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Pandemic Puzzles: The Evolution and Impact of Monkeypox

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ABSTRACT

Monkeypox virus (MPXV), belonging to the Orthopoxvirus genus of the poxviridae family, was first identified in 1958 following outbreaks in monkey colonies. The first human case was recorded in 1970 in the Democratic Republic of the Congo. MPXV is a double-stranded DNA virus with a genome size of 197kb, and it presents with symptoms such as fever, muscle aches, lymphadenopathy, and characteristic rashes. Rodents and primates suspected as potential reservoirs, particularly in endemic regions such as Central and West Africa. Transmission can occur through contact with bodily fluids, skin lesions, or respiratory droplets of infected animals directly or indirectly via contaminated fomites. Furthermore, important environmental factors influencing transmission are host density and mobility patterns. There are multiple routes of transmission for the monkeypox virus all of which involve direct contact with infected humans or animals. Epidemiological data show a male predominance in recent outbreaks, particularly among men who have sex with men (MSM). The 2022 outbreak led to the declaration of monkeypox as a public health emergency of international concern by the WHO, which was lifted in 2023, though cases continue to be reported globally. The virus progresses through incubation, prodrome and encephalitis. Prevention strategies include vaccination, with the JYNNEOS (Imvamune/Imvanex) vaccine proving effective in both pre- and post-exposure scenarios. There is no specific antiviral treatment for monkey pox; however supportive care and antivirals such as tecovirimat may be considered in severe cases. Control measures emphasize early detection, public awareness, and vaccination of high-risk population. This review aims to provide a comprehensive understanding of the epidemiology, pathogenesis, clinical features, and preventive strategies for monkeypox, highlighting the importance of continued vigilance and research to combat this emerging public health threat.

Keywords: MPXV, Zoonotic disease, Vaccination, Public Health, Epidemiology

INTRODUCTION

The Monkeypox Virus (MPXV) belongs to the Orthopoxvirus subgroup of the Poxviridae family. The history of Monkeypox goes back to 1958, when breakout occurred in two colonies of monkeys in Africa. Despite it being named Monkeypox now, the origins were unknown. Following the small pox eradication worldwide, monkeypox emerged as the most significant OPXV for public health.(1)The first case in humans was

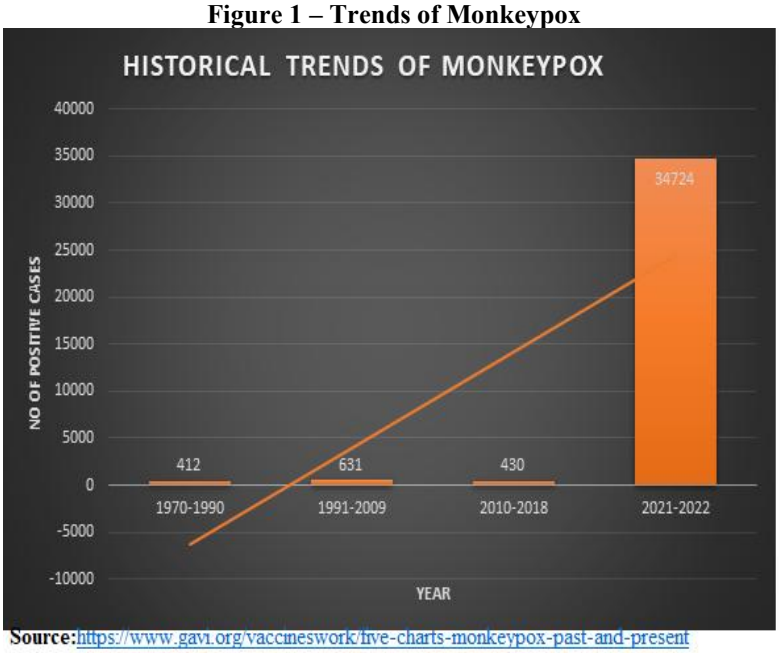
recorded in the Democratic Republic of the Congo 1970.(2) Monkeypox virus is a 200–250 nm sized, brick or oval-shaped double-stranded Deoxyribonucleic acid (DNA) virus with a 197-kbps genome.(3) Common symptoms include fatigue, muscle aches, fever, and enlarged lymph nodes, following rash with crusts and blisters. However, atypical presentations have been common in the present outbreak, including oral, perianal, and genital lesions as well as pharyngitis and proctitis.(4,5) Although the reservoir of the virus is unknown, it is believed that rodents (squirrels, Gambian pouched rats and dormice) play a role in its transmission in endemic countries.(6) Other members of the poxvirus family that infect humans are variola (smallpox), vaccinia, camelpox and cowpox.(7) Since 2022, the Democratic Republic of the Congo has experienced a surge in MPXV cases and fatalities. In certain regions, a new variant of clade I, known as clade Ib, has been spreading through human-to-human transmission. By mid-2024, this clade had also been detected in other countries. As of August 26, 2024, 120 countries have reported MPXV between Jan 2022 and Aug 2024, with over 100,000 laboratory-confirmed cases reported and over 220 deaths among confirmed cases.(8)On 14th August 2024, World Health Organization (WHO) Director-General Dr Tedros Adhanom Ghebreyesus declared the Monkey Pox outbreak a public health emergency of international concern (PHEIC). (9) As a result, it is crucial for both clinicians and the general public to be informed about the diagnosis, management, and control of the disease. This review will explore the current understanding of human monkey pox, with a focus on its epidemiology, pathogenesis, clinical characteristics as well as strategies for prevention and control.

