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Monkeypox: An Update on Current Knowledge and Research Advances

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ABSTRACT

The resurgence of the disease in humans that is very similar to smallpox called monkeypox (MPX) disease, caused by the monkeypox virus (MPXV), is the dominant topic of discussion in the scientific and popular press around the world right now. This is taking place as the world celebrates the historic accomplishments made in the fight against the Coronavirus Disease (COVID-19) pandemic MPX is currently thought to pose a risk to the general public's health, particularly in areas with high rates of MPXV infection and close human-wild animal contact. Despite the rarity of MPX outbreaks, they are often caused by human-to-human transmission, especially in households and healthcare settings. Recent decades have seen recurrent outbreaks of the MPX after the smallpox disease was declared eliminated and the

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consequent cessation of smallpox vaccination programs. MPX has presently spread to several countries throughout the world and posed a global public health emergency, with nearly 45000 confirmed cases in 96 countries and locations, and 12 deaths as of August 24, 2022. Even though this viral illness is thought to be self-limiting, its consequences and feasible pandemic potential seriously jeopardize public health. The main approach to avoiding MPX is to adopt appropriate prevention and control measures, increase awareness of risk factors, and inform the public of the steps they may take to reduce viral exposure. Scientific studies are currently looking at the viability and suitability of the MPX vaccination. This article presents a general introduction to MPXV / MPX along with progress in diagnosis, treatment, vaccination, and prevention and control strategies for tackling this global health emergency.

1 Introduction

Monkeypox (MPX) is a viral zoonosis illness caused by the monkeypox virus (MPXV) that has been linked to detrimental effects on both human and animal health, and currently posed a global public health emergency (Banerjee et al. 2022; Lai et al. 2022; Meo and Jawaid 2022; Mohapatra et al. 2022; Saied et al. 2022a). Its symptoms are similar to those of smallpox, although it is clinically less severe. Even though smallpox was eradicated over 40 years ago and smallpox immunization was discontinued, MPXV has emerged as the most important Orthopoxvirus for public health (Adler et al. 2022; Kozlov 2022). Monkeypox virus (MPXV), a member of the family Poxviridae, is the zoonotic pathogen responsible for MPX. Chordopoxvirinae and Entomopoxvirinae are two subfamilies of the Poxviridae family. The Chordopoxvirinae subfamily is comprised of 18 genera, including those that are known to infect vertebrates (Orthopoxvirus, Capripoxvirus, Parapoxvirus, Avipoxvirus, Suipoxvirus, Cervidpoxvirus, Yatapoxvirus and Leporipoxvirus). The Entomopoxvirinae subfamily consists of four genera that cause disease in arthropods (Gammaentomopoxvirus, Betaentomopoxvirus, Deltaentomopoxvirus, and Alphaentomopoxvirus). There are 10 recognized species of Orthopoxviruses at present, including MPXV and variola (smallpox). However, despite being a DNA virus, MPXV does not replicate outside of the cytoplasm of infected cells (Cheema et al. 2022; Harris 2022).

It was first identified in 1958, after an outbreak of the virus among monkeys in a Danish research facility. A nine-month-old boy in the Democratic Republic of the Congo (DRC) contracted the disease in 1970, despite smallpox having been eradicated there in 1968. This brought attention to the disease for the first time (Mohapatra et al. 2022; WOAH 2022). The genetic lineage of MPXV can be broken down into two subgroups: the West African clade and the Congo Basin clade. Although MPXV is mainly prevalent in the Congo Basin, incidences of MPX in both humans and wildlife have also been documented in other Central and West African countries. However, conducting effective surveillance in endemic areas is difficult due to a lack of epidemiological and ecological research infrastructure. The fatality rate in the West African clade is 3.6 percent, while it is 10.6 percent in the Congo basin clade (Bunge et al. 2022; Kumar et al. 2022; WHO 2022a). Patients with immunodeficiencies may have a higher case fatality rate. The incubation phase normally lasts 6 to 13 days, although in exceptional situations it can last up to 21 days. The most likely source of MPXV is rodents. Close contact with an infected person or animal, or with contaminated objects or surfaces, is regarded to be the major route of viral transmission to humans. Human-to-human transmission may occur via droplets, bodily fluids, or infected surfaces. Importantly, MPX may not always be correctly diagnosed. Concurrent infections with varicella zoster virus (VZV) and MPXV are thought to be very common, although they have only been reported seldom (Kozlov 2022; Okyay et al. 2022; WHO 2022b).

