Mpxox

Introduction

Mpxox is an infection caused by monkeypox virus, an orthopox virus previously associated with sporadic cases in Africa that usually involved contact with an animal reservoir (Figure 1).[1] In May 2022, an mpxox outbreak characterized by human-to-human transmission via primarily close physical contact spread throughout more than 100 countries not typically affected by endemic circulation.[2] Clinical episodes in the context of this 2022 outbreak most frequently involved sexual transmission of mpxox among men who have sex with men (MSM).[2,3,4] Polymerase chain reaction (PCR) testing on samples obtained from mpxox lesions is available for diagnosis and should be used in populations and circumstances with clinical suspicion of mpxox. Vaccination as prevention should be prioritized for vulnerable groups. Although most patients improve with supportive care, multiple investigational therapies are available for treatment, especially in severe disease and in immunocompromised individuals.
Epidemiology

Global Mpox Epidemiology

Mpox virus was first identified as a cause of human disease in the 1970s in West and Central Africa, primarily associated with exposure to animal hosts in which the virus circulates. Since then, increased rates of cases across that region have been seen, and mpox was reported as endemic in multiple African countries, with most cases occurring in the Democratic Republic of the Congo.[5,6] Two clades of the virus have emerged in this context based on geography in Africa; Clade I has been associated with more severe disease than Clade II.[7] Previously, outbreaks in the United States have occurred primarily as spillover events from imported mammals from West Africa or as travel-associated cases without associated transmission.[8,9,10]

- **Clade II Global Outbreak**: In 2022, a global outbreak of Clade II mpox occurred, with cases identified in non-endemic countries, including across Europe and the United States.[2,3,11] Since January 2022 through December 27, 2023, there have been more than 92,546 confirmed cases globally, of which the majority have been in locations that have not historically reported mpox.[12]

- **Clade I Outbreak in Democratic Republic of the Congo**: Although Clade I mpox has not been reported as part of the current global outbreak, since January 2023 more than 12,000 suspected cases of Clade I mpox have been reported in the Democratic Republic of the Congo.[13] Clade I mpox has previously been observed to be more transmissible and to cause more severe infections than has been observed with Clade II infections. During this DRC outbreak, a cluster of Clade I infections was associated with sexual contact, the first such description of Clade I mpox spread.[13] To date, no Clade I mpox infections have been reported in the United States. For patients with a clinical illness who report travel to the Democratic Republic of the Congo within 21 days of the illness onset, the CDC recommends clinicians pursue monkeypox virus clade-specific testing.[14] From an infection prevention and control standpoint, Clade I monkeypox virus is regulated as Category A under hazardous materials regulations (select agents) requiring special handling of samples and waste. Vaccination with either ACAM2000 or MVA is expected to be protective against Clade I. There is no difference in management and/or treatment options for Clade I virus.

Mpox in the United States

The Centers for Disease Control and Prevention (CDC) has provided updated mpox epidemiology data (Figure 2).[10,15,16] In the United States, from January 2022 through January 11, 2024, there have been more than 31,000 mpox cases with 56 mpox-associated deaths.[15] Cases in the 2022-2023 outbreak have disproportionately affected men who have sex with men (including gay, bisexual, or other men).[3,17] Approximately 40% of those diagnosed with mpox also had HIV, and another 40% had been diagnosed with a reportable sexually transmitted infection (STI) in the previous year.[18] Among cases reported at the height of the outbreak, more than 90% were among cisgender men, and the highest number of cases have been reported in persons 31 to 35 years of age.[4,16] Transgender and gender-diverse adults were disproportionately affected, accounting for nearly 2% of cases in the United States despite representing about 0.5% of the population.[19] Among all age and gender groups, Hispanic/Latino and Black persons were disproportionately affected, accounting for more than 60% of cases, despite representing only about one-third of the United States general population.[4,16,19]
Virology, Pathogenesis, and Transmission

Virus Classification and Structure

The monkeypox virus, the causative agent of mpox disease, is a member of the Orthopoxvirus genus in the family Poxviridae.[20,21,22] Orthopoxviruses are characterized by an ovoid brick-shaped morphology as seen on cryo-electron tomography. Monkeypox virus is 360 x 270 x 250 nm in size and contains linear double-stranded DNA of approximately 197 kilobases (kb). This genome encodes more than 200 proteins that are essential for the virus life cycle, virus assembly, and evasion of host immune defenses. Monkeypox infectious virus can exist in two distinct forms: extracellular enveloped virus (EEV, also abbreviated as EV) and intracellular mature virus (IMV, also abbreviated as MV) (Figure 3).[20,21,23]

Life Cycle

Monkeypox virus infects and replicates within host cells as follows (Figure 4):[20,21,23]

1. **Virion Entry:** Monkeypox virus can attach to and enter a host cell in the form of an extracellular enveloped virus (EEV) or a mature virus (MV). The entry and fusion of the MV envelope with the plasma or endocytic membrane involves multiple viral proteins.

2. **Early Transcription and Translation:** Some monkeypox DNA is immediately transcribed and translated to produce early proteins, including growth factors, immune response modulators, and factors needed for DNA replication. This early step occurs in the host cell cytoplasm.

3. **Uncoating:** After cell entry, the uncoating of the viral core occurs, with shedding of the outer membranes and release of the core into the cytoplasm. The uncoating of the core facilitates DNA replication.

