**Review Article**

# Monkeypox Disease Outbreak (2022): Epidemiology, Challenges, and the Way Forward

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The biggest-ever outbreak of monkeypox disease in non-endemic countries started in May, 2022. Though no monkeypox case has been reported from India, till mid-June, 2022, yet, considering the rate of spread to the non-endemic countries, there is an urgent need of better understanding of the monkeypox virus and disease epidemiology to help clinicians, public health specialists, and policymakers to be prepared for any eventuality. This review summarises the monkeypox disease epidemiology, clinical features, therapies, vaccines and outlines the measures for preparedness and response for a possible outbreak. The disease is known to cause severe outcome in children, pregnant women, and immunocompromised hosts and this group need to be given special attention. The Monkeypox disease outbreak (2022) in non-endemic countries should be used as an opportunity by India and other low and middle income countries to strengthen public health surveillance and health system capacity for outbreak and epidemic preparedness and response.

**Keywords:** *COVID-19, Monkeypox, Outbreak, Smallpox, Vaccines, Zoonoses*.

Monkeypox has been endemic in 11 countries in Western and Central Africa since the 1970s [1-2]. In May, 2022, the biggest-ever monkeypox disease outbreak in non-endemic countries had started and by June 15, 2022, around 36 non-endemic countries had reported monkeypox in their territories [3,4]. Though a mild and self-limiting disease for most of the people affected, Monkeypox is known for having comparatively severe outcomes in pregnant women, children and immunosuppressed individuals. In this review, the authors describe the epidemiology, clinical features, and preventive measures and clinical case management of monkeypox. The article also analyzes the epidemic and pandemic potential and possible steps for preparedness and response for India and other non-endemic countries.

## METHODS

A desk review of literature was conducted to collect, collate, synthesize and analyze information on the epidemiology and impact of the monkeypox virus (MPXV) and disease. The information from credible and reliable sources such as websites of the World Health Organization (WHO), the Centre for Disease Control and Prevention (CDC), and the publications in peer-reviewed journals were reviewed. Recommendations and updates from international and national scientific and government bodies were searched for relevant information.

## EPIDEMIOLOGY

Monkeypox disease is an infectious zoonotic disease caused by the monkeypox virus (MPXV), which belongs to the Orthopoxvirus genus of the Poxviridae family, the same genus as that of the smallpox virus [4-7]. It is a double stranded deoxy ribonucleic acid (dsDNA) virus. The MPXV was first detected in 1958, in a group of monkeys in a laboratory in Denmark [8,9]. The first human case was identified in a 9 month-old child, during the intensive search for smallpox cases, in the Democratic Republic of the Congo (then known as Zaire) in 1970 [10]. Ever since, the disease has been endemic in nearly 11 countries of the Central and Western African regions with thousands of cases being reported annually [11-13]. Though various animal species have been identified as susceptible to the monkeypox virus, uncertainty remains on the natural host of the monkeypox virus and further studies are needed to identify the reservoir(s) and how virus circulation is maintained in nature [13,14].

The case fatality rate of monkeypox ranges from 0-11% [4,15], slightly lower at around 0 to 3% for the West African clade and 0 to 11% for the Central African (Congo basin) clade, in comparison to the high fatality of 30% for smallpox virus [16]. To date, deaths in the endemic countries have mainly been reported mostly in young children and people with human immunodeficiency virus/Acquired and Immunodeficiency syndrome (HIV/AIDS) or other immunocompromised hosts [17].

### Cases in non-endemic countries and Ongoing outbreak:

In 2003, there was first-ever MPXV outbreak outside the endemic countries, in the USA with around 70 confirmed or suspected cases [18-20]. This outbreak was linked to the importation of Gambian giant rats, squirrels from Ghana, which had transmitted the virus to prairie dogs that were then sold and transported to the USA as pets [18]. There were no confirmed cases of person-to-person transmission [19]. Imported monkeypox infections in humans following travel have been reported in the United Kingdom, Israel, and Singapore in 2018-19 and then in the US again in 2021 [3,4, 20].

