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Monkeypox - An Overview of Transmission, Clinical Manifestations and Treatment Approaches

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ABSTRACT: Monkeypox (MPX) is a zoonotic viral disease with symptoms like smallpox but less clinical severity. It is an enveloped double-stranded DNA virus that belongs to the Orthopoxvirus genus of the Poxviridae family. Monkeypox is usually a self-limited disease with symptoms lasting from 2 to 4 weeks. However, the extent to which asymptomatic infection occurs is unknown. Since humans are not the causative organism of the monkeypox virus, rodents and primates are the most likely sources of the virus' transmission to humans. Crowded living quarters, poor hygiene, discontinuation of the smallpox vaccination, and decreased herd immunity are implicated in the human-to-human transmission of a disease that earlier was thought to be transmitted via animal contacts. Further, there are high similarities between this disease and smallpox in their pathogenesis except for the mode of viral entries. Due to inconsistencies in the epidemiological investigations, precise and adequate information regarding the virulence and transmissibility of the human monkeypox illness is scarce. Although smallpox vaccinations are believed to be efficacious against monkeypox, there are no known therapies for monkeypox infection that have been experimentally shown. However, the access to the vaccination must be carried out in a collaborative approach between the researchers and health authorities to ascertain the need to enable scale-up for their capacity to curb this infectious illness.

INTRODUCTION

While the world is still getting used to dealing with the SARS-CoV-2's changing variations and effects, a new menace has emerged, further raising global unease. Monkeypox is a chronic disease that is common in several African countries. It is caused by an encapsulated double-stranded DNA virus that is a member of the *Orthopoxvirus* genus of the *Poxviridae* family. However, the outbreak has raised concerns throughout the world, and on July 23, the World Health Organization (WHO) proclaimed the fast spread of the monkey pox outbreak to be a public health emergency of international concern (PHEIC). More than 76 different nations have reported more than 35,000 cases of monkeypox so far this year (Cohen, J., 2022).

A 1958 shipment of sick monkeys from Singapore to a Danish research centre led to the first inaccessibility and identification of the monkeypox virus (MPXV). The first instances of human monkeypox were discovered in 1970, and WHO researchers diligently examined the disease throughout the 1980s. Although the virus was identified from a young boy in the Democratic Republic of the Congo who was thought to have smallpox in 1970, that marked the first known instance of the disease in a human (Ladnyj, I. D., et.al, 1972).

Indications of significant outbreaks of human monkeypox cases in the Democratic Republic of the Congo during 1997–1998 sparked concerns about whether monkeypox was potentially replacing smallpox as a serious illness. The reports of a significant number of cases of human monkeypox in 1997 were extensively reported and created concern (Meyer, H., et.al, 2002). As the research progressed, it became evident that a vast percentage of the cases were chickenpox, and there was no evidence to support the idea that the virus had changed its nature. However, until very recently, field research could not be conducted due to civil conflict. There are approximately 13 MPXV strains with fully sequenced genomes that range in size from 196 to 206 kb (Chen, N., et.al, 2005; Haller, S. L., et.al, 2014).

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In India, the first two MPXV cases were discovered and their genomes were characterized by ICMR-NIV researchers. They were travellers from the United Arab Emirates to India in July 2022. The study, was accepted by the Institutional Human Ethics Committee of the ICMR-NIV, Pune, India, under the project "Providing diagnostic support for referred samples of viral haemorrhagic fever and other unknown aetiology and outbreak investigation," was published on August 23 this year in the *Journal of Infections*. There are currently 11 confirmed instances of monkeypox in the nation, along with one fatality. The report proposes that MPXV infection in India was introduced due to travel after analysing the two instances of confirmed monkeypox there (Shete AM, et.al, 2022; Mascarenhas A., 2022).

