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Monkeypox virus – from endemic to pandemic: a review

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ABSTRACT:

With over 27,814 confirmed cases and 11 deaths (3 outside Africa) spread across the globe, the monkeypox virus is having a good run outside its historically endemic regions. A rare zoonotic disease caused by a member of the orthopoxvirus genus, similar to the causative agent of the previously eradicated smallpox disease but with milder symptoms, has transitioned to be a pathogen of public health emergency of international concern. The waning population-wide immunity provided by the smallpox vaccination, global connectedness, climate change, civil conflicts, and poverty are the likely factors contributing to the global spread. Despite 52 years having passed since it was first discovered in humans, there are gaps in knowledge regarding the ecology of the virus in the wild, host reservoirs, and definitive transmission modes; this is probably due to neglect from both regional and global authorities. The unusual prevalence of human monkeypox in men having sex with men (MSM), gay and bisexual, has generated a renewed concern regarding the possible evolution of the virus regarding sustained human-human transmission. This review highlights the epidemiology, host reservoir, transmission, diagnosis, clinical presentation, and management and prevention of human monkeypox, with further emphasis on the factors responsible for the global spread, the burden, and the neglect of the virus. In the absence of definitive therapy, a strong public health policy will help in curtailing the virus while we close the knowledge gaps that will help us eradicate and prepare for such zoonosis outbreaks.

Keywords: *Monkeypox, Virus, Zoonosis, Endemic, Pandemic, Review.*

INTRODUCTION

Human monkeypox is a rare zoonotic infectious disease caused by the monkeypox virus, a member of the orthopoxvirus genus, the same as the causative agent of smallpox disease. It was first discovered in captive monkeys in Denmark in 1958, and it was not until 1970 that the first human case was documented in Zaire (now the Democratic Republic of Congo); it was discovered as a result of intense last-phase surveillance of global smallpox eradication program in Central and West Africa[1-4]. It is endemic in the tropical rainforests of Central Africa and West Africa, with a larger fraction of the reported cases coming from the Congo Basin. Genomic analysis of the virus has shown two distinct clades-the Congo Basin (CB) clade and the West Africa (WA) clade[2,5]. The former is reported to have better transmission potential between humans and a high case fatality as high as 10% compared to the West African clade, which has a mortality rate lower than 1%[5,6].

Direct contact with dead infected animals, eating poorly cooked bushmeats, and human-to-human transmission have been described as possible routes of infection. The latter route has been reported[5] both in endemic and non-endemic areas. The concerns over sexual transmissibility of the monkeypox virus are underlined by

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the recent outbreak across Europe, where it has a higher occurrence among men having sex with men (MSM)[6,7]. The clinical symptoms of monkeypox are closely related to that of smallpox, with lymphadenopathy a distinguishing feature of monkeypox; others include fever with chills, rashes with a unique mode of formation, and secondary bacterial infections, which are common in immunocompromised patients[3,8,9]. A person is considered to be most contagious at the onset of maculopapular rashes, pneumonitis, encephalitis, and eye-related complications are uncommon features[10].

There is no specific treatment for monkeypox at the moment, although the smallpox vaccine has been recommended[11] by the Centers for Diseases Control and Prevention (CDC) within two weeks of exposure to a possible source of infection, it has been shown[11] to confer about 80% protection against monkeypox virus. Antivirals such as Tecovirimat and Brincidofovir, with strong activity against poxviruses, have been used in a few human monkeypox infection cases, with the former being more effective[3,9]. Yet there is a need for urgent effort to find a definitive cure to this emerging treat that looks very likely to thrive in previously uncharted territories.

Despite the eradication of smallpox long ago with the vaccinia virus vaccine, which provides cross-immunity to other poxviruses, there has been no less than a 20-fold increase in the monkeypox incidence in West Africa since 1986[12]. The recent rise of monkeypox incidence is due to the waning herd immunity as the number of naive individuals is increasing due to the cessation of routine smallpox vaccination[4,5]. Increased accessibility to remote, globalization, and increased economic, trade, and cultural relations have increased the human-human and human-animal interaction[5,7]. These factors favor the exportation of the virus into new environments, as shown by the first two outbreaks in the western hemisphere.