EPIDEMIOLOGY

The first recorded epidemic of monkeypox occurred in 1958 among a group of monkeys in Africa, presenting as an unexplained illness characterized by skin blisters. The monkeypox virus was subsequently identified through examinations of the infected monkeys.(10) Surveillance data from endemic regions between 1970 and 2015 indicated that 51% to 67% of MPXV cases were male, while 71% to 83% involved children under the age of ten. During the 2017–2018 outbreak in Nigeria, 64% of cases were male, with a median age of 29 years. In contrast, the 2022 multi-country outbreak saw a significant increase in male cases, with 96.8% being male and a median age of 34 years (interquartile range: 29–41) according to the World Health Organization (2022). Notably, while children aged 0 to 9 constituted less than 1% of cases in Europe and the Americas, they represented 23.08% of MPXV cases in Africa.(11) In addition to non-human primates, the monkeypox virus (MPXV) can infect various rodent species, including squirrels, Gambian pouched rats, and dormice. However, it remains unclear which specific host is primarily responsible for transmitting MPXV to humans. The virus has an incubation period ranging from 6 to 13 days, followed by an infectious phase lasting 1 to 2 days. Human-to-human transmission largely occurs through large respiratory droplets, necessitating close contact between individuals.(12) India reported its first case of MPXV linked to a traveller from an outbreak-affected country. Currently, there are 10 confirmed cases in India (5 in Delhi and Kerala) and 8 suspected cases across Delhi, Telangana, Bihar, and Uttar Pradesh. As the population experiences increasing "pandemic fatigue," the rise in cases from another virus complicates public health planning and interventions. The initial case in India was identified in Kerala on July 14, 2022, with subsequent cases reported mainly within one to two days. Among those affected, only two were female (ages 31 and 22), while the majority were men who had travelled abroad within the previous 21 days.(13,14) In July 2022, the WHO

declared monkeypox a public health emergency of international concern; however, this declaration was lifted in May 2023. Since the declaration, the WHO has documented 99,176 cases and 208 deaths attributed to monkeypox across 116 countries. The last reported case was identified in March 2024, with India recording a total of 30 cases since the WHO's initial announcement.(15) Preventive measures include vaccination especially for high-risk populations—practicing good hygiene, and avoiding close contact with infected individuals or animals. The smallpox vaccine has shown effectiveness against monkeypox due to similarities between the two viruses. Currently, there is no specific antiviral treatment for monkeypox; instead, supportive care aimed at alleviating symptoms is the primary approach. In severe cases or for high-risk patients, antiviral medications such as Tecovirimat may be considered.(16)

