



The 2022 Global Monkeypox Outbreak: A Focused Review

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Abstract

The first human infection with monkeypox virus was reported in 1970, and infections have subsequently been recorded in endemic areas such as Central and West Africa or linked to international travel to these regions. However, the emergence of the 2022 monkeypox outbreak has involved multiple non-endemic countries and continents without links to travel to endemic areas. The first cases in the current outbreak were reported in May of 2022. The primary mode of transmission is atypical and is thought to occur through direct contact with infected skin lesions. The rapid increase in case numbers prompted the World Health Organization to declare this disease outbreak as a public health emergency of international concern. Robust efforts are being made by global public health authorities to develop effective antiviral treatment options and vaccination strategies to reduce the spread of this disease. The objective of this manuscript is to provide a comprehensive review of the 2022 mpox outbreak with respect to its unique epidemiology, clinical features, complications, and management options.

Introduction

Monkeypox is a zoonotic disease caused by monkeypox virus, an orthopoxvirus member of the *Poxviridae* family that has been declared a public health emergency due to global outbreaks occurring in non-endemic areas^{1,2}. In November 2022, the World Health Organization (WHO) announced that “mpox” would be used as a preferred term instead of monkeypox due to racist and stigmatizing language associated with the disease. There are two known clades of the Monkeypox virus: the Central African (Congo Basin) clade, now referred to as Clade I, and the West African clade, now known as Clade II. Clade II is subdivided into two subgroups, known as IIa and IIb. Evolutionary divergence between the two clades has resulted in nucleotide variations that have led to differences in the viral proteins responsible for viral persistence and immune system evasion. Thus, phylogenetic and clinical differences distinguish the Clade I virus from the Clade II virus^{2,3}. Clade I is responsible for causing more severe illness, but Clade II has demonstrated higher rates of human-to-human transmission, accounting for most of the cases in the current outbreak¹⁻³.

Epidemiology

The CDC estimates that as of December 2022, there have been approximately 82,200 confirmed cases reported worldwide, with over 98% of those reported in non-endemic regions, including North and South America, Europe, and Asia. The United States (US) makes up over 29,000 of those cases. New infections in the US appeared to reach a peak in the summer months (July-August) of 2022, reaching a 7-day average of over 400 confirmed cases, and have been down trending in the recent months^{1,2}.

Human-to-human transmission occurs via contact with contaminated bodily fluids, materials such as clothing or bedding, or skin lesions of an infected person⁴. Initially, it was postulated that this virus can spread through respiratory droplets, but subsequent research has shown that the viral load in oropharyngeal swabs was approximately 17-fold less than in swabs of skin lesions, making this a less likely route of transmission⁵. Cases have been disproportionately reported in communities of men identifying as having sex with men (MSM), where close skin-to-skin contact is hypothesized to facilitate transmission of the virus. Women and children are less commonly affected^{1,6}.

Clinical Features

The mean incubation time for monkeypox virus from contact to symptom onset was found to be between 6 and 9 days in recent studies⁷. Classically, the first symptoms of mpox infection involve a nonspecific prodrome that most commonly includes fever, fatigue, myalgia, and lymphadenopathy⁸. The current outbreak of mpox has presented with atypical clinical characteristics, with many patients facing symptoms deviating from those previously described⁷. Most notably, there is frequent absence of the prodromal symptoms of fever, headache, adenopathy, and malaise before cutaneous involvement^{9,10}. Additionally, emerging data suggests that a large proportion of mpox infections are transmitted during the pre-symptomatic period, from 1 to 4 days before the appearance of any initial symptoms⁷.

One to five days following the prodrome, an eruption of painful vesiculopustular lesions of variable sizes is typically noted (Figure 1). The location of the rash is often dependent on the site of infection. The rash may present as macules, papules, or vesicles in the early stage (day 1-2 following the prodrome) which then evolve into firm pustules (day 7) and resolve into scabs with crusting. These lesions can be found on the face, hands/feet, and oral

mucosa, and if present in multiple areas of the body, they often present simultaneously and in the same stage^{8,11,12}. Though recent presentation has predominated in areas of sexual contact, such as the anogenital or the oral regions, it remains unknown whether the infection is sexually transmitted^{9,10,13}. It is also unclear why some patients may present with disseminated monkeypox infection whereas infection in others is limited to one area of the body.

