

Review

A Systematic Overview of Monkeypox: from Origin to Treatment

Sheikh Rezzak Ali¹, Shahnaz Alom^{1,2}, Shuby Kumari¹, Farak Ali^{1,3}, Jakia Afruja⁴, Gireesh Kumar Singh⁵, Hans Raj Bhat¹, Surajit Kumar Ghosh¹, Anshul Shakya^{1*}

¹Department of Pharmaceutical Sciences, School of Science and Engineering, Dibrugarh University, Dibrugarh, 786004, Assam, India

²Department of Pharmacology, Girijananda Chowdhury Institute of Pharmaceutical Science, Tezpur, 784501, Sonitpur, Assam, India

³Department of Pharmaceutical Chemistry, Girijananda Chowdhury Institute of Pharmaceutical Science, Tezpur, 784501, Sonitpur, Assam, India

⁴Chaitanya Deemed to be University Pharmacy, Warangal, Telangana, 506001, India

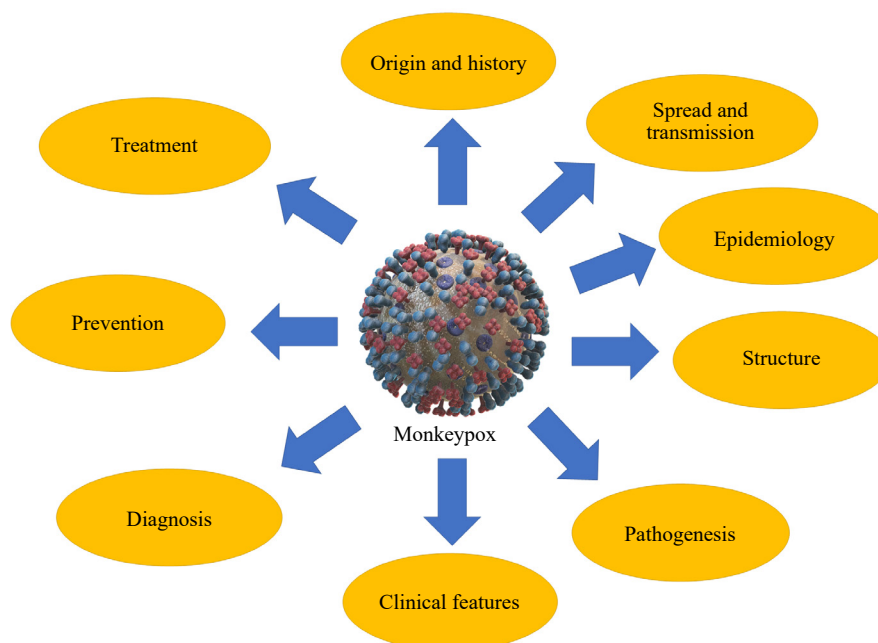
⁵Department of Pharmacy, School of Health Science, Central University of South Bihar, Gaya, 824 236, Bihar, India
E-mail: anshulshakya@dibru.ac.in

Received: 18 January 2023; **Revised:** 11 April 2023; **Accepted:** 18 April 2023

Abstract: The objective of this paper is to analyze existing data related to the monkeypox virus, its genomic characterization, transmission, prevention, and treatment available considering the current scenario of the monkeypox outbreak globally and posing a threat to public health. The literature search was performed in databases including PubMed, Science Direct, and Google Scholar up to September 2022. The monkeypox virus is a re-emerging threat to international travel and public health that poses fresh difficulties. Due to these effects, the World Health Organization (WHO) declared a human monkeypox public health emergency of international concern on July 23, 2022. The illness can spread from animals to humans, from humans to animals, and possibly from humans to humans. However, human-to-human transmission of the monkeypox virus is much more uncommon than animal-to-human transmission. During the outbreak of monkeypox in 2022, 5 continents have shown test positive in less than three months. Most of the cases were in men who have sex with men. There are several methods for diagnosis like genetic method, phenotypic method, immunological method, and electron microscopy. To prevent the spreading of the monkeypox virus, numerous precautions can be taken such as avoiding direct or indirect contact with an infected person, vaccination, or specific medication.

Keywords: genomic, transmission, diagnosis, vaccination, outbreak

Graphical abstract



Abbreviations

ACIP	Advisory Committee of Immunization Practices
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus Disease 2019
CPAP	Continuous Positive Airway Pressure
DNA	Deoxyribonucleic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EUA	Emergency Use Authorization
FDA	United States Food and Drug Administration
HIV	Human Immunodeficiency Virus
Ig	Immunoglobulin
IND	Investigational New Drug
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MPXV	Monkeypox Virus
MVA	Modified Vaccinia Ankara
PCR	Polymerase Chain Reaction
PEP	Post Exposure Prevention
PPPE	Proper Personal Protective Equipment
RNA	Ribonucleic acid
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
UK	United Kingdom
USA	United States of America
VIG	Vaccinia Immune Globulin
WHO	World Health Organization

1. Introduction

Public health experts are worried after the appearance of a new outbreak brought on by the MPXV which could pose a new threat while the world continues to be confronted by the COVID-19 pandemic [1]. The variola, cowpox, vaccinia viruses, and MPXV all come under the genus Orthopoxviruses [2]. Monkeys were the first primates to be infected with monkeypox, although it may also infect other species including Gambian pouched rats, squirrels, and dormice [3]. The family MPXV is the Poxviridae family which causes a zoonotic illness known as monkeypox. The Chordopoxvirinae subfamily of Poxviridae is further divided into other categories including Leporipoxvirus, Avipoxvirus, Capripoxvirus, Cervidpoxvirus, Orthopoxvirus, Suipoxvirus, Yatapoxvirus, Parapoxvirus. The Entomopoxvirinae subfamily of Poxviridae is further divided into four genera - α , β , δ and γ . Entomopoxvirus and these are acknowledged to infect invertebrates. The Orthopoxvirus genus contains 10 species, including monkeypox and smallpox. Despite being a DNA virus, monkeypox completes its entire cycle of life in the cytoplasm of diseased cells [4, 5].

