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# Monkeypox – A Review

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## Abstract

The recent past emergence of pandemics has made the world prepare for all the worst-case scenarios. First COVID-19 pandemic caught us unaware, and since then, diseases like Dengue and Monkeypox are making us take steps to avert the casualties caused by these infections. Monkeypox is a viral disease caused by orthopoxvirus. It spreads from close personal contact with the patient. The disease is severe among children, pregnant, and immunosuppressed patients. Recent outbreak among men who have sex with men (MSM) group has added it to be amongst sexually transmitted infections. It is usually self-limiting, but severe disease-causing deaths have been reported by infection, particularly with central African types. Prevention is possible by vaccination with smallpox vaccines. Treatment is still evolving, with new drugs like tecoviramet showing promising results

**Key words:** Monkeypox; Orthopoxvirus; Sexually transmitted infection; Tecoviramet

## Introduction:

On July 23rd, 2022 World Health Organization (WHO) declared monkeypox disease to be a public health emergency of international concern.[1] Monkeypox is a zoonotic viral infection. It spreads from animals to humans and now human to human as well as environment to human spread has also been reported.[2]

## Etiology and Transmission

Monkeypox virus is an enveloped double-stranded DNA virus belonging to the orthopoxvirus genus of the Poxviridae family. There are two phylogenetically distinct clades. One is thecentral African (Congo Basin) clade,and the other is the west African clade.The central African clade is reported to cause more severe disease than the west African clade.[3] Monkeypox can infect various animal species, but its natural host is unknown. Rope squirrel, Tree squirrel, Sooty mangabey, and Gambian pouched rat are some of the known animal hosts of this virus. Human transmission occurs when a person comes into contact with the virus from an animal, human, or contaminatedmaterial. The virus enters the body throughbroken skin, respiratory tract, andmucous membranes. Spread from animals to humans occurs through animal bite or scratch, direct or indirect contact withthe secretions from body or cutaneous lesions. Human-to-human transmission occurs after direct contact withrespiratory secretions or skin lesions. A prolonged face-to-face exposure or contact with contaminated objects of the infected person.[1,2]

## Epidemiology

In 1959 monkeypox virus was first isolated among monkeys shipped from Singapore to Denmark. Human monkeypox was first reported in 1970 in Congo in a 9-month-old boy.[4] Since then, it has been reported in many African countries. Many cases were diagnosed in several non-endemic countries across the world in May 2022.[5] WHO has reported 16016 laboratory-confirmed cases with 5 deaths from 75 countries worldwide since then.[6] In a recently published multicountry study by Thornhill *et al*. of 528 monkeypox infections of which 527 were men and 1 was a woman, in 5 continents and 16 countries between 27 and 2022 and 24 June 2022. The median age of patients was 38 y (range 18–68 y); 98% of the people with infection were gay or bisexual men, 75% were white, and 41% had HIV infection. Most of the HIV positive patients (95%) were on antiretroviral therapy with undetectable viral load. History of foreign

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travel was present in 28%, and coexistent sexually transmitted infection (STIs) were present in 29%. The major transmission was through sexual activity in 95% of the patients. In this study, monkeypox DNA was detected in 29 of the 32 people in whom seminal fluid was analysed; but whether this was a replication-competent virus was not established. Nine percent of the study patients reported a prior history of smallpox vaccination. No deaths were reported.[7]

In India, 4 cases of monkeypox were reported in 2022. They were all males. The first case was reported on 14 July 2022. Three of them were from Kerala with a history of foreign travel, but one case from Delhi had no history of foreign travel.[8]

## Clinical Features

The disease's incubation periodranges from 5 to 14 days (upto 21 days). The contagious period lasts from the start of symptoms till crusts fall off.[9,10] There are two phases of illness the invasion period and the skin eruption period. The invasion period or prodromal phase lasts from 0 to 5 days. It starts with the onset of fever which can be ≥38.5°C. Other symptoms include headache, myalgia, fatigue, sore throat, cough, and gastrointestinal symptoms (nausea, vomiting, and diarrhoea). There is submandibular, axillary, and/or inguinal lymphadenopathy. Lymphadenopathy can be unilateral or bilateral.[2,9]

