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Mpox Virus: Insights into Pathophysiology, Prevention, and Public Health Significance

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SUMMARY

This review paper details a comprehensive overview of Mpox virus, focusing on its epidemiology, etiological pathways of disease transmission, and pathophysiology of disease. Even though previously confined to Central and West Africa, Mpox has emerged globally, highlighting its potential for widespread human-to-human transmission. The disease's clinical presentation, viral mechanism, and progression are explored in depth. Emphasis is placed on its public health significance, especially in the context of global outbreaks, emergency preparedness and risk among vulnerable populations. Current prevention strategies, including vaccination efforts, are discussed. The paper concludes by outlining key research gaps and future directions to improve surveillance, therapeutic development, and preparedness for potential re-emergence of the virus on a global scale.

Keywords: Respiratory system diseases, Public health epidemiology, Infection risk, Mpox, Viral disease

INTRODUCTION

Monkeypox (mpox) is a rare viral disease, belonging to the poxviridae family [1]. This virus can be contracted by humans through close contact with bodily fluids from a carrier such as saliva, mucus, or skin lesions. This disease presents symptoms such as fever, muscle pain, headache, and rash. This rash begins as a small bump that evolves into raised bumps filled with fluids. Bumps caused by mpox may manifest anywhere on the body, but usually observed on the face, hands and feet. In severe cases, this illness may lead to complications such as sepsis and pneumonia which could eventually turn fatal [1].

The first virus was isolated and identified in 1959 when monkeys shipped from Singapore to Denmark research facility fell ill [2]. However, the first mpox case was confirmed in 1970, in a child in the Democratic Republic of Congo, which was initially suspected to be a smallpox case [3]. First reported human cases in the African countries were regarded endemic, but later between 1996-1997, the human to-human transmission became severe [4].

The two clades of mpox that are identified are the Central and West African clades. The Central African clades are more virulent compared to the West African [5]. A higher morbidity, mortality viremia and continuous transmission in humans was observed to be associated with the Central African clade during the 2003 outbreak in the United States (U.S) [5].

Moreover, this Central African clade is found to be more severe and fatal (10%) compared to the West African clade, which has a fatality rate of 4% [6].

Mediators of transmissions include long term close contact with contaminated personal items, respiratory droplets, and direct contact with the rash region of the infected individual. After approximately thirty years, U.S reported a mpox case-outside the African continent-due to animal importation and travel from African countries [7]. From this point on, there have been mpox cases confirmed occasionally worldwide. In 2022, mpox outbreak spread rapidly and became an international concern, and was declared as a global, health emergency independent of travel issue [8]. During this time, the World Health Organization (WHO) suggested using "mpox" instead of "monkeypox". On 16th January 2023, WHO presented the "2022 Mpox Outbreak" reporting mpox in 110 countries, territories and areas [9].

Initially, mpox was reported to be similar to a smallpox infection but with less fatality. However, with

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years, the virus became more pathogenic and caused outbreaks with many concerns being unanswered [7].

The main objective of this research paper is to provide a comprehensive literature review of the mpox virus, and exploring into its descriptive epidemiology, etiologic pathways, disease mechanism, prevention efforts and future direction of research.