The WHO has classified monkeypox as one of several infectious diseases that have the potential to spread and become endemic or pandemic, along with MERS-CoV, SARS-CoV, SARS-CoV-2, smallpox, Crimean-Congo hemorrhagic fever, influenza, yellow fever, Lassa fever, Ebola, Zika, Nipah, Hendra virus, Marburg virus infection [6, 7]. With a genomic size of about 200 kb, two virus lineages were recently found in the contemporary monkeypox rash in non-endemic nations, according to researchers [8]. The case involving travel in 2021 from Nigeria towards Maryland is connected to the branch or clade that has undergone the most sequencing to date and shows striking similarities to the genomes of the primary MPXV epidemic in 2022. Another clade is connected to the virus that was brought to Texas, USA, in 2021 by a traveler from Nigeria. In the year 2005, researchers examined the clinical, biochemical, and biological characteristics of proven cases of human monkeypox and concluded that the viral clade was relevant to the pathophysiology of human diseases are West Africa and Central Africa. By analyzing the proteins of several clades of the MPXV, it was conceivable to identify which viral proteins would be accountable for the observed variances in human pathogenicity [9].

The first instance of the MPXV was a pox-like sickness in 1959 inflicted on monkeys kept in a research institution in Copenhagen, Denmark [10]. The first monkeypox instance in humans in documented medical history occurred on September 1, 1970, when a child nine months old was brought to the Basankusu Hospital of Congo. A virus similar to the MPXV was revealed to be the source of the boy's ailment, which resembled smallpox [10-13]. Between 1970 (October) and 1971 (May), six human MPXV cases were documented in Nigeria, Liberia, and Sierra Leone. The very first human MPXV occurrence in Nigeria was noted in 1971. From that time until 1978, ten cases were reported [14]. Infections have occurred all across the world as a result of the MPXV's resurgence and spread. Before the 2022 outbreak, there had only been a small number of cases outside of Africa that were connected to either heading to Africa or taking diseased animals. In addition, the bulk of patients in the latest outbreaks are men, which sets them apart from earlier ones, the average age is in their thirties, and sexual transmission is quite likely. Anogenital lesions and rashes dominate the clinical appearance, which is rare and abnormal and largely spares the face and limbs [15].

2. Origin and history of monkeypox

The sporadic viral disease recognized as monkeypox affiliated with the Orthopoxvirus family is instigated by the MPXV and is endemic to places with rainforests, such as West Africa. The first MPXV was founded in 1958 by researchers at Copenhagen, Denmark and Africa's State Serum Institute. After the initial outbreak in the USA in 2003, which was connected to infected pet prairie dogs, it has spread globally. The utmost occurrence of monkeypox was recorded in Africa, in the period from February 1996 until February 1997. Instead of monkeys, numerous rodents and small animals have been proposed as the virus's likely origins. Monkeypox attracted widespread attention in the 1970s, following the worldwide elimination of smallpox, albeit its true ancestry is uncertain. The native prairie dogs kept alongside imported rodents from Ghana and Western Africa, where the sickened individuals contracted the disease through interaction with pet prairie dogs, are the main cause of the outbreak [16]. When a three-year-old girl was sent to the hospital in central Wisconsin on May 24 having a fever following a prairie dog bite on May 13, a mystery sickness was first noted. The mother of that girl felt unwell once more on May 26, 2003, and it was determined that a lesion on

her skin was caused by the poxvirus. Wisconsin experienced 11 confirmed and probable cases of monkeypox on June 6, 2003. These cases were connected through direct contact with prairie dogs. So, from May 29 to June 9, 2003, this virus was at its peak, 72 cases of the MPXV were documented as of July 30, 2003. This is how diverse test results from individuals with different diagnoses revealed a worrying situation as the biggest epidemic. Since 2003, there have been several instances of monkeypox recorded in several nations, with the greatest outbreak being in Nigeria in 2017 [17].

3. Spread and transmission of the disease

Monkeypox is not a familiar illness, it may spread either by being bitten by an animal or coming into close touch with its bodily fluids or sores. There may be a significant role for direct mucocutaneous contact and pulmonary exposure in the transmission of the MPXV from rodents to humans [16]. The risk factors for transmission include interacting skin, face, and mouth. It may also spread through respiratory droplets, direct contact, contaminated surfaces, contaminated bedding, living in the same home, or direct exposure to mucocutaneous abscesses on an affected person. Additionally, contamination of clothing or lines with infectious skin particles on them, etc., can cause transmission to the human body [18]. The virus may pass from animal to person, from one animal to another, or even from one human to another but transmission between people is, however, much less frequent than transmission between animals and people. The majority of human infections occur from bites, scratches, eating improperly cooked meat from infected animals, or close contact. The oropharyngeal and respiratory mucosal is disclosed as the site of inoculation following viral transmission, as well as the virus subsequently travels to the adjacent lymphatic system as primary viremia. The secondary viremia will allow the viral burden to circulate to far-off organs and lymph nodes. The overall process resembles incubation, which lasts for 7 to 14 days but is not contagious [16]. Monkeypox's precise host reservoir is unknown. Uncertainty surrounds the virus's ability to spread from animal to person, however, it is known that the virus can move from one animal to another before entering a human through an intermediary host [17]. There are various ways that the MPXV spreads, but the precise method is still being investigated. Humans may contract the disease from infected animals through bites and scratches. The MPXV is thought to be spread in a variety of ways, although the most frequent mechanisms of transmission are thought to include direct or indirect contact with sick humans or animals. Intimate skin or mucosal contact during sex may spread this disease, while the role of direct sexual transmission is unclear or not yet understood whether monkeypox is sexually transmissible or not [19].

4. Epidemiology of the MPXV

The MPXV occurred years ago, it was first recognized in a 9-month-old kid in 1970 in the Democratic Republic of Congo and then it affected people from many countries [13]. Among them, there are two different classes accountable for outbursts in central and west Africa, the West Basin clade and the more severe illness-causing Congo Basin clade [20]. The whole first incidence of monkeypox was reported in 1971 in a four-year aged girl, and the second instance was confirmed by the mother of the girl who was infected by her child [21]. For almost 40 years no case of monkeypox was recorded and then it re-emerged in September 2017 in Nigeria with 68 confirmed cases [21]. From 2017-2019, MPXV cases were reported in the 21-40 aged group with the verified cases in Nigeria having a 3:1 male-to-female ratio [22]. No MPXV cases were reported in 2020 owing to several variables, including the relocation of staff and resources from monitoring and responding to the MPXV to more lethal viral infections, such as COVID-19 [23].