4. **DNA Replication:** Most of the monkeypox DNA replicates to form concatemeric DNA (long continuous DNA molecules that contain the same DNA sequence linked in series). This process occurs in a localized cytoplasmic region denoted as the viral factory.

5. **Intermediate Gene Transcription and Translation:** Within the viral factory region, the newly replicated (progeny) monkeypox viral DNA can undergo intermediate transcription and translation, generating intermediate proteins that include transcription factors required for late transcription. In addition, late proteins are generated, with some contributing to the viral structure and others playing a role in early transcription and translation.

6. **Late Gene Transcription and Translation:** Also, within the viral factory region, the progeny monkeypox viral DNA can undergo late transcription and translation, which produces late proteins, including some that contribute to the viral assembly process.

7. **Assembly:** The monkeypox DNA is resolved into a single genome and packaged into the core along with proteins necessary for early transcription.

8. **Morphogenesis:** The assembled core is moved out of the viral factory region where it obtains an outer membrane and becomes a mature virus (MV). The MV generally remains trapped within the cell, except in the rare event of cell lysis.

9. **Wrapping:** Some portion of the total virus particles produced is further wrapped by trans-Golgi/late endosomal double membranes to form the intracellular enveloped virus (IEV). During this process, the viral p37 protein interacts with the cellular proteins Rab9 GTPase and TIP47, which together stimulate the wrapping of the MV to form the IEV.

10. **Exocytosis:** The IEV migrates to the cell periphery on microtubules and is released by exocytosis to become cell-associated enveloped virus (CEV). The CEV can infect neighboring cells. Approximately 1% of CEV are released into the extracellular space via motile actin tail formation to become extracellular enveloped virus (EEV). EEV are responsible for long-range dissemination of the virus.

Transmission

Most mpox infections in the 2022-2023 outbreak have occurred through close contact, including close contact
that may occur during sex.[16] Transmission has also occurred among household members and through needlestick exposures.[24,25,26,27,28,29] Person-to-person transmission of monkeypox virus occurs primarily through direct contact with an active lesion or sore (skin), contact with mucosal surfaces (e.g., throat, anus, or rectum), or through body fluids.[3,10,28] Although cases have been reported after sexual contact with a partner who had not yet developed signs or symptoms of infection (i.e., presymptomatic), there are no reported cases of transmission from a person who never developed mpox symptoms.[30] Replication-competent monkeypox virus has been detected in human samples of skin, saliva/oropharyngeal isolates, anorectum, semen, urine/urethra, and conjunctival/ocular fluid. In addition, PCR-detectable monkeypox virus DNA has been found in samples of blood/plasma/serum, respiratory tract isolates, feces, and vaginal isolates.[10] Monkeypox virus has been detected in the upper respiratory tract and environmental samples, demonstrating that airborne viral transmission is possible, but available data suggest person-to-person respiratory transmission likelihood appears to be low.[31] Though not felt to be a predominant source of transmission, contact with contaminated surfaces or objects, particularly soft, porous items, such as sheets and linens (without appropriate personal protective equipment), can result in infection.[32,33,34,35,36]
Clinical Manifestations

Mpox can cause a range of clinical syndromes in adults, both systemic and local. Characteristic lesions of mpox frequently start at the presumed site of inoculation, resulting in rash, proctitis, urethritis, and/or pharyngitis. In persons who develop symptomatic infection, the incubation period for mpox infection is anywhere from 4 days to up to 3 weeks, with symptoms typically lasting 2 to 4 weeks.[3,28,37,38,39] Mpox disease is self-limited in most patients.

Systemic Symptoms

Systemic symptoms frequently occur early on in illness and include fever, malaise, chills, lymphadenopathy, headache, abdominal pain, and myalgias.[3,4,28,40,41]

Rash

Rash is the most common manifestation of mpox in various series and can occur with or without systemic symptoms. Lesions can appear anywhere on the body. Among cases reported in the 2022 mpox outbreak, lesions most frequently involved the anogenital region but were also commonly found on the mouth, hands, face, feet, or chest.[3,4,41] Sometimes, lesions first form on the tongue and in the mouth, known as enanthem.[42] Lesions typically progress through six stages over 2 to 4 weeks, though lesions may be present at different stages of development at the same time (Figure 5).[42]

Anorectal Symptoms

Many patients in the 2022 outbreak reported rectal symptoms, including rectal pain, rectal bleeding, tenesmus, pus/blood in stool, and proctitis.[3,4,43] These may or may not be associated with visible lesions in the anogenital area.[44] Pain is often the most prominent manifestation of anorectal involvement and can require hospitalization for pain management.