In the ongoing outbreak, the West African clade is responsible for the unprecedented rise of cases [3]. As per the latest WHO update, till June 15, 2022, around 2,039 laboratory confirmed cases of Monkeypox disease have been notified from 36 non-endemic countries worldwide [3,4]. Majority of the cases (84%) have been reported from WHO European region. However, cases have been reported from WHO Region of the Americas; Eastern Mediterranean and Western Pacific Region. Amongst the endemic countries, an outbreak of monkeypox disease is ongoing in Nigeria since 2017. [21].

### Transmission and pathogenesis

The incubation period – the period from the exposure to development of first symptoms- of MPXV is usually from 6 to 13 days (range from 5 to 21 days) [4]. A person is not contagious during the incubation period. The MPXV, primarily infects animals [4,14]. Human-to-human transmission occurs primarily through direct skin-to-skin contact with lesions (skin and mucocutaneous) and bodily fluids (such as pus, fluid, or blood from skin lesions) [3,20,21]. Transmission can also occur via the placenta from mother to foetus (which can lead to congenital monkeypox) or during close contact during and after birth [4,20,21]. During the ongoing multi-country outbreak, most of the cases have been reported among men who have sex with men, (MSM) though there is variable evidence of its sexual transmission [3,4]. The virus multiplies at the site of inoculation before entering the bloodstream. [22]. Lesions usually start in the oropharynx then appear on the skin. Serum antibodies are often detectable by the time lesions appear [16].

## LABORATORY AND DIFFERENTIAL DIAGNOSIS

Polymerase chain reaction (PCR) by testing of samples from skin lesions, is the preferred diagnostic test due to its higher sensitivity even in presence of bacterial contamination of patient's specimen. PCR in blood is usually inconclusive [10,20,23].

An important differential diagnosis is illnesses which manifest with rashes i.e., chicken pox, measles, bacterial skin infections, scabies, syphilis, and medication-associated allergies [4,13,20]. The differences in the clinical features of monkeypox with chickenpox and measles are shown in **Table I.** Monkeypox has a typical rash pattern and lymphadenopathy during the prodromal stage of illness. [3,4,20,21].

## CLINICAL FEATURES

The clinical presentation can be divided into two phases. First, the invasion period or the febrile stage that lasts between 0–5 days and is characterized by fever, intense headache, lymphadenopathy, back pain, and myalgia or muscle pain. Lymphadenopathy is a distinctive feature of monkeypox compared to other diseases that may initially appear similar (chickenpox, measles, smallpox) [3,4]. Second, the skin eruption phase, which usually begins within 1–3 days of the appearance of fever. The rash tends to be more concentrated on the face and extremities rather than on the trunk. It affects the face (95%), palms of the hands and soles of the feet [3,4]. Other areas that may be affected are oral mucous membranes, genitalia and conjunctivae as well as the cornea. The rash evolves sequentially from macules to papules to vesicles, pustules, and then forms crusts which dry up and fall off [3,4,13,16]. The number of lesions may vary from a few to several thousand. The complications commonly observed are conjunctivitis and

corneal scarring, vomiting and diarrhea, encephalitis, sepsis, and bronchopneumonia [13]. Full recovery may take days to weeks after the rashes subside **(Box I).** [3,4,23,24].

**Outcome of infection and risk in children**

Monkeypox is usually a self-limiting disease and remains mild but severe cases occur among children, pregnant women, comorbid and immunocompromised hosts [4,13,10,25,26]. The transplacental transmission of monkeypox has resulted in miscarriages and fetal deaths. However the association between severity of maternal illness and these outcomes is unclear [27,28]. Over the years, there has been a shift in the median age of monkeypox disease in Africa, which was 4 and 5 years old children in the 1970s and 1980s to 10 and 21 years old in the 2000s and 2010s [19]. In an outbreak in the US in the past, among the confirmed cases 10 out of 34 (29%) were in younger than 18 years of age [29]. However, during the first year of the ongoing outbreak in Nigeria, in 2017-2018, children formed around 8% of the 91 cases [29,30].

