

Perspective

Mpox, HIV Infection, and Genital Skin Disease: Triple Burden, Threats and Challenges from an Epidemiological Perspective

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ABSTRACT

The expansion and transformation of Mpox (MPX) disease alongside HIV and genital skin diseases has led to an increase in global morbidity and mortality in a relatively brief period. These diseases have a similar transmission pathway through sexual intercourse (mainly MSM/men-sex with males). This review aims to provide a concise, evidence-based overview of MPX, HIV, and genital skin disease coinfections, and to identify epidemiological threats and challenges. Our investigations revealed that from January 2022 to July 2023, there was a significant increase in the number of MPX cases, which reached a total of 88,600, resulting in 152 deaths across 113 countries. There have been case reports of triple-burden disease in six different areas of the world, with at least 52% of reported cases occurring in men who have had sexual activity with other men, 84.1% of whom do not use condoms and do not take pre-exposure prophylaxis (PrEP). In addition, the highest number of deaths due to co-infection with MPX, HIV infection, and genital skin diseases occurred in vulnerable groups (LGBTQIA2S+), especially in men who had sex with men, up to 90.9%, and experienced an increase in the frequency of triple burden diseases to 104.9%. From an epidemiological standpoint, this condition generates several threats and challenges, including an increasing burden of infectious diseases, an increase in immunocompromised populations, an increase in overlapping risk factors, diagnostic difficulties, an increase in interactions and comorbidities, and relatively complex treatment challenges. To suppress these outbreaks and pandemics, comprehensive control and prevention should be proposed collaboratively, including collaboration with the education sector to conduct better research and investigation using one health in complex settings. Epidemiological modeling can be used in the future to accelerate the control of these diseases.

KEYWORDS

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INTRODUCTION

Mpox (MPX) formerly known as monkeypox is a rare viral disease, similar to smallpox. It is primarily found in Central and West African countries but has also been reported worldwide [1]. MPX can be transmitted to people through contact with infected animals (sylvatic cycle) or human-to-human transmission [2]. The speed of transmission and various new clinical features have caused concern for the global health system regarding prevention and control. The presence of MPX contributes to the annals of infectious diseases that can affect immunocompromised individuals. Co-infection with human immunodeficiency virus (HIV) and genital skin diseases can make it more challenging to control MPX [3–5]. HIV impairs the immune system, making people more prone to infections including MPX infections. By impairing the skin barrier, genital skin diseases such as herpes simplex infection can also make people more susceptible to infection [6]. The triple burden of MPX, HIV, and genital skin diseases creates a complex situation that necessitates a multifaceted approach to control. Treatment should address all three conditions concurrently to reduce the risk of complications and transmission [7].

The combination of MPX, HIV, and genital skin diseases has resulted in several potential complications, such as the presence of disseminated MPX, which can lead to systemic infections and cause complications in various organs including the liver, pancreas, lymph nodes, and lungs. In addition, a weakened immune system in people infected with these three diseases may increase skin tissue injury, resulting in exposed wounds that serve as entry points for opportunistic infections. Moreover, there is potential organ damage, including nephropathy in the kidneys, cardiomyopathy in the heart muscle, neurocognitive impairment in the brain and sepsis [8,9]. Therefore, it is essential to understand the future of intricate and interrelated complications.

The World Health Organization (WHO) declared the worldwide outbreak of MPX a global health concern in 2023, with 88,600 reported cases in 113 countries as of July 24, 2023, both endemic and sporadic, and 152 deaths [8]. Evaluations conducted by the WHO indicate that the risk of MPX disease is moderate, particularly in Africa, the Eastern Mediterranean, the United States, and Europe [10]. In contrast, danger is minimal in Southeast Asia and the Western Pacific [8,11]. Epidemiological characteristics show that almost 99% of reported MPX cases occurred among men, 94% of men who had sex with men (MSM) in the past three weeks, 52% of them were HIV-positive, 46% reported the presence of one or more genital skin diseases and genital lesions, and 42% reported the presence of typical prodromal symptoms as the first symptom; therefore, the presence of a low immune system triggers an increased risk of opportunistic infections, including genital skin disease and MPX in people with HIV [8,12,13].

