HISTORY OF MONKEYPOX

Monkeypox virus was first identified in 1958 among monkeys in a Danish laboratory, hence its name. The first human case was diagnosed in 1970 in a nine-month-old boy in what is now the Democratic Republic of the Congo (DRC). The virus has remained endemic in the DRC and was also found to be endemic in multiple other African nations.

The two distinct phylogenetic clades of monkeypox virus are: Clade I (previously known as the Central African/Congo Basin clade) and Clade II (previously known as the West African clade). The clade names were changed to avoid stigmatization of these regions. Clade I has higher transmissibility and mortality rates compared to Clade II, which produces a more self-limited disease with lower mortality rates. Clade II is further divided into Clade IIa and Clade IIb, with the latter referring to the currently circulating international variant.

Prior to the current outbreak, monkeypox cases outside of endemic regions were due to international travel or importation of infected animals. In 2003, the United States recorded the first monkeypox cases outside of the African continent. Forty-seven cases were discovered across six different states, spread from imported pets to pet prairie dogs to humans. Travel-related cases have been documented in Israel, the U.K., and Singapore.

For years, concerns have been raised about the possibility of more significant outbreaks given increased population growth, encroachment on animal reservoir habitats, increasing human movement, and enhanced global interconnectedness. Monkeypox virus isolates from the 2022 outbreak in the United States appear to be phylogenetically different, raising concern for increasing mutation rates and transmissibility; alternatively, the virus may just have reached a population whose behaviors allow it to spread more quickly.

VIROLOGY

Monkeypox virus, the causative agent of monkeypox, is a double-stranded DNA virus of the genus Orthopoxvirus and within the family Poxviridae. Variola virus, the causative agent of smallpox, is also contained in the genus Orthopoxvirus; a common clinical mimic, molluscum contagiosum, is in the family Poxviridae, but as a different genus does not cause false positives for monkeypox testing. Monkeypox virus is a zoonosis capable of infecting multiple mammalian species, including rodents, non-human primates, and humans. Although the primary animal reservoir is not definitively known, rodents — not monkeys — seem to represent the largest population hosting the virus.

The current monkeypox outbreak is being transmitted through human contact, specifically skin-to-skin contact, fomite transmission such as contact with clothing or bedding of infected individuals, and respiratory secretions. This outbreak has disproportionately affected men who have sex with men (MSM), and risk factors of infection include young age, HIV seropositivity, a history of prior sexually transmitted infection (STI), and engaging in high-risk sexual activity such as condomless sex. In this particular outbreak, concerns have been raised as to whether there is direct sexual transmission of the monkeypox virus. Studies have shown viral shedding present in seminal fluid, but currently there is insufficient evidence showing significant infectivity of this fluid.

CLASSIC MONKEYPOX VS. 2022 OUTBREAK: CLINICAL DIFFERENCES

Classically, monkeypox presents with generalized prodromal symptoms such as fever, headaches, chills, malaise, and lymphadenopathy, followed by a characteristic rash. Signs and symptoms generally reflect a milder form of smallpox. The rash usually starts in the
mouth and spreads to the face and extremities without sparing the palms and soles. Lesions begin as macules, then progress to umbilicated papules, vesicles, pustules, and finally scabs (see Fig. 1). Pain can be present, but not in every case. Pruritus is common during the healing process. Lesions are similar in size and present at the same stage. They number between 10-150 total and can persist for up to four weeks. The incubation period is generally thought to be around 7-14 days but could last as long as 21 days. Individuals are infectious from the onset of prodromal symptoms until a new layer of skin forms after the final scab falls off. Severe complications are rare, with exact incidences unclear, but include bacterial superinfection, encephalitis, pneumonitis, and conjunctivitis/keratitis.12

The disease presentation in the 2022 outbreak is somewhat different. The characteristic rash is still present, but it can be limited to genital, perigenital, and perianal areas; it often spares the face; and it may be in different stages of development. There may be mild or no systemic prodromal symptoms, and the systemic (previously prodromal) symptoms may begin after rash onset. Systemic symptoms include fever, lymphadenopathy, pharyngitis, headache, lethargy, myalgia, low mood, and proctitis.13

The Centers for Disease Control and Prevention (CDC) categorizes severe illness from monkeypox as developing one of the following from the infection: sepsis, encephalitis, periorbital infection, abscess formation, confluent skin lesions, and lesions located in the oropharynx and anogenital regions that can cause severe pain. Mild to moderate infections encompass all other infections; the distinction between mild and moderate is clinical and not well defined.

