INTERNATIONAL JOURNAL OF
PHARMACEUTICAL AND HEALTHCARE INNOVATION
journal homepage: www.ijphi.com

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Review Article

Monkeypox: Advances in Understanding, Spread, and Management

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Article Info

Article history:

Manuscript ID:

IJPHI1318192024
Received: 13- September -2024
Revised :18- September -2024
Accepted: 19- September 2024
Available online: September 2024

Keywords:
Monkeypox virus, Poxviridae family, clinical management, Smallpox, myalgia

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Abstract

The infectious agent responsible for monkeypox is the Monkeypox Virus (MPXV), a family member of the Poxviridae genus of viruses. Mpox, formerly endemic to West and Central Africa, has had a notable increase in incidence beyond these countries since 2017, resulting in its resurgence as a global health issue. This review provides a comprehensive analysis of MPXV's virology, epidemiology, and clinical management. MPXV is genetically similar to the variola virus, the causative agent of smallpox, with a genomic similarity of 96.3%. Despite this, notable differences in virulence and host range exist. Infected animals can infect humans through direct touch or their excretions; the virus mostly affects rodents and small mammals. A possible factor in the rise of mpox has been the end of smallpox immunization. Symptoms such as a rash, fever, headache, and myalgia are part of the clinical presentation. Although no specific antiviral drugs are approved for mpox, treatments like tecovirimat, cidofovir, and brincidofovir are used in severe cases. Smallpox vaccination offers cross-protection against mpox. Effective management involves diagnosis through PCR assays, symptomatic relief, isolation, and stringent hygiene practices. Public health measures are crucial for controlling outbreaks.

Introduction

The monkeypox virus (MPXV) is the causative agent of monkeypox. As a member of the Poxviridae family and the Chordopoxvirinae subfamily, the Orthopoxvirus (OPXV) is a kind of dsDNA virus. Additional viral components found in this genus include VARV, CPXV, VACV, CMLV, TATV, and ECTV, among others(1-4). There are two distinct groups within MPXV, known as Clade I and Clade II, with Clade IIa and Clade IIb serving as subgroups within Clade II. There was an erratic spread of MPXV from West and Central Africa to non-endemic areas for more than half a century. But since 2017, mpox cases in non-endemic regions have been on the rise, changing the disease's epidemiological characteristics in endemic regions at the same time(3-5). This event may have set the stage for the 2022 outbreak and subsequent resurgence of MPXV in countries where the virus is already prevalent(1). The purpose of this research is to elucidate what is already known about the features of MPXV and mpox, such as the biology of infection, molecular pathogenesis, clinical symptoms, diagnostic tools, epidemiological trends, and treatment approaches pertaining to mpox. The worldwide genesis and re-emergence of mpox are investigated in this review, which will analyse the roles of viral, host, and anthropogenic variables. With a genetic resemblance of 96.3% with the variola virus the causative agent of smallpox monkeypox is classified under the Orthopoxviruses of the Poxviridae family. In 1958, monkeys brought in from Singapore for research were the first to be positively identified as having MPV in a Danish laboratory(5-8). However, the exact evolution of MPV is still a mystery. Squirrels, prairie dogs, monkeys, rats, mice, and other tiny rodents are the usual hosts for this virus, despite its moniker. Aerosol, indirect, and direct contact with either live or dead animals are all considered potential routes of transmission to humans; however, the exact mechanisms are not well understood. In the 1970s, six African countries—Sierra Leone, Cameroon, Côte d'Ivoire, Liberia, Nigeria, and the Democratic Republic of the Congo—recorded occurrences of MPV(2). In the 1970s, monkeypox virus (MPV) was reported in 48 cases, with over 800 cases in the Democratic Republic of the Congo alone. Along with Nigeria, Cameroon, Côte d'Ivoire, and Liberia were the other five African countries hit hard. As smallpox vaccination efforts came to a halt in the 1980s, cross-protective immunity began to decline, and as a result, monkeypox has spread rapidly across Africa. Research suggests that the smallpox vaccine can avert monkeypox cases by around 85%. Despite their same genetic background, MPV and the variola virus show significant differences in the genomic regions that affect virulence and host range(2). It is anticipated that more than 70% of the population has never been vaccinated against monkeypox, which is a contributing factor to the increasing number of MPV cases. In smallpox epidemic situations, those who had already been vaccinated had milder rash symptoms, were less likely to develop lymphadenopathy, and died from the disease as a result. From 1980 to 2000, most occurrences occurred in African nations. However, as the new century began, the illness spread rapidly across the continent, leading to 20,000 probable cases reported by the Democratic Republic of the Congo(3). The United States reported 48 instances of monkeypox in 2003, the first incidence outside of Africa; the cases were linked to prairie dogs that had contracted the disease via imported Gambian pouched rats, illustrating the dynamics of rodent-to-host transmission. Extremely uncommon epidemics have been greatly aided by the increase in worldwide travel and the flood of goods from Africa. Multiple nations have reported instances; the most recent being the United Kingdom with seven from 2018 to 2021, followed by Singapore with one from 2019, and finally the United States with two (2021). In spite of this, 650 documented cases and nine fatalities in Nigeria between 2017 and 2022 show that monkeypox is still endemic in African countries(4-8). The number of confirmed cases worldwide has risen to almost 50,000 in 100 nations as of August 2022, with 13 deaths recorded. In light of the alarming increase in cases, the World Health Organisation has designated the monkeypox pandemic as a global health emergency. Worries about MPV becoming a more effective human illness linger despite the fact that it has a lower death and transmissibility rate than smallpox(8-12). As of October 2022, 109 countries had registered more than 75,000 cases of MPV, and 12 nations had reported 34 fatalities for the whole year. Clade I of MPV is found in Central Africa, whereas clade II is found in West Africa. The virulence of lineage I, which includes the Congo Basin lineage, is higher than that of Clade II, with a mortality rate of 10.6% compared to 3.6%. The elevated rates of disease, mortality, H1N1 transmission, and viremia are further characteristics of Clade I. Various doses of strains