The skin eruption period usually begins within 1-3 days of the appearance of fever. It has two phases: enanthem and exanthem. Enanthem presents with mucosal lesions in the oral cavity and tongue, which persist for 1-2 days before the generalized skin rash develops. Exanthem starts from the face in most cases and then spreads centrifugally to limbs, palms, and soles. The lesions develop synchronously and not as crops. They are 2-10 mm firm deep-seated lesions. The rash affects the face in 95% of cases and palms and soles in 75% of cases. Oral mucosa is involved in 70% of cases, genitalia in 30%, and conjunctiva and cornea in 20%.[2,9]

The exanthem has different stages. Macules appear at the first stage of the rash, and last for 1-2 days, followed by papules. They also last for 1-2 days. Vesicles appear in the third stage, and last for 1-2 days. Next, pustules with umbilication appear, leading to ulceration. This stage lasts for 5-7 days. Finally, crust formation sheds off after 7-14 days.[11] Meta-analysis conducted by Beniteset al. found that the skin lesions were monomorphic primarily (79%, 95% CI: 68–88%), instead of pleomorphic (38%, 95% CI: 12–68%), with a centrifugal distribution (81%, 95% CI: 59–96%), rather than centripetal (3%, 95% CI: 2–4%). Regarding the number of lesions,50% (95% CI: 36–64%) there were < 100 lesions, and 50% (95% CI: 36–64%) had ≥ 100 lesions. Regarding the lesion distribution, these were located at the head/neck (74%, 95% CI: 49–92%), palms (80%, 95% CI: 53–97%), foot soles (72%, 95% CI: 58–84%), arms/hands (71%, 95% CI: 38–95%), chest/abdomen (69%, 95% CI: 28–97%), legs/feet (61%, 95% CI: 36–83%), pelvic area and groins (45%, 95% CI: 16–76%), oral cavity (39%, 95% CI: 21–59%), mucosae of genitals (34%, 95% CI: 25–44%), and at the entire body (35%, 95% CI: 20–50%).[12]

