

Monkey Pox Pathogenesis, Diagnosis, Treatment: A Comprehensive Review

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ABSTRACT

Human monkeypox is a zoonotic *Orthopoxvirus* with a presentation similar to smallpox. Clinical differentiation of the disease from smallpox and varicella is difficult. Laboratory diagnostics are principal components to identification and surveillance of disease, and new tests are needed for a more precise and rapid diagnosis. The majority of human infections occur in Central Africa, where surveillance in rural areas with poor infrastructure is difficult but can be accomplished with evidence-guided tools and educational materials to inform public health workers of important principles. As the fear of the coronavirus disease 2019 (COVID-19) pandemic subsides, countries around the globe are now dealing with a fear of the epidemic surrounding the prevalence of monkeypox cases in various regions. Previously endemic to regions of Africa, the majority of monkeypox cases associated with the 2022 outbreak are being noted in countries around Europe and in the western hemisphere. While contact-tracing projects are being conducted by various organizations, it is unknown how this outbreak began. Monkeypox virus is one of the many zoonotic viruses that belong to the *Orthopoxvirus* genus of the *Poxviridae* family. Monkeypox cases received global attention during the 1970s, after the global eradication of smallpox. The smallpox vaccine provided cross-immunity to the monkeypox virus. Upon the cessation of smallpox vaccine administration, monkeypox cases became more prevalent. It was not until the 2003 US outbreak that monkeypox truly gained global attention. Despite the virus being named monkeypox, monkeys are not the origin of the virus. Several rodents and small mammals have been attributed as the source of the virus; however, it is unknown what the true origin of monkeypox is. The name monkeypox is due to the viral infection being first witnessed in macaque monkeys. Though human-to-human transmission of monkeypox is very rare, it is commonly attributed to respiratory droplets or direct contact with mucocutaneous lesions of an infected individual. Currently, there is no treatment allocated for infected individuals, however, supportive treatments can be administered to provide symptom relief to individuals; Medications such as tecovirimat may be administered in very severe cases. These treatments are subjective, as there are no exact guidelines for symptom relief. Contemporary epidemiological studies are needed now that populations do not receive routine smallpox vaccination. New therapeutics and vaccines offer hope for the treatment and prevention of monkeypox; however, more research must be done before they are ready to be deployed in an endemic setting. There is a need for more research in the epidemiology, ecology, and biology of the virus in endemic areas to better understand and prevent human infections.

Keywords- Monkeypox, Outbreak, Small pox, Epidemic.

I. INTRODUCTION

The start of 2022 was marked re-emerging of the viral zoonosis; the monkeypox virus. The Monkeypox virus cases have increased from one case detected in the UK on May 7, 2022 to 1,285 cases detected in 28 countries by June 8, 2022. As of July 23, 2022, a total of 2,891 cases have been detected in the United States of America. The rapid spread of the Monkeypox virus has sparked concerns

about the start of a new epidemic[1]. Monkeypox virus is an *Orthopoxvirus* from the family of *poxviridae*. The disease has been largely limited to western and central African countries since its discovery in 1958. One of the unique things about the 2022 pandemic is that some cases had no travel history to endemic areas or history of coming in contact with anyone from endemic areas of the monkeypox virus[2]. This presents a possible unknown transmission chain that may help spread the monkeypox

virus further. A meta-analysis study showed that the case fatality rate was 10.6% for the central African variant while it was 3.6% for the western African variant. The overall case fatality rate was 8.7% (7.0-10.8, 95% CI). According to a systematic review, the case fatality rate in monkeypox patients was found to vary from 1% to 11%[3].

With the first human case reported in 1970 in a nine-month-old boy from the Democratic Republic of Congo, monkeypox is once again causing reason for panic as outbreaks are occurring across the western hemisphere[4]. Endemic to central and western Africa, human monkeypox is a rare viral zoonosis that has been associated with the 2003-04 outbreak in the United States (US).

Monkeypox belongs to the same genus that causes smallpox. Many common viruses belong to this genus, including cowpox, horsepox, camelpox, and alaskapox. The variola virus is the most common and well-known member among all the viruses present in this genus. The World Health Organization (WHO) formally declared the eradication of smallpox in 1980[5].