from Central and West Africa have been tested for their pathogenicity in non-human primates, specifically cynomolgus monkeys. While monkeys given smaller dosages of the Central African strain showed significant illness, those given higher doses died out entirely(12).

The environment, potential hosts, organs, and cells

Despite the moniker, monkeypox does not really originate in monkeys. Numerous animal species can contract MPXV via natural or experimental routes (Table 1); yet, the specific natural host reservoir is yet to be determined(13). While unique host-cell receptors facilitate cell tropism, We still don't know what causes MPXV. Possible components that influence the viral cellular and tissue tropism include the monkeypox inhibitor of complement enzymes (MOPICE) and the complement control protein (CCP). The possibility of MPXV establishing reservoirs in animals outside of endemic areas can be explained by the wide range of tissues and hosts that the virus is thought to infect(14). Several organs have been shown to exhibit tropism for MPXV, including the ovaries, kidneys, heart, brain, pancreas, liver, and lungs. Figure 1 shows that the specific viral ligands have not been found yet. The failure to isolate particular viral ligands and their associated host receptors crucial to MPXV tropism implies that the virus could utilised multiple alternative ligands to effectively infiltrate host cells, or that the host receptors display functional redundancy regarding the viral ligands(16). Zoonotic transmission to humans may come from changes in wildlife habitats. This transmission can take happen through many paths, including aerosolization, direct contact, and fomite transfer. It is suggested that the MPXV epidemics recorded in Africa previous to 2022 were the consequence of spillover events from animals to humans. Consequently, there exists a likelihood of MPXV being maintained in spillover dynamics due to the vast geographical dispersion of MPXV hosts(17). The pathogenic virus has the potential to transmit to humans via intimate interaction with excretions from an infected individual, inclusive of saliva, mucus, or dermal lesions. The clinical presentation is characterized by manifestations such as pyrexia, cephalalgia, myalgia, and a dermal eruption that initiates as diminutive papules and subsequently progresses to elevated vesicular lesions containing fluid(15-20). Lesions attributable to monkeypox can appear on various regions of the body; however, they are predominantly located on the facial area, hands, and feet. In severe instances, the viral infection may culminate in grave complications, including pneumonia and sepsis, which may pose a risk of mortality. Presently, there exists no targeted therapeutic intervention for monkeypox; nevertheless, palliative care, including pharmacological agents aimed at alleviating fever and discomfort, may facilitate symptom management(18). The effectiveness of the smallpox vaccination against monkeypox is uncertain, but it can offer some protection. The risk of monkeypox can be significantly reduced by practicing good hygiene, which includes frequent hand washing and staying away from those who are sick (table 2). Classification of the genetic changes found in the Monkeypox Virus (MPXV), which caused an epidemic in several nations in 2022 (table 3) (20-23). Conventional wisdom holds that smallpox was the progenitor of monkeypox (Table 2). But there are a lot of chromosomal changes between the two viral species, according to genetic investigations. While the viral core sections are almost similar (96.3% identity), the viral capsids encode different proteins, which might explain why the two viruses are so different in their pathogenicity. Two genes that provide resistance to interferon (IFN) are found in the variola virus but not in monkeypox: C3L and the elongated version of E3L. A lower capacity for the viruses to transmit from person to person is associated with the lack of these genes in monkeypox and their reduced expression in variola. On the other hand, monkeypox is thought to encode a β-binding protein (IL-1), which is vital for reducing the severity of the virus-induced illness (table 4) (24).