The data demonstrated that genital skin diseases and MPX outbreaks affected HIV-positive people. A combination of these three diseases poses a high risk. It has affected lesbian, gay, bisexual, transgender, queer, questioning, intersex, asexual, and two-spirit (LGBTQIA2S+) people. However, MSM are at high risk and have been shown to simultaneously increase the incidence of HIV and other sexually transmitted infections (STIs) [3,13]. WHO data showed that 52% (16,631/32,019) of HIV-positive patients who received MPX had symptoms such as rash and lesions (90%), fever (55.2%), and systemic or genital rashes (53.9% and 47.5%, respectively) [8,13]. This finding indicates that a combination of these three diseases (MPX, HIV, and genital skin disease) has the potential to increase if not treated immediately.

Research and identification of possible threats and challenges are necessary to develop effective strategies to control this disease. This includes understanding the epidemiology of MPX, HIV, and genital skin diseases; identifying risk factors for infection; and developing practical diagnostic tools and treatment options for people with coinfections. Finally, there is a need to address the social determinants of health that contribute to the triple burden of MPX, HIV, and genital skin disease. A comprehensive approach that addresses these factors is necessary to control this disease and to reduce its impact on vulnerable populations. This study aimed to identify recent evidence related to the triple burden of infection caused by MPX, HIV, and genital skin diseases as well as the threats and challenges that may arise from an epidemiological perspective. This research must be carried out to add insight related to the triple burden disease that is currently ongoing and has been reported in several regions. Predisposing factors have not been explicitly observed; therefore, the information generated from this perspective can be used

to study MPX, HIV, and genital skin diseases from an epidemiological perspective, and the lessons learned from this condition. Thus, this information is expected to provide the latest information related to reducing morbidity and mortality due to the three burdens of disease in the community

PERSPECTIVE

Triple Burden, Threats and Challenges from an Epidemiological Perspective

Triple-burden disease currently poses a hazard to the entire human population. The simultaneous prevalence of triple-burden diseases, including MPX, HIV, and genital skin disease, has become a new cause of concern, as MPX spreads across multiple nations. The prevalence of MPX and genital skin disease in HIV-positive people has increased, with a reported prevalence of 52% compared with that in people infected with a single disease (48%) [8]. This new danger warrants further investigation. Various case reports and case series in various countries indicate that a combination of MPX, HIV, and genital skin disease (genital lesions or anal lesions) was found and dominated by MSM within the past three weeks and who subsequently appeared to exhibit symptoms that are indicative of MPX and STI [8,13–15]. This combination of infections presents significant control and management challenges for health outcomes.

Mpox disease can be transmitted through the sylvatic cycle from primates to infected people and vertically to infected people [9,16–18]. MPX disease develops in HIV-positive individuals, and the weakened immune system worsens health conditions that trigger opportunistic infections, such as genital skin diseases characterized by genital lesions on the penis and vagina, anal lesions in the rectal area, and skin lesions [13,14]. This damages the health of an infected individual and poses a threat to healthcare professionals providing treatment.

Recently, global health authorities such as the WHO have reported that endemic and sporadic cases of MPX have spread across numerous countries. According to the most recent report, the number of confirmed cases reached 88,600 between January 1, 2022, and July 24, 2023. The number of probable cases was 1,087, with one or more symptoms resembling those of MPX. The prevalence of genital or anal lesions in HIV-positive individuals aids in establishing the diagnosis of the disease. To date, 152 cases of pox-related fatalities have been reported in immunocompromised individuals [14,15]. The number of weekly cases has been reported to increase to 104.9% globally by week 29 of 2023 [8].

According to the WHO report, the top ten countries reporting the highest MPX outbreaks were the United States ($n = 30,404$), Brazil ($n = 10,967$), Spain ($n = 7,559$), France ($n = 4,147$), Colombia ($n = 4,090$), Mexico ($n = 4,039$), Peru ($n = 3,812$), the United Kingdom ($n = 3,761$), Germany ($n = 3,691$), and Canada ($n = 1,496$), which together accounted for 83.5% of the global cases. The countries that reported the highest number of deaths were the United States ($n = 45$), Mexico ($n = 30$), Peru ($n = 20$), and Brazil ($n = 16$). A map of the cumulative distribution of MPX cases and deaths in each country is shown in Figure 1. The curves of MPX cases and deaths in each region until July 24, 2023, are presented in Figure 2 [8].