The virus is divided into two lineages: the Congo Basin lineage and the West African lineage. The Congo Basin lineage, also known as lineage I, and the West African-derived lineage, also known as lineage II, are two MPXV lineages that may be distinguished based on their geographical location. Significantly, the virulence and transmissibility of MPXV lineage I and lineage II differ from one another. lineage II strains produce less severe illnesses than MPXV lineage I infections, which have a greater mortality rate (about 10%) in experimentally infected humans and animals (Likos, A. M., et.al, 2005). Both humans and nonhuman primates exhibit varying degrees of severity of illness, with the West African lineage producing an illness with significant morbidity and infrequent person-to-person dissemination (Chauhan, R. P., et.al, 2020; Wachtman, L., et.al, 2012). Due of global delays in identification and reaction, local health systems have become overburdened. Instead, numerous countries have implemented powerful and successful curative measures that have reduced the number of fatalities since the pandemics' inception (Dubey, A. K., et.al, 2020). Given that monkeypox is a contagious and communicable illness, it will be important to suggest and implement appropriate precautions to avoid it as much as feasible. Even if physical intercourse is considered to be the least likely method of infection, it is nonetheless conceivable. It is therefore advised to engage in protected sex. The relevance of sewerage systems and monitoring has been demonstrated by the prevalence of monkeypox DNA in urine and faeces specimens, as determined by the team of researchers (Peiró-Mestres, A., et.al, 2022; Singla, R. K., et.al, 2022). However, to the best of our knowledge, despite the abundance of publications emphasizing illnesses, epidemiological studies, propagation, pathogenesis, prognosis, and clinical characteristics, no prior state-of-the-art has made any significant efforts to repurpose as well as novel treatment interventions at the present state of the worldwide defining characteristics.

TRANSMISSION

The monkeypox virus can be transmitted from one individual to another by physical intimacy with blisters, bodily fluids, coughing and sneezing, and infected objects like bedding. Monkeypox typically takes 6 to 13 days to incubate, although it can take anywhere between 5 and 21 days (Centers for Disease Control and Prevention, 2022a). The monkeypox virus has been shown to infect many kinds of animals. There is still uncertainty regarding the monkeypox virus's natural history, and further research is required to pinpoint the precise reservoir or reservoirs as well as the mechanisms sustaining viral circulation in the environment. A potential risk factor is consuming meat that has not been properly prepared and other animal byproducts from diseased animals (Guidelines for management of Monkeypox Disease, 2022).

The incidence of MPXV infections in humans is underestimated since the majority of the data that researchers currently have come across are from passive surveillance, which frequently misses specific occurrences. Despite such, contemporary scientific publications based on passive surveillance (although limited in number) demonstrate that human MPXV infections occurred commonly. There isn't enough information available to determine if other aspects, such the rate of transfer from person to person, the rates of morbidity and mortality, or the patterns of transmission, have changed. It is clear that monkeypox incidence has increased (Rimoin, A. W., et.al, 2010).

Although no research has yet definitively discovered a reservoir or host for the MPX virus, hamsters and mammals other than humans have been revealed to be potential natural reservoir-related hosts of this viral infection. Studying host-pathogen interactions, the impact of agroclimatic change on MPX virus, and the biology of the virus are all made more challenging by the size of the natural reservoir (Bunge EM, et.al, 2022; Al-Tammemi AB, et.al, 2022). Due of its widespread distribution throughout many tissues, the MPX virus lacks any distinct tissue tropism. Non-human primates (NHP) have experienced natural epidemics of MPXV both in the wild and in practical trials. The natural host is unknown, but the virus can naturally infect squirrels, rodents, rabbits, and other NHPs (Parker, S., et.al, 2013). Researchers established that ground squirrels functioned as the primary reservoirs of the monkeypox virus in nature and that man only sometimes contracted the disease (Farahat, R. A., et.al, 2022). Gigantic pouched rats (*Cricetomys spp.*), squirrels (*Funisciurus spp.*), and African dormice (*Graphiurus spp.*), as well as perhaps additional wild rodents, thought to be among the most likely reservoirs hosts relying on data from several surveys and research studies (**Figure 1**). However, the researchers found that even while the virus was considerably less infectious than smallpox, it could still be transmitted from person to person. Furthermore, the research showed that even in people who had never had a vaccination, the virus could not be expected to propagate indefinitely (Rimoin, A. W., et.al, 2010; Sklenovská, N., et.al, 2018).