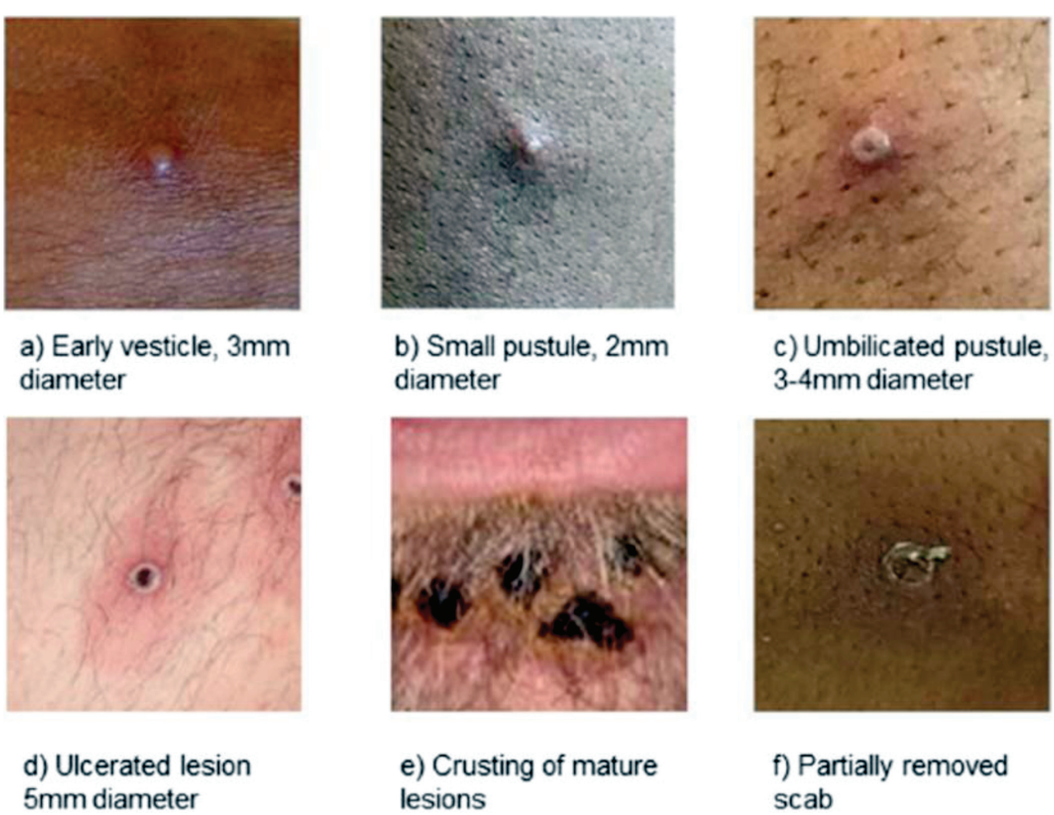


**Figure 1:** Images of individual monkeypox lesions.11Photo credit: UK Health Security Agency

The disease's severity is measured by the number of lesions in the same way as devised for smallpox severity. It is divided into: mild: less than 25 skin lesions, moderate: 25 - 99 skin lesions, severe: 100 - 250 skin lesions, and very severe: more than 250 lesions.[13] Severe disease is most likely to be seen in neonates, infants, and children, and the immunocompromised. The studies showed that in those patients who had very high rash burden, which means that lesions were >250, the interleukin-10, which is an anti-inflammatory marker, was markedly elevated.[14] In compromised skin, secondary infection sites and breaches on the mucosal surfaces can cause superinfections, cellulitis, and possibly sepsis. Scarring can also occur in bacterial superinfection.[15,16]

The lesions heal with post-inflammatory hyper- or hypopigmentation or scarring. Maculopapular lesions are itchy, whereas pustular lesions are painful. Total number of lesions may vary from a few to thousands.[17] The patient becomes non-infectious after shedding crusts. The disease process last from 3-4 weeks after the development of symptoms. Lesions predominate on the face but may develop on the palms, soles, and dorsal hands and feet.[18,19] Genital and peri-genital lesions have been reported in the recent 2022 outbreak. When monkeypox is sexually transmitted, there may not be classical prodromal fever and rash. The rash may begin in the genital or perianal region or localized to the lips and surrounding area. The more classical systemic features and rash distribution follow later.[20,21]

In the outbreak of monkeypox, there was an analysis of national cases conducted by a United Kingdom Security Agency that estimated the mean incubation period of monkeypox disease at 9.22 days.[22] Another European Centre for Disease Prevention and Control-WHO analysis of data from 660 patients showed that 71.4% of the patients had systemic symptoms like fever and headache, 49.0% of the patients had a localized lymphadenopathy. Further, it was also found in the same analysis that 97.7% of the patients developed a rash during the eruptive phase of the disease, 70.5% had mucosal and lesions on the anogenital skin, and 7.0% of the patients showed skin, oral and mucosal lesions. However, in the recent outbreak, skin lesions are also being seen without a prodromal phase in many patients.[23] Patel *et al*. found that 13.7% of patients presented with mucocutaneous manifestations even in the absence of any systemic features.[24]

Antinori*et al*. found that the number of lesions on the skin in monkeypox patients is highly variable. Some patients present with only a few painless lesions. The cutaneous lesions are asynchronous, ranging from single or clustered spots to papules that are umbilicated along with progressive central ulceration and finally there is development of scabs.[25] Different studies showed that the pattern of lesions on the skin is unusual, often in anal, genital, and perianal areas without the typical centrifugal distribution[7,26-28,] andcases of proctitis and pharyngitis have also been described. Thornhill *et al*. found that mucosal lesions were reported in 41% of the patients.[7] Involvement of the anorectal mucosa was reported as the presenting symptom in 12% of cases, with anorectal pain, proctitis, tenesmus, diarrhea, or a combination of these symptoms. Rectal pain or pain on defecation is commonly reported. Oropharyngeal symptoms, including pharyngitis, odynophagia, epiglottitis, and oral or tonsillar lesions, were reported as the initial symptoms in 5% of the cases in that study. Tarin *et al*.[29] conducted a study in Spain in which 43.1% of patients had lesions in the oral and perioral region.