Based on the trend of MPX cases in various countries and regions, the Americas, Europe, and Africa are the main highlights because, in addition to contributing the highest confirmed cases, they also reported the highest total deaths, with changes in the last three weeks (July 1–24, 2023) reaching 88–294% [8]. The results of epidemiological surveillance in different countries indicate that MPX is extremely dangerous for immunocompromised individuals, particularly HIV-positive individuals and those with genital skin diseases [13–15]. Numerous case reports have affirmed that HIV-positive individuals are at a high risk of contracting both MPX and STIs simultaneously. This was reported by 84.1% (26,111/31,031) of men who did not use condoms or preexposure prophylaxis (PrEP), whereas 7.8% (2,029/26,111) were bisexual [8,19,20]. The proportion of MSM and sexual orientation by region are shown in Figure 3.

Figure 3 shows that 31,034 confirmed cases came from male people who had MSM, mostly from Europe and the US. Meanwhile, MPX among heterosexual individuals is most commonly reported in the Americas. The incidence of MPX and genital skin disease in HIV-positive people is predominantly transmitted through sexual contact at 82.1% (16,562/20,171), travel history at 15.8% (3,635/20,171), and hospitalization at 8.8% (4,311/20,171) [8]. People infected with MPX, HIV, and genital skin disease simultaneously had the highest mortality rate (90.9%) compared to

those infected with MPX or genital skin disease alone [8,14,15]. Efforts to accelerate the control of infectious diseases and identify potential threats and challenges are, therefore, centered on the issue of triple-burden disease.

