

A Brief Report on Monkeypox Outbreak 2022: Historical Perspective and Disease Pathogenesis

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Clinical Pathology
Volume 15: 1–6
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DOI: 10.1177/2632010X221131660



ABSTRACT: Monkeypox is a zoonotic disease caused by the monkeypox virus (MPXV). It was an epidemic infection among African countries over the last few decades. In 2022, MPXV has been broke through in Africa, America, Eastern Mediterranean, Europe, South-East Asia, and Western Pacific region. This widespread infection of MPXV has created panic across the nations, and the WHO has declared a global public health emergency due to the multi-country MPX outbreak. We prepared this brief report on the MPX outbreak 2022 by extracting data from Scopus, PubMed, and website databases. We manually read all the relevant articles from our target databases. The rapid spread of MPX infection in around a 100 countries has threatened the global healthcare systems. The available epidemiological data revealed that sexual orientations and encounters are potential contributing factors for monkeypox infections. However, it has not been categorized as a sexually transmitted infection. Also, MPXV can transfer from 1 individual to others in many ways. The empowerment of this old foe has created additional pressure and threat on the healthcare authorities during the ongoing Covid-19 pandemic. Effective preventive measures, social awareness, and therapeutic approaches can reduce this extra burden on the healthcare system across the countries. Focusing only on sexual orientations and encounters as risk factors for MPX infection might increase stigma that will be another barrier to controlling and preventing MPXV spread. Therefore, we should be careful in delivering messages about MPX infection to the general population. Also, we recommend repositioning the existing smallpox vaccines and antivirals in MPX infection until the development of specific antiviral agents against this infection.

KEYWORDS: Monkeypox, monkeypox outbreak, monkeypox virus, poxvirus, poxviridae, orthopoxvirus, zoonotic disease

RECEIVED: August 19, 2022. **ACCEPTED:** September 22, 2022.

TYPE: A brief report

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Background

The monkeypox virus (MPXV) is responsible for the illness of monkeypox (MPX). MPXV belongs to the poxviridae family of the orthopoxvirus genus. MPX is a zoonotic viral infection that can transmit from animals to humans. It can also pass from one individual to another.¹ Two genetically distinct viral clades (West African clade and Congo Basin clade) are available for MPX infection. The Congo Basin clade was assumed to be more contagious and able to create disease severity.² MPX infection was an epidemic in several African countries for several decades before this ongoing multicountry outbreak. A total of 89 countries reported confirmed cases with few fatalities of MPX to the World Health Organization (WHO) from 1st January 2022 to 7th August 2022. Among the six WHO regions, the African region reported confirmed 375 cases and 7 deaths, the American region reported confirmed 10,815 cases and a single death, the Eastern Mediterranean region reported confirmed 31 cases with zero death, the European region reported confirmed 16,495 cases and two deaths, South-East Asian region reported confirmed 13 cases with one death, and the Western Pacific region reported confirmed 85 cases with no death.¹ Here we aimed to report the origin, evolution, and epidemiology of the MPXV. Also, we have discussed how this old foe has become so powerful for threatening global public health and diagnosis, treatment, and preventive measures. To do this review, we searched articles

from Scopus, PubMed, and website databases. We manually read all the relevant articles and extracted the necessary data from them.

Historical Perspective

The MPXV was initially discovered in 1958 after a vesicular disease outbreak among wild monkeys brought from Africa to Copenhagen, Denmark, for scientific research. Thus, the terminology is called “monkeypox.”³ MPXV had to travel a long way since its identification to become so powerful for threatening global public health in 2022.⁴

1970 to 1990

Bokenda, a small village in the Democratic Republic of Congo (DRC) reported the first human MPX case in August 1970. A 9-month-old kid with suspected smallpox was hospitalized at Basankusu Hospital.⁵ After that, a sample received from the smallpox reference center of WHO in Moscow revealed MPXV by viral isolation.⁶ The inquiry revealed that the kid was the only member of the family who had not taken the smallpox vaccine.⁵ There were 350 and 346 cases documented overall between 1980 and 1986. Between 1981 and 1986, the WHO active monitoring program discovered 338 confirmed cases of MPX and 33 fatalities. Primary human cases were mainly responsible for human-to-human transmission and to a



little extent for secondary cases.⁷ The next occurrence rate for domestic interactions in the years 1971 to 1980 was 12% and the years 1981 to 1986 was 9.28% which indicates the ability of the virus to spread remained unaffected.⁸ 72% of cases were due to primary animal infections, whereas 28% were due to human-to-human transmission.² In 1987, outbreaks were detected in Gabon in Africa. Between 1987 and 1992, outbreaks were detected in the DRC.²