Oropharyngeal Symptoms

Oropharyngeal symptoms reported include pharyngitis, odynophagia, epiglottitis, and oral or tonsillar lesions. Pain and difficulty with swallowing may limit oral intake and thus may be another indication for hospital admission.[28,41]

Ocular Manifestations

Ocular manifestations include conjunctivitis, keratitis, periorbital cellulitis, and blepharitis; these may be as a result of autoinoculation from an infected peripheral lesion.[3,4,28,41] Ocular manifestations can be vision threatening.[Q] Mpox Clinical Manifestations

Other Complications

- **Pain**: Significant pain has been noted to be a complication among the listed presentations above, especially in those with anorectal and penile involvement. Pain management (described below) is a cornerstone of therapy.[3,4,41,45]
- **Secondary Bacterial Infections**: Secondary skin and soft tissue infections, including cellulitis and balanitis, have been reported, though not in most cases.[3,46,47] Given the overlap between mpox lesions and systemic symptoms and symptoms concerning secondary bacterial infection, it can be difficult to differentiate between the two.
- **Concomitant Sexually Transmitted Infections**: In a large global case series, concomitant STIs (gonorrhea, chlamydia, and syphilis) were found in nearly one-third of those who were tested.[3]
• **Severe Complications**: Among those with significant immunocompromise or advanced HIV, severe complications have been noted. These include bowel obstruction secondary to tissue edema, rectal wall perforation in severe proctitis, urethritis, paraphimosis, necrotizing lymphadenopathy, myopericarditis, and others.[48,49,50,51,52]

• **Severe Necrotizing Mpox in Advanced HIV**: In people with advanced HIV (CD4 counts less than 200 cells/mm$^3$), a severe necrotizing form of mpox has been characterized by significant fulminant manifestations, including necrotizing skin lesions, visceral involvement (including lung and gastrointestinal tract), secondary infections, sepsis, and a high mortality rate (25% among those hospitalized in a global case series).[22,53,54]
Laboratory Diagnosis

Primary confirmation of an mpox diagnosis is done by PCR analysis on samples taken from active lesions and/or infected areas of the body. Serologic tests are not useful for diagnosing active infection and are mostly used for research purposes. Prior to collecting the sample, it is important to check with the local laboratory that will be processing the sample to confirm the specific requirements for swabs and transport media, as this may vary. Appropriate PPE, as described below in infection prevention and control, should be worn. Collection methods for samples are outlined as follows (Figure 6).

- Swabs of intact skin lesions, as well as samples of lesion crusts, are best. Intact lesions should not be unroofed prior to swabbing. Samples should ideally be collected from two different lesions in different body parts that are in different stages.
- Swabs made of synthetic materials like nylon or Dacron, may be sent either dry or in viral transport media. Two swabs should be sent for each lesion.
- The swabs should be pressed firmly against the lesion and vigorously rubbed back and forth on the lesion 3 times; rotate the swab 180° so that the other side of the swab is in contact with the skin and repeat rubbing back and forth on the same lesion 3 more times.
- Place the swab in an appropriate container with appropriate transport media.
- If a patient has no skin lesions but mpox is still suspected, virus may be detected in other areas like the throat, rectum, or urine, although testing at these sites is not FDA-approved and may not be available from commercial labs.\[55\] Testing these additional sites along with skin lesions does not increase the chances of making a diagnosis when visible lesions are present.\[56,57\][Q]
Treatment

Most patients with mpox recover completely, regardless of whether they receive treatment. Although the FDA has not approved any specific therapies for mpox, supportive care measures are commonly used to manage pain. Some medications originally developed for treating smallpox have been repurposed as medical countermeasures and are used for mpox. These medications may be helpful for patients who are at higher risk of developing severe disease, such as those with compromised immune systems, severe symptoms, or lesions in critical areas. It is important to note that none of these medications have been definitively proven to have a clinical benefit.

Supportive Measures

Supportive care recommendations are primarily based on expert consensus and are targeted to symptoms. For proctitis, using stool softeners can help alleviate pain during bowel movements, and additional comfort can be provided using topical treatments like sitz baths and lidocaine gels. It is important to exercise caution when using topical steroids as they can suppress the local immune response. Over-the-counter pain relievers such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen are often sufficient for managing pain, although some patients with severe pain may require prescription pain relief with gabapentin or opioids. For individuals with pharyngeal disease, viscous lidocaine and saltwater gargles are commonly trialed.[58]

Medications Used for the Treatment of Mpox

Tecovirimat

Tecovirimat, an antiviral medicine initially developed to treat variola virus, targets and inhibits the activity of p37, a viral envelope-wrapping protein found in monkeypox virus (and other orthopoxviruses), and this inhibition prevents the formation of the enveloped virions (Figure 7).[59,60,61] In 2018, the Food and Drug Administration (FDA) approved tecovirimat under the Animal Efficacy Rule, which allows the approval of drugs when conducting efficacy trials in humans is not feasible or ethical. Prior to the recent outbreak, only safety studies involving humans had been conducted for tecovirimat.[62] For those requiring treatment, tecovirimat has been the first-line treatment through the CDC’s expanded access investigational new drug (EA-IND) protocol.[63] More than 6,800 courses have been distributed in the United States and while safety data from cohort studies is encouraging, efficacy data is mixed, and there is currently no randomized controlled human efficacy data.[64,65,66] In a retrospective, cross-sectional interview based study from King County, Washington, investigators reported that early treatment (within 5 days of symptom onset) with tecovirimat when compared with later treatment, resulted in more rapid symptom improvement among persons with severe illness, but not among those with less severe illness.[67] In addition, early tecovirimat did not impact illness resolution.[67] Epidemiological surveillance in Los Angeles, California, identified six cases that did not improve on tecovirimat therapy and found a wide range of tecovirimat resistance levels in patients with HIV who had a CD4 count less than 200 cells/mm$^3$, suggesting selection for resistance.[68] The CDC has identified 50 isolates from 26 patients with a resistant phenotype, all of whom were exposed to tecovirimat. Transmitted phenotypic resistance has also been reported in individuals not exposed to tecovirimat.[69] The possibility of resistance to tecovirimat should be considered in patients who fail to respond to therapy or who develop recurrent disease.