A recent longitudinal study from the Democratic Republic of Congo showed that among 216 admitted patients of monkeypox from the year 2007 till 2021, half were in the age group of 0-12 years [31]. Available data shows that the risk of children developing disease may have gone down over the years; however, they continue to be more vulnerable group given the possibility of adverse outcomes in this population. The prognosis is related to the extent of virus exposure, infection with Congo Basin clade of virus, patient's health status and nature of complications [32-33]. The complications and long term sequelae of the disease are listed in **Box 1** [4,34].

## THERAPEUTICS

Treatment of monkeypox disease is mostly symptomatic with management of complications and prevention of long-term sequelae. Fluids and adequate nutrition are necessary to improve overall recovery [4,20]. A drug named Tecovirimat, originally researched and developed for smallpox, was approved for MPXV in a few countries in early 2022; however, it is not yet widely available [4,20]. Two other antiviral drugs Cidofovir and Brincidofovir, also developed to treat smallpox and working by inhibiting the viral DNA polymerase, have shown efficacy in animal studies [3,22,24]. However, data is insufficient on their effectiveness for treatment of monkeypox disease in humans [23, 24]. Research is also in progress on monoclonal antibody combinations. Vaccinia Immunoglobulins (VIG) shown some

efficacy against other Orthopoxviruses and is licensed by the US Food and Drug Administration [35]. VIG plays a role in post exposure prophylaxis and reducing the severity of the disease, but further studies are needed [3,24].

**Vaccination**

In observational studies, the vaccination against smallpox had shown upto 85% cross protection and reduced severity of monkeypox disease [19]. However, in the current outbreak, immunity from the past smallpox vaccination may not be useful as firstly, it is limited to those who were administered the vaccine by or before the 1980s and secondly, there is every possibility of further waning of the protective effect in that population, over last four decades [4,20]. Smallpox vaccines have not been available to the public since its eradication in 1980. It is also believed that vaccination, upto 14 days after exposure and four days before appearance of symptoms, may also prevent from disease or reduce it's severity, as monkeypox disease has long incubation period [20].

A third-generation smallpox vaccine, MVA-BN (Modified vaccinia Ankara -Bavarian Nordic strain) was approved against monkeypox in 2019. This vaccine is based on a strain of vaccinia virus and is considered protective against MPXV [3,4,15]. As of June 11, 2022 MVA-BN smallpox vaccine is available in many European countries, USA and Nigeria, mostly for 'off-label' use [36]. An interim guideline from WHO has recommended that local authorities may consider the use of approved smallpox and/or monkeypox vaccines in response to ongoing outbreak [36]. Only second and third generation smallpox vaccines can be used for the ring vaccination in monkeypox outbreak, guided and determined at local level [24,36] A summary of key features of approved smallpox /monkeypox vaccines is provided in **Web Table I** [36].

These vaccines may be used for pre-exposure and post-exposure prophylaxis for specific groups; however, vaccination of general population is not recommended. The guidelines suggest that safety and reactogenicity data on the available vaccines should be considered by the technical experts to assess the 'need- risks -benefits' before arriving on a decision and choice of the vaccine [36].

For pregnant and breastfeeding women, non-replicating (MVN-BN) and minimally replicating (LC16) are preferred. For children, MVA-BN and LC-16 are preferred. Only approved vaccine for infants and children is LC16; however, MVA-BN, which is approved for adults, can also be administered as off-label use in children in different settings [3,36].