1990 to 1999

Cameroon was the third country that described the MPX outbreak in 1990. Between 1993 and 1995, no cases were reported. In the DRC, there was a chronic MPX outbreak between 1996 and 1997. The village of Akungula reported the first incidence in the middle of February 1996. The outbreak was not recognized until the last period of July when new citizens infected it. All of the available sera were examined and found to contain orthopoxviruses.² There were 511 suspected cases in 54 villages of the Katako-Kombe health zone and 24 in the Lodja health zone from February 1996 to October 1997.² The disease was very mild, with a 1% to 5% mortality rate, and a substantially greater incidence of subsequent cases (about 78%) than had previously been described.⁹ The Lodja and Katako-Kombe zones have had the highest documented group of suspected patients during this epidemic.²

2000 to 2009

Until 2001 no suspected cases were reported. In 2001, 2002, 2003, and 2004 reported cases were 380, 545, 783, and 1026, respectively. Only 171 clinical specimens from 136 individuals were collected because surveillance efforts were hampered by the civil war.¹⁰ Ministry of Health of DRC received 1265 cases from 1 January 1998 to 31 December 2002. Most of these incidents happened in areas where tropical forest is present. In 2003, the USA became the first country in which an outbreak occurred outside of Africa because of the shipment of animals from Ghana which were already infected. The disease was connected to local prairie dogs living with African rodents at an Illinois pet retailer. The disease was connected.² In April 2003, the first MPX outbreak was reported in the Republic of Congo (ROC) from the village of Impfondo in the Likouala district.¹¹ Five villages in Unity State, Sudan (dry savannah environment), first reported 30 MPX cases between September and December 2005. During this outbreak, no deaths occurred.² During this outbreak, the strain of MPXV was isolated, and thought that it has a variant of a novel genomic structure that was related to the Congo Basin.¹² Seven hundred sixty laboratory-ensured MPX cases were found in 9 health zones that participated during the active MPX monitoring project in the DRC between November 2005 and November 2007. There

were no identifiable seasonality and the highest prevalence was seen in areas with the most forest region.¹³

2010 to 2022

In 2010, 10 cases were reported in the Likouala area of ROC. This outbreak is believed that it is connected to the flow of DRC refugees into ROC via the Ubangi River.² Two MPX cases were verified in the Central African Republic (CAR) in June of the same year (2010). After capturing and consuming a wild rodent, the disease emerged. In 2001, the strain which was isolated was the same as the one linked to an outbreak that occurred at the border between CAR and DRC.¹⁴ According to information from the DRC Ministry of Health, more than 2000 cases were recorded each year between 2010 and 2014. After more than 40 years, a MPX outbreak was discovered in Sierra Leone in 2014. In Bangassou of the CAR, at least 12 persons contracted MPXV between December 2015 and February 2016; 3 of them passed away. The laboratory of the Health Ministry confirmed the disease. As of August 2016, the provinces of Basse-Kotto and Haute-Kotto in the CAR reported at least 26 more suspected cases.² Through the DRCs passive surveillance program, 587 suspected MPX cases were recorded from September 2014 to February 2016. The outbreak of 88 cases of MPX was recorded from January to August 2017 in the ROC's Likouala region where 18 villages in 5 districts were affected. In 2017, CAR reported 2 outbreaks. In February 2017, the province of Mbomou confirmed the first outbreak. In April 2017, the Mbaki district reported the second outbreak. Accounting for out of 3 cases, 1 laboratory was confirmed. In March 2017, Pujehan district of Sierra Leone confirmed a single case of MPX. After being monitored for 13 days, it was discovered that none of the 13 close contacts had experienced any febrile illness in the 1st 21 days following the final exposure. From September 2017 and April 2018, a total of 244 cases were spread across 25 states and Nigeria. In Liberia, sixteen cases of MPX were stated from 2017 November to December, and 2 deaths were recorded. In CAR 20 MPX cases were stated between 17 March and 24 April 2018, although no deaths were recorded. Between 30 April and 30 May 2018, Cameroon recorded 16 cases of MPX.²

