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# Monkeypox emerges on a global scale: A historical review and dermatologic primer



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The current monkeypox outbreak reawakens the concern that *poxviridae* have a high potential for zoonotic spillover and causing a pandemic. Much fieldwork and research have been done by health care and public health workers in Africa during previous human outbreaks, and their knowledge should inform our global response to the current outbreak. However, unusual clinical presentations now have potential implications for recognizing the disease. In addition, infections from *poxviridae*, such as monkeypox, have common cutaneous signs that occur early, may be related to periods of transmissibility, and can leave scarring. Therefore, dermatologists will play a key role in recognizing and diagnosing infections and educating and preparing frontline health care workers for the early detection of new cases and clusters of monkeypox. (J Am Acad Dermatol 2022;87:1069-74.)

**Key words:** complex medical dermatology; dermatology; infectious disease; monkeypox; pandemic; *poxviridae*.

## INTRODUCTION

Although the emergence of SARS-CoV-2 and the COVID-19 pandemic has brought more widespread attention to zoonotic diseases, infections, and novel pathogen risks, scientists have long monitored pathogens and evaluated their risks. To predict viruses with pandemic potential, in 2021, epidemiologists and infectious disease experts ranked 887 zoonotic viruses for spillover potential or the likelihood that a virus that primarily affects animals can transmit to humans. Twelve families of viruses accounted for the 50 highest ranked viruses for spillover potential, with *poxviridae* representing 2 of the top 50 viruses. Monkeypox virus and cowpox virus ranked 24 and 28, respectively.<sup>1</sup> With the unusually widespread outbreak of monkeypox cases in humans starting in May 2022, a renewed, more thorough, and widespread shift in attention to this family of viruses may be warranted. Much fieldwork and research have been done by health care and public health workers in Africa during previous human outbreaks, and their knowledge should inform our global response to the current international outbreak. Unlike SARS-CoV-2,

infections from *poxviridae* have common cutaneous signs that occur early in disease progression, may be related to periods of transmissibility, and can leave scarring. Dermatologists will play a key role in recognizing and diagnosing infections and educating and preparing frontline health care workers to detect new cases and clusters of monkeypox early.

## Monkeypox history

In 1958, captive colonies of cynomolgus monkeys transported from Africa and kept in Copenhagen developed a vesicular rash determined to be an orthopoxvirus similar to but distinct from smallpox.<sup>2</sup> Despite first being discovered in captive monkeys, the name is a misnomer in that it was subsequently documented in diverse mammals such as squirrels, rats, mice, and prairie dogs, and small forest mammals are thought to be the primary driver of zoonotic transmission.<sup>3,4</sup> The first case of monkeypox in humans was described in the Democratic Republic of the Congo in 1970, and since then, cases have been reported primarily in central and western African countries, with the majority of infections having

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occurred in the Democratic Republic of the Congo.<sup>2</sup> In 2003, 47 cases were identified in the United States across 6 states in the Midwest and represented the first monkeypox outbreak outside of Africa. Infected people became ill after having contact with pet prairie dogs that were exposed to sick, small mammals from Ghana.<sup>5,6</sup> Other cases outside of Africa have been described in Israel, Singapore, the UK, and the United States, but cases in and out of Africa typically occurred as single cases or clusters of 2 to 7 cases.<sup>2,5</sup> Although there have been larger, more persistent human outbreaks, the most recent being over 80 cases in 2017 to 2018 in Nigeria, the current is the first to become internationally widespread with multiple foci and evidence for widespread human-to-human transmission beyond close family members. From the 2017 to 2018 outbreak, researchers constructed a phylogenetic tree from 29 monkeypox virus isolates and 23 other orthopoxvirus isolates and determined that there are 2 clades of monkeypox virus, the West African clade and the Congo Basin clade, with the West African clade thought to be less virulent than the Congo Basin clade, and associated with case fatality rates in the range of 1% to 3% compared with the Congo Basin clade around 10%.<sup>4</sup>