The complications of monkeypox are secondary bacterial infections, and corneal scarring, with loss of vision which can occur in 25% of cases, other complications like pulmonary distress or bronchopneumonia, and rarely encephalitis can occur in severe disease.[11,19] Sklenovska*et al*.[30] conducted a study that showed that the genetic clade 2 monkeypox virus causes mild disease, and there is less than a 1% case fatality ratio. Patients are hospitalized due to secondary bacterial infections such as cellulitis involving genital and perineal region. The other complications requiring hospitalization included severe anal and digestive involvement with rectal pain, penile edema, severe angina, and epiglottitis; and ocular involvement with blepharitis, conjunctivitis, and keratitis.[31]

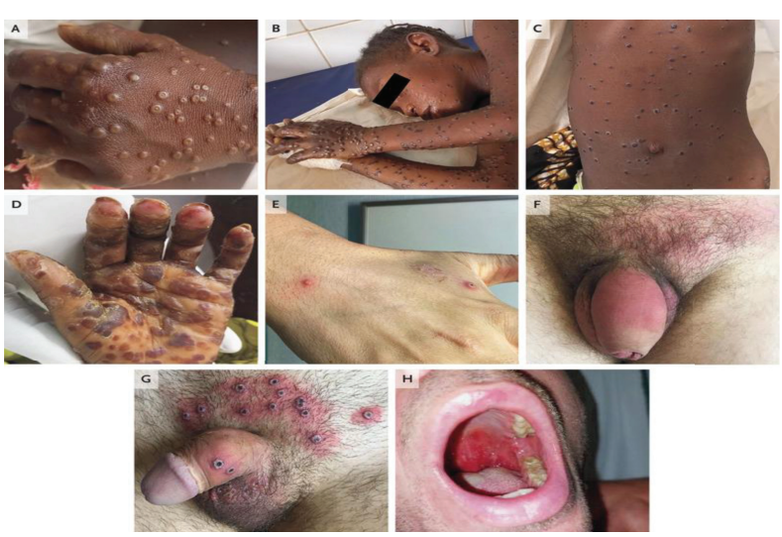


**Figure 2:** Characteristic cutaneous and mucosal manifestations of monkeypox.[31]

Panel A shows numerous skin lesions with umbilicated papules on the left hand of a young girl with confirmed monkeypox infection in the Central African Republic. In Panel B, extensive, disseminated papular lesions are present on a young girl's the hands, arms, and face. Panel C shows disseminated skin lesions at different stages of evolution, including papules and crusts, on the abdomen of a young girl. In Panel D, numerous skin lesions with hyperpigmentation, crusts, and desquamation are evident on a women's left hand with confirmed monkeypox infection. Panel E shows synchronous skin lesions on the right hand of a man who had sex with a man with a confirmed monkeypox infection. A fresh pustular lesion and an umbilicated papule with progressive central ulceration are present. Panel F shows penile edema in a man who had sex with a man who had confirmed monkeypox infection; erythema and swelling extend to the left inguinal region. In Panel G, genital lesions, including scrotal and penile lesions, are present in a man who had sex with a man. Panel H shows pharyngitis in a man who had sex with a man.[31]