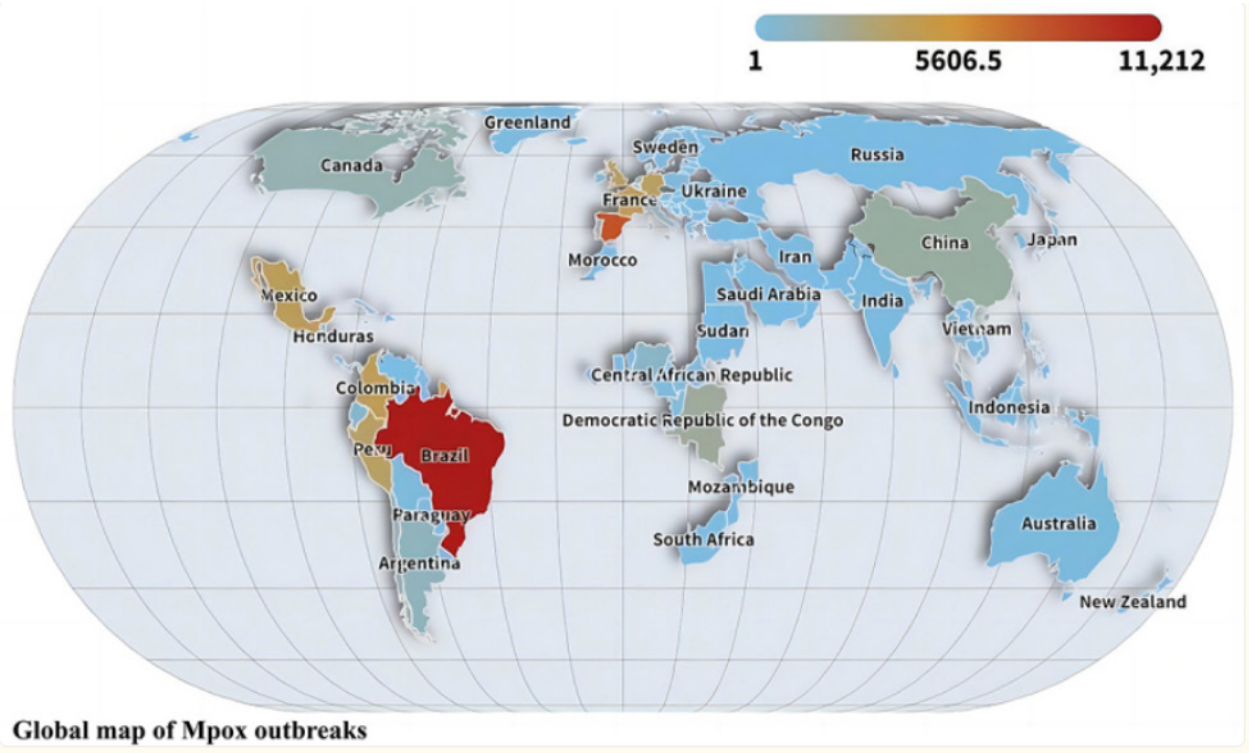
Descriptive Epidemiology

Human mpox received minimal global attention until its first outbreak that occurred in the U.S, outside of Africa in 2003 [10]. Forty-seven mpox cases were reported, with 37 confirmed, and 10 suspected. In the same year, the Republic of Congo reported the first outbreak of human mpox, where 11 patients were confirmed and probable, all of whom were 18 years or younger. Among these patients, one death was reported [11]. In 2005, between September and December, ten confirmed and nine possible patients of mpox were detected in 5 villages-Modin, Nuria, Wang Kay, Bentiu, Rubkona. From 2010 to 2018, several African countries-including the Democratic Republic of the Congo (DRC), Central African Republic (CAR), Cameroon, Liberia, Sierra Leone, and the Republic of the Congo-documented differing numbers of mpox cases. Later in 2017, Nigeria experienced a mpox outbreak, with 122 confirmed or suspected cases of human mpox reported between September 2017 and September 2018 in 17 states. Moreover, six individuals died from mpox (case fatality rate 6%) [12-14].

The Mpox outbreak has infected several individuals around the globe in 2022, which followed several sporadic cases outside of Africa, particularly United Kingdom [15], Singapore [16, 17], U.S [18]. In the UK, several cases of mpox were identified during May 2022. On epidemiologic investigation it was found that the infected individual had a recent travel history to Nigeria. The confirmed mpox cases in other countries such as Spain, Canada, and Portugal were 7, 13, 14 cases, respectively. On 18th May the U.S reported its first mpox case of 2022. Sweden and Belgium confirmed their first cases in 2022 [11]. On May 20th two patients were diagnosed with mpox in Australia both of whom had a recent travel history to Europe [15]. The first cases were later reported in France, Germany, Netherlands and France [19]. The first cases were confirmed in Israel and Switzerland, and the patient was documented by Israeli Ministry of Health as the first Asian case [20]. Furthermore, after May 2022 large number of patients were identified in non-endemic countries worldwide and the WHO declared mpox as an international public health emergency [21]. Figure 1. describes the global mpox outbreaks, with Brazil and Morocco having the highest disease burden as of October 6, 2024 [22]. Across all six WHO regions there were 57, 995 mpox cases with laboratory diagnosis reported in more than 100 countries or regions. A total of 18 deaths in 9 countries were reported [11].

During the height of the outbreak in August 2022, the rate of mpox cases was significantly higher among

*Figure 1. Global map of mpox outbreaks**



* Source: [22]

non-Hispanic Black and Hispanic or Latino males (RR=6.9) compared to White males (RR=4.1) [23]. The mpox outbreak previously disproportionately impacted, the gay, bisexual, and other men who have sex with men (MSM), along with racial and ethnic minority communities, as they experience higher rates of infection [24].