The patient is considered infectious until there is re-epithelialization of all open vesiculopustular lesions on the skin^{11,14}. In addition to the skin findings, features of the mpox enanthem observed during this outbreak include pharyngitis, myocarditis, epiglottitis, as well as proctitis or anorectal pain.

The lesions caused by the monkeypox virus may appear similar to other infectious vesiculopustular lesions, so multiple differential diagnoses may be considered when a patient presents with skin findings concerning for mpox. In particular, mpox lesions must be differentiated from the erythematous vesiculopustular lesions seen in smallpox infection, and other infections such as varicella, disseminated herpes simplex virus, coxsackie virus, and molluscum contagiosum. Disseminated herpes simplex infections can be distinguished by smaller monomorphic lesions. Coxsackievirus infections affect palmoplantar surfaces, presenting with football-shaped vesiculobullous lesions. Most notably, molluscum contagiosum and smallpox exhibit similar vesiculopustular lesions found in mpox that are difficult to derroof and often do not display fluid contents¹¹. However, unlike the clustered vesicles found in these diseases, mpox lesions appear larger, as well as more isolated, umbilicated, and crateriform⁸.

Diagnostic Testing

The WHO and Centers for Disease Control and Prevention (CDC) recommend that all individuals who present with rash and fever or lymphadenopathy be screened for suspected mpox infection^{15,16}. Clinicians should refer to diagnostic guidelines set forth by the CDC and WHO when addressing diagnosis. The confirmation of an mpox infection may be reached following detection of non-variola orthopox DNA through real-time polymerase chain reaction (RT-PCR) and is further distinguished through monkeypox-specific RT-PCR testing or sequencing of specimens retrieved from the individual¹⁷. Specimens for such tests may be collected through vigorous dry swabbing of lesions in the oropharynx, anorectal region, or other areas of disease. Importantly, de-roofing is not essential. Although not readily indicated, Tzanck smears may allow for the rapid cytological interpretation and ruling out of other conditions that present similarly, such as molluscum contagiosum and herpes virus infection¹⁷. Per the recommendation of the CDC, culturing monkeypox



Figure 1: A young male presenting with discrete vesicles and pustules with central umbilication on the left dorsal hand. A polymerase chain reaction was positive for non-variola orthopox virus.

specimens for the purpose of diagnosis should not be performed for routine diagnosis¹⁶. While performing these diagnostic tests, personal protective equipment and careful collection of samples must be prioritized to avoid autoinoculation or transmission of the virus.

Management

Most mpox infections are mild and resolve without specific therapies within 2-4 weeks following infection¹¹. Primary treatment upon hospitalization has consisted of supportive management of mucosal lesion pain, proctitis, and mitigation of secondary infections of the skin^{18,19}. Considerations for general pain control include over-the-counter medications (OTC) such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). Oropharyngeal pain may be managed with rinses of viscous lidocaine along with oral antiseptics to suppress bacterial infection¹⁵. Treatment of proctitis associated with this infection is challenging. Along with OTC medications, sitz baths and application of topical analgesics such as lidocaine may provide some relief.

Antiviral medications approved for treatment of smallpox, including tecovirimat and brincidofovir, may be useful in those at risk of severe disease manifestation, such as children, immunocompromised individuals, and pregnant women¹¹.

Tecovirimat is the first antiviral treatment approved by the US Food and Drug Administration (FDA) for both pediatric (≥ 13 kg) and adult smallpox, taken orally at varying doses depending upon body weight for 14 days²⁰. Orthopoxvirus viral envelope protein VP37 is inhibited by tecovirimat, hindering viral release from infected cells and thus further viral dissemination²¹. Its use has been allowed through the Expanded Access Investigational New Drug application (EA-IND) for potential treatment of other orthopoxviruses such as monkeypox. Although there has been relatively little administration of antiviral therapy during the current outbreak, a few cases of immunocompromised persons have noted disease resolution upon receiving tecovirimat²⁰. However, experimental data have suggested that tecovirimat may have a low barrier to resistance, and there have been emerging reports of tecovirimat-resistant mpox cases²². Of the two cases of tecovirimat resistance first reported by the CDC, both patients were immunocompromised and had progressive and disseminated mpox infection that was not adequately controlled by prolonged treatment with tecovirimat. A proposed mechanism for tecovirimat-resistance is due to F13L mutations in the viral genome²².