Figure 1 – Trends of Monkeypox



Source:https://www.gavi.org/vaccineswork/five-charts-monkeypox-past-and-present

VIROLOGY

Monkeypox is a member of the genus Orthopoxvirus, which belongs to the Poxviridae family. The orthopoxvirus genus also contains smallpox and cowpox.(17,18) . Monkeypox is a large virus measuring approximately 200–250 nm in size with an ovoid or "brick-like" appearance.(3,19) It has a lipoprotein membrane and is a double-stranded DNA virus. Depending on the type of host cell and species, several proteins are required to initiate the replication cycle of MPXV. Furthermore, the infection process becomes more complex as the virus evolves new mechanisms to evade the immune system. The MPXV virus uses four different kinds of proteins to attach to the host cell. It enters the host cell primarily by three processes: fusion, endocytosis, and micropinocytosis. The termini of the genomes carry out interactions between the MPXV virus and host cells, whereas the middle section of the genome carries out transcription and virus assembly.(20) It has been estimated that the incubation period and the length of manifestations are 5-21 days and 2-5 weeks, respectively.(21,22) . Replication of the MPXV virus in fibroblasts and keratinocytes following respiratory or skin-to-skin contact is the main mechanism of MPXV infection.(23,24) Animal models of aerosolized MPXV infection have revealed that the tonsils, mediastinal, and mandibular lymph nodes are the first sites to be involved during the pathogenesis of MPXV

infection. Lymphatic distribution of the virus can lead to the spread of lesions and dissemination to other organs, such as the spleen, heart, kidneys, and cerebrospinal fluid (CSF)(25,26)

PATHOGENESIS

Monkeypox is typically a self-limiting disease, with the severity of infection influenced by factors such as the viral strain, the individual's immune status, and the occurrence of potential complications.(27)The route of entry and the clade of monkeypox virus might affect how the illness manifests. In the respiratory tract, the monkeypox virus can infect airway epithelial cells, whereas in the skin, the virus infects keratinocytes, fibroblasts, and endothelial cells, establishing productive and cytopathic infection.(28)The virus then disseminates throughout the body via tissue-resident immune cells and draining lymph nodes.(12,29)

This marks the latent period of MPXV virus infection, which typically lasts upto two weeks. During this phase, infected individuals remain asymptomatic and do not develop any lesions. Following the latent period, infected individuals begin to display early prodromal symptoms, including fever, chills, headache, muscle pain, and lymphadenopathy. These initial symptoms generally persist for approximately three days. After the onset of fever and lymphadenopathy, a rash begins to develop, initially appearing on the head and face before progressively spreading across the body. The rash evolves through distinct stages, starting as papules, then transforming into vesicles and pustules, before ultimately forming crusts that heal, often leaving scars. This rash phase typically lasts between 2 to 4 weeks.(30,31)

TRANSMISSION

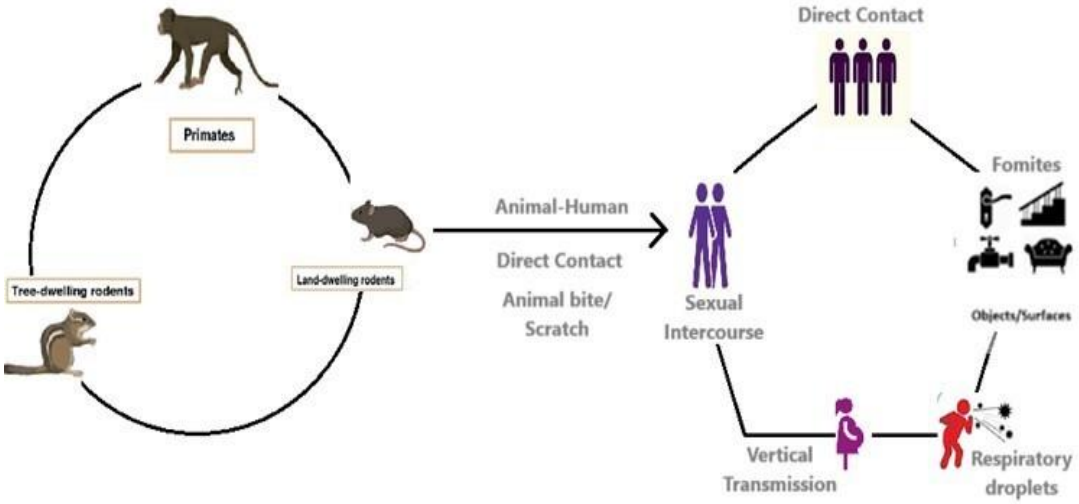
MPXV is a zoonotic virus with rodents and primates suspected as potential reservoirs, particularly in endemic regions such as Central and West Africa. The virus can jump from animals to humans, with initial transmission likely occurring through handling infected animals or consuming wild food products.(32)The primary method of transmission of the infection virus from one individual to another is the immediate interaction with lesions on the skin exudations of respiration of a diseased individual or the object that has been recently contaminated. In a cohort of 595 confirmed cases of MPXV in Spain in 2022, 99% of cases were found to be in the MSM population, with the lesions predominantly affecting the genital, perineal, or perianal areas. The study also identified inguinal lymphadenopathy as a predominant feature suggesting that sexual transmission was the main mode of transmission.(33) In July 2022, the multi-country outbreak of MPXV was declared a PHEIC as it spread rapidly via sexual contact across a range of countries where the virus had not been seen before.(34)