Etiological Pathways

Within the Poxviridae family, under the choropoxvirinae subfamily, orthopoxvirus genus, with its specific species identified as the mpox virus. Under the electron microscope, the virus appears as a brick-shape which is encompassed by a lipoprotein with a linear double stranded DNA, measuring 200-250 nanometers [4, 25]. The mpox virus is a zoonotic disease that is transmitted from animals to humans. The animal reservoirs identified are monkeys, rats, squirrels, and other primates, pigs, hedgehogs, prairie dogs and mice-primarily found in the African regions where the virus is historically prevalent [4].

The primary culprit of spread of is human-to-human transmission via respiratory droplets, direct contact with rashes or infected lesions, or fomites. A recent study published an analysis that detected high concentrations of the virus in bodily fluids such as saliva, feces, urine, and semen. Additionally swabs from the oropharynx and rectum confirmed that sexual transmission plays a significant role in the spread of the illness [26]. Another study recorded that the infection could also be acquired through the consumption of undercooked meat [27], or through bites or scratched from infected animals [28]. Infected mothers can spread the infection to their newborns through vertical transmission [29, 30]. Previously, mpox was only detected when an individual was either travelling to a region affected by mpox or came in contact with an infected animal [31]. Recently, majority of reported mpox cases from outbreaks have been among bisexual and gay men. This group contributed to approximately 98% of mpox cases, where 41% were coinfected with human immunodeficiency virus (HIV) and 73% had lesions on their genital or anal regions [32].

Pathophysiology

Mpox is a transient disease for most individuals but the severity of the infection depends on various factors such as strain of infection, the immunity of an individual etc., [33]. Previous literature highlights the lifecycle of the mpox virus, the first is the virus invasion, second is the viral replication and synthesis and the final is the virus assembly, maturation and release [27].

The period of incubation among mpox cases is approximately 7 to 14 days, where symptoms are observed to be present for 14 to 21 days [34]. Accurate diagnosis becomes difficult if the incubation period is prolonged, leading to delay in seeking medical care, worsening of the infection and increased risk of the spread [35].

Fever, pain, lymphadenectasis (inguinal lymphadenectasis), and fatigue are some of the common symptoms observed [36]. Lymphadenectasis usually seen to be present in mpox virus cases and can help differentiate from other orthopoxviruses [37]. After exposure through fluids from an infected individual the virus invades surrounding tissue of broken skin. Further, it disseminates throughout the body by way of local immune cells and nearby lymph nodes. [38]. During the latent period, the mpox case is usually asymptomatic and has no lesions present. On completion of the latent period the individual enters the symptomatic period where early symptoms are experienced, these prodromal symptoms-such as fever, headache, lymphadenectasis, chills, and muscle pain-persist for about three days. As the disease progresses, a rash begins to appear on face and the head region, which is later seen to spread throughout the body. From the rash, papules arise and are seen to develop, followed by the formation of vesicles and then pustules. The lesions crust over and heal, often resulting in scarring. This period of the rash usually lasts for 2 to 4 weeks [4, 39].

Individuals with weakened immune systems are generally at a greater risk of developing severe forms and complications of mpox. Moreover, these immunocompromised populations could contribute as a vital factor in driving the evolution of the mpox virus, enabling it to better adapt to human hosts and increasing the likelihood of broader transmission [40]. Complications of mpox includes inflammation of vital organs, necrotic disease, septicemia, obstructive disease, and hemorrhagic disease. In non-epidemic regions, the case fatality rate was approximately 0.04% in the year 2022 [41].

Prevention

The treatment of mpox depending on the stage of the lifecycle of the mpox virus has proved to be beneficial [27]. Cidofovir and its derivative Brincidofovir, Ribavirin are few drugs of choices used when the virus is in the second stage. Tecovirimat is a promising drug of choice for the third stage of viral assembly and maturation [27]. Even though immunopathology caused by the mpox virus can result in negative clinical outcomes, immunotherapy offers potential to lessen the severity of the illness. Polymerase Chain Reaction (PCR) is the laboratory method used to diagnose mpox by detecting the virus, even though alternative techniques such as immunological assays and virus isolation through cell culture exist, they are less commonly used [42].