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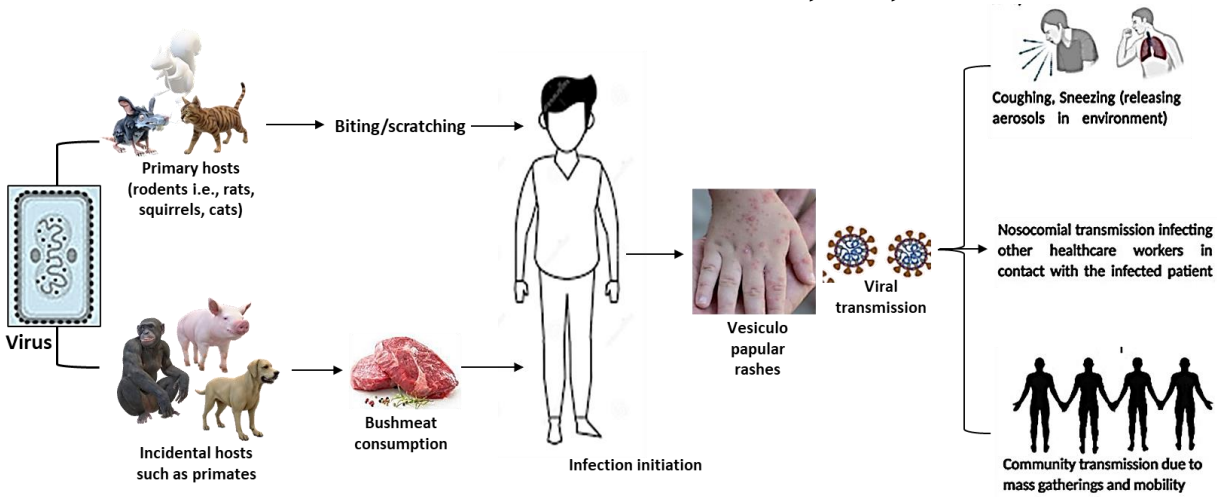

Figure 1: **Transmission routes associated with monkeypox infection.**

Smallpox (*Variola major* and *minor*), *Molluscum contagiosum*, cowpox, and the vaccinia virus all belong to the same family as monkeypox. Skunk, raccoon, camel, and buffalo pox are some more mammalian related animal orthopox diseases (Haller, S. L., *et.al*, 2014). The Democratic Republic of the Congo (DRC) experienced a return of monkeypox, which is linked to the capturing, processing, and ingestion of infected animals and other NHP. Monkeypox was once prevalent in Ghana and Zaire (Fox, J. G., *et.al*, 2015).

The virus is naturally occurring in animals the continent of Africa where infection has been documented in at least 10 NHP species and four squirrel species. Squirrels are believed to be the major disease reservoir in Africa. The virus has a broad host range of Asian, African, and South American non-human primates including select apes, and New and Old-World monkeys (Wachtman, L., et.al, 2012). Most of the infections of captive nonhuman primates have involved Asian macaques (Fenner F., 990). The dry season appears to be when the sickness is more prevalent. 84% of incidents involve children younger than the age of ten. The monkeypox vaccine protects against smallpox. In several nations, as well as within afflicted homes, clusters of cases have been seen. Seven human-to-human transmission events may have taken place (Ligon B. L., 2004). There were no instances of potential tertiary dissemination. Intimate domestic connections who were vulnerable experienced a 10% secondary attack rate, whereas all susceptible contacts experienced a 5% secondary attack rate. Compared to the incidence of smallpox, typically ranges from 25 to 40%, which is far lower (Jezek, Z., et.al, 1983).

The possibility of MPXV acquiring changes that improve its survivability in intermediate hosts and increase its transmissibility, virulence, and pathogenic potential may perhaps grow with higher occurrence in humans, especially in people with weakened immune systems. This presupposes that the population lacks vaccine-derived immunity, which is the case in the present day because smallpox immunization has been discontinued (Weaver, J. R., et.al, 2008). The probability of diverse landscape by visitors increases with higher human-to-human transmission, hence it is important to investigate whether this is the reason of the increasing occurrence of monkeypox (Sklenovská, N., et.al, 2018).

PATHOPHYSIOLOGY

The virus can spread to close contacts through oropharyngeal secretions as a result of replication in mucosal surfaces. The likelihood of transmission is probably influenced by the number of oropharyngeal lesions, the length of time and proximity of the encounter, and the virus' ability to survive despite the immune system's responses. Following transmission from infected individuals, monkeypox starts with an infection of either the dermis or the respiratory epithelium (after transmission from an infected person). Initial viremia and systemic infection ensue from the virus' lymphatic system-wide spread. Skin and mucosal lesions are caused by epithelial infection brought on by secondary viremia (Burrell, C. J., et.al, 2017). A histopathology report of a prairie dog stated that conjunctivae, tongue, and bronchial epithelial cells were the primary targets of monkeypox viral infection. Affected epithelial cells had considerable inflated deterioration and thick, eosinophilic cytoplasmic granules that were difficult to identify from keratohyalin bodies histopathologically (Xiao, S. Y., et.al, 2005). For diagnostic reasons, eosinophilic, ground-glass staining in the nuclei of epithelial cells that occasionally merged to form syncytia must be distinguished from herpetic inclusions. Immunohistochemistry was used to identify the eosinophilic cytoplasmic granules as viral inclusions (Guarnieri-like inclusions), and electron microscopy analysis supported these results (Guarner, J., et.al, 2004).