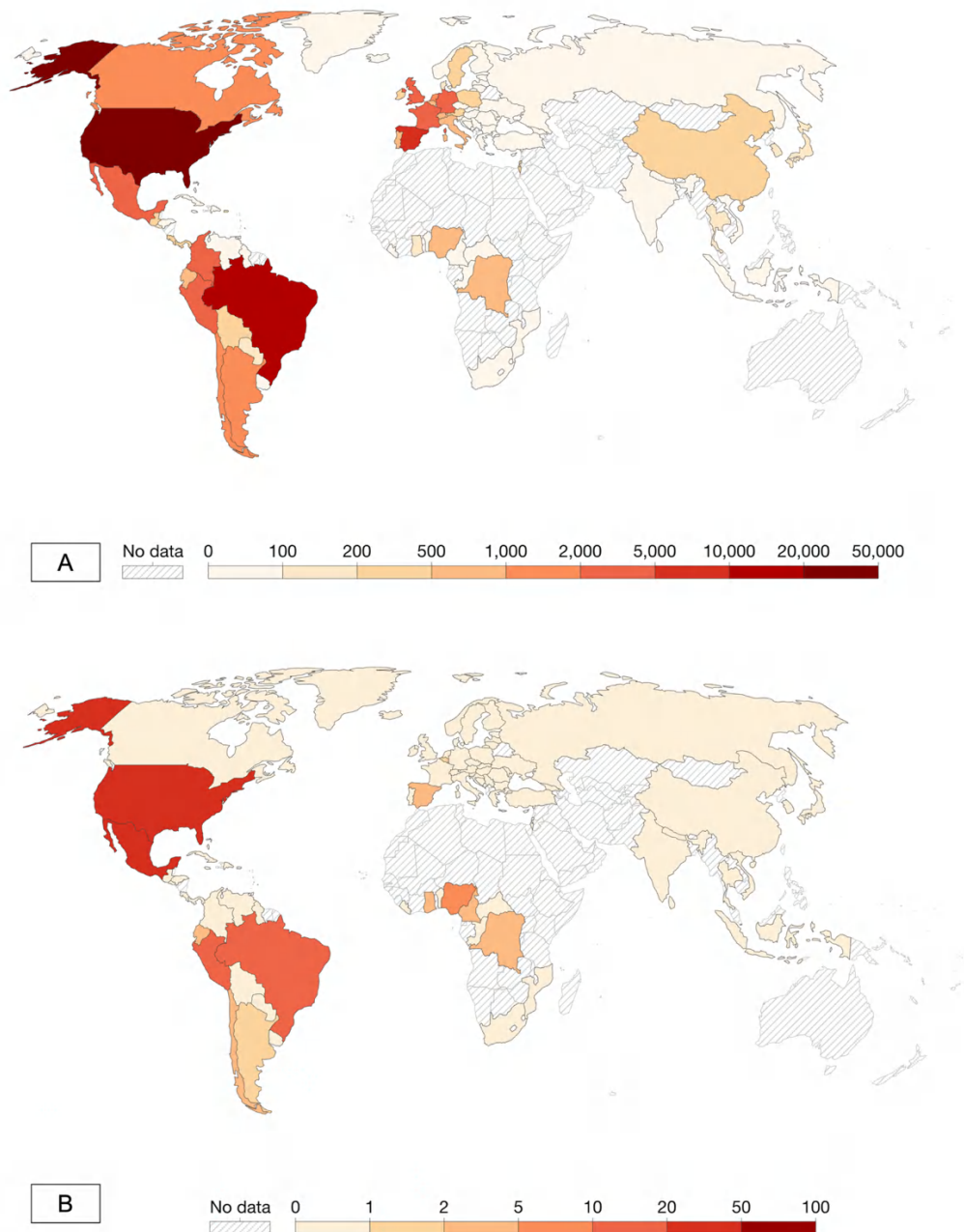


Figure 1. Map each country's cumulative distribution of monkeypox cases (A) and deaths (B) [8].

However, data on the proportion of HIV-positive individuals infected with MPX and genital skin diseases have not yet been reported. This is because diagnosis and management have not been carried out simultaneously; therefore, data reports are relatively late. In addition, the different onset times in each patient and region were the leading causes of this data delay. Epidemiologically, the number of HIV-positive cases has increased cumulatively between 1990 and 2022, reaching 39 million in all age groups, while the number of HIV-positive deaths has reached 630,000. The highest number of cases and deaths were reported in Africa (25.6 million), the Southeast Asian Region (3.9 million), the Region of the Americas (3.8 million), the European Region (3.0 million), and the Western Pacific Region (2.2 million), while the lowest cases were in the Eastern Mediterranean Region (490,000). A map of the distribution of HIV-positive cases and deaths worldwide from 1990 to 2022 is shown in Figure 4 [21].

