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Monkeypox: A Comprehensive Overview of Emerging Zoonotic Disease

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Abstract

Monkeypox, a rare zoonotic disease caused by the Monkeypox virus (MPXV), has garnered increasing attention due to sporadic outbreaks in Central and West Africa. This review article provides a concise overview of the etiology, epidemiology, clinical manifestations, and control strategies associated with monkeypox. Drawing on current scientific literature, the article explores the origins of the virus, its natural reservoirs, and the mechanisms of transmission to humans. The epidemiological landscape of monkeypox, including prevalent regions and historical outbreaks, is discussed to highlight the geographical distribution and potential risk factors. The clinical spectrum of monkeypox in humans, ranging from mild to severe cases, is outlined, with a focus on symptoms, progression, and complications. Additionally, preventive measures, such as vaccination strategies and public health interventions, are explored to elucidate current efforts aimed at controlling and mitigating the impact of monkeypox outbreaks. The review concludes with an emphasis on the importance of ongoing research to enhance our understanding of the virus, improve diagnostic tools, and develop effective therapeutic interventions.

Keywords: *Monkey pox, Small pox, Vaccines, Cidofovir, Vaccinia Immune Globulin*

INTRODUCTION

Monkeypox is a rare and emerging zoonotic disease that belongs to the family *Poxviridae* and the *Orthopoxvirus* genus, which also includes variola virus, the causative agent of smallpox. The disease was first identified in 1958 when outbreaks occurred in monkeys kept for research, hence the name "monkeypox." Since then, the virus has been reported in both animals and humans, with sporadic cases and outbreaks documented primarily in Central and West African countries [1]. However, in recent years, there has been an increase in reported cases, and the geographic distribution of the virus appears to be expanding. This has raised concerns about the potential for the virus to spread to new regions and become a global health threat. The origin of monkeypox can be traced back to the rainforests of Central and West Africa, where the virus circulates among wild animals, including rodents and primates. The natural reservoir of the virus remains unknown, but it is believed that the disease is transmitted to humans when individuals come into contact with the blood, bodily

fluids, or lesions of infected animals [2,3]. Furthermore, the consumption of undercooked meat from infected animals has been identified as a potential source of infection in human cases. Additionally, human-to-human transmission can occur, particularly in settings where close contact with bodily fluids or respiratory droplets is common.

Monkeypox in humans manifests with symptoms similar to but milder than those of smallpox. The incubation period ranges from 5 to 21 days, after which flu-like symptoms such as fever, headache, muscle aches, and fatigue may develop [4]. This is often followed by the appearance of a rash, which progresses to pustules and then scabs over a period of several weeks. While monkeypox is generally a self-limiting disease, severe cases can occur, particularly in individuals with weakened immune systems [5,6]. The clinical presentation of monkeypox is diverse, with a spectrum of illness ranging from a mild febrile illness to severe and potentially fatal cases. The severity of the disease can vary based on factors such as the individual's immune status and the presence of underlying health conditions [7].

The global community has become increasingly vigilant about emerging infectious diseases, and monkeypox is no exception. Given its potential for human-to-human transmission, international health organizations and governments are closely monitoring and responding to outbreaks to prevent further spread. Surveillance systems have been strengthened to detect and manage cases promptly, and research efforts are underway to better understand the virus, develop diagnostic tools, and explore potential vaccines [8,9].

ETIOLOGY OF MPXV

Monkeypox, an infrequent ailment induced by MPVX infection, arises from the infiltration of enveloped, linear, virions. These virions, characterized by a brick-shaped structure and double-stranded deoxyribonucleic acid (DNA), are members of the Poxviridae family, a diverse group affecting various animals like birds, reptiles, insects, and mammals [10,11]. The family encompasses two subfamilies, Chordopoxvirinae and Entomopoxvarinae. Owing to its broad host range, the monkeypox virus has perpetuated within wild animals, occasionally triggering sporadic spillover events that result in disease in humans. Monkeypox disease, resembling smallpox, is associated with the variola virus, and its emergence traces back to 1958 when monkeys in Denmark were identified as carriers. The first documented human case occurred in 1970, involving a toddler in the Democratic Republic of the Congo, with monkeypox exhibiting a higher lethality and case fatality rate than its variola counterpart. As a DNA virus, the MPX virus experiences less frequent and substantial alterations in its inherited traits [12,13].