In less than three months, tests on five continents during the 2022 monkeypox outbreak came back positive, and the majority of cases were in guys who had sex with other men [24]. Around May 17, 2022, the Laboratory Response Network of the Massachusetts Department of Public Health verified the existence of Orthopoxvirus DNA collected from lesion swabs of Massachusetts people by PCR. After those 9 states have shown a positive test of the MPXV [25]. Over 1,300 MPXV confirmed cases have been rising in at least 40 countries other than African countries in Europe, Asia, and Latin America as of June 10, 2022 [26]. Since the end of June 2022, cases are increasing globally affecting people from many countries, as it shows the sign and dangers of the widespread spreading, accordingly the WHO acknowledged the monkeypox epidemic, an international public health emergency. By July 23, 2022, there has been confirmation of over 17,000 cases throughout Asia [27]. Figure 1 indicates the global outbreak of monkeypox till June 2022 excluding

endemic African countries [28].

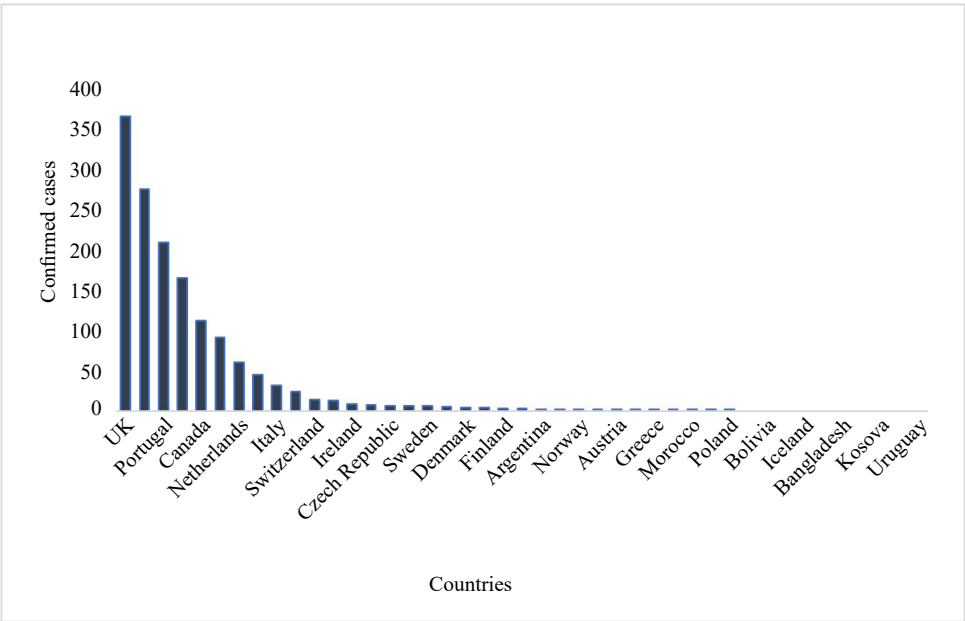


Figure 1. The global outbreak of monkeypox in 2022

5. Structure of the MPXV

MPXV comprises of large DNA genome, structurally similar to a smallpox virus. The capsid, an enormous and intricate protein cage, houses its vast DNA genome. It has surface tubules at the outer envelope. The lateral body comprises of palisade layer, core, and DNA. It has core fibrils surrounded by DNA. The detailed structure of the MPXV is shown in Figure 2.

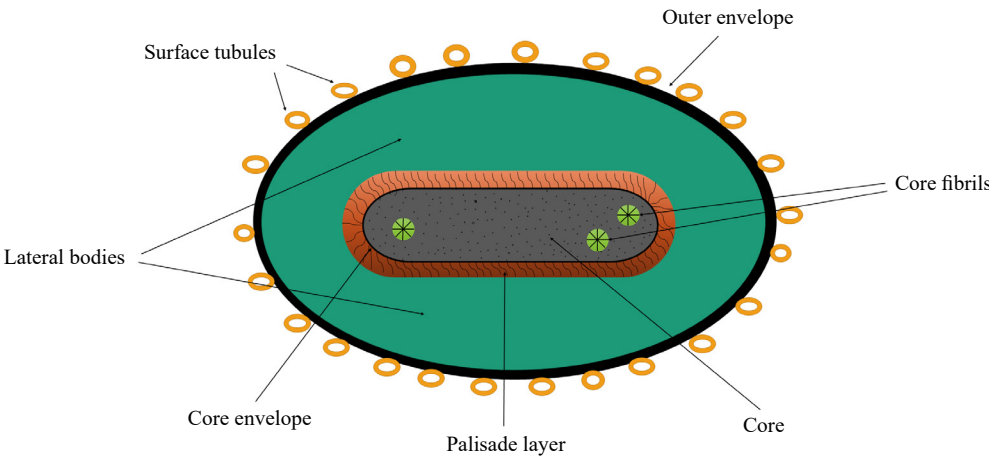


Figure 2. Structure of the MPXV

6. Pathogenesis of the MPXV

There are several potential ways that the MPXV can spread, but they are all thought to involve direct contact with infected people or animals. Although it can be difficult to pinpoint the exact exposure of a human case in areas where animal contact is common owing to rat infestations in dwellings and the hunting or processing of bushmeat from a variety of species, human illnesses have been linked to animal contact [29]. Direct engagement with or exposure to sick animals can result in the transfer of an animal's illness to humans. The most prevalent culprits for this are bodily fluids including saliva, excretions from the lungs, or exudate from cutaneous or mucosal sores [30]. In areas with a dearth of resources, such as food, households are compelled to kill and prepare small animals, increasing their chance of exposure to this virus. Extended face-face interaction, coughing or sneezing, and interaction with sores on an infected person are typical sources of human-human transfer [31]. Using the same bedding, residing in the same residence, and employing the same utensils for drinking or eating are significant risk factors for viral transmission among family members. In the continuing monkeypox epidemic, it has also been noticed that men who have sex with other males are more likely to get sick [32]. The pathophysiology and pathogenesis of monkeypox begin with this transfer, regardless of whether the virus transmission is human-human or animal-human.