SYMPTOMS

The clinical manifestations of monkey pox symptoms are very similar to smallpox symptoms. After exposure and infection, there is an approximate 10-to-14-day incubation phase that is

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accompanied by an approximate two-day prodrome period. An infected individual within the initial 0-5 days of the infection may have fever, myalgias (muscle aches), chills, malaise, headache, backache, sore throat, dyspnea (shortness of breath), and lymphadenopathy (enlarged lymph nodes during the prodrome phase), which is the time before the appearance of a rashes (**Figure 2**) (Di Giulio, D. B., et.al, 2004; Weaver, J. R., et.al, 2008).

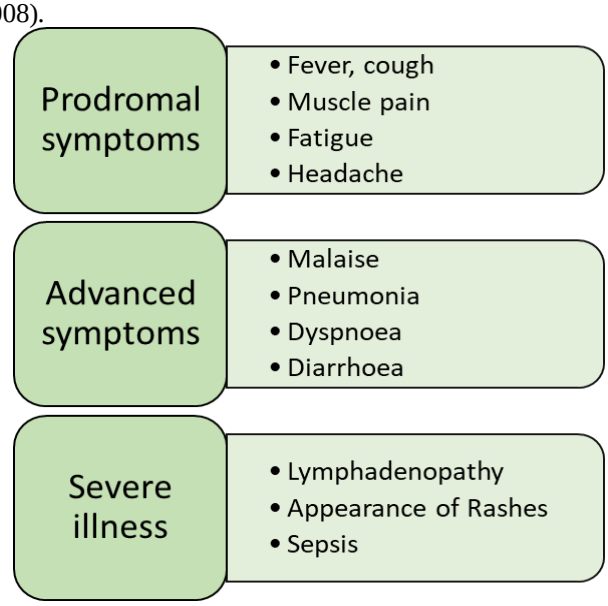

Figure 2: **The symptoms of Monkeypox infection**

A gradual maculopapular rash with lesions diameters ranging from 0.2-1 cm develops after 1-3 days of fever onset (prodrome stage). The infected individual is also thought to be among the most infectious at this time. Commencing on the facial and neck and moving to the appendages with inclusion of the palms and soles, lesions spread throughout the body in a centrifugal pattern (McCollum, A. M., et.al, 2014). Instead of the neck, the rash is more frequently found on the face and limbs. In 95% of instances, it affects the face, and in 75% of cases, it affects the palms of the hands and the bottoms of the feet. Along with the cornea, oral mucous membranes, genitalia, and conjunctivae are all also impacted in 70% of instances (Harris E., 2022).

Acanthocytes have intracytoplasmic eosinophilic aggregates that are visible. The characteristic pock lesion is created by vesiculation and umbilication. Over the course of 4 to 14 days, substantial cutaneous transitions happen (**Table 1**) (Chen, N., et.al, 2005). Over the course of two to four weeks, lesions advance through a number of stages, from macules (flat, firm lesions) through papules (slightly raised, firm lesions), vesicles (clear fluid-filled lesions), pustules (yellowish fluid-filled lesions), and ultimately a crusting phase that involves flaking skin and desquamation (stage when the crusted lesions peel off and reveal new skin underneath) (Weaver, J. R., et.al, 2008; Nalca, A., et.al, 2005).

Table 1: **Stages of lesions development in monkeypox disease (Source: www.cdc.gov/)**

Stage	Duration	Characteristics
Macules	>24 hours	Macular lesions appear
Papules	2−4 days	Lesions typically progress from macular (flat) to papular (raised).
Vesicles	After 5 days	Typically, vesicular lesions develop after that (raised and filled with clear fluid).
Pustules	6−7 days	When this happens, lesions frequently develop into sharply elevated, normally rounded, and firm to the touch pustular lesions (filled with opaque fluid) (deep seated). Lastly, the center of lesions often becomes depressed (umbilication). Until they start to crust, the pustules will last for around 5 to 7 days.
Scabs	7−14 days	Pustules hardened and scabbed over by the second week's end. Before they start to fall off, scabs will last for around a week.