It is imperative to distinguish between monkeypox and benign epidermal monkeypox (BEMP), a poxviral malady in primates triggered by the tanapox virus, an antigenically unrelated member of the Yatapoxvirus genus within the Poxviridae family. Monkeypox transmission occurs through exposure to contaminated objects or bodily fluids, via tiny droplets, or potentially through the air. Natural reservoirs, including nonhuman primates, squirrels, dormice, Gambian pouched rats, and monkeys, play a pivotal role in the disease's circulation. Humans can contract the disease through bites, scratches, close contact, and consuming undercooked meat from infected animals. The three primary modes of human-to-human transmission involve large respiratory droplets, direct exposure, and contaminated fomites [14,2]. Additionally, the virus may sporadically spread through the placenta, leading to congenital monkeypox. Intimate skin and mucosal contact during sexual activity facilitate dissemination, though the exact significance of direct sexual transmission remains uncertain. Congenital MPX cases have been documented due to vertical transmission from mother to foetus or infant [15].

EPIDEMIOLOGY

The human illness known as monkeypox was initially identified in 1970 in the commune of Basankusu in the Democratic Republic of the Congo. There was another unanticipated human illness epidemic in DRC/Zaire in 1996–1997 [16]. In the United States, there was a transient increase in monkeypox in human’s cases among breeders of prairie dogs in 2003. There was an epidemic of monkeypox in Unity, Sudan in 2005, and there have been sporadic instances ever since. During a community outreach drive among refugees arriving in the Republic of Congo from the Democratic Republic of the Congo in 2009, two cases of monkeypox were detected and verified. There were 26 cases and two fatalities of monkeypox in the Central African Republic during August and October of 2016. When predicting outcomes, factors such as vaccination circumstances, multiple disorders, immune system responses, proportion of viral exposure, and severity of repercussions are usually considered. There is no difference in the frequency of poxvirus infections between males and females based on nationality [10, 17]. Nearly one-third of the diseases were found to be sub-clinical. The increase in cases was attributed to the civil war, which promoted the slaughter of squirrels and other woodland animals believed to harbour monkey pox. Monkey pox may eventually go extinct due to a drop in the disease's intermediate hosts

or main reservoir. This is because extensive agricultural practices have replaced hunting and trapping, leading to better lives brought about by increasing urbanisation [16, 18].
As of July 24, 2022, there had been four reports of the virus; the first MPX case was recorded in India on July 14, 2022. There were four males among them. The last instance, from Delhi, had no prior evidence of travel abroad, in contrast to the three cases that had come before it, all of which were from Kerala. In both endemic and nonendemic areas, recurrence of monkeypox has been linked to high-risk behaviours such as sexual activity, alterations in the biologic attributes of the virus, variations in climate, a reduction in the immune system after smallpox vaccination, an increase in abroad travel after the removal of COVID-19 travel limitations, and an end of smallpox vaccination. Phylogenetic analysis indicates that the MPX causing the current outbreak belongs to clade 3, which is extremely comparable to the strain of virus which triggered the Baltimore, USA, sporadic case in 2021 and was linked to the clade 2 viruses that prompted the Nigerian outbreak in 2017–2018. The tightly clustered gene sequences of all the viruses involved in this outbreak indicate that it may have started in a single place. Although adult male homosexuals have been the majority of those affected thus far, it is anticipated that the disease will eventually spread to women, children, and people of all ages [16, 19]. Healthcare workers are more susceptible to infection. An additional issue is that humans may spread diseases to animals, which might serve as a recurring source of disease.