Cidofovir and Brincidofovir

Cidofovir and its lipid prodrug, brincidofovir, are antiviral medications that work by inhibiting the activity of DNA polymerase (Figure 8).

- Cidofovir has been approved by the FDA for intravenous treatment of cytomegalovirus retinitis. Although animal studies have shown potential effectiveness against orthopoxviruses), there is currently no human data confirming its efficacy for treating mpox. Due to the significant risk of
nephrotoxicity associated with cidofovir, intravenous cidofovir for the treatment of mpox has primarily been reserved for individuals with severe disease and significant immunosuppression. Case studies have suggested improvement after cidofovir administration.[70,71] For the treatment of mpox, cidofovir has also been administered as a topical cream applied directly to lesions and as a solution directly injected into a lesion.[72][Q Cidofovir Toxicity

- Brincidofovir, available through an FDA EA-IND, is believed to cause less renal toxicity but may cause diarrhea and hepatotoxicity. Animal studies suggest that the combination of tecovirimat and brincidofovir may act synergistically, and this pairing should be considered for patients with severe immunosuppression or progressive disease.[73]

**Vaccinia Immunoglobulin (VIGIV)**

Vaccinia Immunoglobulin (VIGIV) is a treatment that involves transferring antibodies against the vaccinia virus, which is believed to provide some level of protection against mpox. This treatment may be beneficial for immunocompromised individuals, who are unlikely to mount an antibody response, especially those with advanced HIV. Some case reports have shown improvement in patients with severe mpox who received VIGIV, suggesting that it should be considered for evaluation in individuals with advanced HIV and severe mpox.[74]

**Trifluridine Eye Drops**

Trifluridine eye drops are approved by the FDA for treating eye infections caused by the herpes simplex virus and are also thought to have activity against orthopoxviruses.[75,76,77,78] Therefore, they should be considered as a treatment option for patients with ocular disease from mpox.

**Recommended Treatment of Mpox**

Given the limited data available, tecovirimat, through a clinical trial, should be offered to patients, with the EA-IND available to those with severe disease or at risk of severe disease who are unable to enroll in a trial.[63,79,80] Tecovirimat should be considered for use in the following situations:[48,80,81]

- Patients with severe mpox disease, including hemorrhagic disease, large number of lesions, ocular or periorbital infection, sepsis, encephalitis, or other manifestation that requires hospital admission.
- Patients with mpox involvement of an anatomic area in which serious adverse sequelae may result, including scarring or strictures.
- People who are at high risk of developing severe mpox-related disease, including immunocompromised individuals, children (especially those younger than 8 years of age), pregnant or breastfeeding people, and people who have a medical condition that affects skin integrity.

**Oral Therapy**

Tecovirimat is the preferred medication to treat mpox and should be given orally if possible. Oral tecovirimat is available in a 200 mg capsule formulation and in a liquid formulation.[48,80,81] The absorption of tecovirimat is contingent on coadministration with a moderate or high-fat meal.[81] Adverse events are primarily limited to headache, nausea, and vomiting.[81] The dosing of tecovirimat is weight-based.[80] The standard treatment duration is 14 days, though, in certain cases of severe disease and immunocompromised individuals, the course may be extended in discussion with an expert.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Weight (lbs)</th>
<th>Oral Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Recommendations listed in this table are based on Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®)</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Page 9/45
Weight (kg) | Weight (lbs) | Oral Dosing
---|---|---
25 kg to <40 kg | 55 lbs to <88 lbs | 400 mg (2 capsules) every 12 hours
40 kg to <120 kg | 88 lbs to <264 lbs | 600 mg (3 capsules) every 12 hours
≥120 kg | ≥264 lbs | 600 mg (3 capsules) every 8 hours

Additional Instructions for all oral dosing:

1. Tecovirimat capsules should be taken within 30 minutes after a full meal containing moderate or high fat.
2. Carefully open the required number of capsules and mix contents of capsule(s) with 30 mL of liquid (e.g., milk, chocolate milk, water) or soft food (e.g., apple sauce, yogurt). Administer the entire mixture within 30 minutes of preparation.

Source:


**Intravenous Therapy**

Tecovirimat is also available as an intravenous formulation for those unable to tolerate the oral formulation or the fatty meal required for absorption. It is contraindicated in persons with severe renal dysfunction (creatinine clearance less than 30 mL/min) and should be used with caution even in those with mild-moderate impairment, due to the risk of accumulation of hydroxypropyl-β-cyclodextrin, an added ingredient in the intravenous preparation.[48,80,81] Adverse events are generally injection site-related, including pain, swelling, erythema, and extravasation.[81] Similar to oral dosing of tecovirimat, dosing of intravenous tecovirimat is weight-based. Once able to tolerate oral intake, those receiving IV tecovirimat should transition to the oral formulation to complete the standard 14-day course. Table 2.
### Tecovirimat Recommended Intravenous Dosing for the Treatment of Mpox in Adults*