On May 7, 2022, a confirmed case of the West African lineage of MPXV was discovered in the United Kingdom (UK), and subsequently, the MPXV has drawn considerable interest worldwide. United States of America (USA), India, Australia, Canada, Israel, and many European countries, including the UK, Portugal, Sweden, Spain, Italy, France, Germany, Netherlands, and Belgium have all reported cases (CDC 2022a; Sah et al. 2022). Since January 1, 2022, nearly 45000 confirmed MPX cases from 96 countries and locations along with 12 deaths have been reported as of August 24, 2022 (Adalja and Inglesby 2022; Adegboye et al. 2022; CDC, 2022a; Mohapatra et al. 2022). We still do not fully understand the natural history of the virus, its origins, or which animals serve as its reservoir hosts. We will be able to better understand how the MPXV spread from animals to humans by closely monitoring it in regions where it is prevalent. The current review updates knowledge on MPX's early pandemic transmission pathways, pathophysiology, clinical manifestation, therapy, and prevention.

2 Etiology

In the same family as cowpox (CPX), variola (VARV), and vaccinia (VACV) viruses, MPXV is among the Orthopoxviruses. Typically, the structure of these viruses often has a lipoprotein

envelope and are either oval or brick-shaped, measuring 200–400 nm in size when viewed under an electron microscope (Mohapatra et al. 2022). MPXV shares various features with other members of the *Orthopoxvirus* genus, including variable number tandem repeats and putative telomere resolution sequence, with its 6379-bp terminal inverted repetition (Yang et al. 2020). There are two ways in which MPXV might enter the host cell: first, by binding to chondroitin or heparan sulfate on the viral envelope and then dispersing into the plasma membrane; or second, through macropinocytosis, which uses actin to enter the cell. Viral proteins and enzyme factors are released from the virus into the cytoplasm and weaken cell defenses, encouraging early gene transcription and DNA replication and the formation of intermediate transcription factors (Kumar et al. 2022).

The literature suggests that the MPXV clade that originated in the Congo Basin is more lethal than its West African counterpart. This is due to differences in genomic architecture, which result in greater virulence and higher fatality rates in the Congo Basin clade (Kabuga and El Zowalaty 2019). Notable virulence features include an inability to replicate in human cells and a propensity to inhibit inflammatory cytokine production by human cells (including interferon-gamma (IFN-γ) and tissue necrosis factor-alpha (TNF-α)). Another important immune-modulating component that contributes to the higher virulence of this strain comes from a gene in the Congo Basin lineage that inhibits complement enzymes. However, contrary to what was previously believed, studies have shown that neither a decrease in major histocompatibility complex (MHC) expression nor a decrease in cellular transport is connected to MPX virulence (Cheema et al. 2022).

3 Transmission routes and infectivity

MPXV has been proven to be transmitted from animals to people, but how it gets from humans to humans remains a mystery. Rats, squirrels, and dormice, as well as a wide variety of monkey species, are the most common vectors of the virus. It has been shown, however, that the virus can be passed from person to person, both within and outside of Africa. The most common route of MPX transmission from animals to people is believed to be through contact with infected animals, either indirectly or directly (touch, bite, or scratch). Bushmeat consumption and open wounds in the skin, mouth, or throat are probable avenues for the virus to infiltrate and infect the human body. Direct or indirect contact with bodily fluids or lesions, contaminated surfaces, or materials (e.g., clothing or linens) is the most common means of human-to-human transmission (Parker and Buller 2013; Angelo et al. 2019; Bunge et al. 2022). MPXV can also be transmitted from mother to fetus by vertical transmission, resulting in congenital MPX (Fahrni et al. 2022). As reported, the pregnant women who contracted MPX experienced spontaneous early miscarriages (Khalil et al. 2022). Human MPX infections may carry a high risk of spontaneous miscarriage, premature birth, and fetal death (Fahrni et al. 2022). However, limited data is available to support the probability of vertical transmission of MPX in pregnant women. Males who have sex with other males are likewise more prone to get the disease. Even though MPX can be spread by direct physical contact, this does not qualify as evidence that it is sexually transmitted. Close contact with patients over a long period makes hospital employees and their families more susceptible to illness. Nosocomial transmission has been shown to take place, according to the available evidence (Bisanzio and Reithinger 2022; Heskin et al. 2022). Without proof to the contrary, the human-to-human transmission alone cannot sustain MPX infections in the broader human population. The R0 value for MPX is between 1.10 and 2.40 in areas with low levels of exposure to Orthopoxviruses; this value suggests that an outbreak is likely if imported human or animal cases are present (Okyay et al. 2022).