The nasopharynx, oropharynx, and intradermal pathways are all ways that MPXV might infect a host. Similar to smallpox, the infectious process for the MPXV starts with exposure to the host's oropharyngeal or respiratory mucosa. In human-human transmission, the oropharyngeal and respiratory mucosa assist as the inoculation site, where the virus multiplies following viral entry. The infection rate grows and subsequently extends to the nearby lymph nodes in primary viremia. In secondary viremia, the infection rate distributes to distant lymph nodes and tissues through the circulatory system. The overall process simulates the incubation stage, which usually lasts 7-14 days but may last as long as 21 days [4, 33]. The incubation stage does not show any clinical symptoms; hence this period is not spreadable. The medical symptoms and signs emerge in the prodromal stage, and secondary viral replication extends to the eyes, skin, digestive system, and lungs from the lymphoid organs. The prodromal period is supposed to be when a person is most contagious. This is partly because of signs like lymphadenopathy and mucocutaneous lesions, among other non-specific symptoms (headache, fever, backache, myalgia, chills, rushes). The non-specific, characteristic symptoms of the virus begin 1-2 weeks following exposure to the virus [34]. The prodromal stage is characterized by the onset of fever, lymphadenopathy, myalgias, and other immune system-stimulating symptoms. Because it lacks specificity, a person who is sick can mistakenly believe that these early symptoms are those of the common cold or seasonal flu. When the immune system is first aroused, the lymph nodes in the cervical, maxillary, and inguinal regions will always enlarge, and this will happen concurrently with the development of fever [32]. Rashes characteristically started to show up 1-3 days after the arrival of fever and lymphadenopathy before the 2022 pandemic. According to Harris, prodromal symptoms for some patients at the beginning of these unusual cases may be slight or barely noticeable, noting that certain people might not have any indications at all until the symptoms develop [34]. Typically, the fever will start to go down the day after the rash appears or even up to three days later. The rash will initially occur on the face before spreading fast in a centrifugal pattern across the body [29, 32].

The Congo clade, also recognized as the Congo Basin clade, which originated in Central Africa, is more aggressive than the West African clade [9]. Congo MPXV causes T-cell activation via the TCR (T-cell receptor). It's interesting to note, though, that when human cells are produced from people carrying the MPXV, inflammatory cytokine production is decreased. This shows that the monkey poxvirus may create a modulator that inhibits the responses of the host T-cells [35]. According to reports, the Central African monkeypox clade's capacity to specifically control the host's apoptosis suggests that, in contrast to the West African clade, it downregulates specific host responses [36]. A detailed pathogenesis of the MPXV is shown in Figure 3.