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Weight (lbs)</th>
<th>Recommended Dose</th>
<th>Volume of IV Tecovirimat</th>
<th>Volume of Diluent</th>
<th>Total Volume for Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35 kg</td>
<td>&lt;77 lbs</td>
<td>6 mg/kg every 12 hours by IV infusion over 6 hours</td>
<td>0.6 mg/mL/kg</td>
<td>1.2 mL/kg</td>
<td>Varies by weight</td>
</tr>
<tr>
<td>35 kg to &lt;120 kg</td>
<td>77 lbs to &lt;264 lbs</td>
<td>200 mg every 12 hours by IV infusion over 6 hours</td>
<td>20 mL</td>
<td>40 mL</td>
<td>60 mL</td>
</tr>
<tr>
<td>≥120 kg</td>
<td>≥264 lbs</td>
<td>300 mg every 12 hours by IV infusion over 6 hours</td>
<td>30 mL</td>
<td>60 mL</td>
<td>90 mL</td>
</tr>
</tbody>
</table>

When clinical improvement has occurred, patients should be switched to tecovirimat oral capsules to complete the standard 14-day treatment course as soon as oral therapy can be tolerated.

*Recommendations listed in this table are based on Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Non-Variola Orthopoxvirus Infections in Adults and Children. IND No. 116,039 CDC IRB No. 6402 Version 6.3 Updated on December 19, 2023*

Source:

[Q] Tecovirimat
**Infection Prevention and Control in Health Care Settings**

The following summarized key recommendations regarding infection prevention and control in health care settings.

- **Rooming**: Patients with suspected or confirmed mpox should be placed in a single-person room; special air handling (a negative pressure isolation room) is not necessary, except during intubation, extubation, and procedures that may spread oral secretions (e.g., induced sputum collection). Ideally, there should be a dedicated bathroom for mpox patient use. When a patient leaves the room, all exposed lesions should be covered, and the patient should wear a well-fitting medical mask.\(^{[82]}\)

- **Personal Protective Equipment (PPE)**: Prior to entering a patient's room with either suspected or confirmed mpox, health care providers should perform hygiene and then don PPE as follows: a fit-tested, NIOSH-approved respiratory mask (equipped with an N95 filter or higher), eye protection (with coverage of front and sides of face), gloves, and a gown (Figure 9).\(^{[82]}\)

- **Cleaning**: Perform standard cleaning and disinfection with an EPA-registered disinfectant from List Q: Disinfectants for Emerging Viral Pathogens. Soiled bedding, towels, and clothing should be handled while in PPE and subsequently contained; shaking or handling should be avoided so as not to aerosolize infectious particles. Avoid dry dusting, sweeping, vacuuming, or other cleaning methods. Soiled material may be disposed of in the same way as any other infectious medical waste. After cleaning the room, new patients may be placed in the same room. This guidance applies to the monkeypox virus clade associated with the 2022 mpox outbreak.\(^{[82]}\)

- **Health Care Exposures**: Asymptomatic health care personnel not wearing full PPE who have an exposure to a patient with mpox and should self-monitor symptoms for 21 days but can continue to work if they remain asymptomatic. Health care workers with higher risk exposures (i.e. unprotected contact with broken skin, mucous membranes, mpox skin lesions, or soiled material) may be recommended to receive postexposure prophylaxis JYNNEOS vaccination.\(^{[82]}\)\(^{[Q]}\)
Prevention of Mpox Infection

Reducing Exposure

A key component of mpox infection prevention is avoidance of close contact, including intimate and sexual exposure, with people with mpox, as well as any objects and materials that a person with active mpox infection has used. In the context of the 2022 outbreak, men who have sex with men (MSM) adopted strategies for mpox prevention, including increased condom use, decreased number of sex partners, reduced number of one-time sex encounters, and decreased frequency of sex with partners met on dating apps, sex venues, or group sex.[83] Reducing exposure is an important bridge to primary prevention strategies like vaccination.

Mpox Vaccines Before Exposure to Mpox

Currently, there are two vaccines available for prevention of mpox infection: modified vaccinia Ankara (JYNNEOS) and ACAM2000. The JYNNEOS vaccine is an attenuated, non-replicating vaccinia virus vaccine that is FDA-approved for the prevention of mpox (and smallpox) disease in persons 18 years of age and older who are at high risk for monkeypox virus infection.[84,85] Since August 2022, the FDA also authorized use of the standard dosing administration (subcutaneous route) of JYNNEOS for persons younger than 18 years of age under an Emergency Use Authorization.[86] The JYNNEOS vaccine is the preferred mpox vaccine in the United States and is recommended by the Advisory Committee for Immunization Practices (ACIP) for all people 18 years of age and older who are at risk for mpox infection.[87,88] The replication-competent smallpox vaccine (ACAM2000) is FDA-approved for the prevention of smallpox infection, and it has been made available in the United States for prevention of mpox under an Expanded Access Investigational New Drug Application (EA-IND).[86] The ACAM200 is not the recommended mpox vaccine in the United States, primarily because this vaccine contains replication-competent virus, which, in the first three weeks after vaccination, could risk autoinoculation of the vaccinia virus from the inoculation site to other body sites, as well as potential transmission to others.[89] In addition, ACAM2000 should not be used in persons with immune deficiencies, persons with HIV, during pregnancy, persons with active eczema (risk of eczema vaccinatum), and in persons with multiple major cardiac risk factors (risk of myocarditis and/or pericarditis).[90,91,92]