4 Clinical symptoms

The incubation period for MPX is 8 days (average), and the duration of symptoms is 2 to 4 weeks. Headache, back pain, malaise, tiredness, lethargy, and low-grade fever are all symptoms that typically appear during the prodromal phase of a viral infection. The vesiculopustular rash begins on the face and trunk and then moves outward in a circular pattern to the hands and feet 12 to 16 days after exposure. The rash then radiates outward to affect various parts of the body, including the palms and soles. Macular, papular, vesicular, and pustular lesions are the morphologically distinct stages of the rash. The pustules will crust over in a few days, and then they will fall off in a week or two. In contrast to smallpox, MPXV infection is characterized by painful maxillary, cervical, and inguinal lymphadenopathy, when it is found in 84 percent of unvaccinated people and only 54 percent of vaccinated patients (Petersen et al. 2019; Adler et al. 2022). Lymphadenopathy suggests that MPXV may elicit a stronger immune response and be more easily identified than VARV. Patients with immunocompromised conditions, prolonged viral particle exposure, and other sequelae, such as bronchopneumonia, encephalitis, and corneal infection-induced blindness, have worse clinical outcomes. Additionally, scarring, hypo-hyperpigmentation, dehydration (as a result of nausea and vomiting), and septicemia are all possible side effects (Bragazzi et al. 2022).

Unvaccinated people (74 percent) are more likely than vaccinated people (39.5 percent) to suffer from the side effects of monkeypox infection. The routine vaccination against smallpox has been discontinued in the modern world due to the disease's eradication (Hofer 2022). Cross-immunity protects persons who received smallpox vaccinations before the 1970s against the adverse effects of MPXV infection. Additionally, septic shock and necrotizing fasciitis would arise because of highly exaggerated immune

responses. Lifelong consequences are quite unusual in MPX because the sickness is self-limiting (Petersen et al. 2019; Okyay et al. 2022).

5 Animals susceptible to MPXV

As evidence of acute or past infection in many animals continues to mount, it is difficult to pinpoint the MPXV's primary reservoir species. Mice, rats, woodchucks, jerboas, and numerous rat and raccoon species have all tested positive for MPXV infection (WHO 2022a). MPXV was discovered by Kabuga and El Zowalaty (2019) in two different wild animals: a sooty mangabey (*Cercocebus atys*) and a rope squirrel (*Funisciurus anerythrus*). Multiple species of non-human primates (NHPs) are susceptible to infection by MPXV. These include short-tailed opossums (*Monodelphia domestica*), southern opossums (*Didelphia marsupialis*), prairie dogs (*Cynomys laudovicianus*), and African hedgehogs (*Atelerix* spp.). The main primary hosts of the African orthopoxvirus include the sun squirrel (*Helioscuitius* spp), giant pouched rat (*Cricetomys* spp.), the rope squirrel (*Funisciurus* spp.), and the African dormice (*Graphiurus* spp.) (Kumar et al. 2022). Chimpanzees (*Pan troglodytes*), macaques (*Macaca fascicularis*), marmosets (*Callithrix jacchus*), orangutans (*Pongo pygaeus*), and sooty mangabeys (*Cercocebus atys*) are all susceptible to infection after receiving an intravenous injection of MPXV. Pet prairie dogs close to ill exotic animals brought from Ghana, West Africa, caused an outbreak of encephalitis in the USA in 2003. Despite this, MPXV has made its way to the cause of a multi-country outbreak, causing concern. African rats, which are commonly kept as pets, are known to be susceptible to MPXV, raising fears that the virus could be passed to humans (Adler et al. 2022; Bragazzi et al. 2022). Although many mammals are susceptible to MPXV however the actual animal host for human transmission is unclear. But recently, an Italian male dog is reported to be infected first time with MPX from an infected MSM patient which suggests human-to-dog transmission of MPX virus. The MPX-infected people should avoid close contact with their pets, and domestic animals to prevent further spreading of the MPX virus (Seang et al. 2022). Zoonosis and reverse zoonosis of MPXV as observed for severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2) causing the ongoing coronavirus disease 2019 (COVID-19) pandemic demands advanced global surveillance and tracking system for emerging and re-emerging viruses for limiting animal-to-human and human-to-animal transmissions (Dhama et al. 2020; Pramod et al. 2021; Sharun et al. 2021a; Sharun et al. 2021b; Afrooghe et al. 2022; Chakraborty et al. 2022a).