Due to the immune cross-protection shared among orthopoxviruses, smallpox vaccines based on the vaccinia virus have been recommended for use during the current mpox outbreak [18]. Rimoin et al. reported a significant rise in monkeypox cases in

the Democratic Republic of Congo occurring three decades after the end of smallpox vaccination efforts [43]. Literature highlights the increased protection from mpox infection among individuals that were vaccinated against smallpox vaccine even though the vaccine was administered more than 25 years ago. The 2013 U.S mpox outbreak showed that the smallpox vaccination appears to demonstrate a protective effect against the West African clade by offering cross protective immunity [11]. In order to reduce the risk of contracting mpox, Center for Disease Control and Prevention (CDC) recommends avoiding close contact with infected individuals, especially skin contact with individuals that developed rashes and vesicles. Items and surfaces that have been used or touched by an infected person should be avoided or cleaned thoroughly. Additionally, the use of alcohol-based hand sanitizers before eating or touching their face, and washing their hands regularly, especially after using the restroom should be practiced [44].

Approximately 85% protection against mpox virus is offered by the first generation live vaccinia vaccines, as they trigger cross-reactive antibodies that help in responding to various orthopoxviruses [11]. On evaluating the benefit of the aerosolized mpox virus in cynomolgus macaques, studies showed that a single dose of the ACAM2000 vaccine offered full protection [45]. The JYNNEOS in the U.S, the IMAMUNE in Canada, and the IMVANEX in the European Union received approval in the year 2019 for use among individuals aged 18 years and older, who are susceptible to smallpox or mpox, in order to prevent both the diseases. Amid the ongoing global disease burden of mpox, pharmaceutical companies rush to develop mpox-specific vaccines similar to the COVID-19 response. Moderna has revealed that they have started exploring the possibility of creating an mRNA vaccine for mpox due to increasing vaccination demand, although no additional details have been provided so far [11].

Public health implications

One of the most effective strategies to prevent the spread of mpox infection is vaccination. Additionally, another crucial component is contact tracing and early detection of infected individuals to prevent further transmission. These screening efforts include monitoring individuals with symptoms consistent with mpox. Public health authorities, or epidemiologists may encourage targeted screening in high-risk populations such as close contacts of confirmed cases or areas that are experiencing an outbreak. Local, state and national health departments should increase surveillance efforts [46] that include syndromic surveillance improved case reporting, laboratory surveillance and rapid data analysis. These analyzed findings should be interpreted and communicated to the public in a timely manner to increase disease awareness and prevention efforts. Furthermore, One Health approach strategies that incorporate animal health monitoring can offer early indicators of potential spillover events from wildlife to humans [47]. Studies show that communication across multiple platforms such as media and news channels successfully engage diverse audiences and improve awareness and prevention strategies [42]. Increasing capacity is essential for improving readiness and response to outbreaks. It is important that healthcare professionals are trained in the correct application and removal of personal protective equipment (PPE) to reduce the likelihood of infection during patient interactions [48]. Developing and low- to middle-income countries (LMICs) should adopt to health policies that allow the emergent utilization of mpox vaccines, especially since conducting large-scale efficacy trials in these populations may not be feasible [49].

Future Research

Although mpox has become more prevalent globally, many still view it as a newly emerging infection. Therefore, continued investment in research and funding is crucial to improve public understanding and awareness, especially in areas outside of Africa where the virus is now spreading. There is currently a limited amount of research dedicated to the development of vaccines specifically targeting mpox infection.

Numerous countries have recently reported cases of mpox infection, yet there is a lack of comprehensive studies detailing the strategies used to control its spread. Publishing research on emergency preparedness is crucial, especially for developing and underdeveloped countries. Such research can inform the creation of emergency programs and training that provide these regions with the essential resources and skills needed to effectively manage and control future outbreaks.

Although progress has been made in understanding the virus and developing vaccines, significant knowledge gaps remain-particularly in areas such as viral pathogenesis, long-term immunity. Investigating the immune responses elicited by mpox infection will be vital for improving current vaccines and creating new, more targeted immunization strategies. Additionally, there is a lack of research exploring the vaccines development for immunocompromised individuals. Research should also explore the genetic determinants of virulence and host range, which could lead to the design of safer and more effective vaccine platforms.

CONCLUSION

Mpox is one of the diseases that the WHO has declared as an emergent illness worldwide, apart from COVID-19 and polio. Initially confined to Africa, mpox has now emerged as a global public health issue with cases reported internationally as well as found in communities within individual countries. The rise in mpox infections, driven by a combination of natural

and human factors, highlights an urgent need for further research. The comprehension of immune response and the mechanism of mpox virus is essential as it could offer valuable strategies and insights for advancing the development of vaccine, which is a dire need at the moment. Moreover, further research is urgently needed to develop vaccine strategies for individuals with severe immunosuppression, particularly those that do not rely on CD4-positive T cell assistance. This research is crucial to address existing gaps in vaccine development, especially given that the severe complications of mpox can be fatal.

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