Mpox Vaccine Indications

The following summarizes the 2024 ACIP recommendations for mpox vaccine.[87,88] The JYNNEOS vaccine is recommended for any person 18 years of age and older who is at risk for mpox infection.[86,87,88] Risk factors for mpox infection include:

- Persons who are gay, bisexual, and other MSM, transgender, or nonbinary people who in the past 6 months have had:
  - A new diagnosis of at least 1 sexually transmitted disease
  - More than 1 sex partner
  - Sex at a commercial sex venue
  - Sex in association with a large public event in a geographic area where mpox transmission is occurring
- Persons who are sex partners of the persons described above.
- Persons who anticipate experiencing any of the situations described above

Mpox JYNNEOS Vaccine Dosing and Schedule

Vaccine Administration and Schedule

The FDA-approved immunization with JYNNEOS against mpox requires two vaccine doses given 28 days (4 weeks apart), using a standard subcutaneous administration (0.5 mL per dose). The alternative administration
is an intradermal dose of 0.1 mL per dose (approved under an Emergency Use Authorization) for persons 18 years of age and older (Figure 10). If vaccine shortages exist, intradermal administration may be preferred over subcutaneous vaccination, since only one-fifth the amount of the vaccine is required, and available data indicate equivalent immune responses to intradermal and subcutaneous dosing.[93,94] With intradermal dosing, however, adverse cutaneous reactions occur more often and are more likely to be severe. If a patient has received one subcutaneous vaccination dose, the second dose can be administered as either a subcutaneous or intradermal injection, and vice versa. Patients with a history of developing keloid scars should be offered subcutaneous over intradermal administration to minimize the risk of scarring.[Q] JYNNEOS Vaccine

Acceptable Intervals Between Doses

The recommended time between vaccine doses is 28 days (Figure 11). The second dose may be given up to 4 days early and up to 7 days late. There are, however, no recommendations to restart the vaccine series if the second dose is given earlier than day 24 or later than day 35.[86]

Contraindications and Precautions

The JYNNEOS vaccine is produced using chicken embryo fibroblast cells to grow the monkeypox virus; the final vaccine product also contains small amounts of gentamicin and ciprofloxacin. JYNNEOS vaccine is contraindicated in persons who have experienced a severe allergic reaction after a previous dose of JYNNEOS.[87] In addition, precaution is advised for persons with a history of severe allergic reaction (e.g., anaphylaxis) to any of the components in the vaccine, including chicken protein, egg protein, gentamicin, or ciprofloxacin.[86][Q] JYNNEOS Allergic Reaction

Mpxo Vaccine Special Considerations

- **Persons Who Previously Received Smallpox Vaccination**: Vaccination is recommended against mpxo in eligible groups regardless of prior smallpox vaccination status, given the possibility of waning immunity.
- **Persons with HIV**: In persons with HIV, the MVA vaccine is both safe and effective. In studies, patients with HIV and CD4 counts greater than 350 cells/mm³ had similar antibody responses to those without HIV; total antibody titers were lower in people with more advanced disease (CD4 between 200 and 350 cells/mm³) though still present.[95,96]
- **Vaccine Co-administration Considerations**: Vaccine may be administered at the same time as any other vaccines, though ideally in different limbs. Providers and patients may consider waiting 4 weeks after vaccination against COVID-19 vaccines because of the rare side effects of myocarditis or pericarditis associated with both those vaccines and ACAM2000, a live smallpox vaccine.[91,97] Recent data suggests the risk of myocarditis associated with JYNNEOS is extremely low.[98]
- **Persons with Prior Mpxo**: For persons who develop mpxo disease, there is no recommendation to subsequently receive any mpxo vaccination doses.
- **Vaccination as Mpxo Postexposure Prophylaxis (PEP)**: MVA vaccine is indicated for persons who have recently had close contact with someone with mpxo. Those receiving mpxo PEP should ideally receive vaccination within 4 days of a known exposure to mpxo. If more than 4 days have elapsed since the exposure, PEP vacation can be considered if the exposure was within 14 days, but vaccination after day 4 is less likely to be effective than if given within 4 days of the exposure.[99,100][Q] JYNNEOS Postexposure Prophylaxis

Impact of Mpxo Vaccination on Disease

The rationale for vaccination in prevention of mpxo disease has been supported by data from the 2022 outbreak. A comparison of mpxo incidence from July to September 2022 demonstrated mpxo incidence 14 times higher in a group of vaccine-eligible but unvaccinated men as compared to those who had received at
least one dose of JYNNEOS; later data extending to 43 United States jurisdictions demonstrated increased risk reduction among those who had received both JYNNEOS doses versus one.[101,102] Later case-control studies also demonstrated increased vaccine effectiveness with two doses versus one dose, but there were no statistically significant differences in efficacy based on route of administration or immune status.[101,102] Peak immunity is expected around 2 weeks after the second dose of the vaccine. The duration of protection is currently unknown. There is increasing evidence that mpox infection can occur in those previously vaccinated, with early data suggesting that infection after prior infection or vaccination may be less severe.[103,104,105]
Counseling and Education

Counseling for Patients Awaiting Test Results

The following counseling recommendations are for those individuals who have been evaluated for mpox and are awaiting test results.