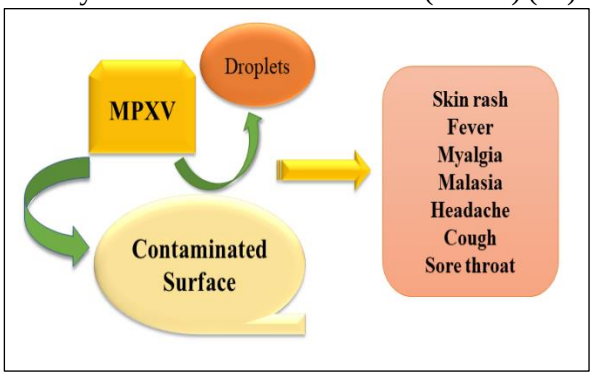

Figure 1: *The pathogenesis and prevalent clinical manifestations associated with the monkeypox virus are of significant interest. Transmission of the virus occurs via respiratory droplets, with an incubation period ranging from 7 to 21 days, averaging approximately 14 days. During this interval, the*

infected individual does not possess the capacity to transmit the contagion to others. Subsequent to this phase, the occurrence of viremia is noted, accompanied by the emergence of clinical manifestations. At this juncture, the individual is capable of transmitting the infection and facilitating the dissemination of the virus within the community.

Table 1: The pathogenesis and prevalent clinical manifestations associated with the monkeypox virus.

SKIN	LYMPH NODES	MUCOUS MEMBRANES	SEQUELAE
Scalp involvement	Unilateral or bilateral enlargement	Mouth, tongue, oropharynx, tonsils, involvement	Abcess, erysipelas, cellulitis, and gangrene are examples of local infections that can affect skin or soft tissues.
Pustules	Compression	Ulcers	Patchy alopecia
Engagement of the hands and feet	Swelling without redness	External genitalia, pelvis involvement	Pitted scars

Table 2: An analysis of various vaccines presently employed across diverse nations, categorized by type, mode of administration, intended demographic, and suggested dosage regimen.

Type	Vaccine	Route of administration	Recommended number of doses
JYNNEOSTM/MVA-BN	Vaccinia virus (Ankara strain) including MPX antigens (third generation)	Subcutaneously	2 doses within 28 days
ACAM2000	Second generation live attenuated	Percutaneously	single dose
LC-16	Biologically attenuated third-generation	Percutaneously	2 doses within 28 days

Table 3: The classifications of the genetic alterations that have occurred in the Monkeypox Virus (MPXV) responsible for the 2022 epidemic across various nations.

Three high-priority mutations	Four medium-priority mutations	Two low-priority mutations
The B21/B22 protein has three mutations: D209N, P722S, and M1741I.Rats were more severely afflicted and died more quickly after this protein was introduced to nonvirulent cowpox strains. All three of these types of herpesviruses contain the T-cell inhibitor: horsepox, camelpox, and cowpox.	The severity of rabbitpox is increased when the C23L(S105L) gene, which is a chemokine-binding protein, is removed from the virus.	***C9L(R48C):*** Vaccinia virus replication drops dramatically if the interferon-stimulated gene product antagonist is removed.
	C22L(S54F): Mice with severe lung disease are more susceptible to ectromelia virus-induced infections when a gene similar to the Tumour necrosis factor (TNF) receptor-like protein is deleted.	***A46L(H221Y):*** Reducing the pathogenicity of the virus in mouse models is achieved by eliminating the vaccinia virus gene.