Although the mode of zoonotic transmission of monkeypox to humans is unknown, contact with small forest animals is presumed responsible for most monkeypox infections in humans.<sup>2</sup> A study conducted after the 2003 US outbreak indicated that the 47 human cases primarily resulted from touching a sick animal, being bitten or scratched with a break in the skin, cleaning the cage, or touching the bedding of a sick animal, although some infected individuals reported merely being in the same room as an infected animal.<sup>5-7</sup> As with related smallpox virus, transmission between people is thought to occur primarily through contact with infected bodily fluids and large respiratory droplets,<sup>2-5,8</sup> although aerosol transmission between infected animals has been demonstrated.<sup>3</sup> Additionally, emerging reports suggest that the monkeypox virus may be found in semen and other body fluids,<sup>9</sup> although the role of seminal fluid in the transmission of the monkeypox virus is still being explored. Contagiousness, if any, from presymptomatic and asymptomatic carriers is unknown.<sup>5</sup> Anecdotal reports from frontline providers shared on social media also suggest

that patients may experience few or no prodromal symptoms, which may play a role in allowing more widespread infection via asymptomatic hosts.<sup>10</sup>

### Diagnosis, disease progression, and prognosis

After an incubation period of 4 to 21 days, averaging 7 to 14 days, illness often begins with anonspecific prodrome, including 1 to 5 days of fever, chills, headache, fatigue, sore throat, myalgia, and lymphadenopathy.<sup>4,5</sup> Typically, within 1 to 5 days from the onset of fever, a rash evolves and resolves over a 2 to 4 week period of time. First, the rash appears as macules (1-2 days), then develops into papules (1-2 days), followed by vesicles (1-2 days), and ultimately pea-sized, hard pustules (5-7 days) before crusting, scabbing, and eventually fall-

ing off (7-14 days).<sup>3-5</sup> Once the eschar has fallen off and the wounds have healed with a fresh layer of skin, the patient is no longer considered infectious, about 2 to 4 weeks from the first lesion.<sup>5</sup> Of the 47 infected individuals in the 2003 US outbreak, all had respiratory and systemic symptoms, with 39 (83.0%) having >4 respiratory symptoms and 30 (63.%) having >4 systemic symptoms; ultimately, 14 (31.1%) required hospitalization.<sup>6</sup> Photographs shared on social media and in early publications from the current outbreak also demonstrate larger, almost crateriform vesicles that may erode and lead to crusted erosions. Lesions tend to show the same stage of evolution on each body part. Lesions often first appear in the mucosa (mouth and genitals) and/or face, then appear on the hands and feet, followed lastly by the trunk.<sup>4,5</sup>

Based on clinical symptoms alone, a probable monkeypox diagnosis can be made with high sensitivity (93%-98%) and low specificity (9%-26%), as previously demonstrated with a cohort of 645 individuals.<sup>4</sup> Reports from the current outbreak suggest that the classic prodrome may be less severe, and the characteristic vesicular lesions may be present in the genital and perineal region more frequently and potentially limited to solely that anatomic site.<sup>10-12</sup> This may make the detection of cases more challenging, and monkeypox should be in the differential diagnosis for new genital lesions and evaluation for potential sexually transmitted infections. Although the main clinical differential

### CAPSULE SUMMARY

- This article reviews existing and emerging literature on monkeypox.
- The current outbreak includes infections in new geographic regions, different patterns of transmission, and different prodromal symptoms and cutaneous manifestations. Therefore, dermatologists must take careful histories and add monkeypox to their differential diagnosis of vesicular and pustular rashes.

*Abbreviation used:*

EA-IND: Expanded Access Investigational New Drug Protocol

diagnosis is smallpox, important clinical differences help differentiate monkeypox. Namely, the presence of lymphadenopathy and crop-like, less-centrifugally distributed lesions may indicate monkeypox.<sup>4</sup> Other differential diagnoses include rashes with vesiculopustular presentation (Table 1). However, herpes infections, including both herpes simplex virus and varicella-zoster virus, tend to have smaller individual lesions and more frequently occur in limited anatomic areas (eg, 1 site or 1 dermatome for shingles). Widespread primary varicella-zoster virus or disseminated reactivation varicella-zoster virus can be challenging to distinguish clinically, but herpes-family infections may reliably be diagnosed by rapid polymerase chain reaction testing. Histologically, monkeypox is similar to vaccinia and cowpox, although markedly different from other pox viruses. Namely, these orthopoxviruses demonstrate proliferation of basal keratinocytes, necrosis of the epidermis with spongiosis, keratinocyte pallor, and dense inflammatory cell infiltration.<sup>13</sup> This also highlights the utility of genetic testing by polymerase chain reaction and immunologic testing by enzyme-linked immunosorbent assay in confirming monkeypox diagnosis.