The 2022 outbreak of monkeypox involving multiple countries in both endemic and nonendemic regions has generated significant international interest. A once-neglected zoonotic virus endemic to West and Central Africa, monkeypox virus was first identified in 1958 in nonhuman primates kept for research in Denmark. The first case in humans was reported in 1970 in the Democratic Republic of Congo. Over the past 50 years, sporadic outbreaks have been reported mainly in African countries, with several thousand human cases recorded to date. Occasional cases and limited outbreaks linked to travel or importation of animals harboring the virus have also been described in nonendemic countries[6]. It has long been a theoretical concern that monkeypox virus and other zoonotic poxviruses could over time expand to fill the ecological niche once occupied by the closely related variola virus. The combined effects of deforestation, population growth, encroachment on animal reservoir habitats, increasing human movement, and enhanced global interconnectedness have made this possibility more real in the last 20 years[7].

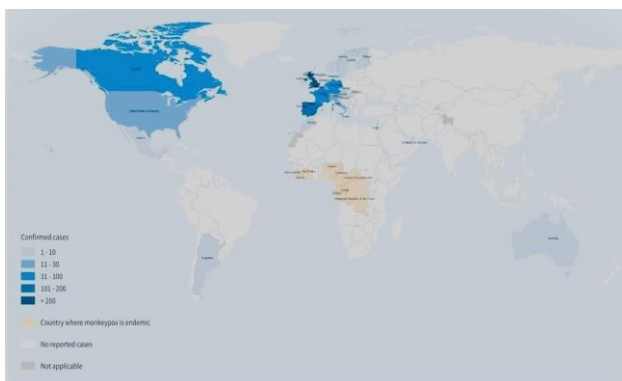


Figure 1: Geographic distribution of Monkeypox virus (Data source- WHO)

II. EPIDEMIOLOGY

Monkeypox is endemic in the tropical rainforest regions of Central and West African countries, notably Cameroon, Central African Republic, Cote d'Ivoire, Democratic Republic of the Congo (DRC), Gabon, Liberia, Nigeria, Republic of the Congo and Sierra Leone. Most cases arise sporadically or occur in the context of localized outbreaks[8]. Cases outside of endemic countries are typically linked to international travel or importation of animals infected with MPXV. Before 2022, cases outside of Africa had previously been reported in the United States, United Kingdom (UK), Israel, and Singapore. There are 2 distinct genetic clades of the *MPXV*: the Central African clade and the West African clade. Infection with the West African clade typically results in a more self-limited disease, with case-fatality ratios estimated to be approximately 3–6%, whereas the Central African (Congo Basin) clade has historically been associated with higher transmissibility and case-fatality ratios as high as 10%. Cameroon is the only country where both clades have been confirmed[9]. Cumulatively, more suspected cases of the Central African clade have been reported to date than cases due to the West African clade due to the high number of cases recorded in historical and ongoing outbreaks in the DRC. The West African clade of *MPXV* has been isolated from cases in newly affected countries in the 2022 multi-country outbreaks.

The transmission of monkeypox in endemic and nonendemic settings is summarized in Figure 2. Animal-to-human transmission occurs via bites and scratches from infected animals. Preparation and handling of infected animal products may also result in transmission. The definitive animal reservoir of *MPXV* has not been identified[10]. The virus has been isolated from several animal species including small mammals and nonhuman primates. In the reported instances in which *MPXV* has been isolated from wild animals, the animals demonstrated pox-like lesions consistent with active infection. It is not known whether asymptomatic carriage of *MPXV* occurs in animal reservoir. Serological surveys have been conducted on wild mammals in endemic regions. These studies have found several animal species with detectable antibodies to *OPXV* in the absence of detectable viremia on polymerase chain reaction (PCR) testing. This suggests exposure to and circulation of zoonotic *OPXV* in many wild animal species. Human-to-human transmission is thought to occur via direct skin-to-skin contact with lesions on the skin, as well as through indirect contact with contaminated fomites, such as bedding or clothing. Transmission can also occur at close proximity through exchange of respiratory secretions containing live virus[11].