SIGNS AND SYMPTOMS

Although less severe, the initial signs and symptoms of monkeypox in humans are similar to those of smallpox. The earliest signs and symptoms of monkeypox include a high body temperature, headaches, muscular pains, and tiredness. There is one main difference between smallpox and monkeypox symptoms: smallpox does not induce lymphadenopathy, but monkeypox does. Incubation periods for monkeypox normally range from 7 to 14 days, although they can reach 21 days. The infection may be divided into two phases using the invasion time (0–5 days) and the skin eruption period (between 1-3 days following emergence of fever). Period of Invasion: The illness starts with a high temperature, shivers, enlarged lymphatic nodes, headache, muscular pains, and back discomfort. The patient has a skin eruption period, which lasts for one to three days following the commencement of the fever. During this time, the patient often gets a rash on their face that eventually spreads to other parts of their body. The face, hands, and soles of the feet are the most commonly afflicted regions. It may require three weeks before the crusts are entirely removed [20,21]. The following phases are experienced by lesions as they develop: eruptions, granules, papules, vesicles, pustules, and scabs.

TRANSMISSION

The two possible MPV transmission methods are animal-human transmission and human-human transmission. Research has shown that droplets from respiration, exposure to body fluids, contaminated patient settings or items, and lesions on the skin from an infected individual are associated with human-to-human transmission. Individual-to-person transmission is more common for the monkeypox virus, which belongs to the Central African clade and is more virulent than the West African clade [22]. Bed linens and doorknobs, for example, might act as a vehicle for transmission of smallpox since the viruses can live a long period outside of the body. Zoonotic transmission can occur by close interaction with or ingestion of one of the endogenous infectious hosts, as well as by physical contact with serum and other body fluids, in addition to injection through the mucocutaneous lesions of an infected animal. Additionally, nosocomial transmission has been reported. The sex geographic distribution of illnesses in the present outbreak shows a significant bias, with over 95% of cases recorded in young males (under 40 years old) [12,23]. While there has been evidence of a spread among men who engage in sexual activity with other men (MSM), heterosexual relationships should also be considered. This kind of MPV diffusion among MSM groups may inadvertently come into contact with a community. Prior research has indicated that individuals with genital and vaginal lesions who are infected may have acquired the illness via intercourse. It has been reported that the number of cases in the Democratic Republic of the Congo increased twentyfold between the 1980s and the mid-2000s [22].

DIAGNOSIS AND DETECTION

Detection

The most common differential diagnosis is chickenpox. Monkeypox is distinguished from chickenpox by a prolonged prodromal phase, lymphadenopathy, and circumferential distribution of the rash, while chickenpox has a brief prodromal period, centripetal distribution of the rash, no lymphadenopathy, and a quicker pace of rash spread. Alternatively diagnosed illnesses that might be mistakenly identified as MPX include molluscum contagiosum, drug eruptions, measles, hand, foot, and mouth disease, and second-degree syphilis [24].

Nucleic acid amplification testing

Detecting particular MPXV viral DNA sequences and determining MPXV infection are mostly accomplished using nucleic acid amplification tests). This is accomplished by either traditional or real-time polymerase chain reactions [25]. The WHO states that in nonendemic countries, if a specific MPXV test is not available, a positive polymerase chain reaction result for the orthopoxvirus is considered confirmation [26].

Antibody detection

Diagnosing a disease only using serum or plasma antibodies is not recommended. Acute and convalescent samples that are specific for the MPXV virus can be used to identify both immunoglobulin M and immunoglobulin G [24]. It is possible to detect specific IgG and IgM antibodies against MPX 5 and 8 days after infection by utilising an enzyme-linked immunosorbent assay (ELISA). However, they are genus-specific and do not differentiate amongst the many pox viruses. IgG positivity may also result from prior smallpox exposure or vaccination.

Electron microscopy

Although MPXV and poxvirus cannot be differentiated using electron microscopy, it can be employed to detect potential poxvirus in a given specimen. Additionally, this method requires extensive infrastructure and technology, has a low recognition sensitivity, and is very technical and complicated. Recombinase polymer amplification (RPA), loop-mediated isothermal amplification (LAMP), restriction-fragment-length polymorphism (RFLP), and RT-PCR are a few of the genetic testing methods. Real-time PCR (RT-PCR) testing on samples from lesions on the skin, throat tissue, bloodstream, and urine may determine the presence of MPX with a high degree of sensitivity and specificity. Despite being costly, these tests are really not carried out on a commercial basis.