6 Public health threats

MPX, a zoonotic disease with animal spillover events is a moderate risk to human health and is currently a global public health threat creating high alert (Banerjee et al. 2022; Kumbhar and Agarwala 2022; Raheel et al. 2022). Since its discovery more than six decades ago (1958), MPX had received little attention because it was assumed to be a rare and self-limiting disorder, however, the recent re-emergence with posing global health concerns has speeded up the research on this virus (Meo and Jawaid 2022; Mohapatra et al. 2022). MPX is on the rise as a serious zoonotic health threat. Many more people are becoming infected with MPX as a result of increased human-wild animal contact in recent years, and the virus is now recognized as a significant threat to public health. There is a risk of international spread if there is unregulated trading in wildlife or its products (CDC 2022b; Kozlov 2022; Zumla et al. 2022). The onset, timing, and distribution of smallpox are all comparable to those of MPX, however, the scarring, complications, and mortality of MPX are often less severe than those of smallpox. While the smallpox vaccine successfully eradicated the disease around the world around 40 years ago, a startling similarity between smallpox and MPXV has lately emerged. During outbreaks, differentiating MPX from chickenpox, another herpesvirus illness, has been challenging. The potential for zoonotic infection from other Orthopoxviruses is something that must constantly be considered (Harris 2022; WHO 2022c). As reported, people having uncontrolled HIV had worse MPX outcomes. A Nigeria-based study reported that four HIV patients with features of AIDS died due to MPX (Yinka-Ogunleye et al. 2019). Another study of MPX cases with HIV patients suggested significant longer-lasting skin rashes, genital ulcers, and secondary bacterial infection (Ogoina et al. 2020). Keeping in mind, the British HIV Association suggests that HIV patients should be considered at higher risk for MPX (Ortiz-Martınez et al. 2022). Moreover, the coinfection of MPX and syphilis have been reported in HIV patients (Bízova et al. 2022). It is highly recommended to investigate the possibility of a combination of MPX with COVID-19 or other diseases which might be dangerous and may increase the fatalities (Farahat et al. 2022).

7 Diagnosis

An ideal specimen for laboratory testing is a sample of dried and sterile exudate or crust taken from skin lesions and kept at a low temperature (without the use of any viral transport media). The best way to get a viral culture is via an oropharyngeal or nasopharyngeal swab. An intact vesicular lesion, or at least a portion of its roof, is an excellent source of skin biopsies for research. An electron microscope, PCR, culture, and sequencing are all necessary for high-containment laboratories to make a conclusive diagnosis of MPX infection (Petersen et al. 2019; McCarthy 2022). Acute and convalescent samples must be matched within 5 days after the presentation for serologic detection of MPXV-specific immunoglobulin M (IgM) or IgG. Papular lesions may exhibit necrosis of keratinocytes, acanthosis, and basal

vacuolization in addition to a superficial and deep dermal perivascular lymphohistiocytic infiltration. Cell degeneration and signs of vasculitis appear in the vessels (e.g., multinucleated epithelial cells, necrosis of the epidermis). Squash-shaped intracytoplasmic aggregates of 200 to 300 mm in diameter are seen in the cytoplasm (Guarner et al. 2022; Haris 2022).