Table 4 : Major differences between monkeypox and smallpox

Causative organism	Monkeypox	Smallpox
Reservoirs	Monkeys and rodents	Humans
Prodromal period	1–4 days	1–4 days
Strains	Congo Basin and West African clades	4 variola major subtypes

Duration of illness	2–4 weeks	Up to 5 weeks
Fever	Low-to-high grade	High grade
Vaccine	JYNNEOS and ACAM2000	ACAM2000 and JYNNEOS (approved for prevention against smallpox)
Fatality	Low	High

Clinical management

Clinical management of mpox involves a multi-faceted approach including accurate diagnosis, symptomatic relief, and infection control(25). Initially, diagnosis is confirmed through laboratory tests such as PCR assays to differentiate mpox from other similar infections. Symptomatic management focuses on alleviating fever and pain with medications like acetaminophen and ibuprofen, while ensuring proper hydration and nutrition. Isolation of patients and rigorous hygiene practices are essential to prevent transmission(26). Although no specific antiviral drugs are approved solely for mpox, treatments used for smallpox, such as tecovirimat, may be considered. Vaccination with the smallpox vaccine provides cross-protection and may be used for those at high risk or for post-exposure prophylaxis(27). Ongoing monitoring for complications and follow-up care, including addressing potential psychological impacts and residual symptoms, are also crucial. Public health measures, including outbreak response and accurate reporting, are vital for controlling the spread of the virus. Currently, there are no antiviral drugs specifically approved for the treatment of mpox. However, certain antiviral agents, originally developed for other poxviruses, may be utilized in managing severe cases or during outbreaks: (28)

- Tecovirimat (TPOXX): Originally developed for smallpox, tecovirimat is an antiviral drug that inhibits the viral envelope protein and prevents the release of new viral particles. It has shown effectiveness against a range of orthopoxviruses, including mpox, and is used under expanded access protocols for severe cases(29).
- Cidofovir is an antiviral medication that is used off-label to treat severe instances of mpox. It inhibits viral DNA polymerase. Because of its broad-spectrum antiviral activity against a range of DNA viruses, including certain poxviruses, it may be examined in cases when tecovirimat is not available or is ineffective.
- Brincidofovir: A prodrug of cidofovir, brincidofovir is designed to have reduced nephrotoxicity compared to cidofovir. It is used in treating smallpox and may be considered for mpox under certain conditions.
- Although it is not an antiviral medicine, Vaccinia Immune Globulin (VIG) can be given to patients with severe mpox to help them recover. VIG is made from the blood of smallpox vaccine recipients and includes antibodies that target orthopoxviruses(30).

Conclusion

The rise in mpox cases globally highlights the need for continued vigilance and research. Despite its lower fatality rate compared to smallpox, the potential for mpox to evolve into a more significant human pathogen remains a concern. The discontinuation of smallpox immunization and heightened global travel have facilitated the dissemination of MPXV outside its customary endemic areas. While no specific antiviral treatments are approved for mpox, existing antiviral agents such as tecovirimat and cidofovir show promise in managing severe cases. Vaccination with the smallpox vaccine remains a key preventive measure. Effective clinical management requires accurate diagnosis, supportive care, and rigorous infection control practices. Public health responses, including outbreak surveillance and reporting, are essential to mitigate the spread of the virus and manage future outbreaks. Continued research into MPXV's pathogenesis, transmission dynamics, and treatment options will be vital for improving global health responses to mpox.

ACKNOWLEDGEMENT

A special debt of appreciation is due to the following institutions: Sam Higginbottom University of Agriculture, Technology and Sciences, Bioorganic , Medicinal Chemistry Research Laboratory, Department of Pharmaceutical Sciences, Prayagraj, India, 211007, Faculty of Pharmacy, Integral University, Dashauli, Kursi Road, Lucknow, UP-226026, India, Faculty of Pharmaceutical Sciences, Rama University, Mandhana, Bithoor Road, Kanpur, Uttar Pradesh-209217, Institute of Pharmacy, Shri Ramswaroop Memorial University, Lucknow

Dewa Road, Uttar Pradesh, India,225003 and Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, India and the author himself.

ETHICAL APPROVAL
NA
INFORMED CONSENT
Not Applicable.
FUNDING
No funding was received for conducting this study.

CONFLICT OF INTEREST
There are no apparent conflicts of interest between the authors' personal relationships or financial interests that may have affected the results of this study, the authors state. There is no conflict of interest, according to the writers. All ideas and opinions expressed in this article are those of the authors.
FINANCIAL INTERESTS
The authors declare they have no financial interests.
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