Brincidofovir is an FDA-approved antiviral medication indicated for the treatment of pediatric (≥ 10 kg) and adult smallpox, working through the inhibition of viral DNA polymerase. It remains under consideration for mpox

treatment under EA-IND as an oral analog of intravenous cidofovir, as it causes lower hepatic and renal toxicity^{20,23}. Similar to tecovirimat, the effects of brincidofovir have not yet been well-documented apart from numbered reports of resolved disease following oral administration of varying doses and frequency²³.

Although the safety of tecovirimat and brincidofovir has been confirmed through human studies, their efficacy has been proved solely in animal models and few patients^{23,24}. Therefore, antiviral use in treating human mpox remains under investigation²⁰. Ongoing studies are needed to provide more evidence for the efficacy of these antiviral therapies in mpox.

An additional therapy for mpox infection may be intravenous Vaccinia Immune Globulin, previously approved for the treatment of vaccinia vaccination complications such as eczema vaccinatum and progressive vaccinia⁸. Such treatment is practical for immunocompromised individuals unable to receive vaccination, and is under consideration for EA-IND.

Individuals who suspect exposure to mpox should monitor their symptoms in the 16-to-23-day period following possible exposure, observing for the appearance of rash, lesions, or the onset of fever or lymphadenopathy^{7,16}. Patients who are actively infected and presenting with mild disease should remain isolated at home until all the lesions have crusted over and the scabs have fallen off with complete re-epithelization¹⁶.

In addition to monitoring symptoms and self-isolation following a suspected mpox encounter, the CDC provides additional guidelines to control and prevent the spread of the monkeypox virus. It is suggested to avoid direct skin-to-skin contact with individuals who have a rash that appears to be mpox, whether it appears on the genitals, trunk, or extremities²⁵. Additionally, avoiding contact with fomites such as utensils, clothing, bedding, or towels of a person with suspected or confirmed mpox virus is also recommended. Finally, prevention strategies such as proper hand hygiene and vaccination are strongly recommended to protect against mpox infection and spread, especially given the emergence of evidence supporting high prevalence of pre-symptomatic transmission^{7,25}. Given the risk of transmissibility through both contact and aerosolization, especially in healthcare settings, it is imperative for healthcare workers to don proper personal protective equipment (PPE) and to use the Identify-Isolate-Inform (3I) tool to manage suspected mpox cases in clinical settings²⁶.

Vaccination

Vaccination is recommended for individuals with known or presumed exposure to monkeypox or those classified as high risk for occupational exposure, such as healthcare

Table 1: Comparison of Currently Available Vaccination Options for Monkeypox

Vaccine Name	JYNNEOS	ACAM2000
Vaccine Type	Live, replication-incompetent modified vaccinia virus Ankara vaccine	Live, replication-competent vaccinia virus vaccine
Regimen of Vaccination	Two dose series, 28 days apart	One dose
Route of Administration	Intradermal injection in the forearm of 0.1 mL ^a Subcutaneous injection in the upper arm of 0.5 mL ^b	Percutaneous scarification of the skin with 0.0025 mL droplet (multiple punctures of skin with a bifurcated needle containing vaccinia virus)
Recommended Population	Intradermal injection (Alternative): < 18 years of age Subcutaneous injection: >18 years of age, or at risk of developing keloid scars	Greater than 12 months of age
Contraindications	Persons with history of severe allergic reactions to vaccine ingredients	Pregnancy; persons with history of severe allergic reactions, or atopic dermatitis, eczema, psoriasis and exfoliative skin disorders; infants; Immunocompromised individuals (HIV, leukemia, transplant recipients); heart disease
Adverse Reactions	Injection site swelling, pain, and redness.	Injection site swelling, pain, and redness; lymphadenopathy, itching, malaise, fatigue; eczema vaccinatum, progressive vaccinia (rare) ^c

^a The alternative regimen is an injection volume of 0.1 mL intradermally for those greater than 18 years of age, decreasing the dosage to improve vaccine availability during the outbreak²⁸.