Real-time PCR and Light Cycler quantitative PCR (targeting the ATI/ A-type inclusion body gene) have substantially improved the detection of MPXV reliably and rapidly. Real-time PCRs, especially TaqMan probe-based assays, have considerably improved our ability to detect a variety of Orthopoxviruses, including MPXV. It is not just that such assays are useful in distinguishing MPXV from another pox (ie., Variola) and herpes viruses (viz., Varicella-zoster) (Maksyutov et al. 2016; Petersen et al. 2019). In addition to PCR, genomic sequencing of viral deoxyribonucleic acid (DNA) will aid in the diagnosis and other elements of the disease. West and Central African clades can be detected using a recombinase polymerase amplification (RPA) assay that targets the MPXV G2R gene specifically. The test has high sensitivity and a considerable detection limit, which is advantageous (16 DNA molecules can be detected per microlitre). When electron imaging reveals stages of virion assembly in the cytoplasm of keratinocytes, immunohistochemistry aids in the detection of viral antigen in afflicted epidermal keratinocytes, follicular and eccrine epithelium, and a few mononuclear cells of the dermis (Bunge et al. 2022; Mauldin et al. 2022).

8 Therapeutics and vaccines

As of yet, the Food and Drug Administration (FDA) has not approved a therapy intended to alleviate the symptoms of MPX. Most cases of MPX infection, fortunately, have a mild and self-limiting course. This results in treatment that is often supportive rather than requiring any sort of specialized care. Some examples of supportive treatment include the use of analgesics to alleviate pain, antipyretics to reduce fever, and antibiotics to treat any secondary bacterial infections that may develop (Adler et al. 2022; WHO 2022b). It is possible, however, that certain patients will require unique treatment. Specialized care may be needed for patients with severe diseases and those with impaired immune systems, pregnant women, and children. Smallpox-era medicines and vaccines have shown promising results against MPXV because of their resemblance to smallpox. Despite a lack of proof, FDA and European Medicines Agency (EMA) have approved the antiviral drug Tecovirimat for the treatment of smallpox in humans. Tecovirimat can be administered intravenously or orally. It is approved for use in the USA for the treatment of MPX by the Centers for Disease Control and Prevention (CDC) (Chakraborty et al. 2022b; Hofer 2022; Rodrguez-Cuadrado et al. 2022). Antiviral medications for cytomegalovirus (CMV) and human smallpox diseases, such as cidofovir and brincidofovir, are also an option. Vaccinia Immune Globulin Intravenous (VIGIV) is an intravenous infusion of a vaccinia-specific immunoglobulin intended to alleviate the symptoms of vaccinia vaccination. As part of an enhanced access protocol, the CDC approves it for the treatment of MPX disease (CDC 2022a; CDC 2022c; Keckler 2022). Of note, considering the prophylactic and therapeutic potential of medicinal herbs, plant metabolites, phytochemicals, immunomodulatory foods, and nutritious dietary elements as well as newer and effective chemical ligands, antiviral medicines, broadly neutralizing antibodies (nAbs), these need to be exploited for managing MPX patients, as found promising for many infectious emerging and/or re-emerging pathogens including deadly viruses affecting humans and animals (Dhama et al. 2018a; Dhama et al. 2018b; Tiwari et al. 2018; Anand et al. 2021; Singh et al. 2021; Calder 2022; Chakraborty et al. 2022b; Saied et al. 2022b).