Human impacts on the environment have also created an avenue for increased interactions with suspected host reservoirs. Expansion of rainforests due to warmer and humid conditions (driven by climate change) enables the monkeypox virus to expand its geographic range, thus leading to a faster rate of dissemination[13]. Large flooding sometimes precedes a monkeypox outbreak, possibly due to the movement of both animals and human to dry land for safety[5]. Deforestation is also a driving force, especially in the known endemic areas[11], since it causes the movement of animals from deep forests; thus, contact is established with humans. Agriculture also plays a part in the storage of foods in the bush before transportation and further distribution into towns and cities, which might have been contaminated by rodents[14]. Moreover, civil unrest, wars, and poverty have led to the movement of people into the forest[14], which further leads to reliance on rodents and monkeys for food[6].

Post-COVID-19 relaxation has led to an increase in human interaction through gatherings, and this has been thought to be responsible for the recent surge in human monkeypox in Europe, as shown by the disproportionate rise in the prevalence among the MSM after attending the gay pride festival[15] that took place in the year 2022 across the globe, with 10 prominent ones among them being the one in Los Angeles (June 12), Tel Aviv (June 10), Sao Paulo (June 19), New York City (June 26), San Francisco (June 26), Madrid (July 9), Berlin (July 23), Amsterdam (August 6), Taipei (October 29) and Sydney (June 2-June 30). Lack of active surveillance for monkeypox coupled with a lack of resources in the endemic areas – mostly impoverished communities – has enabled the virus to remain below the radar, and a lack of globally coordinated efforts has allowed the rare zoonotic disease to transiting to a potentially global threat[16]. Thus, monkeypox virus - the most widespread Orthopoxvirus in humans – is regarded to have the ability to occupy the niche left by smallpox[3,5,12].

In summary, climate change, civil conflicts, poverty, and global accessibility are the likely factors driving the current outbreak[13,14]. With over 27,814 confirmed cases and 11 deaths in 89 different territories globally[17], this has raised the concern of policymakers, health workers, and the public regarding the threat posed by a disease known to affect the most impoverished population. This is underlined by the lack of in-depth knowledge of the virus ecology, as no known definitive host reservoir has been identified[6,16]. As part of the efforts to curtail the virus, WHO on 23 July 2022[4] declared it a Public Health Emergency of International Concern (PHEIC).

This review highlights the factors contributing to the global spread of the monkeypox virus, epidemiology, burden, clinical presentation, therapeutic management, and the need to curb this re-emerging infection to prevent another zoonotic pandemic.

EPIDEMIOLOGY, HOST RESERVOIRS, AND TRANSMISSION

Epidemiology

People living in the tropical rainforest of Africa are presumed to have come in contact with the monkeypox virus, which is native to the mentioned place, through hunting and consumption of bushmeat[18]. The low-level exposure that might have led to subclinical infection and the re-emergence after 1970 is believed to be due to the subduing effects of the smallpox vaccine, and there is a possibility of it being mistaken as another sexually transmitted infection[2,16,19]. Surveillance and improved laboratory diagnosis have led to an increase in the number of reported cases. Reports[2] documented 338 cases between 1981 and 1986, and there was a rate of 22 cases per 1,000 people in the 1997 outbreak in DRC; this represents approximately 96% of the reported global cases after three decades of monkeypox discovery, with the rest distributed in seven other countries across Central or West Africa. However, the geographical range has been expanded recently[2,3]. There were over 18,000 reported cases[3], spanning over two decades, starting from 2000 to 2019, and about 10,545 cases and 362 associated deaths between 2020 and May 2022. Cameroon reported[8] an outbreak in December 2021, and, as of February

2021, there were two deaths, three confirmed cases, and 65 suspected cases. At the same time, the Central Africa Republic reported[8] six confirmed cases and one death on 14 March 2022. Before the 2017 monkeypox outbreak in Nigeria, the last case had been reported in 1978[3,20]. There were 226 confirmed cases from 2017-2021, while 133 cases were confirmed out of 357 suspected cases and three deaths between the 1st of January and 24th of July, 2022[21]. According to the Africa CDC[22], there are about 2,567 cases, and 103 deaths (3.6% case fatality rates). About 72% of the reported cases from the region are thought to be of zoonotic transmission with children (average age: 4.4), mostly at the receiving end, with a mortality rate of 9.8% in non-vaccinated individuals[1].

In 2003, monkeypox cases were reported[13] in the Western hemisphere for the first time, an incident traced to the importation of exotic pets (rodents) from Ghana, a country with no reported case of human monkeypox as of that time[13] with around 71 cases investigated across the midwestern states, the isolated virus belonged to the West African (WA) clade[2,3]. Three different cases were reported in the UK in September 2018; two of them had a travel history to Nigeria, which had an active outbreak back then, and the other person had contact while caring for one of the infected. On the 7th of May, 2022**,** the UK reported an imported case of human monkeypox from a person traveling from Lagos, while two further cases were reported a few days later but not linked to the single imported case, and a case reported was not also linked with contact nor relevant travel history[18,19]. Portugal also reported 23 confirmed cases from 18 May to 20 May, 2022**,** followed by a cluster of reported cases in several European countries, including, Spain, Belgium, the Netherlands, Sweden, Austria, Germany, France, and Italy, bringing the total to about 13, 912 cases across 29 EU/EEA countries as of 8 August, 2022[8,16,23]. The genomic analysis confirmed the spread is due to the WA clade; this raised questions about the probable evolution and mode of transmission of the monkeypox virus as that particular strain is thought to have less efficient human-to-human transmission[23]. However, no new variant has been isolated in the ongoing outbreak, and no reduction has been observed in the genomic composition, which is a predictor of increased virulence in the variola virus, although the CB clade has been hypothesized to adapt better to human transmission[16]. There is still a need to investigate the sexual transmissibility of monkeypox further, as a large proportion of the cases in Europe has been in men who have had sex with other men and may be linked to recent pride festivals[8,18].

Host Reservoirs

Rodents and other small mammals have been implicated as the reservoir for the monkeypox virus in the wild; despite some evidence, knowledge about the definite reservoir is still lacking. This underlined the urgent need to investigate the ecology of the virus in the wild in a bid to achieve full control[5,14]. However, the known relationship between the orthopoxviral genus and rodents, coupled with recent evidence, is a likely indicator of them (rodent species) being the host reservoir[14]. Haider et al[12] reported the isolation of the monkeypox virus from a rope squirrel (*Funisciurus anaerythus*) and sooty mangabey (*Cercocebus atys*), both in the wild animal, the only two occurrences to date.

Its ability to infect a wide range of mammalian taxa, including sciurid, Nesomyid rodent, etc., indicates that there is a presence of more than a single host, and the seroprevalence of monkeypox in squirrels (*Funisciurus spp*) is higher when compared to other suspected hosts[2,14,18]. There are also instances of a monkeypox outbreak in some chimpanzees kept in a wildlife sanctuary in Cote d'Ivoire and Cameroon, and this ability to utilize various hosts has been hypothesized[3] to be necessary for its maintenance in nature. Prediction and prevention of novel spillover are difficult due to the extensive network of poorly defined hosts[23].

Transmission

Monkeypox virus is primarily transmitted to humans through direct contact with infected animals *via* bites, contact with skin lesions and body secretion. Human-to-human transmission has also been observed through respiratory droplets, sexual intercourse (close skin contact), and direct contact with contaminated household materials[6,24]. Perhaps the observed human transmission chains are usually short, and their lack of intrinsic transmissibility mitigates the potential of the monkeypox virus to become established in the human population[14,25]. Vertical transmission and fetal death have been reported[16]. The high prevalence of monkeypox incidence in men who have sex with men, especially in Europe, points to the possibility of its sexual transmissibility, but more studies are required to ascertain its transmission through genital fluids[3,16]. Thornhill et al[16] reported that 169 (32%) and 106 (20%) of the patients said to have visited sex on-site and have been engaged in "chem sex", respectively. Compared to the variola virus, monkeypox is less fatal and has a poor transmission, and the fact that it is a large DNA virus that has lower mutation points and is efficient in repairs also indicates the unlikely evolution that will warrant sustained human transmission albeit concern of it becoming an efficient human pathogen[10,13,23].

Unvaccinated individuals (against smallpox), hunters, people having multiple sex partners, frontline workers, immunocompromised individuals, and young children, especially males, are at risk[1,4,8].

Burden of Monkeypox

More than 1,300 cases of monkeypox have been confirmed in 40 non-African countries[26]. Africa, particularly the sub-Saharan regions, shares the highest burden of human monkeypox both in the past and in this

ongoing outbreak, with already stretched and stained healthcare due to the COVID-19 pandemic containing the ongoing outbreak without external aid will bear them to bones[26]. In the ongoing outbreak, the Democratic Republic of Congo (DRC) shows the highest burden out of the previously-known endemic region with 2,159 cases (84.3% of the total case), while Congo has a case fatality rate (CFR) of 43% more than the sum of the rest of the African Union members[22], and this might be due to the high fatality associated with the Congo Basin clade known to that area.

A retrospective study conducted on the burden of monkeypox in Nigeria (2017-2021) by Ogoina et al[20], reported that the south-south region of the country (Bayelsa and Rivers states) is the hotspot for human monkeypox, not surprising as the former is the origin of the 2017 outbreak in Nigeria, although Lagos (the most crowded city in the country) and Delta were reported to have a medium cluster of human monkeypox[20].

Several factors, such as uncontrolled border immigration, pastoral drifting, and civil unrest across the region, might be inimical to the adoption of good preventive measures, further adding to the burden[27]. Lack of public awareness and the stigma associated with the disease might deter people from seeking medical attention[5].

In Europe and the US, the prevalence among bisexuals and MSM (men who have sex with men)[28] poses a new challenge as the development of a sex-based approach to screening and treatment is still lacking, coupled with the Russo-Ukraine war, which can further spread the virus among men who are known to have the highest risk[29]. The availability of vaccines in the said region and existing robust public health strategies have been identified as important factors in containing the outbreak according to a model for non-endemic countries, the secondary cases would be reduced by up to 86.1%, and the duration of the outbreak by up 75.7% after the implementation of public health measures[28]. The viral metazoan of monkeypox was recognized in Congo Basin and West Africa; the virus from the Congo Basin was found[17] to be more virulent than any other globally. The endemic regions in Africa neither have robust public health nor vaccines to keep the outbreak at bay.

SYMPTOMS, DIAGNOSIS, THERAPEUTIC MANAGEMENT, AND PREVENTION

Symptoms

The symptoms of monkeypox and smallpox are similar with less severe symptoms in monkeypox. The incubation phase lasts for 10-14 days, after which the prodromal phase (1-3 days) begins with accompanying fever, severe headache, sore throats, lymphadenopathy (in the cervical, submandibular, or inguinal region), muscle aches, and then followed the development of maculopapular rashes (rash phase). At the development of rashes, the patient is considered very contagious, although transmission in the prodromal stage has also been observed. The lesion progresses from macules to papules and vesicle pustules, followed by scabbing and shedding within 2-4 weeks. It can spread to the extremities and genitals after starting from the face and trunk[1,8,18]. The slow maturation of the skin lesion can be employed as a differential in other skin lesion diagnoses[30].

Secondary complications include bacterial infection, sepsis, gastroenteritis, and pneumonia, and people with compromised immunity, such as HIV, are more likely to have poor outcomes due to secondary bacterial skin infection[3,16]. Conjunctivitis has also been reported[30]; the scarring of the corneal might lead to extensive and permanent damage to the eyes[30]. Kabuga et al[24], reported death due to high viremia following human-to-human transmission. Moreover, the lesions on the skin can leave lifelong scars[27].

Diagnosis

Definitive diagnosis can be established using real-time polymerase chain reaction (PCR) by taking the sample of the suspected skin lesions, preferably using swabs and aspirated lesion fluids; recent rt-PCR can be used to differentiate between the two clades of monkeypox virus (CB and WA)[8]. Testing for orthopoxvirus antibodies and immunohistochemistry have also been employed in the past and are still in use. However, these methods are relatively non-specific and cannot distinguish monkeypox infection from other orthopoxvirus infections due to antigenic cross-reaction[1,18]. The long and tedious process involved in using electron microscopy as a diagnostic tool precludes its use[1]. Monkeypox infection can be differentiated from other non-viral disorders using a Tzanck smear; that being said, it cannot be used as a differential diagnosis in smallpox or herpetic infections[2]. Rapid diagnostic kits such as Biothreat Alert® (Southern Scientific Limited, West Sussex, United Kingdom) and GeneXpert® (Cepheid, California, USA) have been developed to aid diagnosis in endemic areas with limited access to standard laboratories and personnel[24,30].

Sklenovska and Van Ranst[31] reported that misdiagnosis and co-infection with varicella zoster virus (VZV), the causative agent of chickenpox, is a relatively common occurrence, and anthrax and HIV-related fungal infection are not uncommon misdiagnoses. Thus, it is imperative to conduct laboratory investigations on suspected cases to avoid over/under-reportage, which might be inimical to effective control strategies.

Therapeutic Management

Currently, there are no approved specific treatments for monkeypox. The management is mainly aimed at providing supportive care and relief of symptoms. However, several strategies used include the use of an anti-smallpox agent and the use of the vaccinia vaccine.

Antiviral agents

Brincidofovir (CMX001) and Cidofovir are DNA polymerase inhibitor (broad spectrum against poxviruses) that acts by blocking viral synthesis at the polymerase level after the conversion to the active phosphate form. Both have been reported[1] to have inhibitory activity against monkeypox virus, both *in vivo* and *in vitro*. Brincidofovir use in small studies[9] showed derangement in liver enzymes, and as such, there is a need for close monitoring.

Tecovirimat has been approved[32] for use against orthopoxvirus infection in humans both in the EU and the US, though its efficacy in monkeypox infection is not yet ascertained. It acts by inhibiting the function of a major envelope protein (F13L), which is responsible for the spread and replication of the virus in the cell[1] and has been stockpiled as part of the US strategic National Stockpile to be deployed in an instance of smallpox bioterrorism[8,24]. Other drugs with potential use in monkeypox due to their activity against poxvirus include Ribavirin and Tiazofurin[1]. Therefore, there is a need to intensify the efforts in the search for drug targets for the monkeypox virus to obtain specific therapy[2]. Empirical antibiotic therapy using acyclovir might be initiated if there is a subsequent bacterial infection[27].

Vaccine and immunotherapy

In the absence of a specific vaccine for monkeypox, the smallpox vaccine, which has been reported[8] to have efficacy as high as 85% against monkeypox, has been recommended[8] for use due to its cross-protection against monkeypox, although its post-exposure efficacy has not been fully evaluated[8] even though it reduces the severity of the symptoms. ACAM2000 (Emergent Product Development Inc., Gaithersburg, United States) (first generation) and MVA-BN (Bavarian Nordic, San Diego, USA) (third generation) vaccines have been used to prevent smallpox infection, and the latter has been approved for the prevention of monkeypox infection by the US Food and Drug Administration and European Medicine agency[1,8]. Several efforts[33] have been put in place to develop the newer generation of vaccines, such as MVA-BN, which is devoid of adverse effects and can be employed in immunocompromised individuals and those with atopic dermatitis[1,3]. There have been concerns[2] over the deployment of the live vaccinia virus vaccine in endemic areas with an undefined number of immunocompromised individuals. A specific vaccine against monkeypox has been used in clinical trials in Africa since 2020[32].

Vaccinia immune globulin (VIG) is recommended to be used as a systemic treatment alternative in a patient with T cell immunodeficiency as post-exposure prophylactic against monkeypox, although its benefit is yet to be fully evaluated[18,32].

Prevention

Despite the proven benefit of the vaccinia (smallpox) vaccine in providing cross-protection against monkeypox, mass vaccination is not recommended nor required at this time based on the assessment of risk and benefit. However, it might be offered to individuals when the benefits outweigh the risks; for example, to the frontline health workers and those people (healthy) with a high risk of exposure[33].