## PREPAREDNESS AND RESPONSE

The monkeypox disease cases have not yet been reported from India; however, considering the pattern of spread of MPXV in the ongoing outbreak, there is need for every country to be prepared. The outbreak readiness measures such as the designated isolation facilities and dedicated beds, equipment's and reagents for laboratory diagnosis, and training of group of health care workers as members of rapid response team (RRT) in standard elements of care should be prioritized. The Infection and prevention control measures at the designated facilities should be reviewed and strengthened. Early case identification, contact tracing and as and where possible, the ring vaccination (of close contacts and family members), remains to be mainstay of response. It also needs to be remembered that while laboratory confirmation of suspected cases is needed, it should not delay the public health measures. Similarly, while awaiting the laboratory confirmation, patients and contacts in community need to be traced and further investigated (backward contact tracing).

Risk Communication is another essential but under-used public health intervention for any disease with an outbreak and epidemic potential, as we have witnessed in the coronavirus disease 2019 (COVID-19) pandemic. The concerned health staff needs to be trained in risk communication. once one or more MPXV cases are reported, special efforts should be made to raise awareness about clinical symptoms and prevention of spread. However, it should not be overdone, which may result in panic.

In end May 2022, the Ministry of Health and Family Welfare (MoHFW), Government of India released guidelines on the detection and management of Monkeypox disease [37]. There is emphasis on intensified surveillance and early case identification, using standard case definitions [37]. A laboratory at National Institute of Virology (NIV) in Pune has been designated as nodal laboratory for monkeypox virus testing in India.

An **i**nterim response guideline by the WHO for monkeypox outbreak control, has provided recommendations on preventing the spread and managing monkeypox disease [24]. Key features are summarized in **Box III.**

## DISCUSSION

In the ongoing Monkeypox disease outbreak, other than the index case in the UK, there were no substantial travel links of the cases to the endemic areas in Africa, indicating that community transmission may have already begun in some settings. A majority of population in the non-endemic countries, including those affected in the ongoing outbreak, as well as people in India, do not have natural or acquired immunity to MPXV. Though smallpox vaccine is known to have provided

protection against monkeypox disease; after the eradication of smallpox virus from India in 1978, immunization against smallpox was stopped which makes the people younger than 42 years relatively more susceptible. However, people older than 42 years may not much protection because of waning immunity.

In the monkeypox outbreak, a majority of cases have been detected in men who have sex with men (MSM)[3]. However, this might be linked to early care seeking by MSM and the route of sexual transmission further needs further careful assessment [4]. Experts have argued that sexual contact is just a context which has provided close physical contact and thus opportunity to spread.

Due to the COVID-19 pandemic, the capacity in many countries for conducting genomic sequencing has been strengthened. In case of MPXV, genomic sequencing would be useful to identify the clade and the chain of infection. However, considering that MPXV is a DNA virus which has a slow rate of mutation, the repeated genomic sequencing has limited value. Then, MPXV genome has around 200,000 nucleotide bases, six times larger than the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) and thus genomic sequencing is a bit harder, more time consuming and expensive, with the limited benefits.

A key question is whether the MPXV is capable of causing a pandemic? There are several points which make MPXV disease unlikely to become a pandemic. First, it is not a new virus and has been present globally for five decades. There is a reasonable understanding of the viral structure, transmission and pathogenicity. Second, the virus causes mostly mild illness, as evident from zero deaths occurring since the onset of the ongoing outbreak. Third, it is less contagious and requires close personal contact in contrast to SARS-CoV-2 that had a respiratory spread and a high proportion of asymptomatic cases. In Monkeypox disease, person is contagious only when symptoms start appearing, therefore, chances of transmission going undetected are negligible. Fourth, a few smallpox vaccines are readily available and their ’off-label’ use can be recommended, and production can be ramped across the globe, if required. Fifth, it is relatively stable virus with very slow rate of mutations. It is in this backdrop, most experts on infectious disease believe that monkeypox outbreak would not turn into the pandemic. There is every reason, as of now, to believe that a Monkeypox outbreak can effectively be tackled and virus contained by isolation of confirmed cases, quarantine of contacts and the use of authorised smallpox vaccines as ‘off-label’ for ‘ring vaccination [24, 36,37]. The vaccination of general population is not currently recommended.