Transmission can occur through contact with bodily fluids, skin lesions, or respiratory droplets of infected animals directly or indirectly via contaminated fomites. Furthermore, important environmental factors influencing transmission are host density and mobility patterns. There are multiple routes of transmission for the monkeypox virus all of which involve direct contact with infected humans or animals. Shedding viruses through feces could be an additional route of exposure. In endemic areas with limited infrastructure and resources, exposure to the feces of infected animals can be a significant risk factor. Hunting is the only option in places with limited resources and necessities like food, which raises the danger of monkeypox infection. The transmission rate is higher in animal-to-animal than in human-to-human transmission in areas where people hunt or trade wild animals for food or medicine.(35) Due to the possibility of transmission through men who have sex with men (MSM), the monkeypox virus is more prevalent in males than in females during the current epidemic.(36) These findings

show that sexual interaction contributes to the spread of monkeypox in the confirmed cases. Environmental factors, such as temperature, humidity, and sunlight exposure, can also affect the survival and transmission of the virus. (35)

Investigations have also detected MPXV virus in semen samples.(37) Indeed, genital fluids, including vaginal fluid and seminal fluid, from infected cases consistently contain the MPXV virus.(38,39) In some patients, MPXV virus DNA was detected in seminal fluid even a long time after the onset of clinical manifestations.(40) Moreover, urethral and anal swabs from infected cases can be used to culture viable MPXV virus.(41)These sexual transmission characteristics of MPXV virus have led some researchers to investigate the possibility of classifying MPXV infection as a sexually transmitted infection.(42,43) In recent years, most confirmed cases of MPXV during outbreaks have been reported in bisexual or homosexual men. In this regard, an investigation also showed that 98% of MPXV patients were bisexual or homosexual men, with 41% co-infected with human immunodeficiency virus (HIV).(44)