Virus isolation

The established technique for detecting bacterial infections has been the isolation of MPXV from clinical samples. Nonetheless, only labs equipped with the required confinement infrastructure and education should perform MPXV. This means that this method is insufficient for routine diagnostic procedures [24]. Although P3-level laboratory standards should be adhered to when it comes to individuals wearing personal protective equipment, isolation of viruses is advised to be carried out in P2-level biosafety facilities.

TREATMENT

Nonetheless, the vaccination against smallpox may provide immunity to the disease. For human monkeypox, there are no recognised therapies. Since the widespread immunisation scheme was terminated in the 1980s, more individuals have become cognizant that the monkeypox virus still exists in the human population [28].

Cidofovir

Many skin conditions caused by viruses are treated with cidofovir, a strong antiviral drug. It is used topically or intralessionally to treat DNA virus-induced skin problems. It is effective against practically all DNA viruses, including papilloma, adeno, polyoma, and herpesviruses [29]. Molluscum contagiosum, smallpox, cowpox, monkeypox, camelpox, and other poxviruses susceptible to cidofovir's inhibitory actions are among the confirmed poxviruses.

Brincidofovir

The FDA authorised brincidofovir in June 2021 for the medical management of smallpox infection. It has already been applied to individuals with OPXV, adenovirus, and CMV infections. A patient who had been vaccinated against smallpox and was later diagnosed with acute myeloid leukaemia (AML) was treated with brincidofovir as part of a combination treatment regimen [30]. Following induction treatment with

chemotherapy, the patient experienced progressive vaccinations, for which he or she received six doses of brincidofovir as part of their treatment. Additionally, a 17-year-old kidney transplant patient who developed a disseminated cowpox virus infection that eventually proved deadly was treated with this drug [34].

Smallpox Vaccine

The smallpox immunisation successfully shields recipients from monkeypox when given prior to exposure to the illness. The CDC recommends that the immunisation be given within 4 days after the date of exposure in order to prevent the disease from spreading. Although vaccinations can reduce symptoms of sickness, they cannot prevent disease [31]. Vaccinations should be given between 4 and 14 days following the exposure date. Various types of small pox vaccine used in monkeypox are listed in table 1.

Tecovirimat (ST-246)

Diseases caused by the orthopoxvirus can be effectively treated with ST-246. Human clinical trials demonstrated the drug's safety, tolerability, and lack of serious adverse effects. Tecovirimati has been authorised by the U.S. Food and Drug Administration to conduct Phase II investigations, which are now being conducted in clinical trials. Tecovirimat exhibited a satisfactory tolerability profile throughout phase I studies, devoid of any significant adverse events [32, 33].

Vaccinia Immune Globulin (VIG)

To make vaccine immune globulin (VIG), an array of blood from people who have received the smallpox vaccination is used. In case they develop antibodies in response to the smallpox vaccination, these individuals are isolated from one another and purified [34, 35].

PREVENTION

Whether a patient has a confirmed diagnosis of monkeypox or not, they should be placed in an isolation room. No special air handling is required. If it's safe to do so, it's advisable to keep the door closed. There need to be a separate bathroom in the room. Following usual precautions, people who suspect monkeypox should be treated. Steer clear of portable fans, dry dusting, cleaning, and vacuuming since these activities might resuscitate crusted material from lesions. Moving the patient outside of the room should only be done when it is absolutely required by medicine. If the patient is moved from their room to another, they should wear source control that fits properly (such as a medical mask), and any skin lesions that are exposed should be covered with a sheet or gown [36]. When a patient is transferred from one room to another, they should cover any exposed skin lesions with a sheet or gown and wear a source protection device that fits appropriately, such as a surgical mask [36]. Intubation, exudation, and any other operation that might spread secretions from the mouth should take place in a room designed for the isolation of airborne diseases. Once all lesions have crusted, split apart, and a fresh layer of healthy skin has formed below, it is crucial to continue taking isolation precautions. Patients with mild diseases who are kept alone at home can use the same criteria. Medical personnel should always wear personal protective equipment (PPE) when visiting a patient's room. This equipment should comprise a gown, gloves, eye protection (goggles or a face shield covering the front and sides of the face), and a N95/FFP2 or higher respirator. Waste management (i.e., handling, storing, treating, and disposing of dirty PPE, patient dressings, etc.) should be done with due caution. The best practices should be followed while handling soiled laundry, which includes bedding, towels, and personal clothing, to prevent skin contact with any potential lesion material. Whenever feasible, soiled clothing should be confined quickly and carefully in an appropriate laundry bag to prevent the spread of infectious materials. Individuals who were previously exposed to monkeypox, such as healthcare workers and patients, must to be kept apart and closely monitored for 21 days after the last exposure [37].