EPIDEMIOLOGY OF 2022 OUTBREAK

As of November 2022, there have been 77,092 cases of monkeypox worldwide in 109 countries. There have been 28,442 cases in the United States with six deaths, and 800 cases in Pennsylvania.14 Thirteen cases have been diagnosed within the Penn Medicine Lancaster General Health system. Nationally, cases peaked in mid-August and are declining overall, presumably due to education and prevention, diagnosis and treatment, and vaccination.

The highest incidence of cases remains among MSM, with the highest burden in the 31-35 age group (see Fig. 2 on page 70).15 Initially, the most affected racial group was white individuals, but this has transitioned to Black individuals being most affected. Behavioral data collected from gay, bisexual, and MSM through a monkeypox supplemental survey of the American Men’s Internet Survey in August demonstrate active behavioral modification, with 48% of respondents reducing number of sexual partners, 50% reducing one-time sexual encounters, and 50% reducing sex with partners met on dating apps or at sex venues.16

Internationally, specifically in South America and Africa, case numbers continue to rise.17 Given the novelty of the virus outside of endemic regions, likely underreporting/under-identification of cases, potential for spread to new animal reservoirs, and likely return to
pre-outbreak sexual habits in high-risk populations, the
direction the epidemic will take and whether the virus will
become endemic in a larger number of countries remain
unpredictable. Additionally, vaccines are not yet available
in Africa, hampering control in endemic countries, thus
long-term projections are unreliable. However, short-term
epidemic case forecasts published weekly by Chowell-
Puente, an infectious disease modeler out of Georgia
State University, have been generally accurate to date.

PREVENTION

For the general public, the CDC recommends that
people avoid close, skin-to-skin contact with anyone
with a rash that could be monkeypox and avoid contact
with any objects or materials that have come in contact
with a person who could have monkeypox.18 Frequent
handwashing with soap and water is also recommended.

Providers should wear a gown, gloves, eye protec-
tion (goggles or face shield), and an N95 respirator while
interacting with patients with suspected monkeypox in-
fection. Patients should be evaluated and treated whenever possible in a single-person room. While special air
handling is not required for initial evaluation and treat-
ment, any aerosolization procedures, such as intubation
and extubation, should be done in an airborne infection
isolation room.18

Prior vaccination against smallpox appears to pro-
vide some protection against symptomatic and severe
illness from monkeypox. In one study in the DRC, indi-
viduals who were previously vaccinated against smallpox
were shown to have a fivefold lower risk of monkeypox
compared to unvaccinated individuals during a mon-
keypox outbreak in 2010.19 In the United States, data
from the 2003 monkeypox outbreak also suggest that a
history of smallpox vaccination reduced the chance of
symptomatic monkeypox infection.20 However, this im-
munity likely wanes with time and there is insufficient
evidence to evaluate whether previous smallpox immu-
nization confers protection in the current outbreak.

VACCINATION

Two vaccines are available to reduce risk of severe
monkeypox infection. The preferred vaccine is the modi-
fied vaccinia Ankara (MVA) vaccine, which is available
as JYNNEOS in the United States.21 It is an attenuated
pox virus vaccine that has been approved for the preven-
tion of monkeypox and smallpox, and it has a strong
safety profile. It can be given as a two-dose series over
four weeks subcutaneously. Due to supply shortages, the
CDC and Food and Drug Administration (FDA) ap-
proved intradermal administration of this vaccine under
Emergency Use Authorization. The intradermal route
requires one-fifth of the standard vaccine dose, and early
studies show a similar immune response in comparison
to subcutaneous administration.22

The second vaccine available is called ACAM2000.
It was developed as a smallpox vaccine but has been
made available for use against monkeypox under an Ex-
panded Access Investigational New Drug protocol by the
CDC. While large doses of this vaccine are available, it
has both more side effects and more contraindications
than the MVA vaccine.21

Two special populations to consider when counsel-
ling on vaccination include pregnant patients and im-
munocompromised patients. While there are minimal
data available on monkeypox and monkeypox vaccine in
pregnancy, the American College of Obstetricians and
Gynecologists (ACOG) recommends pregnant patients
who are eligible for vaccination receive JYNNEOS be-
cause the vaccine-associated risks in pregnancy appear

Fig. 2. U.S. cases of monkeypox reported to CDC: age and gender.19
to be lower compared to ACAM2000, which is contraindicated in pregnancy. It is unknown if patients who have received JYNNEOS can safely breastfeed, but because the MVA vaccine is replication deficient, it is unlikely to pose a significant risk of transmission to breastfed infants. JYNNEOS is approved for use in immunocompromised individuals who are not recommended to receive other live vaccines.