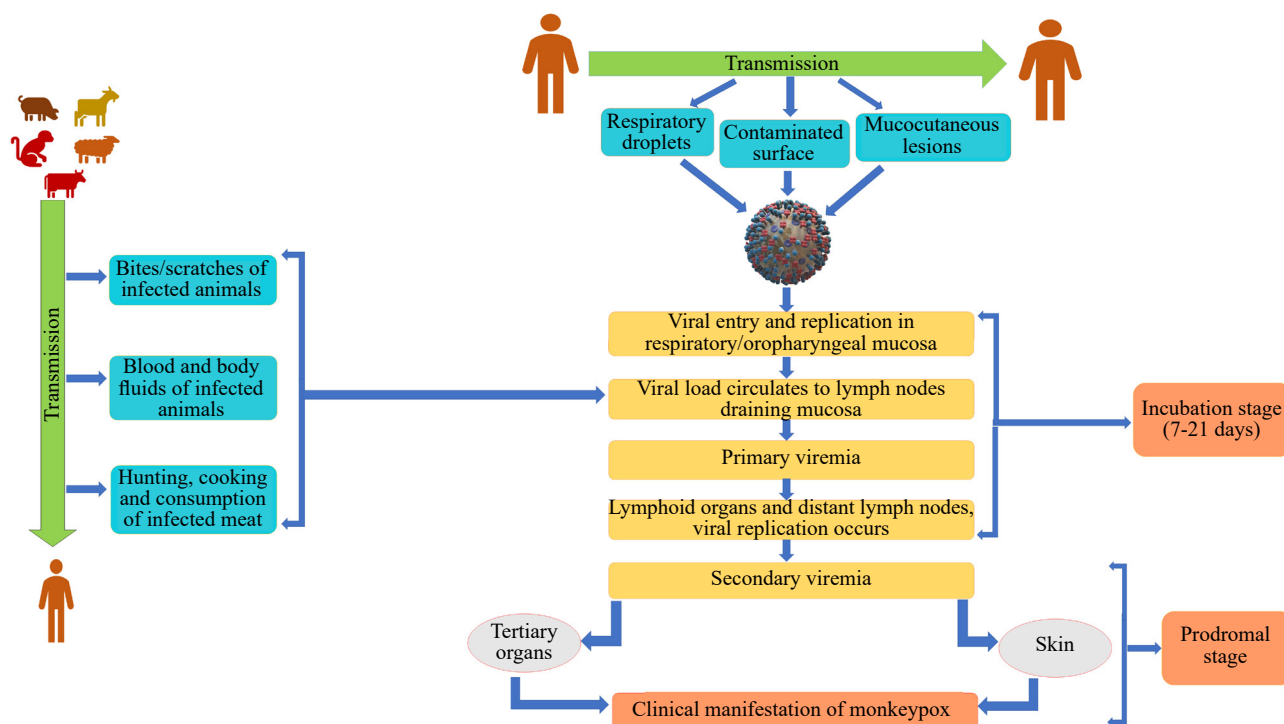


Figure 3. Pathogenesis of the MPXV

7. Clinical features of monkeypox

Even though monkeypox symptoms are less severe, they remarkably resemble smallpox symptoms. Patients frequently report having come into touch with animals or persons who were infected with the MPXV in the past. They first exhibit symptoms that resemble ‘influenza’, then develop skin sores, which manifest as abscesses and scarring after scabs. The MPXV infection progression can be roughly split into two phases: the prodromal phase which lasts for 0-2 days and includes symptoms such as fever, lethargy, headaches, muscle aches, and lymphadenopathy, and the rash phase lasts for 7-21 days. When the rash appears, the patient is contagious, and it frequently appears 1 to 5 days after the fever. The major body parts where the rash is most obvious are the cheeks, hands, the soles of the feet, the oral cavity, the genital area, and the eye. The rash progresses over the course of two to four weeks, the plaque develops into papules, blisters, pustules, scabs, and finally shed skin. Locations with a few to thousands of lesions are possible [5, 37, 38]. The rash has been reported to progress through a variety of stages before the desquamation phase when the scabs start to peel off. These characteristic lesions frequently start out looking like enanthem, macular, or popular lesions before becoming vesicular and pustular, according to research [29, 39]. Crusts gradually form on the pustules, and after one to two weeks, they exfoliate. 54% of patients who have had vaccinations have sensitive maxillary, cervical, and inguinal lymphadenopathy, compared to 84% of uninfected individuals, respectively, distinguishing MPXV infection from smallpox-like first signs and symptoms [29, 40]. Large sections of skin may fall off in severe cases when the lesion areas overlap. Numerous complications may also be present, among them are dehydration driven by vomiting and diarrhea, recurrent bacterial infections, respiratory issues, bronchopneumonia, encephalopathy, and corneal diseases with vision loss [5, 37]. The presence of lymphadenopathy suggests that MPXV may be more strongly recognized by the immune system than variola [29]. Patients with immunosuppressed states prolonged viral particle exposure and the development of comorbidities [40]. Children are more likely to experience severe instances, which also have a case fatality rate of 1%-10% [41, 42]. Clinical signs and symptoms of monkeypox infection are shown in Figure 4.

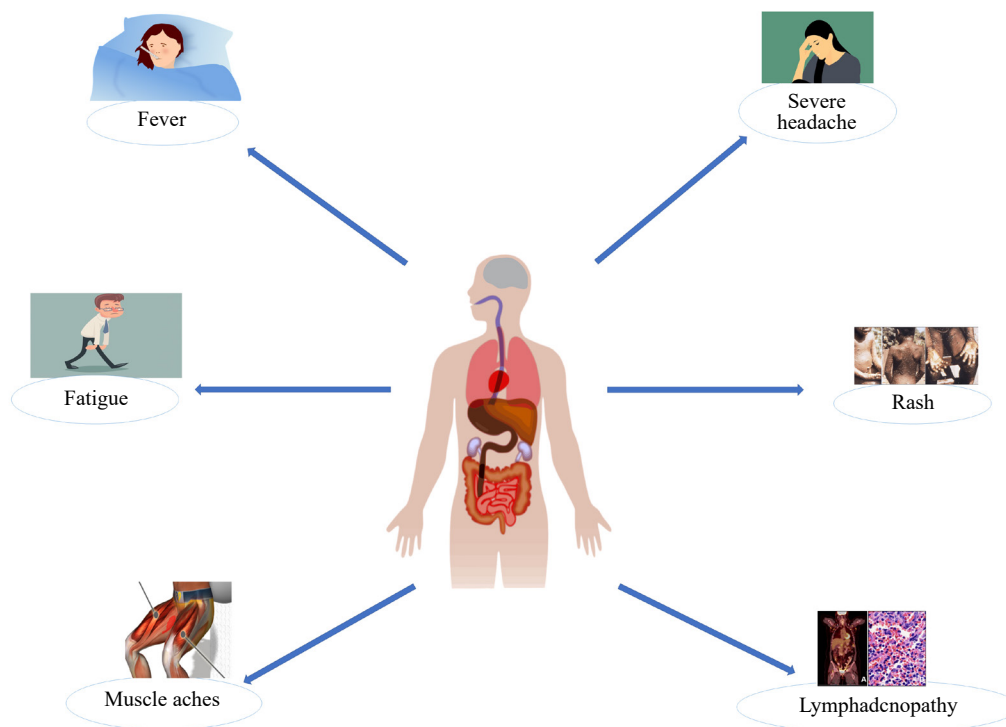


Figure 4. Clinical signs and symptoms of monkeypox infection

8. Diagnosis

8.1 Genetic methods

RT-PCR (real-time PCR) is the most preferred technique for standard diagnosis among the various approaches for MPXV nucleic acid detection currently available [43]. Typically, targets for PCR amplification are chosen based on the retained portions of the outer envelope protein gene named B6R [44], Subunit 18 of the DNA-dependent RNA polymerase named RPO18 [45], DNA polymerase gene named E9L [20], and complement binding proteins such as C3L, F3L, N3R genes [46, 47]. The benchmark for separating MPXV from further Orthopoxviruses is whole genome sequencing [48, 49]. According to the initial genome sequencing and phylogenetic study, the virus from the current monkeypox outbreak is thought to be closely interrelated to the MPXV recovered from the Singapore, UK, and Israel outbursts and is from the mild West African clade [50]. Genome sequencing is expensive, and evaluating the sequencing data subsequently necessitates a lot of processing power. As a result, it might not be the greatest tool for characterization, particularly in sub-Saharan African nations. Even though RT-PCR is still the most popular way for standard diagnosing MPXV, field genome sequencing technologies, such as Oxford Nanopore MinION, must be used in conjunction with it to offer to obtain real-time viral genome data is essential for taking evidence-based epidemiological precautions. In West African settings with limited resources, using MinION during the Ebola outbreak's genetic monitoring was effectively conducted [51]. In addition, technologies including restriction length fragment polymorphism (RFLP), to identify monkeypox DNA, loop-mediated isothermal amplification and recombinase polymerase amplification have both been designed [52-54].

8.2 Immunological methods

The enzyme-linked immunosorbent method can confirm specific IgM and IgG antibodies in the blood of monkeypox patients. Acute and convalescent serum antibody levels that have increased by fourfold can be utilized to diagnose MPXV infection. Because of the MPXV's antigenic cross-reactivity with other poxviruses, the clarity is poor.

As a result, this approach, which is frequently employed in epidemiological research, cannot identify the MPXV reliably [4]. A positive IgG acquisition ELISA demonstrates that the person has already been exposed to monkeypox either by vaccination or spontaneous infection. However, both unprotected and vaccinated people exhibit symptoms of recent exposure to this virus [55, 56].