Occurrences of myocarditis and cases of epiglottitis have both been recorded as significant consequences. An individual with HIV infection who had epiglottitis and a CD4+ cell count under 200cells /mm^3 had tecovirimat treatment and benefited greatly. The myocarditis patients self-limited (resolved in around 7 days) and did not require antiviral medication (Thornhill, J. P., et.al, 2022). Age, dietary state, linked HIV status, immunization history, and skin manifestation all affect it. In societies wherein starvation, parasite diseases, and other serious health-compromising illnesses are frequently prevalent, monkeypox is most common. Any of these circumstances might have an adverse effect on the prognosis of an MPXV patient (Tulchinsky, T. H., et.al, 2014). Typically, monkeypox is a self-limiting illness with symptoms that lasts 2-4 weeks. Children are more likely to experience severe instances, which are connected to the level of viral exposure, the patient's condition, and the kind of problems. The results might be worse if immunological deficits were present (Guarner, J., et.al, 2004).

Although smallpox immunization proved protective in the past, people under the age of 40 to 50 (depending on the country) may now be more vulnerable to monkeypox due to the worldwide discontinuation of smallpox vaccine programs after the illness was eradicated (Mohapatra RK, et.al, 2022). Monkeypox complications can include secondary infections, bronchopneumonia, sepsis, encephalitis, and corneal infections with subsequent vision loss. It is uncertain how widespread an asymptomatic infection could be (Kaler J, et.al, 2022; Stagles, M. J., et.al, 1985).

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DIAGNOSIS

Since smallpox and monkeypox share many clinical traits, laboratory identification is crucial, and improved techniques that take advantage of variations in the host immune responses to *Orthopoxviruses* are now being developed. At reference laboratories, a variety of scientific tests may be run to distinguish between these viruses. Clinical symptoms are crucial in making a differential diagnosis, but historical indicators of monkeypox infection include recent travel to endemic regions, contact with wild animals imported from endemic areas, and caring for an infected animal or human all play a significant role (Li, Y., et.al, 2006).

Real-time polymerase chain reaction (rt-PCR) tests have recently been used to identify a monkeypox virus that specifically targets two genes. A test that concentrates on the DNA polymerase gene, an ortholog to the vaccinia virus strain Copenhagen (COP) E9L gene, may be used to distinguish distinct Eurasian Orthopoxviruses (Tiecco G, et.al, 2022). COP-B5R, an additional ortholog of the vaccinia virus' viral envelope, appears to be the focus of further research. This assay, is sensitive and specific to the monkeypox virus alone, makes use of single nucleotide polymorphisms within a small stretch of the COP-B5R ortholog of the monkeypox virus (Weaver, J. R., et.al, 2008; Li, Y., et.al, 2006).

Since PCR is more sensitive and allows for the distinction of OPV, protein-based techniques for identifying various antigens from clinical samples have also been developed (Hughes, L. J., et.al, 2014; Sklenovská, N., 2020). However, protein-based approaches are frequently reliable and easily adaptable for usage in the field. Two methods, the Tetracore Orthopox BioThreat® and the ABICAP immunofiltration system, were created for the detection of Orthopoxviruses (Townsend, M. B., et.al, 2013; Stern, D., et.al, 2016).

A further method under development that depends on minute antigenic variations between the viruses is a whole-virus enzyme-linked immunosorbent test (ELISA), where antibody titers to the monkeypox and vaccinia viruses are assessed and their ratio is calculated (Hammarlund, E., et.al, 2005). A protein expressed by the monkeypox homologue of the cowpox virus strain Brighton red (BR) 219 gene serves as an illustration of an epitope difference that might be exploited to diagnose monkeypox. This gene purports to encode a membrane-associated glycoprotein, yet the vaccinia virus lacks this protein. This protein's peptide was employed in an ELISA to discriminate between current monkeypox infection and previous smallpox immunization (Weaver, J. R., et.al, 2008; Shchelkunov, S. N., et.al, 2002). However, there are no commercially accessible laboratory assays for monkeypox, including on-site diagnostic tests. This contrasts with the large number of diagnostic tests for clinically important viral illnesses (Stern, D., et.al, 2016).

PREVENTION AND TREATMENT

In order to treat monkeypox symptoms effectively, handle complications, and avoid long-term effects, therapeutic treatment must be properly maximized. There are currently no known, effective therapies for monkeypox infection, however repurposing the therapeutics of smallpox treatment approaches can help in the management of the disease. The method of treatment for viral infections is supportive symptom management. However, precautionary measures are required that may be taken to avoid an epidemic. Liquids and nourishment should be served to patients in order to maintain a healthy dietary condition. As necessary, subsequent infectious diseases should be treated. Keep track on patients for changes in their clinical characteristics. Inform patients of the warning signs and symptoms of problems that necessitate immediate attention. Keep a close watch out for secondary bacterial infections in sores and treat with the proper oral antibiotic medication if they appear.