In recent years, MPX cases have increased in number due to travel, all of which were brought on by Nigerian exposures. Israel reported 1 case in 2018, the UK reported 3 (1 in 2019 and 2 in 2018), and Singapore reported 1 case in 2019.¹⁵ In May 2021, 3 members of a family were infected when came to the United Kingdom from Nigeria.¹⁶ One case occurred in July 2021 with an individual who moved from Nigeria to Texas.¹⁷ One case occurred in November 2021 with an individual who moved from Nigeria to Maryland.¹⁸ Investigations of one instance of MPX that occurred in a human who came from Canada to Massachusetts as of May 2022 are ongoing.¹⁹ Reported MPX cases history was (WHO) between 1st January

and 7th August 2022.¹ In Portugal 14, Spain 7, and Canada 13 cases of MPX infection were recorded on 18 May 2022. On 19th May 2022 first MPXV instances were reported in Belgium, Sweden, and Italy. The 2 cases were reported on May 20 by Australia. Two of them came from Sydney and Melbourne, respectively. Recently they returned from Europe. On May 20, the Netherlands, Germany, and France all reported their first patient. On May 20, the Health Secretary of the United Kingdom (UK) revealed an additional 11 MPX cases, bringing the total to 71. The first nation to impose a 21-day quarantine requirement for MPX was Belgium. On May 21, Israel and Switzerland both reported their first cases. On 18 May 2022, 1st patient with MPX was found in Spain.²⁰ The first case of Denmark was reported on May 23 by a person who had just returned from the Canary Islands. On May 24, 2022, Quebec in Canada reported 15 confirmed cases, and the Czech Republic had just confirmed its first case. In May, a traveler from West Africa who was 29 years old was the first case to be identified in the United Arab Emirates. Nineteen countries have also reported MPXV cases until May 24. Travelers from endemic areas of Africa to North America and Europe brought infections with them, which began in them and later spread throughout the world.²¹ On 23rd June 2022, the WHO stated MPX is an “evolving danger of moderate public health concern” because more than 3,000 MPX cases have been documented since early May 2022 in more than 50 nations across 5 regions.²² Between 1st January and 7th August 2022, WHO has reported 27 814 confirmed MPX cases and 11 deaths from 89 countries or territories in all 6 WHO regions.¹ In the current outbreak, data on sex are available for 73% of cases. Among them, 99% are males with an average age of 36 years. Males between 18 and 44 years are disproportionately (77%) affected by this ongoing MPX outbreak. Among all cases, 39% have known HIV-positive status.¹ Considering the gravity of the ongoing multi-country MPX outbreak, the WHO declared it a Global Public Health Emergency on July 23, 2022.²³

Monkeypox Transmission and Disease Symptoms

MPX is a contagious virus that spreads in many ways. It can spread to anyone by personal, close, skin-to-skin touching, with direct interaction from a person with scabs, MPX rash, and fluids of the body with MPX. It can also spread through touching materials, fabrics (bedding, clothing, or towels), and also by surfaces that someone used with the disease MPX. Moreover, the virus can spread if anyone comes in contact with respiratory secretions. In the case of intimate contact, direct contact can be happened, with touching the genitals or anus or anal, oral, as well as vaginal sex of a person with the disease of MPX. It can also spread through massage, hugging and kissing, and lengthy face-to-face touching. Only 33% of all cases of ongoing MPX outbreaks have disclosed their sexual orientation. Of these,

97% have been identified as gay, bisexual, and other men who have sex with men. Also, information on the mode of transmission is available for 23% of all cases where 91% reported transmission through sexual encounters. Therefore, sexual orientations and encounters are considered major contributing factors to getting MPX infection.¹ However, a pregnant woman can spread this virus to the fetus through the placenta.²⁴ Also, sleeping outside of the home or near the forest can increase the contact risk with animals. Acquiring MPX contact with sick animals every day or cleaning their bedding or cages are also risk factors. It is sufficient to sustain a break in skin by catching or being touched by an infected animal.¹⁵

One of the most common symptoms of MPX is lesions. In the oral cavity, lesions are often noted and it causes trouble with eating and drinking. About secondary bacterial infections of the skin, the huge alarm of the skin raises concerns. The patient's skin has been figured out as being stiff, swollen, as well as painful until crusts seemed. The second febrile phase occurrence happens when the lesion of the skin becomes pustular. During the disease period, secondary infection has been found in the lungs and bronchopneumonia can be happened often late in individuals. Septicemia and encephalitis were diagnosed in one patient and another patient with more than 4,500 lesions. Blindness and scarring of the cornea can be occurred because of ocular infections. The person who survives an infection for those the most common long-term sequelae is pitted scarring.²⁵ However, with vulnerable populations and enhancing case numbers, like less immune active persons, pregnant women, and infants may have a chance to be infected. Difficulties are more common in immunocompromised children compared with healthy adults, with a huge bacterial infection chance, keratitis, respiratory difficulties because of pneumonia, pharyngeal abscess, and encephalitis.²⁶

