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Editorial

Monkeypox: An update

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The story of monkeypox began in 1958 when the pathogen was first identified in laboratory macaque monkeys at the State Serum Institutes in Copenhagen in Denmark.[1] The first human infection was reported in 1970 in a 9-month-old baby boy in Zaire (current Democratic Republic of the Congo).[2]

Till 2003, monkeypox remained endemic to a few nations in West and Central Africa.[3] The first case of monkeypox outside Africa was reported in 2003–2004, in the Unites States of America (US). The epidemiological link in all the 47 confirmed or probable cases was traced to pet prairie dogs. The dogs (believed to be infected when they were housed near rodents shipped from Ghana to Texas, before being sold as pets) infected their owners.[3] It is interesting to note that though rodents captured from Ghana were identified as the source of the US outbreak in 2003, the first human case in Ghana was detected and reported much later (during the current outbreak).[4]

A larger outbreak occurred in Nigeria in 2017, and monkeypox cases were reported in a few other countries as well.[5] However, till May 2022, the only countries outside Africa that reported monkeypox were the US, the United Kingdom (UK), Israel, and Singapore and the infections were documented as imported as they appeared in individuals who traveled to known endemic nations.[6-8]

A disease often considered endemic to a few African nations and that did not receive the necessary attention, became a matter of a global health concern when several countries started reporting human monkeypox cases since May 2022, which forced the World Health Organization to declare it as a public health emergency of international concern on July 23, 2022.[9] Contrary to the history of monkeypox, the current outbreak has mostly affected countries in the western hemisphere and concentrated around Europe.[10] As on September 30, 2022, 106 countries have reported a total of 68,428 monkeypox cases, during the current outbreak. Out of the 106 countries, 99 have diagnosed the infection for the 1st time.[11]

The first monkeypox case in Southeast Asia was reported from the Indian State of Kerala on 15th July 2022.[12] The disease was diagnosed in a 35-year-old man who had traveled from the United Arab Emirates.[12,13] At present, the number of monkeypox cases reported from the country stands at 12 with one death (reported from Kerala).[11,14,15]

MONKEYPOX: A MISNOMER

The disease received the name "monkeypox" as the virus was first identified in monkeys.[1] Available evidence suggests that monkeys, like humans, serve only as an incidental host for the virus.[10] The exact reservoir host remains unknown, though it is believed to be one or several species of rodents or squirrels inhabiting the forest regions of Central Africa.[10]

Monkeypox is caused by a zoonotic virus belonging to the *Orthopoxvirus* genus of the family *Poxviridae*.[10] Poxviruses are large, enveloped, double-stranded DNA (deoxyribonucleic acid) viruses. Rodents, rabbits, and non-human primates serve as the major hosts of poxviruses with occasional transmission to humans. Human-to-human transmission is less common.[10] Monkeypox virus, though similar to smallpox virus, is less fatal.[10] Two genetic clades are identified for the virus, namely, the Central African (Congo Basin) clade and the West African clade. The Central African clade is more virulent with the potential to cause more human-to-human transmission and is associated with a greater degree of viremia, morbidity, and mortality.[10,16] The overall case fatality rate of monkeypox is estimated to be 8.7%. The Central African clade has a fatality rate of 10.6%, while the same for West African clade is 3.6%.[16] The Central African clade attains greater virulence by downregulating the host immune response.[10] The 2003 outbreak in the US, the 2017 Nigerian outbreak, and the current ongoing outbreak are attributed to the West African clade.[10,16,17] The Central African clade is mostly associated with cases reported from the Central African Republic, the Democratic Republic of the Congo (the country that has reported the maximum number of monkeypox cases) and South Sudan.[16]

It is believed that the virus might have been present in sub-Saharan Africa for thousands of years, but was recognized only with the eradication of smallpox. The smallpox vaccination might have offered cross-immunity against the monkeypox virus. With the cessation of smallpox vaccination and the waning of immunity among population against smallpox, the closely related monkeypox virus might have found its targets among humans. The possibility of some of the monkeypox cases being misdiagnosed as smallpox in the pre-eradication era cannot be ruled out. Deforestation and encroachment of humans into forest areas might have also contributed to the animal-to-human transmission.[10]