Table 1. Types of smallpox vaccine used in monkeypox

Type of vaccine	Property
ACAM2000 – live vaccinia virus	A single dosage is administered by puncturing the skin's surface, which also leaves a lesion at the injection site and increases the risk of replication. Pregnant women, those with atopic dermatitis, and people with impaired immune systems should not use this method, may propagate among contacts of the vaccinated. There have been reports of adverse cardiac responses after immunisation.

Modified vaccinia Ankara (MVA) (Jynneos, Imvanex, Imvamune)	Two subcutaneous dosages spaced four weeks apart are administered. The vaccination location is free of lesions. Doesn't grow, therefore those with compromised immune systems are permitted to utilise it. In circumstances of shortage, a single dosage may be given.
LC16m8 (modified vaccinia virus)- licensed in Japan	Given as a single dosage, smaller and safer than ACAM2000 in terms of replication capacity.

Smallpox vaccinations have been discontinued after the illness was declared eliminated in 1980. The protection that the vaccine provides may ultimately wear off, and the proportion of cohorts that have not gotten the vaccination is rising. As a result, there are more vulnerable people in the world, which might provide the ideal conditions for MPXV to spread. In the USA, it is approved to prevent MPXV using the ACAM2000 and JYNNEOS (also known as imvamune or imvanex) immunisations. The live attenuated viral vaccine JYNNEOS has been licenced by the US FDA for use in certain individuals who may be exposed to the poxvirus. However, because of its severe adverse effects, ACAM2000 is no longer licenced in the European Union.

CONCLUSION

In conclusion, the emergence of the monkeypox virus poses a new challenge amid global efforts to combat the ongoing COVID-19 pandemic. This discussion has highlighted the two clades of the human monkeypox virus, its potential for sexual transmission, and the reported cases, especially among men who have sex with men (MSMs). The clinical presentation of human monkeypox, its etiology, epidemiology, and various modes of transmission have been thoroughly examined. The signs and symptoms of monkeypox in humans, although resembling smallpox, have been detailed, emphasizing the importance of distinguishing between the two. The discussion delves into the virus's transmission methods, including animal-human and human-human transmission, with a focus on the biases observed in the current outbreak, particularly affecting young males. As it develops into a primary viremia, this virus travels to the nearby lymph nodes after replicating within the cytoplasm. Bronchopneumonia, dehydration, respiratory distress, encephalopathy, and other consequences are also linked to monkeypox infection. The section on diagnosis and detection explores various methods, including nucleic acid amplification testing, antibody detection, electron microscopy, and virus isolation. The lack of specific therapies for human monkeypox is highlighted, and potential treatments such as cidofovir and brincidofovir are discussed. The importance of the smallpox vaccine in preventing monkeypox, along with other potential preventive measures, is emphasized. There is currently no treatment for infections with the monkeypox virus, according to the Centres for Disease Control and Prevention (CDC). On the basis of the knowledge gained from the smallpox pandemic, the use of the vaccinia vaccine, cidofovir, tecovirimat, and vaccinia immune globulin (IVG) is being examined as a potential treatment for monkeypox. By restricting the viral DNA polymerase, cidofovir exerts its action. The approved vaccines, ACAM2000 and JYNNEOS, are discussed, highlighting their properties and limitations.

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