Therefore, from the aforementioned information, we can see that the MPXV is so much threatening and it has a broad spectrum spreading compared to other viruses and it is so much chronic. It is very much contagious. For these kinds of reasons, the MPXV is very much powerful. Because of the attack of this virus patients undergo severe chronic diseases which can lead to death. Fever, back pain, swollen lymph nodes, muscle aches, headache, and low energy are among the symptoms of MPX that are most frequently observed. The appearance of a rash that might continue for 2 to 3 weeks follows or is present along with this. The rash may appear on the palms of the hands, soles of the feet, neck, eyes, mouth, groin, and genital and rectal parts of the body. Concerns about subsequent bacterial infections in the skin are raised by substantial skin disturbance. Individuals are contagious until all lesions have dried layer, all scabs have peeled off, and a fresh layer of skin has developed underneath. It can lead to death for some people.¹

Diagnosis of Monkeypox Infection

Genetic methods

Real-time polymerase chain reaction (RT-PCR) or PCR is required for this test, and it is recommended that it should be performed at a biosafety level 3 facility.²⁷ From veterinarian materials and clinical as well as from MPXV-infected cell cultures, the gene of the extracellular envelope protein, DNA polymerase, and the E9L are targeted by RT-PCR to routinely identify MPXV DNA.^{28,29} The detection of MPXV DNA also intensifies gene fragments by using Restriction Length Fragment Polymorphism (RFLP) of PCR, although RFLP is labor-intensive and necessitates viral culture.²⁷ The most accurate method for characterizing MPXV and other Oral Polio vaccines (OPVs) is still sequencing the total genome utilizing the method of Next Generation Sequencing (NGS). However, the technique is costly, and analyzing sequencing data afterward needs a lot of computer power.²⁷ Thus, NGS is not appropriate for less developed countries of the African sub-Sahara region. In the West African region, MinION sequencing in the field was effectively employed for genomic observation of the outbreak of Ebola.³⁰

Phenotypic methods

According to clinical diagnosis, MPXV has an incubation period of 4 to 21 days and this is typically ruled by a prodromic sickness with several symptoms like fever, lymph node enlargement, back pain, headache, myalgia, severe headache, malaise, drenching sweats, pharyngitis, and intense asthenia. Lesions in MPXV patients resemble smallpox in appearance and are monomorphic, hard, and pea-sized. The MPXV lesion differs from smallpox in that it has a crop-like appearance and a weak centrifugal force. The distinguishing clinical characteristic between MPXV and smallpox is the presence of lymphadenopathy in MPXV. To identify suspected instances, it is crucial to presume the presence of MPXV based on clinical signs.²⁷

Immunological methods

It involves the detection of IgG and IgM antibodies as well as immunohistochemistry for the detection of viral antigens by applying the Enzyme-Linked Immunosorbent Assay (ELISA). If antibodies of IgM and IgG are found in a person who is not vaccinated, rash history, and has a serious sickness, MPXV may be diagnosed.²⁷ An individual who has a history of smallpox immunization can employ IgM to determine whether they have a MPX infection.³¹ When both IgM and IgG are present in a sample they provide a powerful indication of current OPV exposure in people who have already had a vaccination or have been exposed to natural disease. Therefore, the presence of IgM in people who have had a smallpox vaccination in areas where MPX is prevalent is a sign that they have recently been exposed to MPXV.²⁷

Electron microscopy

Under an electron microscope, MPXV has been seen as a brick-like structure of intracytoplasmic parts and size between 200 and 300 nm. It has a central core as well as lateral bodies. It provides a hint that the virus is a member of the Poxviridae family, even though it cannot provide a conclusive diagnosis because OPV species cannot be distinguished morphologically.²⁷