^b The standard regimen of 0.5 mL subcutaneous administration is recommended for individuals less than 18 years of age, or those at risk of developing keloid scars²⁸.

^c In immunocompromised persons, the vaccine may generate uncontrolled viral shedding at the site of inoculation, leading to progressive vaccinia, a rare adverse event associated with an expanding and necrotic vaccination site. Those with a history of atopic dermatitis may present with eczema vaccinatum, a complication in which the vaccinia virus exploits the already weakened skin-barrier for replication²⁹.

personnel, laboratory workers, and veterinarians. Two vaccines, JYNNEOS and ACAM2000 (Table 1), have been indicated for pre-exposure prophylaxis with 85% efficacy, as well as post-exposure prophylaxis if administered promptly following close contact^{8,11,27}.

ACAM2000 is a live and replication-competent vaccinia virus vaccine, approved by the FDA in 2007 for the prevention of smallpox. Recently, it has also been approved for the prevention of mpox under EA-IND³⁰. Orthopoxviruses, such as monkeypox, vaccinia virus, and Variola virus (smallpox), feature a highly conserved genome, allowing for orthopoxvirus infection or immunization with an orthopoxvirus vaccine to provide a level of immunity against other viruses within the genus³¹. One-dose ACAM2000 has mitigated previous monkeypox outbreaks, demonstrating the cross-reactive immunity potential of the vaccine³². Despite this capability, the vaccinia vaccine has been shown to elicit several unfavorable reactions among inoculated individuals and their close contacts, due in part to its replication competence²⁷.

JYNNEOS is a live and replication-incompetent modified vaccinia virus Ankara vaccine authorized in September 2019 by the FDA for the treatment of smallpox. In August 2022, an Emergency Use Authorization issued by FDA approved the vaccination for mpox²⁸. However, there have been reports of injection site pain, redness, and swelling¹⁸. Unlike ACAM2000, extensive trials regarding adverse events have yet to be conducted²⁷, which is another area that requires additional research.

Post-exposure prophylaxis with these vaccinations holds potential due to the more drawn-out incubation period of mpox⁶. Onset of symptoms usually occurs several days after exposure; thus vaccination is recommended 4 days after known exposure to prevent disease or within 4-14 days to lessen the symptoms of infection^{7,11}.

Complications

Mortality due to monkeypox virus remains low, at an estimated 65 total deaths worldwide according to the CDC in December of 2022¹. The most common complications of this infection may cause significant morbidity, including bacterial superinfection of skin lesions, sepsis, permanent skin scarring, and residual hypo- or hyperpigmentation of the skin³³. Eczema monkeypoxium is a newly identified phenomenon thought to result from predisposition to monkeypox infection due to impairments in the skin barrier secondary to preexisting atopic dermatitis. However, the long-term sequela of monkeypox virus superinfection on atopic dermatitis are not yet fully understood³⁴. Systemic complications such as neurologic, ocular, and pulmonary symptoms have also been emerging throughout the current outbreak. Pulmonary complications are thought to result from inflammation caused by the virus in the lung tissue, most commonly leading to bronchopneumonia². The most commonly reported neurologic complications include headache and mood disturbances, but few cases of severe complications such as encephalitis have been reported³⁵. Ocular manifestations during this outbreak have also been reported to cause morbidity on a spectrum, ranging from

conditions such as conjunctivitis and keratitis to more severe complications such as corneal ulcers and scarring³⁶.

Conclusions

Monkeypox (mpox) remains a global health concern, highlighting the need for continued vigilance and efforts to halt community transmission. Even as reported mpox cases continue to decline, it is imperative for clinicians to remain updated regarding the varied presentations of this viral disease, its clinical mimickers, and guidelines regarding use of antivirals and vaccines while managing this condition. Further research in multiple areas is needed to better understand the transmission of the monkeypox virus during this current outbreak and efficacy of existing antiviral therapies.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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