## Differential Diagnosis

In dermatological practice, many skin diseases that clinically resemble monkeypox lesions have to be ruled out. Chickenpox and smallpox are the most mimicking ones (Table 1). The lesions of chicken pox are mostly in the superficial stage and rapidly progress to the crust stage within 24 hours, also they are unlikely to produce lymphadenopathy. Smallpox has been eradicated since 1977. Also, smallpox presents all the lesions at the same stage;however not present in all the cases of monkeypox.[32-34]

| Characteristic | Chickenpox | Monkeypox | Smallpox |
|---|---|---|---|
| **Incubation period (days)** | 12–14 | 2–21 | 7–17 |
| **Length of prodromal phase (days)** | 0–2 | 1–5 | 2–4 |
| **Stages of lesion development** | Lesions at different stages of development | Usually at the same stage of development but can also be at different stages | Lesions at the same stage of development |
| **Rash distribution** | Centripetal | Centrifugal | Centrifugal |
| **Frequency of lesions on palms or soles** | Rare | Common | Common |
| **Lesion depth (mm)** | Superficial, 2–3 | | |
| **Superficial to deep, up to 6** | Deep, 4–6 | | |
| **Length of time until crusting of pustules (days)** | Within 24 h | 5–7 | 5–8 |
| **Length of time from rash onset to desquamation (days)** | 6–14 | 14–21 | 14–21 |
| **Lymphadenopathy** | Usually absent | Significant | Usually absent |

**Table 1:** Comparison of the clinical characteristics of chickenpox, monkeypox, and smallpox.32-34

In measles, the patient has coryza, Koplick's spots, and a maculopapular rash without becoming vesicular or pustular, which is a differentiating feature of measles. Herpes simplex infection/eczema herpeticum presents with localized grouped vesicles with associated autoimmune dermatoses. Impetigo is a bacterial infection in which lesions are few in number with honeycomb crusting. In secondary syphilis, there is a painless, nonitchy, coppery red rash. Herpes zoster presents with a painful vesicular eruption in a dermatomal pattern. Scabies is a contagious disease with nocturnal itch and positive family history of similar disease. Burrow is a pathognomic sign of scabies. In drug reactions, there is a temporal relation with the intake of medicine.[35] Other differentials include molluscum contagiosum, disseminated gonococcal infection, lymphogranuloma inguinale, granuloma inguinale, cryptococcosis, pustular psoriasis, subcorneal pustular dermatosis and hand-foot-mouth disease, erythema multiforme, anthrax, cowpox, Rocky Mountain spotted fever, syphilis, staphylococcal scalded skin syndrome, Stevens-Johnson syndrome / Toxic epidermal necrolysis.[35,36]

## Laboratory Investigations

The diagnosis of monkeypox is made through polymerase chain reaction (PCR), the preferred laboratory test given its accuracy and sensitivity. The sample is taken from skin lesions,i.e., the roof or fluid from vesicles, pustules, and dry crusts. WHO has recommended nucleic acid amplification tests (NAATs).[1] Enzyme-linked immunosorbent assay (ELISA) can detect monkeypox-specific IgM and IgG antibodies after 5 to 8 days of infection.[4,9] As orthopoxvirusesare

serologically cross-reactive, antigen and antibody detection methods do not provide monkeypox-specific confirmation. IgG can also be positive after smallpox exposure and vaccination. Therefore, serology and antigen detection methods are not recommended for diagnosis or case investigation. Other laboratory abnormalities include elevated hepatic transaminase (AST, ALT), low blood urea nitrogen (BUN), low albumin, elevated WBC,and low platelet count.[9]

## Treatment

Monkeypox is usually self-limiting but may be severe in some individuals, such as children, pregnant women, and immune-suppressed people due to other health conditions. Case fatality rate (CFR) varies between the two clades. Human infections with the west African clade appear to cause less severe disease compared to the Congo Basin clade in the west African clade CFR is 3.6%,whereas in the Congo Basin clade, the CFR is 10.6%.[1,4]