8.3 Phenotypic methods

In conjunction with the clinical diagnosis, the virus takes approximately 4 to 21 days to incubate, and it is often accompanied by a prodromal illness with certain other indications, such as swelling of the lymph nodes, fever, headache, myalgia, back pain, strong asthenia, severe headache, drenching sweats, pharyngitis, and malaise. Vesiculopustular rashes start to begin on the face and progress to other parts of the body within the first ten days after the exanthema phase, which precedes the prodromal phase. Patients with the MPXV have monomorphic, stiff, pea-sized lesions that resemble smallpox. Smallpox cannot be confused with MPXV lesions because of its modest centrifugal propagation and crop-like morphology. Swelling of lymph is the major clinical distinction that differentiates the MPXV from another poxvirus [29, 43, 57-60]. In a cohort study containing 645 subjects, the detailed clinical description of monkeypox has been demonstrated to have high sensitivity of more than 90% and low specificity of below 30% in the absence of laboratory confirmation. Clinical case definition for monkeypox is critical for the spotting of such situations when doing surveillance [61, 62].

8.4 Electron microscopy

The diagnosis may be aided by electron microscopy depending on the morphological characteristics of the MPXV. When observed under an electron microscope, the virus exhibits a brick-like structure with lateral bodies attached to a central core that is between 200 and 300 nm in size. Because the MPXV and other poxviruses cannot be discriminated against based on their morphology, this method can only provide hints that the virus comes under a family named the poxvirus family [29, 57, 59].

8.5 Other tests

MPXV antigen detection methods include multiplexed immunofluorescence imaging and immunochemistry analysis [63]. Viral isolation and culture involve creating and analyzing a live virus from a human specimen, which is also essential for determining a certain diagnosis [37].

9. Prevention strategies for MPXV

While the world continues to be threatened by the COVID-19 pandemic, public health experts worry that the appearance of a new outbreak caused by the MPXV could create a new threat [64, 65]. According to the CDC, supportive care is often enough for individuals with a MPXV infection because there are currently no particular medicines available [66]. Smallpox vaccines, antivirals which are all available after consulting with the CDC, however have been used to manage tiny outbreaks. Monkeypox can be prevented and treated similarly to other Orthopoxviruses infections, and up until it is determined that a case is not monkeypox, all confirmed Orthopoxviruses cases should be handled as such [64].

To prevent the spreading of the MPXV, several precautions can be taken. Among them include avoiding direct contact with animals that might be contaminated with the virus, such as ill or dead animals found in places where monkeypox occurs, avoiding touch with bedding and other items that have come into contact with sick animals, separating affected patients from those who might transmit the virus, and handwashing after coming into contact with infected humans or animals. The virus itself can be used as a vaccine to protect animals in the case of a monkeypox epidemic in a monkey colony. The transmission of the virus outside of Africa can be stopped by preventing the trade in animals that carry the MPXV, for as by restricting or banning the shipping of small African mammals and monkeys. Animals kept in captivity should not receive the smallpox vaccine. Instead, sick animals should be quarantined as soon

as possible and kept apart from the rest of the animals. Animals that may have come into touch with the sick animals should be isolated for 30 days and kept an eye out for symptoms of monkeypox. Without a specific drug or vaccine, the only approach to avoid infection is to raise public knowledge of the risk factors and educate people about the steps they may take to lessen their exposure to the virus [65, 67].

Data suggest that smallpox vaccination can reduce the severity of the clinical indications of illness and provide protection against the MPXV [64]. ACAM2000[®] and JYNNEOS[™] also known as IMVAMUNE, IMVANEX, and MVA-BN are licensed for smallpox; the Aventis Pasteur Smallpox Vaccine could be used for smallpox under an IND protocol. Currently, the US Strategic National Stockpile has three smallpox vaccinations. JYNNEOS[™] is an attenuated, non-replicating Orthopoxviruses that is created from the modified vaccinia Ankara-Bavarian Nordic (MVA-BN strain) [68]. The FDA has officially approved it for use in preventing smallpox and monkeypox sickness in anyone aged 18 and older who has been proven to be at high risk of developing either monkeypox or smallpox disease [69]. According to historical evidence, vaccinia virus smallpox immunization was about 85% effective against monkeypox [70]. The vaccine, known as IMVANEX[®], is approved in Europe for the prevention of smallpox despite being used off-label in the UK to treat instances of monkeypox [64].

ACAM2000[®] is prepared by using live vaccinia virus. It was approved by the FDA in August 2007 and took the place of the earlier Orthopoxviruses vaccine Dryvax[®], which the manufacturer had discontinued [64]. For people who have been shown to have a high risk of contracting smallpox, ACAM2000[®] is recommended for active vaccination against the illness. During an outbreak, the CDC has an emergency access IND protocol that permits the use of ACAM2000[®] for infections caused by non-variola Orthopoxviruses (such as monkeypox) [68].

JYNNEOS[™] and ACAM2000[®] differ from each other in several ways [68]. ACAM2000[®] is a MVA virus that is replication-competent, whereas JYNNEOS[™] is a MVA virus that is replication-deficient. ACAM2000[®], as opposed to JYNNEOS[™], does not result in a substantial cutaneous reactivity at the inoculation site as a result. As a result, using ACAM2000[®] carries a danger of accidental inoculation and autoinoculation, however using JYNNEOS[™] has no such risk. Eczema vaccinatum and progressive vaccinia may develop in some people who receive replication-competent vaccinia vaccines like ACAM2000[®] due to unchecked viral replication [64]. Eczema vaccinatum can occur in people with atopic dermatitis or eczema, although progressive vaccinia is typically found in immunocompromised people. According to recommendations, ACAM2000[®] should be avoided in groups like sex workers and HIV-positive people who are at higher risk of undiagnosed HIV, the population from which the majority of current non-African cases are being identified, and a population from which monkeypox may spread more widely [71]. Additionally, with replication-competent vaccines, unintentional transmission can happen, including vertical co-transmission leading to fetal vaccinia, which can be lethal to the fetus or baby. ACAM2000[®] vaccinees are predicted to have post-vaccination encephalitis and myopericarditis which is estimated to occur in 5.7 per 1,000 initial ACAM2000[®] vaccinees, which are both major side effects that are observed more frequently with ACAM2000[®] than with JYNNEOS[™]. The FDA evaluated ACAM2000[®]'s efficacy by contrasting immunologic responses and acceptance rates between ACAM2000[®] and Dryvax. Similar to this, the FDA evaluated the efficacy of JYNNEOS[™] by contrasting its immunologic response to that of ACAM2000[®] and also considering supportive animal research. JYNNEOS[™] is given in two doses over the course of 28 days whereas ACAM2000[®] is supplied subcutaneously in a single dose utilizing the multiple puncture technique and a bifurcated needle [64].