The ongoing monkeypox outbreak also raises questions about broader global public health response and collaboration. Despite the existence monkeypox disease in 11 countries in Africa for more than five decades, the disease is getting global attention now only when high and upper-middle income countries have been affected. This reflects the inherent bias in global public health, where diseases of low and middle income countries do not get commensurate priority for research and policy interventions [38].

There is a need for technical discussion amongst experts, at all levels, regarding possible use of smallpox vaccines for monkeypox outbreak situation. The national technical advisory group on immunization (NTAGI) in India and the immunization working groups and expert committees of the professional associations should discuss possible target groups as well as come up with technical guidance on possible target groups and to plan, procure, stockpile and if needed deployment of such vaccines.

In India, many viral and zoonotic diseases have emerged and re-emerged in the last two decades [39,40]. With change in the climate across the world, there are estimates of increased risks of cross-species viral transmission and zoonotic diseases [41]. The interventions to tackle those diseases are mostly similar. A stronger primary healthcare system, well-functioning disease surveillance systems, trained public health workforce and focus upon 'One-health' approach where interventions are coordinated to protect the health of humans, animals and ecosystem. [42]. are essential for any such eventuality. In the last one year, the Indian government has launched Pradhan Mantri- Ayushman Bharat Health Infrastructure mission (PM-ABHIM) [43] to strengthen the block public health laboratories and workforce. Then, in April 2022, a guidance document on public health and management cadre (PHMC) was released [44]. An accelerated and timely implementation of PM-ABHIM and PHMC by Indian states will prepare Indian states for epidemic and pandemic preparedness and response including for responding to zoonotic diseases [45].

## CONCLUSION

The emergence of monkeypox disease in non-endemic areas is a reminder that infectious diseases and pathogens are not restricted by the geographical borders. No case of monkeypox virus and disease has been reported from India in the ongoing outbreak; however, there is a need for better preparedness. Strict surveillance at port of entry and early identification, isolation, and case management are the key to response. Disease surveillance, contact tracing and ring vaccination with available smallpox vaccines, authorized for off-label use for monkeypox, for prioritized affected population are the key

strategies. The outbreak in non-endemic countries should be used as an opportunity by India and other countries to strengthen public health surveillance and health system capacity for outbreak and epidemic preparedness and response.

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**Table I Differentiation of Monkeypox from Other Illnesses with Rash**

| *Symptoms* | *Monkeypox* | *Chickenpox* | *Measles* |
|---|---|---|---|
| Fever | 1-3 d before rash | 1-2 d before rash | 3-5 d before rash |
| Rash/ lesions | Single stage | Often in multiple stage | Often in multiple stages |
| Rash development | Slow | Rapid | Rapid |
| Distribution of rash | More dense on face, present on the pal and soles | More dense on trunk; Not present on palms and soles | Starts on face, then to hands and feet. |
| Lymphadenopathy | Yes | No | Rarely |
| Death | Upto 10% | Rare | Variable |

*Adapted from references [3,4,20,21]*

**Box I Risk Factors and Clinical Findings Associated With Monkeypox Severity**

| |
|---|
| *Higher risk of severe disease or complications*<br><br>Children, pregnant women, persons who are immunosuppressed i.e. living with HIV |
| *Signs and symptoms of complications*<br><br>Nausea and vomiting painful cervical lymphadenopathy causing dysphagia, poor oral intake, eye pain, vision abnormalities, hepatomegaly, sepsis, dehydration, respiratory distress/pneumonia, and/or confusion. |
| *Laboratory abnormalities*<br><br>Elevated hepatic transaminases (AST and/or ALT), low blood urea nitrogen (BUN), low albumin, elevated white blood count (WBC), or low platelet count. |
| *Skin lesion severity score From smallpox experience*<br>- Mild (< 25 skin lesions)<br>- Moderate (25–99 skin lesions)<br>- Severe (100–250 skin lesions)<br>- Very severe (> 250 skin lesions). |