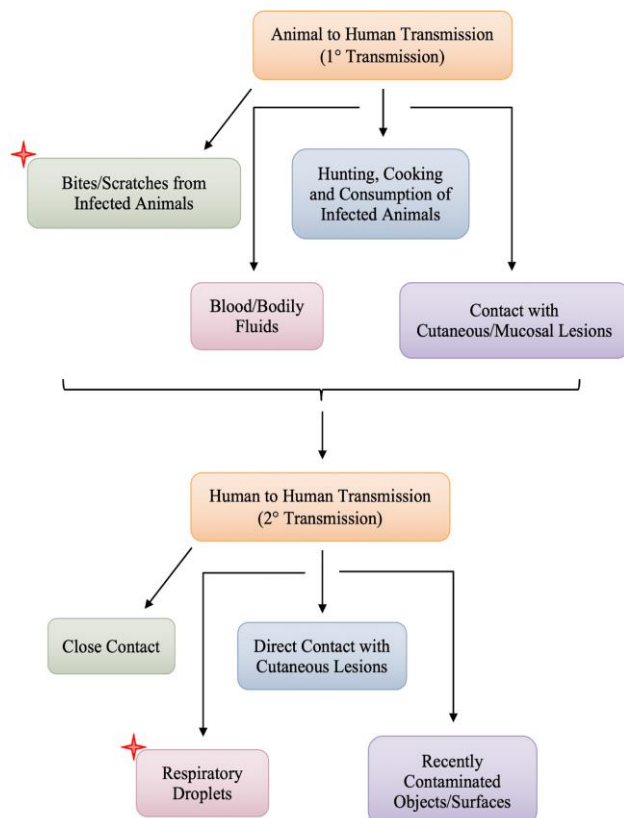


Figure 2: Pathogenesis of Monkeypox

III. DIAGNOSIS

Diagnostic assays are important components to the identification of an *Orthopoxvirus* infection. These tests are most powerful when they are combined with clinical and epidemiological information, including a patient's vaccination history. Given the limited cold chain and diminished resources for sample collection and storage, lesion exudate on a swab or crust specimens still remain some of the best and least invasive acute patient specimens[12]. Viral DNA present in lesion material is stable for a long period of time if kept in a relatively dark, cool environment, an important factor to consider when cold chain is not readily available. Conventional tests such as viral isolation from a clinical specimen, electron microscopy, and immunohistochemistry remain valid techniques but require advanced technical skills and training, as well as a sophisticated laboratory[13]. Specimens can be analyzed using real-time polymerase chain reaction (PCR) to assess the presence of *Orthopoxvirus* or monkeypox virus in a lesion sample. These assays are highly sensitive and can efficiently detect viral DNA. Real-time PCR is currently best used in a major laboratory, thus limiting its use as a real-time diagnostic in rural, resource-poor areas. Advances in technologies may make diagnostic use of real-time PCR more feasible outside of major laboratories[14].

Determining the cause of cases identified retrospectively requires antibody-based diagnostics. Anti-

Orthopoxvirus immunological assays have cross-reactivity to a variety of *Orthopoxviruses*, and these assays may be useful in areas where there is prior evidence as to what virus is causing illness. Anti-*Orthopoxvirus* immunoglobulin G (IgG) alone will not provide a definitive diagnosis for retrospective patients who have been exposed to an *Orthopoxvirus*, including by vaccination, during their lifetime[15]. Alternatively, serological assays that assess anti-*Orthopoxvirus* immunoglobulin M (IgM) are more applicable to diagnose recent retrospective infections, including in individuals with prior vaccination.

IV. CLINICAL SIGNS AND SYMPTOMS

Monkeypox traditionally presents with a typical picture consisting of lymphadenopathy, fever, headache, body pains, and aches. The rash affects the face and periphery more than the trunk. Mucosal membranes may also be involved including the mouth and genitals[16]. Involvement of the corneal and conjunctival mucosa was seen in a small percentage of patients. The rash in monkeypox patients starts off as macular in appearance and then transitions into papules, vesicular, and pustules and finally drying up to form crusts that fall off. The monkeypox lesions take a longer time to develop into crusts as compared to other similar diseases like chicken pox. The number of lesions can also vary from a single lesion to thousand[17]. Lymphadenopathy is considered as a classic feature of the monkeypox virus it can be used to differentiate between monkeypox and other pox diseases. A study found that 84.2% of patients develop fever, 78.9% develop lymphadenopathy and 100% of patients develop fever and maculopapular rash.