The case fatality rate from monkeypox has been reported as 1% to 11% in the general population, although higher in young children and those with certain underlying immunodeficiency conditions.<sup>5</sup> Early genetic data suggest that the ongoing outbreak appears related to the West African clade and therefore is expected to have a lower case fatality rate.<sup>14</sup> Notably, even these mortality numbers may be overestimated, as in the 2003 US outbreak in which there were no deaths,<sup>6</sup> and improved supportive care may lead to reduced mortality. Beyond mortality, monkeypox infection is associated with significant morbidity and potential long-term sequelae. Complications include secondary infections, pneumonia, sepsis, encephalitis, and corneal infection. Even in the absence of secondary bacterial infection, cutaneous and corneal scarring can occur, the latter of which can result in loss of vision.<sup>3-5,13</sup>

### Vaccination and treatments

Primary treatments are supportive, although early identified close contacts may benefit from ring vaccination, either with the vaccinia vaccine

(replication-competent vaccine, approved for smallpox) or the newer Jynneos' Imvamune (replication-deficient vaccine, approved for monkeypox). Because the incubation period of monkeypox is long, early vaccine administration may help decrease symptoms or even prevent the disease.<sup>4,5</sup> However, the replication-competent vaccinia vaccine has a considerable adverse event profile, including 74 complications and 1 death per 1 million primary vaccinations as per the 1968 vaccination campaign in the United States.<sup>3</sup> There are many contraindications to vaccination by vaccinia vaccine, including serious allergy, immunocompromised status, pregnancy or breastfeeding, underlying heart disease, or a history of atopic dermatitis or another exfoliative skin condition.<sup>15</sup> In the case of individuals with a history of atopic dermatitis, a rare and potentially lethal complication known as eczema vaccinatum can occur with vaccination by replication-competent vaccinia vaccine.<sup>15</sup> More recently, the US Department of Defense vaccinated 540,824 military personnel with an updated replication-competent vaccinia vaccine; 1 in 8000 developed myopericarditis.<sup>3</sup> In contrast, the nonreplicating Jynneos vaccine is expected to have much lower rates of adverse events though large-scale trials have not yet been conducted.<sup>15</sup>

Other potential treatments include tecovirimat, an antiviral medication approved for the treatment of human smallpox in adults and certain pediatric patients, and extended via Expanded Access Investigational New Drug Protocol (EA-IND) for treatment of nonvariola orthopoxviruses like monkeypox during an outbreak; cidofovir, an antiviral medication approved for the treatment of cytomegalovirus retinitis in patients with AIDS, and extended through EA-IND for treatment of orthopoxes during the outbreak; Vaccinia Immune Globulin Intravenous for the treatment of vaccinia vaccination complications, and expanded by EA-IND for treatment of orthopoxviruses during an outbreak; and brincidofovir, antiviral medication for the treatment of human smallpox viruses in both pediatric and adult patients, and currently being evaluated for EA-IND for use in treatment for monkeypox.<sup>5</sup>

### Infection control and public health guidelines

Patients diagnosed with monkeypox or exposed to an infected person or animal should follow Centers for Disease Control and Prevention and state/local public health guidelines regarding isolation and symptom monitoring. Centers for Disease Control and Prevention recommend that health care professionals caring for known or suspected

**Table 1.** Clinically differentiating monkeypox from varicella

Clinical feature	Monkeypox	Varicella
Lesion anatomic sites	Mucosal tissues (mouth, genitals, and anus); entire body surface favoring face and extremities	Primary: scattered, widespread Reactivation: dermatomal
Lesion distribution pattern	Centrifugal, primarily with body regions at the same stage of disease progression; possibly local to the anogenital region in some cases	Primary: disseminated individual vesicles, which appear in crops/clusters, with lesions in different stages present at the same time Reactivation: dermatomal clusters
Lesion appearance	Early: large crateriform or umbilicated vesicles Late: pustules rupture and crust and leave hypopigmented scarring	Early: vesicles like a dewdrop on a rose petal Late: vesicles ooze and crust
Illness progression	Prodrome: 1-5 d Macules: 1-2 d Papules: 1-2 d Vesicles: 1-2 d Pustules: 5-7 d Scabs: 7-14 d	Primary: Prodrome: 1 d Vesicles: 1-4 d Crusting/Scabbing: 5-7 d Reactivation: Neuropathic pain and vesicular eruption with the similar time course
Systemic symptoms	Very common: lymphadenopathy, fever, sweats, chills, muscle ache, back pain, headache, and abdominal pain Common: respiratory symptoms (wheezing, cough, rhinorrhea, sore throat, and respiratory distress) Less Common: gastrointestinal symptoms including nausea, vomiting, and diarrhea <sup>6</sup>	Primary: Fever, malaise, and sore throat Reactivation: Pain at site Other symptoms are uncommon but can include headache, fever, and fatigue

