill after being housed with imported rodents shipped from Ghana.^{2,5} There have also been imported cases in Israel, the United Kingdom, and Singapore.

Transmission of monkeypox virus can be animal-to-human or human-to-human through direct contact with infected lesions or body fluids.^{8,9} In this report, we focus on human-to-human transmission. Historically, the virus has not spread efficiently between humans, requiring direct contact with infected body fluids or fomites (ie, bed sheets) or sustained respiratory droplet exposure within 6 feet for 3 hours or more.¹⁰ The unusual nature of the current outbreak is that most of the recently reported cases have not had a direct travel link to an endemic area. Cases have been primarily identified among men who have sex with men.¹¹ The mechanism of transmission likely reflects transmission secondary to direct contact with body fluids and exposed skin lesions. However, further epidemiologic investigation of transmission will be

required to evaluate the question of whether sexual transmission represents a plausible mechanism as this has not been previously reported with monkeypox.⁸ Most important, however, this outbreak highlights the importance of avoiding stigmatization and promoting evidence-based response to an epidemic or pandemic as all communities and individuals are at risk.¹²

CLINICAL FEATURES

The incubation period for monkeypox is usually between 6 and 13 days but can be up to 21 days. The World Health Organization clinically defines monkeypox infection in 2 phases: (1) an initial invasive period (lasting 0 to 5 days), including fever, headache, lymphadenopathy, myalgia, asthenia, and malaise; followed by (2) the skin eruption phase, occurring 1 to 3 days after onset of fever.¹³ The characteristic pleomorphic rash begins on the face and trunk as macules and papules measuring 0.5 to 1 cm, with progressive evolution into vesicular and pustular rash, often with umbilication by day 5 to 7 (Figure).^{14,15} The rash then spreads centrifugally to involve extremities, palms, and soles of feet. Importantly, involvement of oropharyngeal mucous membranes, genitalia, conjunctivae, and cornea is frequently noted. During a period of 2 to 4 weeks, the rash resolves with scabbing and desquamation.¹³ Notably, all skin lesions are relatively the same size and often in the same phase of development, in contrast to chickenpox, in which lesions tend to be in different phases. Severe illness due to monkeypox was defined by Huhn et al⁹ as temperature of 38.3 °C or higher and a rash composed of 100 or more lesions at any point during illness.

During the 2003 outbreak in the United States involving a cluster of 37 patients, the predominant symptom was rash, followed by fever, chills, lymphadenopathy, headache, and myalgia. The median duration of fever was 8 days (range, 2 to 13 days), and rash lasted for 12 days (range, 7 to 24 days).⁹ In the present outbreak, however, “phase 1” prodromal symptoms have not always been present, with rash being the primary symptom at onset.¹¹ In addition, several patients



have been described to have predominant genital or perianal lesions as well as signs of proctitis, initially misclassified as sexually transmitted infections including herpes, varicella zoster, and syphilis.¹⁶

Monkeypox is a self-limited disease lasting between 2 and 4 weeks. However, the clinical course can be severe in children, pregnant women, and patients with immunocompromising conditions.⁶ It would be important for organizations to include specific guidance to these specific patient populations. This should include infection prevention and control measures, like avoiding contact with persons with active infection as well as reinforcing masking in those exposed or infected.

DIAGNOSIS

Diagnostic testing is currently performed at the Centers for Disease Control and Prevention (CDC) or state health departments. The primary method for diagnosis is polymerase chain reaction analysis of specimens collected from infected lesions. Appropriate specimens include skin/crust from the surface of the lesion or a swab obtained from the vesicular lesion.⁶ Electron microscopy of samples collected from skin lesions may reveal a characteristic poxvirus, but this is not typically

performed for diagnostic purposes. Serologic testing is not recommended because of cross-reactivity between orthopoxviruses and the possibility for false-positive results in those with prior smallpox vaccination.⁶

To facilitate diagnostic testing in suspected cases, 2 swabs of skin lesions should be collected (1 used for screening, the second for additional testing at the CDC). If skin/crust from the surface of the lesion is collected, it must be submitted along with a paired swab of the lesion. A sterile, dry polyester or Dacron swab should be used to vigorously sample the lesion. The swab should then be placed in viral transport medium or in a sterile, dry container and shipped at refrigerated temperature (4 °C) to a testing laboratory. Initial testing at a participating laboratory will include screening polymerase chain reaction analysis for orthopoxviruses; if the response is positive, the second swab may be sent to the CDC for additional testing.

INFECTION CONTROL AND PUBLIC HEALTH CONSIDERATIONS

The disease is transmitted through direct contact with infected material or exposure of mucous membranes to large droplets.