Prevention of Monkeypox Infection

Prevention of MPX outbreaks in endemic places is very much stimulating, and it is controlled by circumventing any interaction with primates and rodents as well as restraining direct contact with blood as well as improperly cooked meat. For increasing common consciousness as well as for advising on exact management of species of the animal reservoir (protecting cloths, gloves), evading intimate with someone affected enormous health education campaigns are needed. In health-care infection control actions are so important for preventing human-to-human spreading. It is needed instruction with proper benefits for developed nursing (gloves, protecting cloths, hand gloves) and practices of quarantine. Organizing immunization against individuals suffering from MPX should be considered by national health authorities.³ Throughout an outbreak, quarantining a minimum of six weeks isolation from the previous exposure date, the sick animals as well as detecting their contacts may control the spread of the MPXV.³² From the authorities of global public health to local authorities' obedience to specific rules is mandatory. In first-world countries at hospitals, when this disease is diagnosed the infected person directly to be placed in a private room. Standard, contact, and droplet precautions should all be taken.³

Repositioning of Antiviral Agents

Vaccination

Irregular vaccine program for smallpox has made an ecological blank where a population growing quantity has either nonexistent immunity or waning to MPXV.³ Patients who had been vaccinated against smallpox before against MPXV were recognized to have 85% protection.³³ Center for Disease Control and Prevention (CDC) recommends the smallpox vaccine (ACAM2000TM), during the 2003 USA MPXV endemic, it is shown to reduce the symptoms. For preventing MPX for adults, Food and Drug Administration has given a license of IMVAMUNE diminished third generation, Modified Vaccinia Ankara, found to be risky of VARV and MPXV exposure. Therefore, these 2 vaccines provided active safety in the case of MPXV.²⁷

Antivirals

A Tecovirimat (ST-246 or TPOXX or 4-trifluoromethylphenol derivative which are approved by FDA, and using an animal model it has undergone clinical trial. In the infected

animals, the drug showed effectiveness. It prevents the secretion of the virus that lives intracellularly. With Tecovirimat the human clinical trial recommended that the drug was safe and tolerable as a CDC report. In the same way, applying Cidofovir and Brincidofovir, in vitro studies and animals, showed to be effective. The viral DNA polymerase is inhibited by these two drugs.^{34,35} Against MPXV and CPV (Chicken Pox Virus) in vitro, the Brincidofovir showed better antiviral activity and greater cellular toxicity than Cidofovir. Because of its better efficacy, Brincidofovir has a huge selective index which was a minimum of 25-fold greater than Cidofovir. Better transformation to the active form together with increasing cellular uptake by intracellular enzymes is liable for greater efficiency perceived in Brincidofovir. The phosphorylated cidofovir is designed by intracellular kinases of cidofovir via the conversion after Brincidofovir has passed into cells by the endogenous fluid uptake passage which is secreted by cleavage. Apart from the above-mentioned drugs, Iseni and Delaune did fairness in evaluating the opportunity of various potent drugs against poxviruses which has activity against the virus. The additional potential drug called NIOCH-14 was tested against poxviruses. For the future NIOCH-14 which has significant activity against the virus for its potent antiviral activity as well as its creation is simple. Depending on their antiviral activities, Baker et al, tested potent drugs in contrast to OPV (Oral Polio Virus) and also assembled those drugs into five groups (DNA polymerase inhibitors, S-adenosylmethionine, Inosine Monophosphate (IMP) dehydrogenase, protease blockers and reverse transcriptase (RT)), 2 IMP dehydrogenase inhibitors (Ribavirin and tiazofurin), showed for inhibiting of all OPVs replication with MPXV which are higher sensitive compared to additional viruses. By inhibiting viral replication [(S)-9-(3-hydroxy-2-phosphonomethoxypropyl) adenine] and Cidofovir proved activity against PXVs. Consequently, against MPXV, antiviral drugs or effective vaccination are needed for preventing the spread from asymptomatic ones to others.²⁷

Conclusion

MPX was mainly confined across central and western Africa over several decades. The current multi-country outbreak shows that MPX disease is not a rare zoonotic disease now. It continues its spreading and has infected about 100 countries far away from Central and West Africa.³⁶ Also, it is now not confined among the travelers but rather spreading locally among the local communities. The chance for human-to-human spreading is alarming for family members along with providers caring for contaminated persons. Moreover, the world is passing its most critical time in history due to the ongoing Covid-19 pandemic, economic instability, and political tension. Therefore, the global healthcare authorities should prioritize health safety measures, create awareness, and emphasize the implementation strategies to avoid another pandemic turn of this ongoing multi-country MPX outbreak.

Author Contributions

PPDC, MAH, BA, and MT conceived the study and wrote the first draft. MRI revised and gave intellectual inputs in the manuscript. All the authors approved the final version for submission.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics Statement

It was an analysis of online available aggregate data. No Ethical approval was needed.

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