MODES OF TRANSMISSION

The estimated reproductive ratio (R0) or the degree of transmissibility of monkeypox virus is 1.10–2.40 in countries without a history of significant exposure to the virus. This means that each affected individual can transmit the disease to 1–2 others and this, in turn, indicates that imported human or animal cases can precipitate an epidemic.[10]

The disease transmission can be primary (animal-to-human) or secondary (human-to-human).[10] The most common mode of transmission is exposure or direct contact with the saliva, respiratory secretions, and exudates from cutaneous and mucosal lesions of an infected animal.[10] The 2003 outbreak in the US identified "touching a sick animal or its bedding, receiving a bite or scratch that broke the skin, and cleaning the cage of a sick animal" as activities associated with disease transmission.[3] The disease can be acquired through exposure to the feces of infected animals while sleeping outdoor on the ground (in resource poor settings) or while visiting forests inhabited by several infected animals.[10] The disease is reported to occur in the war ravaged areas of Africa where households with scarce resources are forced to hunt and cook small mammals.[10] Human-to-human transmission, though less efficient, is known to occur through droplet inhalation (following prolonged face-to-face contact with an infected person) or through contact with the cutaneous or mucosal lesions of the affected.[10] Secondary attack rate among household contacts (who are unvaccinated against smallpox) is estimated to be about 8% (0–11%), which is much less than the same noted for smallpox (35–88%).[18,19] However, a secondary attack rate of 50% was reported in a disease outbreak among 16 households.[20] "Sleeping on the same bedding, contact with contaminated objects or surfaces and eating or drinking from the same dishes as an infected individual" can lead to household transmission.[10]

During the current epidemic, the disease predominated among males who have sex with males. Thornhill *et al*., after studying human monkeypox infections documented in 16 countries during April–June 2022, reported that in 95% of the affected, the transmission followed sexual activity. Among the affected, 98% were gay or bisexual men, 95% had rash, 64% had less than 10 skin lesions, 73% had anogenital lesions (out of which 54 had single genital lesion), 41% had human immunodeficiency virus (HIV) infection, and 29% of those tested had other sexually transmitted infections.[21] One of the patients (who presented with monkeypox in the period between 2018 and 2021) in the series reported by Adler *et al*., suffered from persistent inguinal lymphadenopathy even after the resolution of the rash. Approximately 6 weeks after discharge, he suffered a relapse that clinically manifested as an increase in the inguinal lymphadenopathy and was associated with pustular and ulcerating skin lesions. The exacerbation followed his first sexual intercourse after the illness. Polymerase chain reaction (PCR) analysis of skin lesions and swab from the upper respiratory tract showed positivity for monkeypox virus; there was no evidence of viremia. The authors suggested the possibility of a genital reservoir for the virus.[22] Along with this, the predilection noted for the infection among males who have sex with males during the current outbreak and the detection of monkeypox virus DNA in the seminal fluid of 29 of the 32 patients tested (as reported by Thornhill *et al*.) suggests the need for further research to assess the link between sexual activity and transmission of monkeypox.[21] However, currently, there is no conclusive evidence to consider monkeypox as a sexually transmitted infection. The close contact during sexual activity might have resulted in the transmission of infection during the latest outbreak.[10] Condom use is recommended for

8 weeks after resolution of disease, though more information is needed in this regard.[21]

A prolonged PCR positivity (22–39 days) in blood and swabs from upper respiratory tract and inguinoscrotal ulcers was noted in some patients diagnosed and treated in the UK before the current outbreak; however, the significance of the same in disease transmission remains unclear.[22]

Vertical transmission and fetal deaths were documented following monkeypox infection in pregnancy.[23]

Although, animal-to-animal transmission, animal-to-human transmission, and human-to-human transmission of monkeypox are well reported in literature, the data on human-to-animal transmission are scarce. Seang *et al*. have recently reported transmission of monkeypox from infected humans to their dog.[24]