monkeypox cases don gowns, gloves, eye protection, and a National Institute for Occupational Safety and Health-approved respirator with N95 filters or higher.<sup>5</sup> One should be especially mindful of activities that could resuspend dried material from lesions, such as the use of fans and sweeping. Dried material from smallpox lesions can remain infectious for many years,<sup>16</sup> although it is unknown if this is true for monkeypox. While Centers for Disease Control and Prevention have not yet made recommendations regarding domesticated animals as potential sources of infection, on May 23, 2022, the European Centre for Disease Prevention and Control recommended that pet rodents such as mice, rats, hamsters, and guinea pigs exposed to confirmed cases of human monkeypox should “ideally be isolated in monitored facilities, complying with respiratory isolation (eg, a laboratory) and animal welfare conditions (eg, government facilities, kennels, or animal welfare organizations), and tested (by polymerase chain reaction) for exposure before quarantine ends. Euthanasia should only be a last resort reserved for situations where testing and/or isolation are not feasible.”<sup>17</sup> Other mammalian pets exposed to monkeypox should be isolated at home when possible.

### Conclusions and commentary

Fortunately, and in contrast with SARS-CoV-2, monkeypox is not a novel pathogen and has been markedly less transmissible. However, it is important to act quickly to halt community transmission and avoid the establishment of additional animal reservoirs, potentially leading to further outbreaks. If we hope to contain monkeypox while minimizing unintentional harm, we must acknowledge and act upon several key features.

First, early identification of monkeypox cases allows public health officials to identify contacts, evaluate their risk of exposure, isolate as appropriate, monitor for symptoms, and potentially implement ring vaccination. Dermatologists should add monkeypox to their differential diagnosis when evaluating patients with new papulovesicular or vesiculopustular lesions. Patients should be queried for exposure history, and public health systems engaged rapidly if the diagnosis is suspected or confirmed.<sup>18</sup> To support this, governmental resources informed by public health authorities should focus on providing financial support to those quarantined because of monkeypox or exposure, particularly to account for the pathogen’s extensive incubation and infectious periods.



Second, the observation that most cases in the current outbreak have occurred among men who have sex with men can most likely be explained by an early cluster. More specifically, this outbreak was likely seeded by “highly interconnected sexual networks within the men who have sex with men community, where it can spread in ways that it cannot in the general population.”<sup>19</sup> There may also be some degree of ascertainment bias because of high rates of health-seeking and experience with routine evaluations for sexually transmitted infections among men who have sex with men, so cases among other populations may not yet be accurately captured.<sup>19</sup> Along these lines, David Heymann, MD and former director of emergencies for the World Health Organization, recently said, “We know monkeypox can spread when there is close contact with the lesions of someone who is infected, and it looks like sexual contact has now amplified that transmission.”<sup>20</sup> So far, Dr Heymann’s statement has evolved into headlines such as: “Expert: Monkeypox likely spread by sex at 2 raves in Europe;”<sup>20</sup> “Monkeypox outbreak is primarily spreading through sex, World Health Organization officials say;”<sup>21</sup> and “Monkeypox outbreak may be blamed on sex at European raves, World Health Organization expert says.”<sup>22</sup> These headlines help demonstrate that health officials and reporters alike must be intentional in their speech and that we must balance messaging regarding possible risks of certain communities while avoiding stigmatization.

With only 3000 cases internationally, it may seem premature to sound alarms about monkeypox. However, in a world still combating another pandemic, we are acutely aware that early intervention and rapid containment are keys to controlling the spread at the community level. Therefore, as monkeypox emerges and spreads in multiple countries, we should all be alert and act quickly to contain it. Furthermore, we should recall that we are all one interconnected species and refocus research and support on neglected diseases.

#### Conflicts of interest

Drs Rosenbach and Freeman serve *Pro Bono* on the Ad Hoc Task Force to Develop Monkeypox Content for the American Academy of Dermatology. This submission does not represent the official views of the Academy.

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