Eligibility for the vaccine is governed by local and state health departments and depends on community prevalence and individual risk factors. In general, the CDC recommends prioritizing post-exposure prophylaxis (PEP), which means vaccinating individuals after known exposure. PEP vaccination should ideally be done within four days of exposure to prevent disease but may be considered up to 14 days after exposure to decrease disease morbidity.

Secondarily, public health entities are encouraged to consider expanded post-exposure prophylaxis (PEP++) when resources are available. PEP++ refers to the vaccination of individuals who may have had exposure to monkeypox, individuals who have had experiences that may increase their risk of monkeypox exposure, or individuals who live in a defined geographic area where monkeypox transmission is occurring at high rates.

Lastly, pre-exposure prophylaxis (PrEP) is vaccination before exposure to monkeypox and has been largely restricted to people in occupational risk groups, such as laboratory workers, health care workers, and public health responders directly handling viruses or treating patients with monkeypox. Locally, vaccination eligibility guidelines are available at www.lghealth.org/monkeypoxvaccine. Vaccination clinics were held at LG Health from August to October (see Fig. 3) but have been stopped as the community need has largely been met. LGHP Comprehensive Care will continue to have a small number of vaccine doses available for patients to start and complete the vaccine series, as needed. The CDC offers a monkeypox vaccine locator online at mpoxvaxmap.org.

Data are emerging regarding vaccine uptake and effectiveness from across the United States. To date, 1,012,283 doses of JYNNEOS vaccine have been administered. A CDC-led, monkeypox-specific follow-up study of the American Men’s Internet Survey found that about one in five respondents received at least one dose of monkeypox vaccine. Uptake was highest among Hispanic or Latino men (27.1%) and lowest among non-Hispanic or African American Black men (11.5). Rates varied considerably between urban (27.8%) and rural areas (5-7%).

Data suggest vaccination is an effective tool in controlling the outbreak. In one monitoring study by the CDC that included data from 32 U.S. jurisdictions among vaccine-eligible males aged 19-49, unvaccinated individuals were at 14 times the risk of acquiring monkeypox compared to their vaccinated counterparts. However, these data were not controlled for age, underlying conditions, or behavior, so larger studies are needed to determine true vaccine effectiveness.

**DIAGNOSIS**

The diagnosis of monkeypox is based on clinical evaluation (see above) and laboratory confirmation via PCR testing from monkeypox lesions. Locally, this is a send-out lab that takes 3-5 days to result. Testing the appropriate patient and testing them correctly is critical because medications for treating monkeypox are distributed by the Pennsylvania Department of Health and only available for laboratory-confirmed cases. For the most part, only patients with a rash consistent with monkeypox should be tested. Providers testing patients should collect swabs from multiple lesions, two swabs per lesion. Collecting samples from lesions on different
parts of the body is preferred, but it is important to keep swabs from lesions, crusts, and exudate in separate specimen containers. The lesion should be swabbed vigorously but not unroofed. If a patient does not have a rash but has systemic symptoms, a high risk of exposure, and pharyngitis or proctitis, an oropharyngeal or rectal swab, respectively, should be collected using the same supplies used for testing of lesions. The sample must be refrigerated within an hour of collection.

Culture-based testing is not recommended for clinical practice or diagnosis. Locally, testing supplies can be requested through the LG Health core laboratory courier. The swabs are polyester tipped and sent in viral transport media; these are the same swabs used for herpes simplex virus testing.

MANAGEMENT
Isolation
Patients diagnosed with monkeypox, and those awaiting test results, should remain isolated for the duration of the illness, which lasts until scabs fall off and a new layer of skin is present for all prior lesions. This typically takes two to four weeks. If a patient is unable to remain fully isolated, they should:
• Avoid crowds.
• Avoid any physical or sexual contact.
• Avoid contact with pets and animals.
• Wear a mask at all times when around other people.
• Cover up all rashes or lesions.
• Avoid sharing utensils or cups.
• Avoid sharing clothing or bedding.
• Wash hands with soap and water frequently.