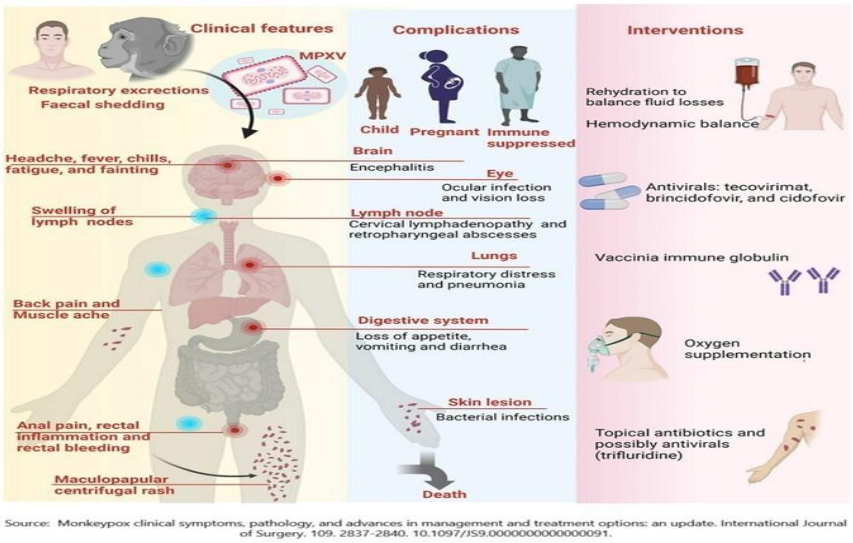
Figure 2 – Transmission of Monkeypox



CLINICAL FEATURES

Monkeypox manifests in a way similar to smallpox, but with a less severe course, starting with a prodromal phase, which includes fever, flu-like symptoms, headache, and myalgia with the addition of lymphadenopathy, which is absent in the latter. (45) Monkeypox affects both children and adults and typically has three phases: incubation, prodrome, and the eruptive stage. (46)After primary infection the incubation period ranges 13 days (3-34). The prodromal stage lasts for 1-4 days and it is characterized by a high temperature, headache, fatigue, and lymphadenopathy, especially in the cervical and maxillary regions. During the eruptive phase, which lasts for 14 to 28 days, skin lesions appear in a centrifugal distribution and progress through several stages: macules, papules, vesicles, and finally, pustules. The lesions are firm and well delimited, they frequently occur on the palms and soles. Symptom severity and disease duration are proportional to the density of skin lesions. The disease is most severe in children and pregnant women. Monkeypox usually follows a self-limiting course, but clinical sequelae, including pitted facial scars, are common. (46) Complications include secondary bacterial infections that can cause bronchopneumonia, encephalitis, keratitis, diarrhea, and even sepsis. People unvaccinated against smallpox are also susceptible to superimposed bacterial infections of the skin. (47)

Figure 3 - Salient clinical features and treatment options for patients with monkeypox



Source: Monkeypox clinical symptoms, pathology, and advances in management and treatment options: an update. International Journal of Surgery. 109. 2837-2840. 10.1097/JS9.0000000000000091.

PREVENTION AND CONTROL

Variola, cowpox, vaccinia, and monkeypox virus all belong to the Orthopox genus. Due to immunological cross-reactivity and cross-protection among the Orthopox species, infection with any one of these species provides some extent of protection against the other. It has been found that vaccination against smallpox offers immunological protection against all orthopox viruses, including monkeypox.(48) Smallpox vaccination can be given prophylactically to prevent monkeypox infection before or after a suspected or confirmed viral exposure. However there are no licensed treatments for human monkeypox infection as of today, but a few drugs namely, tecovirimat, brincidofovir, and cidofovir have shown benefits in the therapeutic management of this infection.(49) Pre-exposure prophylaxis (Pre-EP) is indicated only in high-risk groups, such as immune-compromised persons or medical personnel who are frequently exposed to orthopox viruses, it is indicated when prolonged high exposure contact has taken place. Exposures requiring Pre-EP include unprotected direct mucocutaneous contact with an infected patient's skin, body fluids, contaminated fomites, as well as standing within 6 feet radius of an infected patient without personal protective equipment during any procedure that may produce aerosol from a patient's secretions, body fluids, and dry exudates.(50) . They are advised to follow safety measures and use effective personal protective equipment, such as respirator masks, disposable gloves, face shields, and long-sleeved gowns.(51,52)

VACCINATION

Small pox vaccines especially third generation vaccines such as Modified Vaccinia Ankara (MVA) strain have been found effective in preventing monkey pox infection, when administered pre-exposure or within early days post exposure.(53,54) The U.S FDA- approved JYNNEOS (Imvamune or Imvanex in other regions) , a non-replicating MVA- based vaccine, is specially authorized for monkeypox prevention and has been widely used in outbreak response scenarios. Studies indicate that vaccination may offer immunity lasting several years, though further research is needed to confirm the durability of protection against monkeypox in varying population.(55)

CONCLUSION

Monkeypox has emerged as a significant public health issue, particularly after smallpox was eradicated. Since it was first introduced by animals in endemic areas, it has spread to humans, especially among high-risk populations. While vaccination

with smallpox vaccines such as JYNNEOS has shown promise in mitigating the spread of monkeypox, there is a need for further research to assess long-term immunity, safety, and accessibility in diverse populations. Efforts to control the spread must focus on targeted vaccination strategies, robust contact tracing, and prompt treatment of cases to minimize morbidity and mortality. Education, early diagnosis, and efficient isolation are important public health tactics. Understanding changing epidemiology, enhancing prevention, and getting ready for future outbreaks require constant research, surveillance, and international cooperation. A global action protocol rooted in collaboration, is essential to control the spread of MPXV and prevent future outbreaks. Implementing these measures can enhance preparedness and resilience against emerging zoonotic diseases.

Declaration by Authors

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