- Patients with possible mpox should stay isolated if possible. This means staying at home and separated from others without attending work, school, or other public settings.
- Patients should be counseled to avoid public or other group transportation, if possible. If use of public transportation is unavoidable, they should wear a mask, ensure all lesions are covered, and avoid any physical contact with others.
- Persons awaiting test results who need further medical care should inform their medical provider that they have been tested for mpox. If there is an unavoidable need to seek medical care (for example, for further medical testing or treatment), the patient should ensure the rash is fully covered and wear a mask during the entire medical visit.
- If possible, consider isolation from pets such as dogs, as human-to-dog transmission has been documented.[106, 107]

Counseling for Patients With Positive Mpox Test Results

The following counseling recommendations are for those individuals who have been evaluated for mpox and have positive test results:

- Persons with mpox should follow isolation instructions as described above for patients awaiting test results.
- If someone with mpox cannot fully separate from others in the household, they should wear a face mask, avoid physical contact, and cover any lesions when in shared spaces. They should try to use a separate bathroom if available. Utensils, clothing, towels, bedding, and other similar items should not be shared.
- Patients should wash their hands often with soap and water, or use an alcohol-based hand sanitizer. Any item that has been touched should be cleaned; clothing items should ideally be machine washed.
- Patients should stay isolated until any rash is fully resolved, all scabs have fallen off, and new skin is forming underneath. This usually takes 2-4 weeks. If they did not have a rash, they should be counseled to stay isolated until all symptoms (e.g., rectal pain, urethral pain) have fully resolved.
- There is limited data to inform counseling on the time period after infection in which resuming sexual activity is safe. The World Health Organization has recommended condom use for up to 12 weeks after infection; CDC has no formal recommendation. Available data suggest detection of mpox virus is of shorter duration in semen than in perianal skin.[108, 109]
Summary Points

- In 2022, an mpox outbreak occurred in non-endemic countries including across Europe and the United States at much higher rates than seen prior. This outbreak was associated with close contact, including sexual contact.
- Person to person transmission of mpox occurs primarily through direct contact with an active lesion or sore, or contact with mucosal surfaces or bodily fluids.
- Mpox can cause a wide array of symptoms, including systemic symptoms, a characteristic rash, as well as anorectal, oropharyngeal, and ocular manifestations. Serious complications including severe pain, stricturing, and others may occur, especially in those with significant immunocompromise, including advanced HIV disease.
- The diagnosis of mpox is confirmed by PCR testing of samples taken from active lesions or infected areas.
- Primary treatment cornerstones are supportive care; several antiviral options exist with emerging data, including tecovirimat, cidofovir, brincidofovir, and others. Tecovirimat is the preferred option.
- There are two available vaccines in the United States for prevention of mpox disease, ACAM2000 and JYNNEOS; of the two, the JYNNEOS vaccine is the preferred option and demonstrates high efficacy.
- To prevent the spread of mpox to others, patients with active mpox should stay isolated and keep lesions covered until full resolution of the lesions has occurred.
Citations


48. Centers for Disease Control and Prevention (CDC). Mpox. Clinical Considerations for Treatment and Prophylaxis of Mpox Infection in People Who are Immunocompromised. Updated September 1, 2023 [CDC] -


63. Centers for Disease Control and Prevention (CDC). Mpox. Tecovirimat (TPOXX) IND Information. Updated July 6, 2023


78. Perzia B, Theotoka D, Li K, et al. Treatment of ocular-involving monkeypox virus with topical
[PubMed Abstract] -

79. Centers for Disease Control and Prevention (CDC). Mpox. Demographics of Patients Receiving Tecovirimat (TPOXX) for Treatment of Mpox. August 7, 2023
[CDC] -

[CDC] -

[CDC] -

[CDC] -

[PubMed Abstract] -

[PubMed Abstract] -

85. US. Food and Drug Administration. JYNNEOS. FDA. Published online October 2, 2023.
[FDA] -

86. Centers for Disease Control and Prevention (CDC). Mpox. JYNNEOS Vaccine. Updated September 1, 2023
[CDC] -

87. Advisory Committee on Immunization Practices (ACIP). Adult Immunization Schedule by Age. Recommendation for Ages 19 Years or Older, United States, 2024.
[ACIP] -

[ACIP] -

[PubMed Abstract] -


99. Fact Sheet for Healthcare Providers Administering Vaccine: Emergency Use Authorization of Jynneos (Smallpox and Monkeypox Vaccine, Live, Non-Replicating) for Prevention of Monkeypox Disease in Individuals Determined to be at High Risk for Monkeypox Infection [FDA] -


[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[CDC] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

References

[PubMed Abstract] -

[PubMed Abstract] -

[CDC] -

[PubMed Abstract] -


- US. Food and Drug Administration. ACAM2000. FDA. Published online September 27, 2022. Accessed June 13, 2023 [FDA] -


Figures

Figure 1 Monkeypox Virus

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Figure 2: Mpox Epidemiology in United States, 2022-2024


This is a dynamic visualization. Please visit our website to experience this dynamic content.