Depending on the individual's medical examinations and local antimicrobial resistance trends, antimicrobial treatment and the medication shall be administered. Monkeypox illness can be prevented with the use of two vaccinations, including the JYNNEOS vaccine, which is licensed to protect against both monkeypox and smallpox. Under an Expanded Access Investigational New Drug (EA-IND) procedure, another candidate, the ACAM2000 vaccine is made available for use against monkeypox in addition to smallpox vaccination (Centers for Disease Control and Prevention, 2022b). However, a license from the FDA has been given to Vaccinia Immune Globulin Intravenous (VIGIV) to treat vaccinia vaccination-related side effects such as eczema vaccinatum, gradual vaccinia, intense generalized vaccinia, vaccinia infections in people with skin conditions, and aberrant infections brought on by the vaccinia virus (except in cases of isolated keratitis). Monkeypox and other Orthopoxvirus epidemics can be treated with VIGIV according to a CDC increased access policy (Centers for Disease Control and Prevention, 2022c).

Several anti-virals have been re-purposed towards strategic treatment and curb of MPXV. Based on investigations from both animal and human research, the European Medicines Agency (EMA) granted Tecovirimat (TPOXX, ST-246), an antiviral drug originally created to treat smallpox, a license to treat monkeypox in 2022. In individuals with impaired immune systems, vigilance is needed since tecovirimat has the possibility of contributing to poxvirus tolerance. However, it is still not readily accessible (Rojek, A., et.al, 2022; World Health Organization, 2022).

Brincidofovir (CMX001 or Tembexa) is a prodrug of cidofovir and an *Orthopoxvirus* nucleotide analogue DNA polymerase inhibitor. This drug smallpox approval in the US, but an expanded access investigational new drug procedure may make it available in the future to treat monkeypox

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(Siegrist EA, et. al, 2022; Andrei G, et.al, 2022). The effectiveness of Brincidofovir in treating instances of monkeypox in humans is still unknown. However, brincidofovir medication may result in increases in blood transaminases and serum bilirubin when liver function tests are performed both before and during the course of treatment (Centers for Disease Control and Prevention, 2022d).

Cidofovir (Vistide), another antiviral nucleotide analogue that is effective against poxviruses is authorized in the US for the treatment of cytomegalovirus (CMV) retinitis, but it is also permitted for emergency use during an epidemic of monkeypox under an improved accessibility experimental novel therapeutic strategy. Cidofovir may be helpful in treating monkeypox, according to in vitro and macaque challenge investigations. However, there is no information available about the effectiveness of cidofovir in treating monkeypox in humans (Stittelaar, K. J., et.al, 2006; Huggins, J., et.al, 2009; Andrei, G., et.al, 2010).

CONCLUSION

Given that a substantial section of the population is suffering monkeypox, with a noticeable fatality rate, in the absence of any effective action, a successful treatment plan, and sufficient wide-spread social isolation. It makes logical to stick with present procedures and government-sponsored healthcare initiatives until potent and effective drugs or vaccines are created. Immunomodulatory foods, emotional support, following regulations, and combination medications will all contribute to long-term efficacy against MPXV. In addition to controlling this pandemic, stringent measures must be put in place since it's likely that zoonotic infections will continue to lead to viral epidemics in the future. Healthcare personnel and children in particular are among the vulnerable groups that need extra safety and prevention measures. Younger generations of individuals were most commonly affected by the early occurrences of epidemic mortality because they had compromised immune systems brought on by altered lifestyles that allow for fast viral infection development. The great vulnerability of the virus, which goes beyond the reach of public-health management techniques, is demonstrated by the increased prevalence of occurrence in farm animals and the identification of novel reservoir species. Therefore, planning and manufacturing MPXV vaccines is as crucial as developing new drugs and carrying out clinical trials on already approved ones. Experiences with SARS-CoV and MERS-CoV indicate that a lot of focus should be placed on creating experimental animals that can capture many aspects of human disease as well as characteristics that impact the security and efficacy of vaccinations.

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AUTHOR'S CONTRIBUTION

AKD: Wrote the manuscript and give consent for publication.

ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. Journal and Publisher will not be responsible for any copyright infringement and plagiarism issue.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY

All the key information is already available in the manuscript, still, authors are ready to share the raw data, if the proper channel for the inquiry will be followed which will be routed through journal and affiliation authorities.

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