CLINICAL FEATURES

Bung *et al*., in a systematic review that assessed the evolution of epidemiology of monkeypox virus from 1970 to September 2020 noted that the median age of the affected was 4, 5, 10, and 21 years in the 1970s, 1980s, 2000s, and 2010s, respectively.[16] This indicates that the disease shows a predilection for the generation that was born after the discontinuation of smallpox vaccination. Routine vaccination against smallpox was withdrawn following the eradication of the latter in 1980.[25] The median age of the affected in the current outbreak (ongoing from 2022 May) is 31 years, which once again underscores that monkeypox shows a predilection for those unprotected by smallpox vaccination.[10]

Existing literature shows that the disease shows a male predilection (>50%), which was more pronounced (>95% affected are men) among the affected in the current outbreak.[11,16]

The disease manifests after a typical incubation period of 7–14 days (the upper limit of 21 days), and this period is non-contagious.[10] A prodromal phase, which is considered as the most infectious stage, follows the incubation period and is characterized by non-specific symptoms such as fever, lymphadenopathy (cervical, inguinal, and maxillary nodes) and malaise, skin, and mucosal lesions, and involvement of eyes, lungs, and gastrointestinal tract.[10] According to the literature before 2022, rash appears 1–3 days after the onset of fever and lymphadenopathy. However, the prodrome before rash was mild or absent in many of the affected in the current outbreak.[10] Fever shows resolution within 1–3 days of appearance of rash. The rash typically starts on face and spreads centrifugally. Mouth and tongue lesions (enanthem) often precede rash and often interfere with food intake. The typical rash of monkeypox is a "disseminated vesiculopustular rash" and passes through macular (1–2 days), papular (1–2 days), vesicular (1–2 days), and pustular (5–7 days) stages before crusting within 2–3 weeks.[10] The affected individual is considered non-contagious once the crusts peel off, leaving underlying new skin (desquamation phase). The rash is painful in all stages, while intense pruritus is experienced when the crusts peel off.[10] Secondary bacterial infection of skin lesions can complicate the disease process.[10]

Thornhill *et al*., in a study of 528 patients from 16 countries during the ongoing outbreak reported anogenital area as the most common anatomical site of rash (73%) with only 25% manifesting face lesions.[21]

According to most of the data before 2022, skin lesions of monkeypox appear similar with respect to the size and the stage of development and show a predilection for face and extremities, though can affect all body sites.[10] Certain atypical features have been documented for the rash among many cases reported during the 2022 outbreak. These include lesions in different stages of development and rash limited to genital, perigenital, and perianal areas.[10,26]

A retrospective observational study from the UK (2018–2021) documented deep tissue abscesses in the left ankle and thigh (PCR analysis of abscess fluid tested positive for monkeypox virus) in one patient and ulcerated inguinoscrotal lesions in two others.[22] During the 2003 outbreak of monkeypox in the US, an affected child was diagnosed with retropharyngeal abscess, though there was lack of adequate laboratory workup for a conclusive diagnosis of monkeypox virus-induced abscess.[11,27]

The clinical features that were commonly reported in the 2003–2004 outbreak in the US were "rash, fever, chills, sweats, cough, sore throat, headache, vomiting, and lymphadenopathy."[28] The clinical manifestations reported to centers for disease control and prevention (CDC) during the current outbreak are rash (95%), fever (72%), pruritus (64%), enlarged lymph nodes (63%), rectal pain (47%), rectal bleeding (29%), tenesmus (24%), proctitis (15%), malaise (69%), chills (67%), headache (64%), myalgia (60%), vomiting or nausea (24%), and conjunctivitis (6%).[3]

Resolution of rash may leave pitted scars or post-inflammatory hypopigmentation or hyperpigmentation.[10] Corneal infection is a dreaded complication of monkeypox as it can lead to corneal scarring and blindness.[10] The other reported complications are secondary infection of skin lesions, cellulitis, vomiting, diarrhea, dehydration, acute kidney injury, bronchopneumonia (usually in those coinfected with influenza virus), respiratory distress, encephalitis, sepsis, septic shock, epiglottitis, and myocarditis.[10,21]