There is also a potential risk of aerosolization of viral particles from certain procedures. Hence, for hospitalized patients, the CDC recommends a combination of contact precautions (gowns and gloves), droplet precautions (protective eyewear in addition to gowns and gloves), and airborne precautions (placement of the patient in a negative air room with adequate air exchanges and an N-95 respirator or higher respiratory protection). However, owing to the evolving nature of this outbreak, infection prevention and control recommendations from public health organizations may change and we encourage readers to refer to these organizational resources for the most up-to-date recommendations. Nevertheless, patients should remain in isolation until all skin lesions have crusted over, which may take up to 4 weeks.¹⁷

As we gain additional understanding of transmission dynamics, it is likely that these recommendations will change. The public health impact of this current outbreak is uncertain. There has been limited person-to-person transmission in the past, largely because the infection is frequently symptomatic, and persons are infectious to others only after the onset of symptoms. It is unclear whether this still holds true as there are suggestions that there may be subclinical infections promoting ongoing transmission. Whereas it is unlikely that we will see widespread transmission as with COVID-19, even relatively small outbreaks could further burden a health care system that is already stressed by COVID-19.

APPROACH TO A SUSPECTED CASE AND DIAGNOSIS

In evaluating a suspected case of monkeypox, the focus should be on establishment of a diagnosis, prevention of spread, and appropriate personal protective equipment for health care workers. Currently, cases have been limited to those with direct contact with known cases, and therefore obtaining an accurate history with a suspected case should raise clinical suspicion for monkeypox. However, this may change if the infection becomes more widespread.

There remain many unknowns with regard to the current outbreak. The exact source of infection, incubation period, and transmissibility compared with past outbreaks are not well defined. From the current outbreak, most transmission seems to be through the contact route. Although transmission has historically been thought to be from large respiratory droplets, the COVID-19 pandemic has demonstrated that the distinction between airborne and droplet transmission is not as clear as it once appeared. Therefore, adequate personal protective equipment for health care workers is important. It is also important to review proper disposal of contaminated waste, contaminated laundry, patient care equipment, and surfaces in the patient care environment.

TREATMENT

Most patients with monkeypox infections have a self-limited course and recover without medical interventions. The primary management involves supportive, symptom-directed care until clinical resolution of illness. Clinicians should be alert to secondary bacterial infections and provide early direct antibiotic therapy as appropriate.⁹ Certain patients may benefit from specific therapies; these include children, pregnant or breastfeeding women, the immunosuppressed, and those with widespread skin or mucosal involvement. These therapies include 2 antiviral agents, tecovirimat (TPOXX) and brincidofovir.

Tecovirimat is an antiviral medication that inhibits the major envelope protein of orthopoxvirus and was approved by the Food and Drug Administration for treatment of smallpox.¹⁸ It has been found to prevent lethal infection from monkeypox virus in nonhuman primate models.^{18,19} Cidofovir and brincidofovir, which inhibit viral replication through selective blocking of viral DNA polymerase, have been found to have in vitro activity against monkeypox in animal models.²⁰ Brincidofovir was also approved in June 2021 for treatment of smallpox.²¹ Adler et al,²² in a retrospective study, described efficacy of tecovirimat in

reducing duration of viral shedding and clinical disease (n=1), whereas brincidofovir failed to demonstrate similar efficacy and was discontinued early because of adverse effects (n=3). At this time, tecovirimat represents the primary treatment of choice. However, the decisions on therapy should be made in consultation with local departments of health and the CDC, given paucity of data on efficacy. Safety data in pregnancy are limited to animal reproductive studies, with no adverse events observed with tecovirimat but fetal toxic effects and adverse pregnancy outcomes reported with brincidofovir.¹⁸

POSTEXPOSURE MANAGEMENT

Because of the relatively long incubation period of monkeypox, the disease can be prevented with vaccination in those thought to have been exposed. In the response to orthopoxvirus outbreaks, an approach of “ring vaccination” is used to vaccinate those with contact with known cases to stop the outbreak. Vaccination with ACAM2000 confers protection against orthopoxvirus diseases including smallpox and monkeypox. As a live virus vaccine, ACAM2000 is not recommended for immunocompromised hosts.²³ In addition, as skin lesions that form because of vaccination with ACAM2000 can spread the vaccine virus to others in contact with fluid from the lesions (including from fomites), those with close household contact with immunocompromised hosts should also not receive this vaccine.²³

A newer vaccine, JYNNEOS (also known as Imvamune or Imvanex), is a replication-deficient viral vector vaccine that confers immunity against orthopoxvirus and can be safely used in immunocompromised patients. JYNNEOS is the preferred postexposure vaccine for the prevention of monkeypox.^{24,25} Although still investigational, vaccinia immune globulin can be considered for use in postexposure prophylaxis for highly immunocompromised patients who may not mount a sufficient immunologic response to JYNNEOS and for whom ACAM2000 is contraindicated.²⁵

Ensuring timely and protocolized access to JYNNEOS or vaccinia immune globulin should be a priority for management of infection in immunocompromised patients should widespread case prevalence become an issue.

CONCLUSION

It is essential to implement the lessons learned during the COVID-19 pandemic. The evidence and understanding are rapidly evolving with the present monkeypox outbreak. Moving forward, focus on preparedness should include plans for infection prevention and control, diagnostics, and management.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests. Dr Sampathkumar, associate editor of the journal, had no role in the editorial review of or decision to publish this article.

Abbreviations and Acronyms: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019

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