A study done in 2004 found similar results. Headache and skin lesions were present in 100% of patients while 82% of patients reported fever, sweating, and chills[18]. Coughing was reported by 73% of patients, lymphadenopathy was reported by 55% of patients and 18% patients reported malaise[19]. Blepharitis, nausea, nasal congestion, back pain, and myalgias were reported in only 9% cases. Another study concluded that nausea, vomiting, and mouth sore were independently associated with hospitalization duration of more than 48 hours[20].



Figure 3: Monkeypox signs and symptoms

V. TREATMENT

Currently, there is no approved treatment for the monkeypox virus infection. A study done in 1988 deduced that the smallpox vaccine was effective in preventing monkeypox. People vaccinated with the smallpox vaccine appear to develop some degree of protection from the monkeypox virus[21]. It has been suggested that antiviral medication developed for smallpox might prove to be beneficial against the monkeypox virus. The ACAM2000[™] was used in the 2003 United States monkeypox outbreak. It managed to decrease the symptoms but was ineffective in the prevention of monkeypox disease[22]. The use of IMVAMUNE in populations with high risk has been recommended by various health monitoring organizations. Tecovirimat a drug that blocks the intracellular release of the virus has shown promising results and has been recommended to be used in immunocompromised patients. European Union (EU) body has already approved Tecovirimat for monkeypox virus while Food and Drug Administration (FDA) has approved it for smallpox[23]. Cidofovir, ribavirin, and tiazofurin have proven to be efficacious in animal and in vitro trials. Brincidofovir has been shown to have a better safety profile than Cidofovir but it has not been shown to be effective in treating Orthopoxviruses in vitro and in animal studies. A study conducted on dormouse showed that the dryvax smallpox vaccine protected against mortality by monkeypox virus[24].

At the moment, there are no specific treatments approved for monkeypox. Fortunately, the clinical course of monkeypox infection is usually mild and self-limiting. Therefore, it seldom warrants specific therapy, and treatment is often supportive[25]. Supportive therapy may include antipyretics for fever, analgesics for pain, or antibiotics for secondary bacterial infections. However, certain patients may require specific treatment. Those with severe disease, immunocompromised patients, pregnant women, and the pediatric age group may require specific treatment. Due to the similarities MPXV shares with smallpox, drugs and vaccines initially intended to treat smallpox have shown signs of efficacy against MPXV. However, limited data is available to support this[26]. Tecovirimat is an antiviral medication approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of human smallpox disease. Tecovirimat is available in oral (200 mg capsule) and intravenous formulations. According to the Centers for Disease Control and Prevention (CDC), it can be used as a treatment for MPXV in the United States. Cidofovir or brincidofovir can also be used; these are the antiviral medications that the FDA approves for treating cytomegalovirus (CMV) and human smallpox disease, respectively[27]. Vaccinia Immune Globulin Intravenous (VIGIV) is an immunoglobulin used to treat complications from vaccinia vaccination. The US CDC allows its use as a treatment for monkeypox disease under an expanded access protocol[28].

VI. PREVENTION

Studies have shown that smallpox vaccination effectively prevents other *Orthopoxvirus* infections, including monkeypox. When administered early in the incubation period, it can prevent disease onset or mitigate the severity of the illness[29]. However, there is a risk of severe adverse effects in immunocompromised patients. The eradication of smallpox in 1980 led to the termination of vaccination efforts against the viral illness, leaving many people susceptible to monkeypox[30]. Next-generation smallpox vaccines, which include ACAM2000 (live vaccinia virus), Modified Vaccinia Ankara (attenuated vaccinia virus), and LC16m8 (attenuated vaccinia virus), with attenuated strains not only offer an improved safety profile compared to first- and second-generation smallpox vaccines but also adequately stimulate antibody production in atopic and immunocompromised patients[31].

Hospitalized patients should be under strict airborne isolation in a negative pressure room. Health personnel should wear appropriately fitted N95 masks, gloves, and eye protection before coming in contact with these patients until the lesions have crusted and scabs have fallen off[32].

VII. CHALLENGES OF MONKEYPOX VIRUS

Comparisons with the COVID-19 pandemic are expected and at this stage some of the challenges are familiar, ranging from stigma against certain societal groups to the need for scaled up (devolved) testing, financial support for those isolating at home and the production of rapid guidance in the face of ongoing clinical and epidemiological uncertainties[33,34].