A more severe infection is seen in disease induced by the Central African clade of the virus, young children, immunocompromised persons, and persons living with HIV infection.[29]

HISTOPATHOLOGY OF CUTANEOUS LESIONS

Histologically, the skin lesions appear as "partial-thickness wounds." The central area of lesions shows epidermal necrosis. The changes intensify in the pustular stage and show progressive ulceration, necrosis, interstitial hyperplasia, prominent edema at the margins of necrotic areas, and formation of clefts (by accumulation of fluid and cellular debris) between cells. Late-stage lesions show predominance of inflammation and necrosis of the superficial dermis with destruction of sebaceous glands and follicles.[10]

DIAGNOSIS

CDC has laid down case definitions for confirmed, probable, and suspect cases of monkeypox for the 2022 outbreak [Table 1].[30]

Swabs from the roof and base of a vesicle, crusted lesions, vesicle fluid, oropharyngeal and nasopharyngeal swabs, blood, and urine are collected from the affected for virology analysis. Best yield is expected from lesional specimens (collected from multiple sites) in the rash phase; however, in recovery phase, the blood samples may give more information.[31] However, those vaccinated against smallpox may show positive serology even in the absence of monkeypox infection.[32]

MANAGEMENT

Management mainly revolves around supportive care and includes ensuring adequate hydration, maintaining electrolyte balance and preventing and treating secondary bacterial infections (with topical and/or systemic antibiotics). Dedicated ophthalmology care should be provided whenever necessary. Moist occlusive dressings may benefit patients with extensive facial rash.[10] As and when indicated, respiratory support and hemodynamic support should be provided.[26]

Most of the patients recover with supportive care. CDC recommends antivirals (tecovirimat, brincidofovir, and cidofovir) for special situations – "Patients with severe disease (conditions such as hemorrhagic disease or other conditions requiring hospitalization, large number of lesions that are confluent, sepsis, encephalitis, ocular, or periorbital infections), lesions on anatomic areas which can produce sequelae such as scarring and strictures, painful anal lesions that interfere with bowel movement, and severe secondary infections requiring surgical debridement" are candidates for antiviral treatment. Antiviral treatment should be considered for "patients with severe immunocompromised status, children (especially those below 8 years of age), pregnant and lactating women, and patients with conditions that compromise the integrity of skin (atopic dermatitis, psoriasis, and infections due to herpes simplex virus and varicella zoster virus)."[33]

A cross-sectional analysis of monkeypox cases treated in the UK from 2018 to 2021, reported three patients who received brincidofovir (200 mg once a week orally) and one who received tecovirimat (600 mg twice daily orally for 2 weeks).[22] All three patients on brincidofovir manifested elevated alanine transaminase and the drug had to be withdrawn. The patient treated with tecovirimat showed a rapid recovery.[22] Available literature suggests that a 5-day course of tecovirimat may attain clinical recovery; however, a 2-week course is needed to ensure humoral immunity and lasting viral clearance.[34] Brincidofovir is considered to have a better safety profile than cidofovir with less chance of renal complications.[26]

Table 1: Case definitions for monkeypox 2022 by Centers for Disease Control and Prevention.

Suspect case	Probable case	Confirmed case
New characteristic rash/a high clinical suspicion for monkeypox and satisfies one of the following epidemiologic criteria Epidemiologic criteria within 21 days of illness onset: Contact with a person or people with a similar appearing rash or who received a diagnosis of confirmed or probable monkeypox/close or intimate in-person contact with individuals in a social network experiencing monkeypox activity/traveled outside the United States to a country endemic for monkeypox virus or with confirmed cases of monkeypox/contact with a dead or live wild animal or exotic pet of African endemic species or used a product derived from such animals	No suspicion of other recent *Orthopox*virus exposure and PCR of a clinical specimen showing *Orthopox*virus DNA/immunohistochemical or electron microscopy testing methods detecting *Orthopox*virus/detectable levels of anti-*Orthopoxvirus* Ig M antibody in patients' serum during the period of 4–56 days after the onset of rash	PCR or next-generation sequencing of a clinical specimen showing monkeypox virus DNA/ monkeypox virus isolated in culture from a clinical specimen