Attenuated vaccinia virus of MVA is unable to complete reproduction in mammalian cells. When the MPXV was administered in lethal doses to primate models, MVA demonstrated protection. However, in primates with substantially reduced T-cell function, this vaccination has not provided protection. Another vaccine modified to stop viral replication is LC16m8, which has demonstrated protection against severe monkeypox disease in non-human primates. In Japan, more than 50,000 school children received the LC16m8 vaccine with little side effects being documented [29].

9.1 Early prevention and care

Vulnerable individuals who run the risk of occupational Orthopoxviruses exposure are advised to get vaccinated, according to the ACIP. It is advised that anyone working in a research facility, a clinical lab performing Orthopoxviruses diagnostic testing, or a member of a selected response team receives vaccinations if they might be exposed to orthodox viruses at work. In addition, based on shared clinical decision-making, immunization can be provided to medical staff who use ACAM2000[®] or treat patients who have replication-competent Orthopoxviruses [64, 72].

9.2 Post-exposure prevention and care

Monkeypox transmission requires protracted close contact with a person who is exhibiting symptoms. PEP is typically not necessary for brief encounters and those carried out with the PPPE and following basic procedures because they do not pose a high risk. To assess exposure risk and make wise choices regarding PEP, the CDC has produced well-informed recommendations. The first dose of the vaccine should be given within four days of being exposed to prevent sickness, according to the CDC. Vaccination may lessen disease symptoms but may not stop disease onset if administered 4-14 days after the exposure date [64]. In the event of unprotected skin-to-skin contact with mucous membranes, skin, lesions, or bodily fluids, such as during sexual contact, accidental splashes of patient saliva into someone's eyes or mouth, or ungloved contact with the patient or contaminated materials like contaminated linen or clothing, as well as being in a patient's room or within six feet of a patient while performing any procedures, it is advised to monitor high-level exposures and receive PEP vaccination. To assess whether the advantages of PEP outweigh the hazards, it would be advised to monitor such exposure to some extent and make informed clinical decisions on an individual basis [55]. Activities that cause sleeves and other areas of a person's clothing to come into touch with a patient's skin lesions, bodily fluids, soiled bed sheets, or dressings are exposure characteristics for a moderate level of exposure. These exposure characteristics include spending three or more hours near a patient who is not wearing a surgical mask for at least six feet [61, 72].

10. Treatments

10.1 Antiviral treatment

Monkeypox infections can be treated with the same antivirals that treat smallpox in animals. Although their efficacy has not been extensively analyzed, some drugs have been studied at human dose levels [73]. The vaccinia vaccine, cidofovir, tecovirimat, and VIG may be useful in treating monkeypox while there are currently no specific medications for monkeypox disease [32, 72]. The EMA granted tecovirimat approval for use against monkeypox in 2022, according to the WHO. It was created to treat smallpox. Since tecovirimat is not currently readily accessible, any usage of it needs to be closely supervised. By blocking viral DNA polymerase, cidofovir has antiviral efficacy against several viruses [17]. Numerous Orthopoxviruses, including variola, vaccinia, cowpox, ectromelia, rabbitpox, and monkeypox, have been reported to be specifically susceptible to tecovirimat [32]. An oral inhibitor of intracellular viral release, tecovirimat, may have therapeutic benefits for treating monkeypox [17].

10.2 Brincidofovir and cidofovir

Although there is no established cure for humans, animal research revealed that antiviral treatment with cidofovir or a similar acyclic nucleoside phosphonate analog is effective. In comparison to the therapeutic use of the smallpox vaccination, antiviral drugs are more effective at reducing animal mortality. Most of the time, supportive care is provided along with the medication. Many animals recover on their own and antiretroviral drugs be helpful in experimental infection. The CDC advises that all animals with suspected monkeypox be put to death to stop the spread of the disease [65]. Since June 2021, brincidofovir has been authorized in the US for the treatment of smallpox. An oral counterpart of the injectable medicine cidofovir, brincidofovir, may have a better safety profile than cidofovir, such as reduced renal damage [64, 74]. These medications function by preventing viral DNA polymerase [75]. Despite the lack of trials exploring its use in treating monkeypox infections in animal models, brincidofovir's effectiveness against Orthopoxviruses infections has been proven [76, 77]. Clinical evidence regarding the efficiency of cidofovir against monkeypox in people is still lacking, despite reports of its in vitro activity and effectiveness against lethal MPXV infections in animals. In addition to probenecid therapy and intravenous saline, cidofovir must be administered. Liver function tests must be done before and during treatment because brincidofovir may cause increases in serum transaminases and bilirubin. Through an IND or EUA, these treatments can be obtained [64, 72].

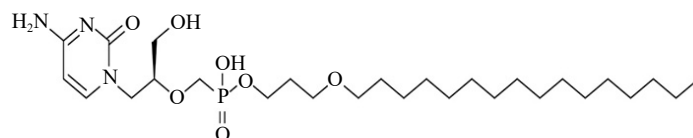


Figure 5. Structure of brincidofovir [78]

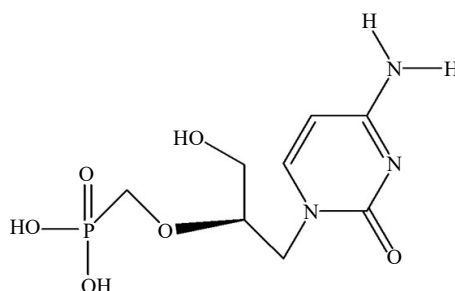


Figure 6. Structure of cidofovir [79]

10.3 Tecovirimat

Tecovirimat, also known as ST-246 or TPOXX, is the first antiviral to be approved for the treatment of smallpox in adults and children weighing at least 3 kg, and it is usually regarded as the best choice [64, 74]. Dual therapy with tecovirimat and brincidofovir may be utilized in patients with advanced illness. By preventing the development and discharge of the virus from the infected cell at its terminal stages, the viral envelope protein VP37, which is inhibited by tecovirimat, prevents the virus from spreading within an infected host [64, 72]. Investigations on animals treated with tecovirimat at various sickness phases have shown greater survival from deadly MPXV infections compared to animals given a placebo, even though its effectiveness in treating monkeypox in people has not been examined [80]. Use of tecovirimat for non-variola Orthopoxviruses infections, such as monkeypox, is permitted under the CDC's Emergency Access Investigational New Protocol. The protocol also authorizes opening an oral capsule and mixing its contents with liquid or soft food for young patients weighing less than 13 kg. The Strategic National Stockpile provides tecovirimat as an oral capsule or an intravenous vial [72, 74].