Contact Tracing
Whenever possible, patients should create a list of close contacts, including anyone with whom they have had close physical contact in the three weeks prior to infection, and notify them of their possible exposure to monkeypox so that those close contacts can be evaluated for vaccination (see PEP and PEP++ above). The state health department will also assist in contact tracing and confidential exposure notification, as needed.

Mild to Moderate Illness: Supportive Care
For many immunocompetent individuals, monkeypox illness is mild and only requires supportive care. Early pain management of skin lesions is key to effective supportive care. Acetaminophen and NSAIDs are recommended as first-line therapies for pain control. Topical steroids and anesthetics, such as hydrocortisone and lidocaine cream, can be effective adjunct agents but must be used carefully in patients with open wounds.

For patients who develop proctitis, stool softeners, Sitz baths, sucralfate enemas (need compounded), or calmol suppositories can be added to the aforementioned pain regimens. Itching can be treated with oral antihistamines or topical antipruritics, such as diphenhydramine cream, calamine lotion, or mild topical steroids. Lesions should be closely monitored for signs of superimposed bacterial infection, abscess formation, or spread to sensitive areas — such as anogenital, ocular, and oropharyngeal lesions — which require more aggressive treatment and closer monitoring.

Severe Illness and Vulnerable Populations: Antiviral and VIVIG Therapies
While there is no specific treatment yet approved for monkeypox, antiviral and immunoglobulin therapies developed for other conditions have been made available to treat monkeypox with the hope that they may help slow the progression of symptoms and curtail the duration of illness, especially in cases of severe illness or in vulnerable patient populations.

Severe illness includes sepsis, encephalitis, periorbital infection, abscess formation, confluent skin lesions, and lesions located in the oropharynx and anogenital regions that can cause severe pain. Patient populations that are susceptible to rapid disease pro-

<table>
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<tr>
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<tr>
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<tr>
<td>Brincidofovir</td>
<td>Smallpox</td>
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</tbody>
</table>

*Yet to be released from Strategic National Stockpile
gression and severe illness who should be considered for these therapies include those living with uncontrolled HIV/AIDS cancer or other immunocompromising conditions, as well as those receiving radiation therapy, immune modulating therapies (TNF inhibitors, high-dose corticosteroids), and transplant recipients. In addition, children younger than 8 years old, pregnant and breastfeeding patients, and patients with skin disease (e.g., psoriasis, eczema, severe acne) should also be considered for these antiviral therapeutics.

In the outpatient setting, patients who meet these criteria can be referred to the LGHP Comprehensive Care practice for treatment. Patients who are admitted though no human data are available to confirm its efficacy. VIGIV was developed to treat complications of smallpox vaccination. It is unknown whether it is effective against monkeypox. As described above, the modes of infection are the same for all individuals: skin-to-skin contact (which can occur during sex), contact with fomites, or respiratory secretions.

The CDC has outlined specific communication recommendations to prevent stigma, which include using inclusive language such as “us” and “we”; avoiding sensational language and images; using language that resonates with the audience; using positive and diverse images; and emphasizing preventive strategies, symptom recognition, and the treatable nature of the disease to allay public fear and promote self-action.

For individuals in high-risk groups, it is beneficial to work with already-established community-specific avenues of communication, such as specific websites, dating apps, and community partners. In these settings, relatable, personal stories can be helpful. Educational materials available from the CDC meet these guidelines. Utilization of these methods will decrease silent spread in the community and the worsening of an individual’s symptoms that can result when fear of experiencing stigma delays presentation for care.

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A CLINICAL PRIMER ON THE MONKEYPOX OUTBREAK


Andrew V.A. Foley, MD, MPH
Family Medicine Residency Program
Penn Medicine Lancaster General Health
540 N. Duke St., Lancaster, PA 17602
717-544-4950
Andrew.Foley@pennmedicine.upenn.edu

Elliott Brady, MD, MPH
Family Medicine Residency Program
Penn Medicine Lancaster General Health
540 N. Duke St., Lancaster, PA 17602
717-544-4950
Elliott.Brady@pennmedicine.upenn.edu

Patricia Carr Reese, MD, MPH, AAHIVS
LG Health Physicians Comprehensive Care
Penn Medicine Lancaster General Health
554 N. Duke St., Lancaster, PA 17601
717-752-2002
Trish.CarrReese@pennmedicine.upenn.edu