PCR: Polymerase chain reaction, DNA: deoxyribonucleic acid. Exclusion criteria: Patient has features of an alternative diagnosis (other than secondary syphilis, herpes, and varicella which can cause diagnostic confusion with monkeypox) which can fully explain the illness OR suspected case not manifesting any rash within 5 days of onset of illness OR high-quality specimens from the suspected case not showing *Orthopoxvirus* or monkeypox virus or antibodies to *Orthopoxvirus*

Vaccinia immunoglobulin intravenous (VIGIV) has been used along with antivirals in the treatment of other *Orthopoxvirus* infections.[26]

VACCINES

Smallpox vaccine offers about 85% protection against monkeypox.[35] ACAM2000 and JYNNEOS™ are the two vaccines licensed in the US against smallpox. ACAM2000 is a live *Vaccinia* virus. Vaccine is inoculated into the skin and the recipient is considered vaccinated within 28 days. The virus can replicate at the site of inoculation and disseminate to other parts of body and other individuals. JYNNEOS™ is a live, non-replicating, modified *Vaccinia Ankara virus* vaccine. The vaccine virus does not spread to other body parts or other individuals and is considered safe in immunocompromised individuals. Two subcutaneous injections, 4-week apart, constitute the vaccine schedule. The recipient is considered vaccinated, 2-week after the second dose. At present, these two vaccines are recommended for pre-exposure and post-exposure prophylaxis against monkeypox.[35] Aventis Pasteur Smallpox Vaccine, produced from replication-competent *Vaccinia Virus,* may be used in emergency situations when the other two vaccines are unavailable.[26]

Pre-exposure prophylaxis is recommended for health care workers managing or identified to take care of patients with *Orthopoxvirus* diseases such as monkeypox and laboratory personnel exposed to *Orthopoxviruses*.[35] According to CDC, smallpox vaccine given within 4 days of exposure to monkeypox virus can prevent the disease, while vaccine received within 4–14 days of exposure may reduce the disease severity.[35] Persons who have not received smallpox vaccine within 3 years may get vaccinated on exposure to monkeypox virus.[35]

VIGIV can be used for prophylactic treatment in an exposed person with severe T-cell immunodeficiency who cannot receive smallpox vaccination.[35]

Exposed persons should be monitored for 21 days since the last day of contact. Suspected or confirmed cases should be isolated in a hospital room or in a separate area (at home) from family members and pets until resolution of rash and formation of new skin.[26]

LESSONS FROM MONKEYPOX

Phylogenetic analysis suggests that monkeypox virus might have been circulating undetected in regions outside known endemic areas for years, often being misdiagnosed as its clinical mimics such as varicella, herpes simplex, secondary syphilis, and hand, foot, and mouth disease.[21] This underscores the importance of laboratory evaluation of all suspicious rash cases. The steady increase noted in the median age of the human monkeypox cases over the years reflects the advancing age of the generation born after the eradication of smallpox.[16] This suggests that future epidemics of monkeypox could affect older individuals. The disease outcome in an aged population (with the attendant comorbidities) could be different from the same observed in healthy, young adults. The medical fraternity should be prepared to meet the challenges of the infection in people with multiple comorbidities and immunosuppression associated with old age (immunosenescence). Anderson *et al*., while reporting a severe monkeypox virus disease in a child described the unique difficulties they had to encounter.[27] Health care workers were reluctant to take care of the patient with an infection induced by an exotic pathogen. In this age of global trade, a foreign travel is not necessary for a person to come in contact with pathogens from different parts of the world. The health care workers should be updated and equipped to meet the challenges posed by novel infections. As the world aims to eradicate more infections such as polio, we need to be vigilant regarding the possibility of emerging and re-emerging infections by related pathogens that move into take the place of the eradicated agent.

Declaration of patient consent

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Conflicts of interest

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