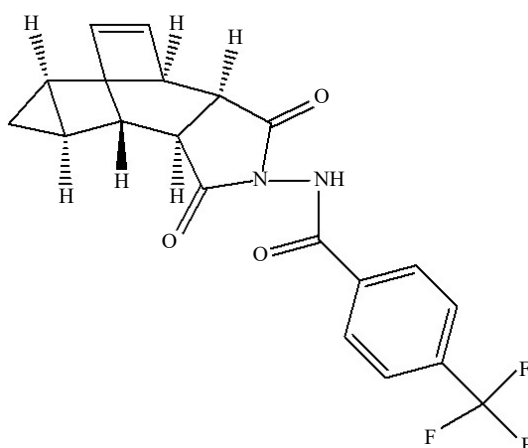


Figure 7. Structure of tecovirimat [81]

11. Additional supportive measure

Despite the suggested treatment options, symptomatic and supportive therapy is the cornerstone of managing a MPXV infection. It's important to understand that there is no known treatment for monkeypox other than symptom management and avoiding complications. Considering the 2003 US monkeypox outbreak and the current global case presentation, more research is needed before any therapeutic or vaccine can be created [64].

The majority of monkeypox patients heal without any medical assistance. To reduce gastrointestinal fluid losses, those who experience gastrointestinal symptoms for example vomiting or diarrhea will need oral or intravenous rehydration [64]. Oral or intravenous antibiotics for prophylaxis, nebulizer therapies, and non-invasive ventilation like CPAP can all be used in cases of symptoms of respiratory distress or bronchopneumonia. As a supportive measure, intravenous or oral rehydration, intravenous or oral antiemetic and antidiarrheal medicines, supplementary oxygen, corticosteroids, insulin, and oral or intravenous antibiotics can be utilized for symptoms of sepsis. In case of symptoms of fever, antipyretic drugs and external cooling can be used; and for symptoms of superinfection skin, oral/intravenous antibiotics, incision, and drainage, advanced wound management such as negative pressure wound therapy can be used. Oral or intravenous anti-inflammatory, analgesic drugs can be used in case of inflammation and lymphadenopathy, likewise for symptoms of corneal infection, ophthalmic antibiotics or antivirals, and corticosteroids can be used. Lastly, the application of moist occlusive dressings for skin scarring or cellulitis or skin lesions can be used as a supportive measure to treat MPXV infection [32].

12. Future prospects

The burden of the disease may upsurge and monkeypox has been estimated as a global emergency. Since monkeypox has not previously been experienced in India, clinicians here have little knowledge of the virus, there are few diagnostic tools readily available, the illness's course and treatment are not well established, and therapies and preemptive dealings are not sound understood. Practitioners should keep an elevated index of concern for this condition and adhere to the procedure for diagnosis, monitoring, and quarantine of patients, as well as dispel public fears and misconceptions. Even though the disease in nonendemic nations has received attention globally, effort should be paid to governing the disease in Africa, where the majority of loss of human beings occurred. Future generations should remember to pay attention to neglected tropical illnesses. No one is safe in the current era of globalization unless everyone is safe. Drug repurposing can be one easy option for finding effective drug molecules against monkeypox. So many antiviral drugs have been known to exist which can be tried against this virus. Molecular docking studies, plant-based phytomedicines, and herbal drug therapy can be suitable options for the development of a drug against monkeypox.

13. Conclusion

Monkeypox is a viral disease which is causing a pandemic-like situation as people have suffered from SARS-CoV-2, MERS-CoV, Ebola, and SARS-CoV. As a result, Monkeypox was considered to be pandemic on July 23, 2022. A study revealed that the first case of monkeypox was found to be in 1958 as well as it re-emerges in 2022 after such a long time. The mode of transmission is an animal bite or direct contact of a human with animal body fluids or lesions. It may also transfer through respiratory droplets, direct contact, contaminated surfaces, contaminated bedding, living in the same home, or direct connection with mucocutaneous lesions on a diseased person. Additionally, contamination of clothing or linings with infectious skin particles can cause transmission to the human body. Development of rashes can be observed in cheeks, palms, oral mucosa, soles of the feet, reproductive organs, and eyes the main areas of the body which may last up to two to four weeks. RT-PCR test is the most preferable way to diagnose monkeypox-infected patients. Apart from RT-PCR, other techniques such as field genome sequencing technologies like Oxford Nanopore MinION and ELISA, phenotypic visualization, electron microscopy, immunofluorescence imaging, and immunochemistry analysis are also used.

To prevent the spreading of the MPXV, numerous precautions can be taken such as avoiding direct or indirect

contact with an infected person, vaccination or specific medication. Earlier, ACAM2000[®] and JYNNEOS[™] correspondingly recognized as IMVAMUNE, MVA-BN, and IMVANEX, were used as effective vaccines against smallpox. Regarding medication against monkeypox, antiviral drugs like brincidofovir, tecovirimat and cidofovir can be chosen drug. These drug work by preventing the polymerization of viral DNA whereas it is advised to take probenecid along with cidofovir. To reduce gastrointestinal fluid losses, those who experience gastrointestinal indications such as vomiting, and diarrhea will need intravenous or orally administered rehydration. Antipyretic medications, outer chilling, and sophisticated wound care techniques, such as negative pressure wound treatment, can be employed in cases of fever and signs of skin superinfection, respectively.

Acknowledgement

The authors are highly thankful to Library, Dibrugarh University, Dibrugarh for providing enriched e-resources for the adequate search of relevant journals.

Conflict of interest

There is no conflict of interest for this study.

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