There are significant differences. This outbreak, although worldwide, was first identified in the United Kingdom, with the first, unrelated cases providing a serendipitous link for astute clinicians[35]. During this outbreak there are some causes for optimism; there has been recent experience of case management in UK hospitals. Treatment and vaccination are already available and are being used, with the latter playing an important role in pre- and post-exposure prophylaxis[36]. Smallpox vaccine confers approximately 85% protection against MPX. Rapid sequencing of the virus has led to speculation that it may have been circulating in humans rather than animal reservoirs for some time and sharing of sequence data from multiple countries has facilitated this[37]. Furthermore, transmission predominating in specific subgroups allows for more targeted health promotion measures.

VIII. FUTURE PROSPECTIVE

Presently, the precise global distribution of MPX is uncertain due to case ascertainment bias (encompassing

a lack of diagnostic testing, clinical mis-classification and incomplete surveillance) in some countries[38]. Although transmission chains have been relatively small in previous outbreaks, a decline in population immunity may lead to sustained epidemics with a basic reproduction rate (R_0) > 1, as evidenced by this ongoing outbreak. For MPX to become endemic in the UK, pathogen sharing must occur with domesticated animals, in particular pet rodents, with transmission into wildlife species[39]. Therefore, current advice from the UKHSA human animal infections and risk surveillance (HARIS) group is for temporary removal of these rodents from infected households for up to 21 days, and testing to exclude infection is recommended.

Within this current outbreak and in the future, MPX should be routinely considered in the spectrum of diseases when assessing patients presenting to genitourinary medicine clinics, as well as expanding multiplex PCR assays to include specific primers for pox viruses, both in the diagnostic laboratory or in rapid diagnostics to be utilized in the clinic[40]. A rapid diagnosis provided by the clinic would be beneficial for patient isolation, infection control and contact tracing.

Considerations for vaccination with smallpox, or even an MPX specific vaccine, are ongoing not only as post-exposure prophylaxis but also as a pre-exposure measure among at risk groups such as patients on HIV pre-exposure prophylaxis (PreP), susceptible healthcare workers in the sector and even among diagnostic laboratory staff handling infectious material[41-44]. Vaccination may become more routine and widespread as the true burden of MPX becomes more apparent.

Ultimately, the future of this outbreak will be determined by similar questions posed by COVID-19 in March 2020; what the extent of the outbreak is, both worldwide and in the United Kingdom, what the current reproduction number is, the extent (if any) of an animal reservoir, and what strategies will be required to drive it down[45-50].

IX. CONCLUSION

Previously endemic to regions of Africa, the monkeypox virus is now becoming a global concern, with sporadic cases being confirmed in regions in the western hemisphere. With human-to-human transmission most commonly occurring via respiratory droplets or direct contact with the mucocutaneous lesions of an infected individual, social distancing and contact tracing is imperative. Monkeypox cases are being confirmed in mid-age individuals. This can be attributed to the loss of cross-immunity from the smallpox vaccine seen in older individuals. This virus replicates within the cytoplasm and matures to create a primary viremia in which the virus spreads to the local lymph nodes. Monkeypox infection is also associated with complications such as bronchopneumonia, dehydration, respiratory distress, encephalitis, etc. Of all the complications, the most feared complication is corneal scarring, as it can lead to vision

loss. It is important to be able to provide the appropriate supportive treatment to ensure that the risk of these complications can be minimized as much as possible. Supportive therapy, such as applying moist occlusive dressings, may be applied in areas where the rash is highly concentrated. As cases of monkeypox cases are still being confirmed globally, organizations are focused on understanding how these cases are sporadically occurring across Europe and the western hemisphere. Investigation into any potential treatments is important, along with understanding the true extent of all the symptoms of monkeypox and the long-term effects of the virus and the symptoms. In the coming months, we will gain more clarity on the magnitude of the current outbreak as case finding intensifies. Acting quickly and proactively will be crucial for containing it. Ensuring that we learn from recent epidemics and share available resources early and quickly will be the key to success. The warning signals on monkeypox becoming a global public health concern have been present for many years. Now is the time to adopt a truly global approach that addresses this problem definitively not only in wealthy countries but also, critically, in the endemic countries that have been responding to monkeypox for decades.

CONFLICT OF INTEREST STATEMENT

The author declare no conflict of interest.

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