The greatest number of mpox cases have occurred among persons who were 31 to 35 years of age.
Figure 3 Monkeypox Virus Structure: Envelope and Mature Virus

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Figure 4 Monkeypox Virus Life Cycle

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Figure 5 Mpox Cutaneous Lesions: Description and Progression

Illustration: Cognition Studio, Inc. and David H. Spach, MD

Lesions typically begin as flat discolorations
Lesions typically become slightly raised and feel firm
Raised lesions fill with clear fluid
Lesions become filled with opaque, yellowish fluid. They are sharply raised, firm-feeling, and round, and often umbilicated
Lesions become crusty scabs and become itchy
After scabs fall off and fresh skin is formed underneath, the person is no longer considered contagious

1-2 days 1-2 days 1-2 days 5-7 days 7-14 days 7-14 days

Total time: 2-4 weeks
Figure 6 (Image Series) - Obtaining Clinical Samples for Mpox Diagnosis (Image Series) - Figure 6 (Image Series) - Obtaining Clinical Samples for Mpox Diagnosis
Image 6A: Swab for Skin Lesion Sample

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Figure 6 (Image Series) - Obtaining Clinical Samples for Mpox Diagnosis
Image 6B: Technique for Collection of Skin Sample

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Figure 6 (Image Series) - Obtaining Clinical Samples for Mpox Diagnosis
Image 6C: Repeat Collection of Skin Sample with Same Swab

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Figure 6 (Image Series) - Obtaining Clinical Samples for Mpox Diagnosis
Image 6D: Placing Swab in Appropriate Container

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Figure 7 Tecovirimat Mechanism of Action Against Monkeypox Virus

Illustration: Cognition Studio, Inc., David H. Spach, MD, and Raaka G. Kumbakar, MD
Figure 8 Brincidofovir Mechanism of Action Against Monkeypox Virus

Illustration: Cognition Studio, Inc., and David H. Spach, MD
Figure 9 Recommended Personal Protective Equipment (PPE) When Encountering a Patient with Confirmed or Suspected Mpox

Illustration: Cognition Studio, Inc. and David H. Spach, MD
**Figure 10 Mpx Vaccine**

This vaccine can be administered as either a 0.5 mL/dose subcutaneous injection or a 0.1 mL/dose intradermal injection. The intradermal dosing is an option only for persons 18 years of age and older.

Illustration: Cognition Studio, Inc. and David H. Spach, MD
**Figure 11 Recommended Mpox Vaccine Schedule**

Illustration: Peter Harrison, MPH and David H. Spach, MD

![Recommended Mpox Vaccine Schedule](image_url)
# Table 1.

**Tecovirimat Recommended Oral Dosing for the Treatment of Mpox in Adults***

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Weight (lbs)</th>
<th>Oral Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 kg to &lt;40 kg</td>
<td>55 lbs to &lt;88 lbs</td>
<td>400 mg (2 capsules) every 12 hours</td>
</tr>
<tr>
<td>40 kg to &lt;120 kg</td>
<td>88 lbs to &lt;264 lbs</td>
<td>600 mg (3 capsules) every 12 hours</td>
</tr>
<tr>
<td>≥120 kg</td>
<td>≥264 lbs</td>
<td>600 mg (3 capsules) every 8 hours</td>
</tr>
</tbody>
</table>

Additional Instructions for all oral dosing:

1. Tecovirimat capsules should be taken within 30 minutes after a full meal containing moderate or high fat.
2. Carefully open the required number of capsules and mix contents of capsule(s) with 30 mL of liquid (e.g., milk, chocolate milk, water) or soft food (e.g., apple sauce, yogurt). Administer the entire mixture within 30 minutes of preparation.

Source:

Table 2.

**Tecovirimat Recommended Intravenous Dosing for the Treatment of Mpox in Adults***

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Weight (lbs)</th>
<th>Recommended Dose</th>
<th>Volume of IV Tecovirimat</th>
<th>Volume of Diluent</th>
<th>Total Volume for Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35 kg</td>
<td>&lt;77 lbs</td>
<td>6 mg/kg every 12 hours by IV infusion over 6 hours</td>
<td>0.6 mg/mL/kg</td>
<td>1.2 mL/kg</td>
<td>Varies by weight</td>
</tr>
<tr>
<td>35 kg to &lt;120 kg</td>
<td>77 lbs to &lt;264 lbs</td>
<td>200 mg every 12 hours by IV infusion over 6 hours</td>
<td>20 mL</td>
<td>40 mL</td>
<td>60 mL</td>
</tr>
<tr>
<td>≥120 kg</td>
<td>≥264 lbs</td>
<td>300 mg every 12 hours by IV infusion over 6 hours</td>
<td>30 mL</td>
<td>60 mL</td>
<td>90 mL</td>
</tr>
</tbody>
</table>

*Recommendations listed in this table are based on Expanded Access IND Protocol: Use of Tecovirimat (TPOXX®) for Treatment of Human Non-Variola Orthopoxvirus Infections in Adults and Children. IND No. 116,039 CDC IRB No. 6402 Version 6.3 Updated on December 19, 2023

When clinical improvement has occurred, patients should be switched to tecovirimat oral capsules to complete the standard 14-day treatment course as soon as oral therapy can be tolerated.

Source:
