

Clinical Features Present, Past & Future Prospective of Monkey Pox: A Orthopoxvirus

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ABSTRACT

Some issues regarding the potential spread of monkeypox have arisen just as the international world is beginning to recover from the initial alarm that was caused by the probable spread of coronavirus disease 2019 (COVID-19). Despite the fact that parts of Africa have traditionally been more susceptible to monkeypox than other regions of the world, the majority of new cases that have been linked to the outbreak that began in 2022 have been reported in countries located in Europe and the western hemisphere. Despite the fact that a great number of organisations are working on contact-tracing activities at the moment, the origin of this outbreak is still unknown at this time. The monkeypox virus belongs to the family of viruses known as Poxviridae and the genus known as Orthopoxvirus. Following the eradication of smallpox across the globe in the 1970s, news of monkeypox caused widespread worry across the globe. Through vaccination with the smallpox virus, individuals were able to develop cross-immunity against monkeypox. After distribution of the smallpox vaccine was discontinued, the number of outbreaks of monkeypox rose. The monkeypox epidemic that occurred in the United States in 2003 was the first time that the disease gained extensive notice in the media. In spite of its name, the virus known as monkeypox is not transmitted by monkeys. Although a number of different kinds of rodents and other small mammals have been suggested as the primal hosts of the monkeypox virus, the virus's true lineage is still a mystery. The virus that causes monkeypox was first identified in macaque monkeys, which is where the disease was first seen. When monkeypox does transfer from one person to another, it often does so through a person's mucocutaneous lesions or through the respiratory droplets that they expel. However, this only happens very infrequently. However, supportive therapy can be given to reduce symptoms, and medications such as tecovirimat may be administered in really severe cases. At this time, there is no specific treatment for patients who have infected the virus; however, supportive treatments can be given. It is debatable whether or not these treatments are successful in reducing symptoms because there are no concrete guidelines to follow in this regard.

Keywords- Monkeypox, viral disease, human to human, genomics.

I. INTRODUCTION

Smallpox and monkeypox are both caused by the same genus of virus. This family of viruses includes

some well-known pathogens as cowpox, horsepox, camelpox, and alaskapox. The variola virus is the most widespread and well-known of the viruses belonging to this genus. The smallpox epidemic was officially

declared over by the WHO in 1980 [1]. Although the monkeypox virus is genetically identical to the smallpox virus, it has a far lower risk of mortality and is much less contagious among close contacts [2,3]. The rash and other symptoms, however, are strikingly similar to those of smallpox. Two clades, clade 1 and clade 2, of the monkeypox virus have been found in Africa. While clade 2 is only found in West Africa, clade 1 is widespread throughout Central Africa and the Congo Basin [2]. The current monkeypox epidemic has been connected to the clade 2 strain, making it an international public health issue. However, a recent study reveals that the presently prevalent strain of the virus has many mutations in its DNA genome, suggesting that the presently prevalent virus is modifying itself for human adaptation and spread. [3] Throughout human history, there have been numerous viral epidemics that had far-reaching effects on health and culture around the world. Epidemic viruses include smallpox, influenza, human immunodeficiency virus type 1 (HIV-1), Ebola, severe acute respiratory syndrome, severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), and monkeypox. The variola virus caused smallpox, a highly contagious and ultimately lethal disease [4]. The human immunodeficiency virus (HIV) is a ssRNA virus that causes AIDS. The immune system is the primary target of the Retroviridae virus family, which leaves humans more susceptible to secondary infections and disorders. The medical disorder known as acquired immune deficiency syndrome (AIDS) arises when the immune system of an individual has been so compromised that it is unable to effectively fend against disease and infection. An estimated 35 million people have died as a result of the HIV/AIDS pandemic so far [5]. The influenza virus causes a respiratory ailment known colloquially as the flu. Severe sickness and even death can result from this extremely contagious virus, especially in the elderly and those with preexisting health issues. The Spanish flu pandemic of 1918-1919, for example, is said to have infected one-third of the

world's population and been responsible for tens of millions of fatalities [6]. The Ebola virus, which produces an illness characterised by high fever, bleeding, and organ failure, is a ssRNA virus of the family Filoviridae. It spreads when a person comes into touch with an infected animal or person's blood or other bodily fluids. The most recent of multiple Ebola outbreaks in Africa occurred in West Africa between 2014 and 2016 and was responsible for over 28,000 confirmed cases and over 11,000 deaths [7]. The SARS-CoV virus causes severe acute respiratory syndrome (SARS). The coronaviridae family is ssRNA viruses. Over 8000 cases and over 750 deaths have been attributed to it since it was first discovered in China in 2002 [8]. The SARS-CoV-2 coronavirus is the next potential pandemic virus after the COVID-19 virus. It is a highly contagious respiratory illness spread by airborne particles and liquid droplets. It was initially discovered in December 2019 in Wuhan, China, and it has already become a global epidemic [9]. Last but not least, a member of the family poxviridae: the monkeypox virus. Disease in monkeys is caused by a double-stranded DNA virus in the family poxviridae. Humans catch it from interacting with infected primates, rodents, and rodentia. Close contact with a carrier's saliva, mucous, or skin sores can transfer the virus to other people. Fever, headache, muscle soreness, and a rash that begins as tiny bumps and progresses to raised lumps filled with fluid are all symptoms of this sickness. Monkeypox bumps show up most frequently on the face, hands, and feet, however they can appear anywhere. Complications from the infection, such as pneumonia and sepsis, can be life-threatening in the worst cases. While there is presently no cure for monkeypox, supportive therapy such as pain and fever relievers can help patients cope. The smallpox vaccine has shown some promise in preventing monkeypox, albeit it is not 100% reliable. Monkeypox can be avoided by practising good hygiene, such as washing one's hands frequently and staying away from sick people, and staying away from infected animals[10].

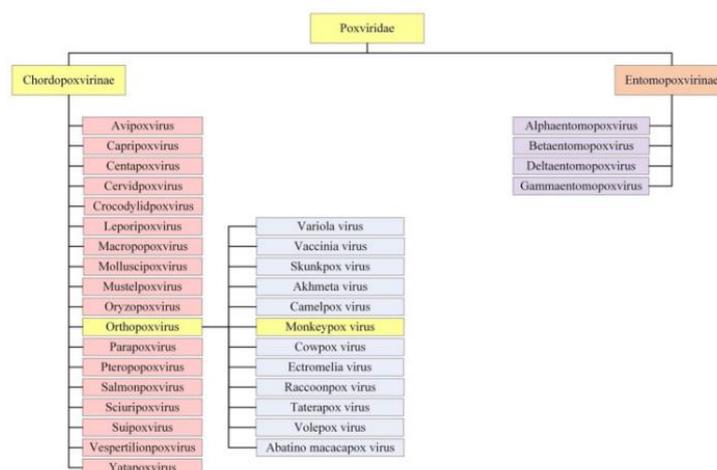


Figure 1: Taxonomy of Poxviridae

II. METHODOLOGY & SEARCH STRATEGIES

PubMed, ScienceDirect, and Google Scholar were used in a search of the literature on monkeypox. "Monkeypox" and either "origin," "spread," "symptoms," "prevention," "treatment," "vaccine," OR "risk to the healthcare worker" were used in the search syntax. This article summarises the findings of a literature review conducted by four medical doctors for ease of reading.

III. PATHOPHYSIOLOGY OF MONKEY POX

The MPXV is an obligatory parasite that exists in two separate strains, one of which originated in the Congo Basin (commonly known as Central Africa), and the other of which originated in West Africa. Transmission from person to person seems to occur more frequently and be more dangerous in the Congo Basin clade (also known as the Central Africa clade) than it does in West African clades [11]. It does its replicating inside the host, which reduces the host's defences against outside diseases. In spite of the many investigations that have been conducted on the pathophysiology of MPXV, the roles of both innate and adaptive immunity remain unclear. Natural killer (NK) cells are the most essential component of innate immunity because of their role in assisting T cells and dendritic cells in the direct elimination of infected cells [12]. During the early stages of an infection, the suppression or activation of natural killer (NK) cells is initiated upon contact between NK cells and their respective ligands, such as the major histocompatibility complex (MHC) I molecule. NK cells are responsible for inducing inflammation by the secretion of cytokines such as IFN- and TNF-. These cytokines, together with the support of dendritic cells, are what activate T-helper (Th) cells [13]. In his discussion of viral tropisms, McFadden distinguished three categories: cellular, host, and tissue tropisms. The fact that MPXV primarily replicates and spreads within infected hosts has a significant bearing on the types of hosts and tissues that are most susceptible to infection by the virus. Histopathology examination revealed that the MPXV antigen was present in the lungs, liver, pancreas, kidneys, ovaries, and heart of the patient. It was found that the MPXV causes the most damage to ovarian tissue [14], which is likely due to the higher viral titers in this tissue compared to other tissues. Zaucha et al. [15] found that MPXV thrives in the lymphoid tissues of the *Macaca fascicularis* (cynomolgus monkey), and that the viral antigen was also present in many other tissues, such as the salivary gland and the sebaceous tissues of the lips. They also found that MPXV thrives in the lymphoid tissues of the cynomolgus monkey. The skin infection

that causes monkeypox might come from monkeys or the respiratory mucosa of a person who is already sick. It is through the lymphatic system that the virus gains access to the bloodstream, which results in primary viremia and a systemic infection [16].

In addition, MPXV is related to poxviruses since it utilises an orthopoxvirus mechanism similar to that of poxviruses. The initial phase of the cytoplasmic replication process for the pox virus involves the virus attaching itself to the surface of mammalian cells. There are two distinct varieties of the virus, which are referred to, respectively, as the external enveloped virus (EEV) and the internal mature virus (IMV) [17]. Both components enter the cell via distinct routes, and their surface proteins and the amount of membranes they are surrounded by are distinct from one another. The fusion process begins once the virion has established a connection with the membrane of the host cell. The inner structure of a virion is instantly discharged into the cytoplasm of a cell when the virion enters the cell. It is not necessary for a virus to attach itself to a particular receptor in order for it to enter a host cell; rather, viral entry happens through fast signalling pathways in many networks of host protein kinases, and this signalling affects later phases of replication [18]. Even though the stimulation of signalling pathways stimulates the synthesis of cell receptors such toll-like receptors (TLRs), which activate antiviral pathways like the release of cytokines and chemokines, some pox viruses have the potential to block TLRs [19]. This is the case despite the fact that some pox viruses have the ability to block TLRs.

The early promoters of the virus are responsible for driving RNA polymerase to produce viral mRNA. This mRNA is then used to release virus core material into the cytoplasm and initiate the initial cascade of gene expression. Second, core uncoating happens when the core structure dissolves because of host and viral mechanisms that are currently unknown [20]. This happens when the core is exposed to the environment. After the viral coat has been removed, the core structure of the virus can be exposed. This exposes the viral DNA, which can then enter the cytoplasm, where it can serve as a template for DNA replication and induce early as well as late DNA transcription activities. The coordination of viral gene expression with host-produced transcription factors during the early, intermediate, and late stages of the transcription process [21] results in an increase in the efficiency of viral gene expression. Microtubule-mediated trafficking is responsible for transporting IMV, an infectious virus formed by the accumulation of late viral genes, to the golgi-derived membrane, where it is then wrapped to become IEV [22]. IMV is an acronym for infectious virus that is generated by the accumulation of late viral genes. The resulting cell-associated enveloped virus (CEV) can be directed towards surrounding cells via actin tail polymerization or released directly as free EEV particles

[23]. This occurs when the IEV establishes a fusion with the cell membrane and loses one of its outer membrane wrappings. The CEV and EEV forms are thought to be particularly significant for rapid cell-cell propagation in

vivo fig 2 [24], whereas the IMV form is anticipated to contribute to virus transmission only after late-stage cell death and membrane rupture.

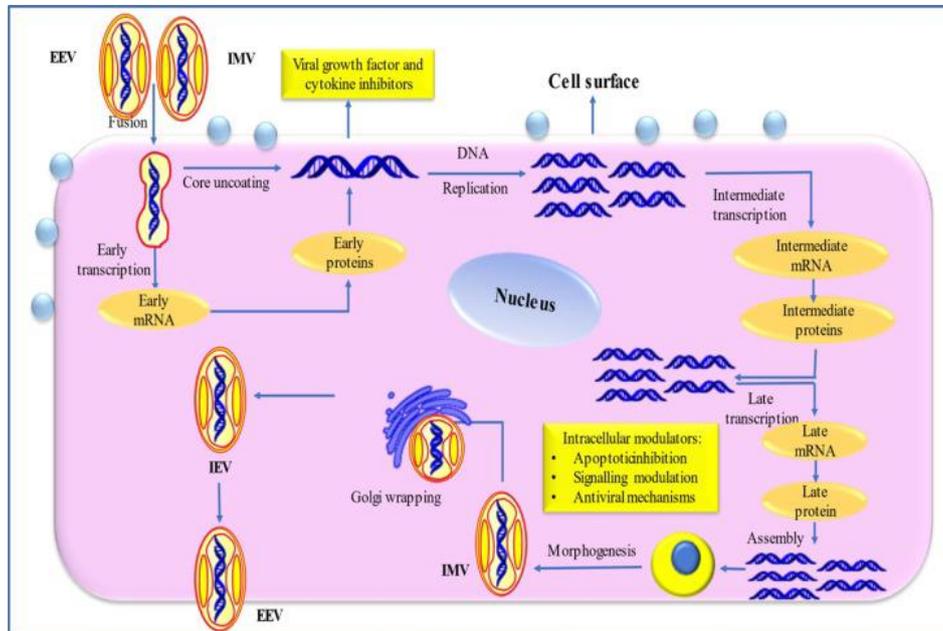


Figure 2: To quickly summarise the pathophysiology of monkeypox virus, the virus replicates inside the host and weakens the immune system. The pox virus replicates within the cytoplasm, and the process starts with the virus attaching to the host membrane and fusing with the host cell. Both the internal mature virus (IMV) and the extracellular enveloped virus (EEV) are considered to be components of the virus. The nucleoprotein core of the virion is then released into the cytoplasm, where RNA polymerase can begin synthesising viral mRNA in response to early promoters. After then, the process of uncoating the core continues. Early and late DNA transcription processes arose from viral DNA being released into the cytoplasm once the virus core structure was uncoated. IMV virions are infectious virus particles formed by the aggregation of late viral genes. which move via microtubule-mediated trafficking and enclose themselves in a membrane formed from the golgi to form intracellular enveloped viruses (IEVs). In order to become the cell-associated enveloped virus (CEV), the IEV form sheds one of its outer membrane wrappings during membrane fusion. Epidemiology of Monkey pox

In 1970, a patient in the Democratic Republic of the Congo was identified as having human monkeypox for the first time[25]. After that, between the years 1970 and 1990, there were approximately 400 documented cases of monkeypox in Africa. The majority of these cases were found in the Democratic Republic of the Congo (DRC),[26] followed by the Central African Republic (CAR) (6 cases),[27] Cameroon (2 cases), Nigeria (3 cases), Ivory Coast (2 cases), Liberia (4 cases), Sierra Leone (1 case), and Gabon (1 case).56 Only one of the four suspected cases of monkeypox that were reported in Cameroon in the year 1990 has been verified as really having the disease.1996 was the year that the Democratic Republic of the Congo (DRC) experienced a prolonged outbreak of human monkeypox. Following the discovery of the disease's first confirmed case in February of that same year, a total of 71 potential cases of monkeypox were found by August of that same year. As of 1999, the Democratic Republic of the Congo (DRC) had recorded more than 500 cases of

monkeypox. Between February and August of 2001, the province of Equateur in the Democratic Republic of the Congo (DRC) reported a total of 16 cases of monkeypox. In the meanwhile, researchers Anne et al[28]. examined vesicle secretions and crusted scabs from 136 people in the Democratic Republic of the Congo who were suspected of having monkeypox during the years 2001 and 2004. There were fifty-one instances of monkeypox that could be confirmed.

Before the first case was discovered in the United States in 2003, people in other parts of the world didn't pay much attention to human monkeypox[29]. There were 47 reported cases of monkeypox, including 37 confirmed cases and 10 possible cases. All of the cases of monkeypox were contracted through intimate contact with captive prairie dogs (*Cynomys* spp.). The number of confirmed cases was 37, while the number of probable cases was 10.70 Among the infected small mammals imported to Ghana from Africa were rope squirrels (*Funiscuirus* spp.), tree squirrels (*Heliosciurus*

spp.), Gambian giant rats (*Cricetomys* spp.), brushtail porcupines (*Atherurus* spp.), dormice (*Graphiurus* spp.), and striped mice (*Hybomys* spp.). Laboratory testing that included virus isolation and PCR amplification determined that one Gambian giant rat, three dormice, and two rope squirrels were all infected with monkeypox. This information was provided by the Centres for Disease Control and Prevention (CDC). The fact that there were no fatalities reported and no evidence of HGT68 was identified was attributed to the fact that the strain originated in West Africa, where there was a lack of transmission.[31]. In addition, studies conducted on the effects of human monkeypox transmission routes discovered that invasive transmission was associated with much more severe symptoms of systemic disease (49.1% vs. 16.7%; $P = 0.041$) than noninvasive transmission.⁷⁰ In contrast to the epidemic that has been sweeping across Africa, the vast majority of cases that have been confirmed so far have been found in adults. In 2003, the Republic of the Congo (ROC) announced the first known instance of monkeypox affecting a human patient. During the course of this outbreak, twelve people were found to have either confirmed or suspected cases of monkeypox, all of whom were under the age of 18. One of these individuals passed away. The monkeypox virus is thought to have passed from human to human on at least six separate occasions; this is the longest chain of transmissions that has ever been observed[32]. Between September and December of 2005, residents of five communities in Unity State, Sudan, reported a total of ten confirmed and nine possible cases of monkeypox. Two of these communities were located in Bentiu, three in Modin, five in Nuria, five in Rubkona, and four in Wang Kay. Between the years 2010 and 2018, there were 73 cases of monkeypox recorded throughout several countries in Africa, including the Democratic Republic of the Congo (DRC), the Central African Republic (CAR), Cameroon (79), Liberia (80), Sierra Leone (81) and the Central African Republic (COA).⁸² In addition, in the year 2017, reports surfaced indicating that an outbreak was taking place in Nigeria. In the two years that passed between 2017 and 2018, 122 instances of human monkeypox were documented throughout the 17 states that make up Nigeria. The fatality rate per case was 6%, and there were a total of six deaths documented. After several years of rare occurrences outside of Africa (United Kingdom, Singapore, Israel,^{91,92} United State), the monkeypox outbreak in 2022 afflicted thousands of individuals all over the world. The outbreak was preceded by several years of rare occurrences outside of Africa (United States). In May of 2022, the United Kingdom saw an outbreak of monkeypox, which resulted in many confirmed cases.² On May 6, 2022, the condition known as monkeypox was identified in a person who had a history of travelling to Nigeria.⁹⁴ On May 12, the United Kingdom Health Security Agency (UKHSA) in London confirmed the

diagnosis of two additional cases of monkeypox. Both of the parties are not linked to one another and have never been to the endemic region. After a week had passed, four further verified incidents surfaced. In a peculiar turn of events, it turned out that none of these patients had any known connections to the cases that had already been authenticated. In a polymerase chain reaction (PCR) analysis, 96 patient swab samples tested positive for the West African clade of the monkeypox virus. This result indicates that this strain was the one responsible for the outbreak that occurred[34].

On May 18th, there were a total of 14 confirmed cases of monkeypox in Portugal, 13 confirmed cases in Canada, and 7 confirmed cases in Spain.[35]. On this day, the United States also reported the confirmation of its first case of monkeypox for the year 2022.¹⁰² On May 19, authorities in Belgium and Sweden reported the occurrence of the first cases.^{103,104} In Belgium, it has been mandated that everyone who has been diagnosed with monkeypox must remain in isolation for a period of 21 days. In addition, Belgium was the first country in the world to require quarantine for individuals who had been diagnosed with monkeypox. At the same time, a tourist who had been to the Canary Islands became Italy's first confirmed case of the disease.¹⁰⁵ Additionally, there has been a suspected case reported from the country of France. Through genetic research, it was discovered that a virus that was isolated from a case of monkeypox that occurred in Portugal was closely related to a virus that was imported from Nigeria in 2018 and 2019[36]. On May 20th, it was discovered that two people in Australia had contracted monkeypox after recently returning from trips to Europe. On the same day, Germany, the Netherlands, and France each confirmed their first cases, bringing the total number of confirmed cases to [37]. The following day saw official announcements made in both Switzerland and Austria regarding the matter. The first known case of monkeypox was found in Asia, and the disease has already made its way to Israel, according to the Israeli Ministry of Health.[38]. After May 2022, there was an upsurge in the number of confirmed cases of monkeypox in non-endemic nations. On June 23, the World Health Organisation (WHO) issued a statement stating that monkeypox is a "evolving threat of moderate public health concern" due to the distinctive character of the outbreak. On July 23, 2022, the World Health Organisation (WHO) issued a declaration that the rapid spread of monkeypox across a large number of countries and regions constituted a "Public Health Emergency of International Concern" (PHEIC).[39] During this time, recommendations for the treatment and prevention of monkeypox have been created in a number of countries.[40]. As of the 13th of September 2022, there have been 57,995 instances of monkeypox virus infection that have been laboratory-confirmed across all six WHO regions (Fig. 3). These cases have been reported from more than 100 nations or regions. As a

direct consequence of this, nineteen persons in nine different countries lost their lives. According to the most recent sources, the first confirmed case of monkeypox occurred on September 6 in Hong Kong.[41]. Epidemiological research indicates that this patient, who was born in the Philippines and had reached the age of 30 when she arrived in Hong Kong on September 5th, originally hailed from that country. In light of this, the government of Hong Kong has initiated a readiness and reaction plan in response to the appearance of

monkeypox in the territory. The four verified cases that have been reported in Taiwan Province, China, are the first ones to be recorded outside of that region. It is important to note that on August 4, 2022, the Centres for Disease Control and Prevention (CDC) in the United States declared a public health emergency declaration owing to the spread of monkeypox. As of the 6th of September, there were a total of 20,733 confirmed cases of monkeypox in all 50 states, making this outbreak one of the worst in the history of the United States[42].

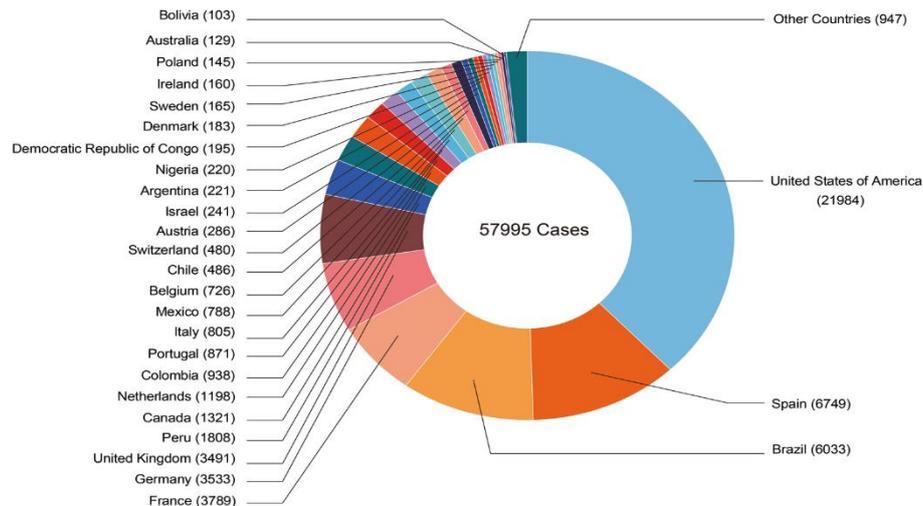


Figure 3: Map showing the spread of the monkeypox pandemic from January to September of 2022 around the world. Cases that have been confirmed may include those that have only been confirmed as orthopoxvirus or as the less severe monkeypox virus. The CDC provided the data given here as of September 12, 2022. GraphPad Prism 9 was used to create this diagram.

IV. HOW MONKEY POX TRANSMITTED TO HUMAN

Before the first case was discovered in the United States in 2003, people in other parts of the world didn't pay much attention to human monkeypox.68,69 There were 47 reported cases of monkeypox, including 37 confirmed cases and 10 possible cases. All of the cases of monkeypox were contracted through intimate contact with captive prairie dogs (*Cynomys* spp.). The number of confirmed cases was 37, while the number of probable cases was 10.70 Among the infected small mammals imported to Ghana from Africa were rope squirrels (*Funiscurus* spp.), tree squirrels (*Heliosciurus* spp.), Gambian giant rats (*Cricetomys* spp.), brushtail porcupines (*Atherurus* spp.), dormice (*Graphiurus* spp.), and striped mice (*Hybomys* spp.). Laboratory testing that included virus isolation and PCR amplification determined that one Gambian giant rat, three dormice, and two rope squirrels were all infected with monkeypox. This information was provided by the Centres for Disease Control and Prevention (CDC). The fact that there were no fatalities reported and no evidence of HGT68 was identified was attributed to the fact that the strain originated in West Africa, where there was a lack of transmission.69 In addition, studies

conducted on the effects of human monkeypox transmission routes discovered that invasive transmission was associated with much more severe symptoms of systemic disease (49.1% vs. 16.7%; $P = 0.041$) than noninvasive transmission.70 In contrast to the epidemic that has been sweeping across Africa, the vast majority of cases that have been confirmed so far have been found in adults.71 In 2003, the Republic of the Congo (ROC) announced the first known instance of monkeypox affecting a human patient. During the course of this outbreak, twelve people were found to have either confirmed or suspected cases of monkeypox, all of whom were under the age of 18. One of these individuals passed away. The monkeypox virus is thought to have passed from human to human on at least six separate occasions; this is the longest chain of transmissions that has ever been observed.72 Between September and December of 2005, residents of five communities in Unity State, Sudan, reported a total of ten confirmed and nine possible cases of monkeypox. Two of these communities were located in Bentiu, three in Modin, five in Nuria, five in Rubkona, and four in Wang Kay. Between the years 2010 and 2018, there were 73 cases of monkeypox recorded throughout several countries in Africa, including the Democratic Republic of the Congo (DRC), the Central African Republic (CAR), Cameroon

(79), Liberia (80), Sierra Leone (81) and the Central African Republic (COA).⁸² In addition, in the year 2017, reports surfaced indicating that an outbreak was taking place in Nigeria. In the two years that passed between 2017 and 2018, 122 instances of human monkeypox were documented throughout the 17 states that make up Nigeria. The fatality rate per case was 6%, and there were a total of six deaths documented. After several years of rare occurrences outside of Africa (United Kingdom, Singapore, Israel, United States), the monkeypox outbreak in 2022 afflicted thousands of individuals all over the world. The outbreak was preceded by several years of rare occurrences outside of Africa (United States). In May of 2022, the United Kingdom saw an outbreak of monkeypox, which resulted in many confirmed cases.² On May 6, 2022, the condition known as monkeypox was identified in a person who had a history of travelling to Nigeria. On May 12, the United Kingdom Health Security Agency (UKHSA) in London confirmed the diagnosis of two additional cases of monkeypox.⁹⁵ Both of the parties are not linked to one another and have never been to the endemic region. After a week had passed, four further verified incidents surfaced. In a peculiar turn of events, it turned out that none of these patients had any known connections to the cases that had already been authenticated. In a polymerase chain reaction (PCR) analysis, 96 patient swab samples tested positive for the West African clade of the monkeypox virus. This result indicates that this strain was the one responsible for the outbreak that occurred.^[38]

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The viral zoonosis known as monkeypox is most prevalent in the tropical woods of Central and West Africa, but it has the potential to spread to other regions of the world. The symptoms of MPXV normally endure between two and four weeks, which indicates that the condition is self-limiting. Case reports were used to assemble together evidence suggesting that MPXV can be transmitted to healthy individuals. Skin-to-skin contact with infected animals or people who have skin lesions caused by MPXV is the route of transmission that is observed to be the most common [43]. The most typical ways that MPXV is passed from person to person are through prolonged and direct skin-to-skin contact, as well as by the inhalation of infectious droplets. Additionally, transmission can take place when the infected individual's personal goods (such a pillow, clothing, or pocketbook), for example, come into contact with another human being [44]. At this point in time, it is uncertain precisely how the virus spreads. The incubation period for monkeypox typically lasts between 6 and 13 days, although in extremely rare instances, it can last up to 21 days [45].

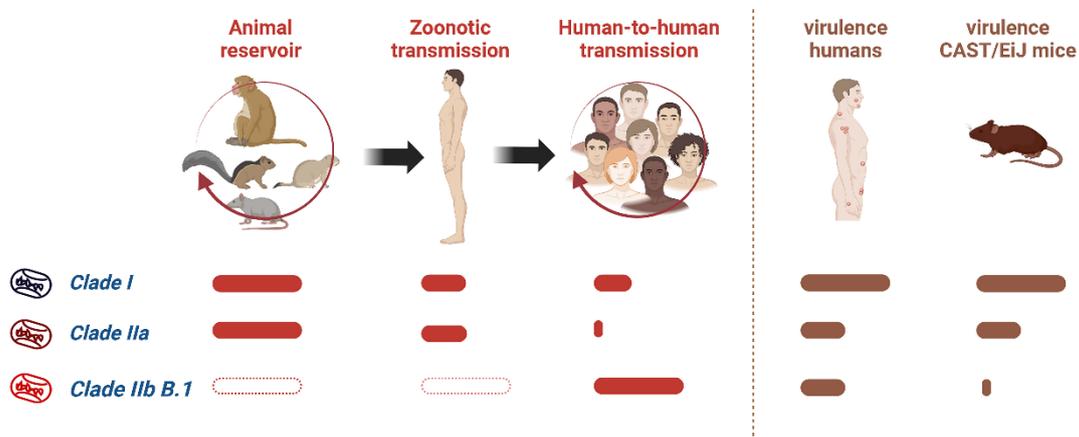


Fig. 3 Mode of transmission of Monkey pox

V. DIAGNOSIS OF MONKEY POX

Only laboratories with a biosafety level 3 should attempt to carry out PCR or real-time PCR. MPXV DNA may be routinely detected by real-time PCR in clinical and veterinary materials as well as in cell cultures with MPXV infection by utilising conserved portions of the extracellular envelope protein gene (B6R), the DNA polymerase gene (E9L), Rpo18, a DNA-dependent RNA polymerase subunit, and the F3L gene[46]. PCR-amplified genes or gene fragments can also be subjected to RFLP analysis, which stands for restriction-length fragment polymorphism. This allows for the detection of MPXV DNA. However, RFLP takes a significant amount of time and requires viral culture[47]. When used in clinical settings when speed, sensitivity, and specificity are of the utmost significance, RFLP analysis of PCR products is less than ideal since it requires the additional stages of enzyme digestion and gel electrophoresis. When it comes to characterization of MPXVs and other OPVs, whole genome sequencing carried out with next-generation sequencing (NGS) technology is still considered the gold standard. The downstream sequencing technology has a lot of positive effects, but it comes with a hefty price tag and a lot of extra work to compute[48].

In regions such as Sub-Saharan Africa, where other methods of characterization may be more readily available, NGS may not be the method that provides the best results. Real-time PCR is still the method of choice for routine MPXV diagnosis; however, this method needs to be complemented by field genome sequencing technology such as Oxford NanoporeMinION in order to enable rapid epidemiological interventions based on evidence from the viral genome. During the Ebola outbreak, resource-limited parts of West Africa were able to effectively utilise MinION field sequencing for genomic surveillance. This was accomplished with great success[49].

According to clinical diagnosis, the incubation period for MPXV is anywhere from four to twenty-one days, and it is frequently accompanied by a prodromal disease that manifests itself with symptoms such as enlarged lymph nodes, fever, myalgia, headache, back pain, acute asthenia, malaise, pharyngitis, and profuse sweating. A vesiculopustular rash appears anywhere from one to ten days after the onset of the prodromal phase, and it gradually spreads to every part of the body during the exanthema phase. The lesions generated by MPXV have a consistent look, range in size from a pea to a sultana, and are extremely hard, very similarly to the lesions caused by smallpox. Crop-like lesions and a mild centrifugal distribution are diagnostic of smallpox, but they are not diagnostic of MPXV[50]. Another way that MPXV can be distinguished from smallpox is through the development of lymphadenopathy. Even in the absence of test results, it is extremely important to make a quick diagnosis of MPX. In a sample of 645

individuals, the clinical criteria of MPX had a high degree of sensitivity, ranging from 93 to 98 percent. The specificity, on the other hand, is not particularly high (only 9-26%)[51]. Immunohistochemistry is utilised in the process of viral antigen detection, whilst enzyme-linked immunosorbent assays (ELISAs) are utilised in the process of IgG and IgM antibody detection. Rather of relying solely on OPVs, an immunochemistry analysis that makes use of either polyclonal or monoclonal antibodies can be used to identify between an infection caused by a poxvirus and one caused by the herpes virus. It has been proven that there is an increase in both the levels of antiviral antibodies and T-cell responses soon before the onset of illness. On the other hand, IgM and IgG antibodies can be detected in the serum anywhere from five to eight days after the rash first occurs. If someone tests positive for MPXV IgM and IgG antibodies but has no history of rash or severe illness, a doctor may still be able to make an indirect diagnosis of MPXV in that person. None of these strategies, on the other hand, are exclusive to MPX. People who have previously had the smallpox vaccination have the ability to employ IgM to detect infection with MPX in addition to other OPV species[52]. IgG capture ELISA results suggest prior exposure to OPV, whereas IgM capture ELISA results indicate recent contact with OPV (possibly MPXV in endemic areas). Prior exposure to OPV is indicated by the presence of antibodies against the virus. Because of this, the presence of OPV antibodies in a sample indicates that the persons who participated in the study had either recently received the OPV vaccine or are at risk of becoming infected with the virus on their own. In regions where the monkeypox virus (MPX) is common, there will be a population of people who have IgM but are not immune to smallpox. In the event that the necessary equipment is readily available, electron microscopy can also be exploited as a laboratory for the purpose of identifying poxviruses[53]. It is possible that this is an early sign of a disease that will reveal itself as a rash. When observed by electron microscopy, typical poxvirus particles will have the characteristic shape that is associated with them. For instance, during the recent epidemic of MPX in the United States, electron imaging revealed that keratinocytes contained both mature virions and immature virions in the stage of synthesis within the cytoplasm (often referred to as "viral factories"). On the other hand, this approach does not make it possible to distinguish between different species of orthopoxvirus. After virus isolation and classification using a number of different PCR approaches, such as restriction fragment length polymorphism testing or amplicon sequencing, the identification of MPXV is frequently believed to be conclusive. In addition to this, real-time PCR tests that use panorthopoxvirus or MPXV-specific targets are now more readily available. Another quick approach for detecting orthopoxviruses is using a DNA oligonucleotide microarray. This particular array

includes the *crmB* gene, which encodes for the TNF receptor [54].

Clinicians should perform a test for MPX in all patients who have a high fever and a rash for no obvious reason, regardless of whether or not there is an outbreak. Rash symptoms often start on the lips, then travel in a circular pattern to other parts of the face, hands, and feet. A accurate diagnosis can be obtained via PCR testing on fluid samples or skin lesions. There is no screening that is done on a large scale, and these kind of testing are only provided by national public health labs [55].

VI. TREATMENT

Supportive Care

Most patients with monkeypox infection recover without medical treatment. Those with gastrointestinal symptoms (e.g., vomiting, diarrhea) will require oral/intravenous rehydration to minimize gastrointestinal fluid losses [56].

Antivirals

Several antivirals may be effective in treating monkeypox infections, although these drugs were approved for the management of smallpox based on animal models. Dose studies for these drugs have been conducted in humans, but the efficacy of these agents has not been thoroughly defined [57].

Tecovirimat

Tecovirimat (also known as TPOXX or ST-246) is the first antiviral indicated for the treatment of smallpox in adults and pediatric patients weighing at least 3 kg and is considered the treatment of choice [58]. In patients with severe disease, dual therapy with tecovirimat and brincidofovir may be used. Tecovirimat works by inhibiting the viral envelope protein VP37, which blocks the final steps in viral maturation and release from the infected cell, thus inhibiting the spread of the virus within an infected host [59]. While the efficacy of this agent in humans against monkeypox has not been tested, studies have reported improved survival from lethal monkeypox virus infections in tecovirimat-treated animals compared to placebo-treated animals at different stages of disease [60, 61]. In an expanded safety study of 359 human volunteers placed on tecovirimat, the placebo side-effect profile was largely similar to that of tecovirimat [62]. In small studies, tecovirimat was used in combination with vaccinia immune globulin (VIG) in patients with complications from smallpox vaccine, such as eczema vaccinatum [62, 63] and progressive vaccinia [64]. The CDC-held Emergency Access Investigational New Protocol allows use of tecovirimat for non-variola orthopoxvirus infection such as monkeypox. The protocol also includes allowance for opening an oral capsule and mixing its content with liquid or soft food for pediatric patients weighing less than 13 kg.

Tecovirimat is available through the Strategic National Stockpile as an oral capsule formulation or an intravenous vial [65].

Brincidofovir and Cidofovir

Brincidofovir has been approved for treatment of smallpox in the US since June 2021 [66]. Brincidofovir (oral) is an analogue of the intravenous drug cidofovir, and may have an improved safety profile, namely less renal toxicity, compared to cidofovir [67]. These drugs work by inhibiting the viral DNA polymerase [68]. While studies evaluating the use of brincidofovir for treating monkeypox infections in animal models are scarce, brincidofovir has been shown to be effective against orthopoxvirus infections [69]. Clinical data regarding the efficacy of cidofovir against monkeypox in humans is lacking, yet in vitro activity and efficacy against lethal monkeypox virus infections in animals has been reported [70, 71]. Intravenous normal saline and probenecid therapy must be given concurrently with cidofovir. For brincidofovir, liver function tests before and during treatment must be done, as brincidofovir may cause increases in serum transaminases and serum bilirubin. These therapies are available under an EUA or IND.

Vaccinia Immune Globulin (VIG)

VIG is a hyperimmune globulin licensed by the FDA for treatment of certain complications of vaccinia vaccination [72]. These include eczema vaccinatum, progressive vaccinia, severe generalized vaccinia, vaccinia infections in individuals who have skin conditions, and aberrant infections induced by vaccinia virus (except in cases of isolated keratitis, e.g., ocular infections) [73]. While a potential treatment, data on the effectiveness of VIG against monkeypox and smallpox is largely lacking, and use of VIG for monkeypox or smallpox has not been tested in humans. Since vaccination with vaccinia virus vaccine is contraindicated in patients with severe immunodeficiency in T-cell function, such patients with exposure history may alternatively be given VIG [74]. Treatment with VIG should be conducted under an IND application [75].

VII. CONCLUSION

The current outbreak of monkeypox has been the subject of extensive epidemiological investigations, which indicated that the reported cases had not been connected to travel to endemic areas. The latest outbreak of monkeypox in 2022-23 largely afflicted MSM, as far as we can infer from the early data that is now available; nevertheless, the clustering of cases has not been limited to this group. In order to avoid attributing a stigma to MSM, careful consideration is required in the process of interpreting these preliminary epidemiologic investigation results.

The ongoing monkeypox outbreak is the focus of persistent efforts that are being made in the hope of

bringing it under control. Nonetheless, in order to accomplish this objective, it is required to carry out continuous monitoring, to locate any and all potential interactions, and to raise levels of understanding and awareness, particularly among those working in the medical field. This technique has the potential to improve the early diagnosis of instances, which would ultimately result in the disruption of transmission networks. Many medical professionals and medical students lack the required knowledge and confidence to appropriately diagnose, treat, and prevent monkeypox, according to research that was conducted recently as well as study that was conducted in the past. As a consequence of this, this area of research requires additional attention in order for effective strategies to be devised to both control the current outbreak and improve readiness for future pandemics.

In the most severe cases, it may be worthwhile to investigate the potential use of investigational medications that have shown promise against orthopoxviruses in animal trials and severe vaccinia vaccination side effects. These drugs may be used. There is insufficient evidence to support the viability of intravenous vaccinia immune globulin, oral DNA polymerase inhibitor brincidofovir, or oral tecovirimat as treatments for MPXV [43]. In the hunt for a treatment to cure monkeypox, the data gleaned from preclinical research concerning the safety and effectiveness of these drugs are essential.

It will be necessary to conduct additional study at the genetic level and through molecular analysis in order to gain a better understanding of the host-viral interaction and pave the path for the creation of a therapeutic antiviral medicine. To get to a conclusion, conducting clinical tests of possible treatment medications and vaccines is absolutely necessary in order to control and prevent the further spread of MPXV.

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