Currently, no specific treatments are available for monkeypox infection, but monkeypox outbreaks can be controlled.Potential treatments includesmallpox vaccine, cidofovir, brincidofovir, tecoviramit (TPOXX or St-246), and vaccinia immune globulin (VIG).[37-44] Clinical care for monkeypox should be fully optimized to alleviate symptoms, manage complications and prevent long-term sequelae.Patients should be offered fluids and food to maintain good nutritional status.Secondary bacterial infections should be treated as indicated. Antiviral agent known as tecovirimat was developed for smallpox and has now been licensed by the European Medicines Agency (EMA) for monkeypox in 2022 based on animal and human studies data. It has yet to be widely available. TPOXX or ST-246 is an orthopoxvirus P37 envelope-wrapping protein inhibitor. It was the first drug approved by the U.S. Food and drug authority to be used for the treatment of monkeypox.[44] It is given as immediate-release oral capsule to be administered twice daily for fourteen days or intravenous formulation. A retrospective observational study in the United Kingdom was done to study the effect of antivirals on monkeypox. They reported the first use of antiviral agents in patients with monkeypox, with one patient receiving tecovirimat. The patient treated with tecovirimat had blood and upper respiratory tract PCR negative 48 hours after starting the treatment, with no adverse events identified before discharge.[42] Headache, nausea, abdominal pain, and vomiting are some of the reported side effects of tecoviramet. Tecovirimat, approved for monkeypox, can be considered under investigational or compassionate use protocols, particularly for those who have severe symptoms or are immunocompromised.[43]

Cidofovir and brincidofovir (CMX001) are other drugs used to treat monkeypox though data are unavailable on the effectiveness of cidofovir and brincidofovir in treating human cases of monkeypox. However, both have proven activity against poxviruses in *invitro* and animal studies. Due to side effects, patients on brincidofovir and cidofovir could not complete the treatment.[44]

A new drug is being developed known as NIOCH-14 since 2001.[13,43] It is similar to tecoviramet and is reported to be effective in animal studies. VIG are antibodies derived from persons who were given the smallpox vaccine. There is no convincing data available on its effectiveness in the treatment of monkeypox after exposure or in severe disease.[44,45]

## Prevention

Vaccines against smallpox are used to immunize against monkeypox. Previous data from Africa suggests that the smallpox vaccine is at least 85% effective in preventing monkeypox. When administered adequately before exposure, they prove effective at protecting people against monkeypox. ACAM2000 and Jynneos$^{tm}$ (also known as Imvamune or Imvanex) are the two currently licensed vaccines in the United States to prevent smallpox. Jynneos is also explicitly licensed to prevent monkeypox.Vaccination after a monkeypox exposure may help prevent or make the disease less severe. Centers for Disease Control and Prevention(CDC) recommends that the vaccine be given within 4 days from the date of exposure to prevent onset the disease's onset. If given between 4–14 days after the date of exposure, vaccination may reduce the symptoms of disease but may not prevent the disease.[44,45]

ACAM2000 is a live virus preparation. It is inoculated into the skin by pricking the skin surface. Following a successful inoculation, a lesion will develop at the vaccination site. The virus growing at the site of this inoculation lesion can spread to other parts of the body. Individuals who receive vaccination with ACAM2000 must take precautions to prevent the spread of the vaccine virus.[45]

JYNNEOS$^{TM}$ is a live virus vaccine that is non-replicating. It is administered as two subcutaneous injections four weeks apart.There is no risk of spreading to other parts of the body or people.People who receive Jynneos$^{tm}$ are only considered vaccinated once they receive both doses of the vaccine.[45]

Vaccine is recommended for clinical laboratory personnel performing diagnostic tests for orthopoxviruses such as smallpox and monkeypox, laboratory people researching the viruses, and healthcare workers who administer the ACAM2000 vaccine or care for patients infected with orthopoxviruses.

Monkeypox can be prevented by creating awareness of factors that increase the risk of contracting the disease. It is suggested that people should avoid close and skin-to-skin contact with patients of monkeypox. Contact with fomites and objects used by patients should also be avoided. The use of hand sanitizers and washing of hands is also recommended. These measures can reduce exposure to the virus.[1,16] Monkeypox is a notifiable disease and should promptly be reported to centersfor disease control for proper public health measures to be adopted.

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