*Adapted from reference [3,4,20,24]. HIV – human immunodeficiency virus, ALT - alanine aminotransforse, AST - Aspartate aminotransferase.*

**Web Table I Key Characteristic of Smallpox and Monkeypox Vaccines**

| *Name and type* | *manufacture and country* | *Licensing status* | *Recommended for* | *Remarks* |
|---|---|---|---|---|
| MVA-BN<br>Third generation;<br>Non-replicating vaccine | Bavarian-Nordic in Denmark | **For Smallpox:**<br>In US and Canada Full market authorization (2019)<br>In EU: exceptional circumstances (2013)<br>**For Monkeypox:** approved and full authorization in US and Canada since 2019 | adult population | Very limited supply.<br>Supplied as Imvanex in EU; Ivmamune in Canada) and Jynneos in US (all TM)<br>Empirical data indicate safety in this group and can be used. Off-label use for children can be considered |
| LC-16<br>Third generation;<br>Minimally replicating vaccine | KM Biologics, Japan | For smallpox: Fully approved in Japan (1975) and special approval in USA 2014<br>Not approved for monkeypox in any country | Approved for all ages including infants, children and adults | Only vaccine approved for infants and children.<br>Can be given to pregnant and lactating women. |
| ACAM2000<br>Second generation.<br>Standard Replicating vaccinia-based vaccine developed by cell culture technique. | Developed in France and USA, | Smallpox:<br>Approved in USA<br>**For monkeypox;** special circumstances approval in USA | Adults in 18-64 years | Contraindicated in immunodeficient; atopic dermatitis and HIV/AIDS etc.<br><br>Not recommended for use in pregnant women, infants and children. |
| Vaccinia/Smallpox vaccines<br>First generation | Multiple countries | Not approved for monkeypox in any country. | Wider age groups. | Not recommended for monkeypox.<br>Ensure strategic reserve for health security and preparedness. |

*Reference [3,20,36].*

**Box II Complications and Sequelae of Monkeypox**

*Complications*

- Bacterial skin and soft tissue infections such as cellulitis, abscesses, necrotizing soft tissue infections
- Subcutaneous fluid accumulation in the crusting phase leading to intravascular depletion and shock
- Skin exfoliation
- Severe pneumonia and respiratory distress
- Corneal infection and vision loss
- Loss of appetite, vomiting and diarrhoea which may lead to severe dehydration, electrolyte abnormalities and shock
- Cervical lymphadenopathy which may lead to retropharyngeal abscess or respiratory compromise, sepsis, septic shock, and, encephalitis
- Death

*Sequelae*

- Complications during pregnancy (miscarriage, bleeding, still birth)
- Congenital disease in newborn born to affected mother.

*Reference [3,4,20,24].*

**Box III Key Recommendations for Monkeypox Management**

***Case management***

- Mild (suspected or confirmed) cases can be isolated at home with adequate infection control measures and supportive and symptomatic care.

  Antipyretics, adequate nutrition and rehydration form the mainstay of treatment.

- Skin lesions, need to be monitored for secondary bacterial infections and treated accordingly.

- Patients with high risk for complications, including children and pregnant women should be admitted to the hospital for closer monitoring and clinical care.

***Pregnant women and children***

- Any pregnant women if presents with mild and uncomplicated case, immediate hospital care is not recommended.

  Complicated cases need to be admitted immediately.

  MPX disease is not a direct indication for caesarean section.

- Children at risk should be completely vaccinated according to routine National immunization schedule.

  Newborn baby born to affected mother should be closely monitored for possible congenital infections.

- Breastfeeding of baby born to affected mother should be decided based on general physical status and severity of disease.

***Post exposure prophylaxis of health workers***

- There should be an assessment and management plan for staff with occupational exposure to MPXV.

*Reference [3,36].*