Public health measures such as avoiding contact with dead or animals that might harbor the virus, isolation of sick animals, proper hand washing with soaps, disinfection of surfaces with alcohol-based disinfectant, use of personal protective equipment (PPE), and avoidance of exposing open wounds when working with animals should be observed[7,32]. Quarantine protocols should be employed on imported animals, not exclusively non-human primates and rodents, as the full range of the virus is not yet known. The infected individuals should be isolated; a six-week period from the date of infection has been reported[2] to be effective, and this is essential in containing the human-human spread. The onus lies in educating the general public to adhere to measures that will help keep the resurging threat at bay.

NEGLECTED OR UNDERRATED?

There have been signs[26] of a possible spillover of monkeypox in non-endemic areas. The 2003 and the 2017 outbreaks in the Western hemisphere were only two among several others ignored[26]. Ebola virus outbreak was ignored for decades until it spread across West Africa and then hit non-African countries, and humans supposed have learnt a lesson from this. As such, the current outbreak outside Africa is thought[29] to have been due to a lack of detection of the virus, which might have established itself and circulated within some host reservoirs. The lack of smallpox vaccine stocks in top countries' national reserves[3,33], in Africa, especially in the endemic regions, points to some degree of neglect by the developed and developing countries, the vaccine which the WHO has promised to roll out but not yet delivered[26]. The lack of intense dedicated research and diversion of grants[34], further contributed to the lack of preparedness for the virus discovered over 52 years ago. All these pointed to a lack of efforts to combat the virus, leaving it to go berserk in the endemic regions.

The virus, which has always been associated with poor African communities, is now spreading in high-income countries globally[19].

The possibility of sexual transmissibility raised by Ogonia et al[20] was grossly underrated, and some pointed out that homophobia might be another reason for the neglect[29]. Several calls by scientists regarding environmental and ecological changes that might further facilitate the improved human transmission of monkeypox were not duly addressed[30,35,36]. Climate change

might be one of the current drivers of most emerging and re-emerging zoonotic diseases[29], possibly due to an increase in the condition that favors the maintenance of the pathogen in the environment[37].

The situation is similar to what happened with coronavirus, about which there have been several warnings[26] since 2005 on the potential danger of bat coronavirus that could get attached to human receptors. Therefore, an infection historically confined to the African forests, can easily reach the Pacific region due to global connectedness[19,30]. Thus, the neglect in Africa is now a global concern, not just a déjà vu[26].

The recent global and regional efforts, the potential rollout of vaccines[33], and the ongoing clinical trials[32] in Africa for monkeypox-targeted treatments are huge strides in curbing this global threat.

CONCLUSIONS

The present outbreak is the largest, and the first time monkeypox-related deaths are happening outside Africa; this has moved the status of monkeypox from a rare zoonotic disease to a disease of international concern. Several factors have been put forward as the likely cause of the present global outbreak, chief among them is the waning herd immunity against poxvirus due to the cessation of routine smallpox vaccination. Others include globalization, zoonotic spillover, and human impacts on the natural environment. The fact that monkeypox cases is prevalent among the MSM, gay and bisexual, calls for further investigation to ascertain if the virus has employed a new transmission strategy. Moreover, some studies[29] have shown that males usually have higher severity and a higher proportion of infectious diseases compared to females. This further underlines the need to investigate male-male transmission.

Effective eradication of this virus is difficult without addressing the gaps in knowledge about the ecology of the virus in the wild and identifying the host reservoirs. This will help to understand the factors fueling the recent spread. Improved surveillance, diagnosis, public education, and collaboration with relevant agencies to implement the One Health approach[27] would greatly help in the absence of a definitive cure. Monkeypox is not as contagious nor dangerous as smallpox or COVID-19, but the wealth of knowledge about orthopoxvirus is an added advantage in the ongoing fights[27]. Despite the known cross-protection offered by the smallpox vaccine, its human efficacy against monkeypox needs to be proven in clinical trials with further pharmacovigilance[19]; further research is required to improve the current arsenal against the virus in case of a resistant strain. Although the developed and developing countries with better resources would respond appropriately to the threat, the same cannot be said of the most ravaged country (the Democratic Republic of Congo), which has been battling spontaneous outbreaks for the past two decades. More funding needs to be directed at zoonotic diseases as they have been the major threat to global health security recently[6].

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