MPX has surpassed smallpox as the most common human Orthopoxvirus infection since smallpox was declared eradicated in 1980, and as a consequence of the cessation of smallpox vaccination, risk factors got triggered for increasing infection with MPXV, especially among the younger population (less than 40-50 years of age) those who did not receive smallpox vaccination (Simpson et al. 2020; Mohapatra et al. 2022). Presently, humans are protected by a vaccine made from a highly attenuated strain of smallpox for up to six weeks following vaccination. While smallpox and MPX vaccinations are now legally available, they are not yet extensively distributed (Simpson et al. 2020). There are now two MPXV vaccines on the market: ACAM2000® (alive, replication-competent vaccinia virus) and JYNNEOSTM (alive, replication-incompetent vaccinia virus). Due to viral replication that goes uncontrolled with ACAM2000®, some persons experience an extremely painful and uncomfortable cutaneous reaction at the injection site, however, this is not the case with JYNNEOSTM. While ACAM2000® has the potential for accidental and self-inoculation, JYNNEOSTM is safe (Keckler 2022; WHO 2022b). The World Health Organization (WHO) has issued a global alert about the current multi-nation MPX outbreak, urging all countries to consider the situation and convene their national immunization technical advisory groups (NITAGs) to examine the available information and formulate vaccine use recommendations suitable to each country's specific circumstances. Before deciding to undergo smallpox or MPX vaccination, a healthcare professional and the person who is being vaccinated should assess the risks and benefits of each immunization individually. This vaccine should be administered in all nations at risk of MPX, to expedite the development of evidence regarding the vaccine's safety and efficacy (Okyay et al. 2022; WHO 2022c).

9 Prevention strategies

The primary strategy for MPX prevention is to raise knowledge of risk factors and educate the public about the measures they may

take to minimize their exposure to the virus. MPX vaccines are now being tested for their ability to prevent and control the disease. People who may be in danger, like health workers, laboratory personnel, and fast reaction teams, are offered vaccines in several countries (Cohen 2022; Saied et al. 2022a). The ability to quickly identify new cases and contain an outbreak is essential. People who come into close contact with infected MPX victims are the most likely to contract the illness. Those in the medical field, as well as their families, are at greater risk of contracting an illness. Health care workers caring for patients with MPXV infection or specimens from them should follow normal infection control procedures (Bunge et al. 2022). People who have been vaccinated against smallpox should be chosen to care for the patient if at all possible. People and animals suspected of having MPXV infection should only be handled by trained laboratory workers (CDC 2022b; CDC 2022c). A patient specimen must be packaged in conformity with WHO guidelines for the transportation of infectious substances to ensure its safety during shipment (WHO 2022a). Non-endemic countries with no direct travel linkages to an endemic area were found in the year 2022 to have clusters of MPX cases. Further study is under place to identify the source of the infection and limit its spread. When determining the origin of an outbreak like this, it is critical to look at all conceivable channels of transmission (CDC 2022d; Haider et al. 2022). Transmission and spread of human monkeypox virus infection have been earlier linked to travelers during previous outbreaks and travelers' perspectives (Bhattacharya et al. 2022).

The majority of human illnesses have transferred from animals to people through personal contact. It is best to stay away from wild animals, especially if they are sick or dead. This also includes avoiding their flesh, blood, and any other body parts. Meat and other animal products must be thoroughly cooked before being consumed. NHPs and rodents are subject to import restrictions in some countries. There should be an urgent quarantine for any animals that may be infected with MPX in captivity. All animals suspected of having come into contact with an infected animal should be quarantined for 30 days and observed for MPX symptoms (CDC 2022e; Saied et al. 2022a; WHO 2022b).

Conclusion and future prospects

Our understanding of MPX is limited since it is based primarily on sporadic reports of cases or outbreaks and on passive intermittent surveillance. In light of the devastation wrought by the COVID-19 pandemic, we must conduct in-depth research into the public health implications of MPX and its potential for a pandemic. Preparedness for public health issues and priority research requires community-led, locally coordinated, interdisciplinary programs centered on capacity building and education. A higher sense of urgency exists in the need to fortify national healthcare systems and develop international rules, regulations, and response mechanisms. Underreporting of MPX may occur in impoverished countries due to inadequate health care infrastructure and scarce resources. To prevent this disease from becoming a source of dread and stigma, swift political and financial backing is required. Healthcare workers and residents alike are worried about the possibility of the disease spreading from one person to another. To better prepare for and respond to future threats to public health, a deeper knowledge of the mechanisms that shaped MPXV's epidemiology, transmission patterns, clinical presentation, and natural habitat is required. Proactive, continuous, and comprehensive surveillance, rapid risk assessments, response measures, early detection, and contact tracing will be required to successfully control emerging or reemerging viral risks. To keep up with the rapidly changing epidemiology of this reemerging disease, there must be concerted efforts on a global scale to enhance the detection and surveillance of MPX cases.

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