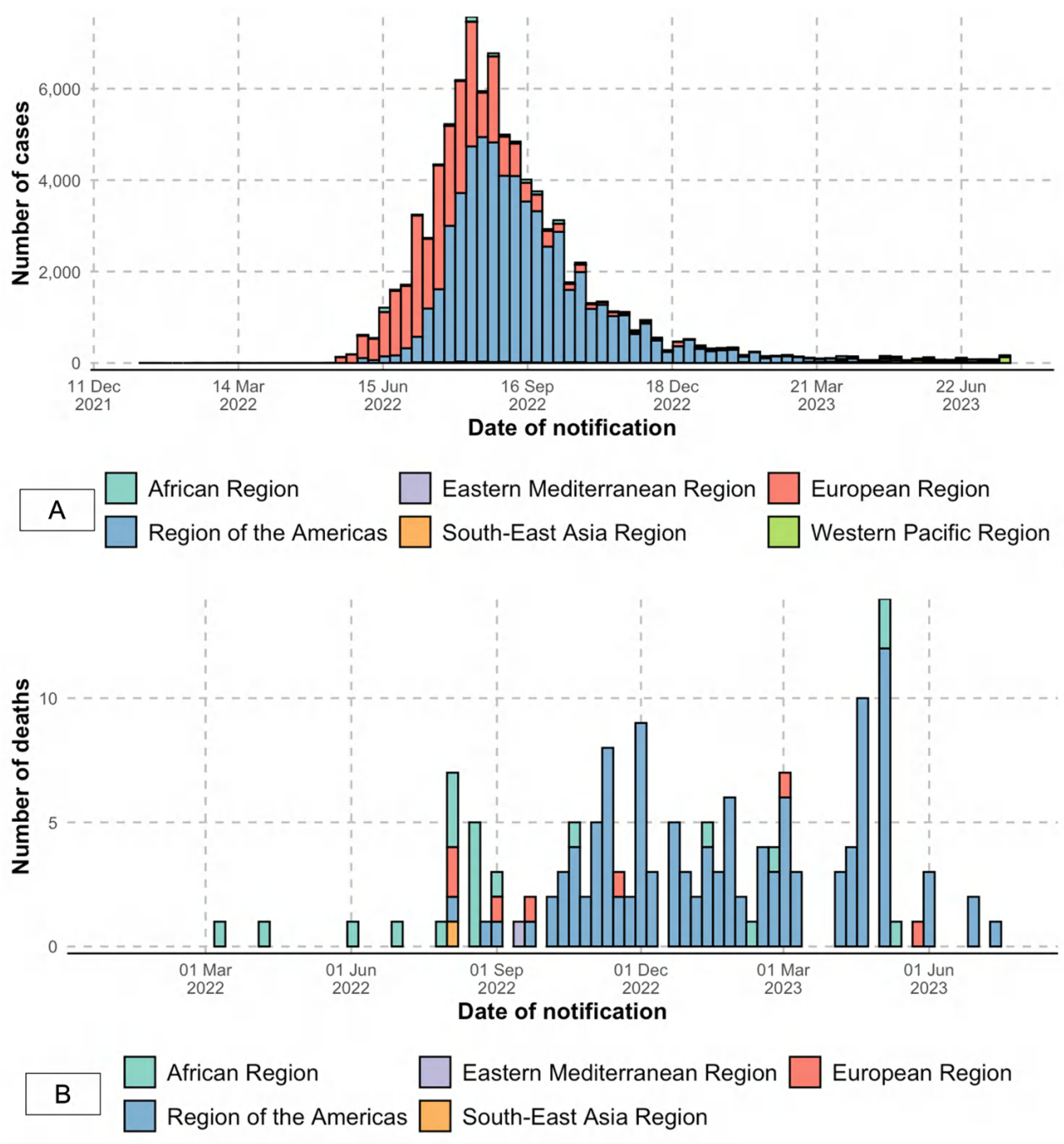


Figure 2. The curve of cases (A) and deaths (B) from monkeypox in each region from January 1, 2022, to July 24, 2023 [8].

Worldwide, MSM have a higher risk of being HIV-positive than the general population. The highest mortality rate occurs at the age of 15–49 years, which is classified as productive age. Some people have unprotected sex, which affects the increase in new cases of HIV-positive people accompanied by STIs [22]. In recent years, the incidence of both MPX and genital skin diseases in HIV-positive individuals has increased throughout the region. In susceptible individuals, weakened immune systems have implications for the simultaneous onset of signs and symptoms, leading to exacerbation of symptoms and an increased risk of mortality from MPX and HIV. Moreover, genital skin diseases can increase the risk of MPX and HIV transmission from infected to uninfected individuals [7,23].

Open sores and lesions on the skin can serve as entry points for viruses and increase the likelihood of transmission during sexual contact or other forms of close contact exposure to infected bodily fluids, including semen, vaginal fluids, anal fluids, and blood [3,6,17]. When these fluids come into contact with mucous membranes or damaged skin, such as genital ulcers, the

risk of HIV and STI transmission increases significantly. Other STIs, such as syphilis, herpes simplex virus (HSV), and chancroids, can cause genital ulcers similar to those seen in monkeys. STIs can also increase the risk of HIV transmission. Genital ulcers disrupt the protective barrier of the skin and mucous membranes, facilitating the entry of HIV and other pathogens [20]. Furthermore, the inflammatory response caused by these ulcers can attract immune cells that are more susceptible to HIV-positive infection and increase the risk of transmission.

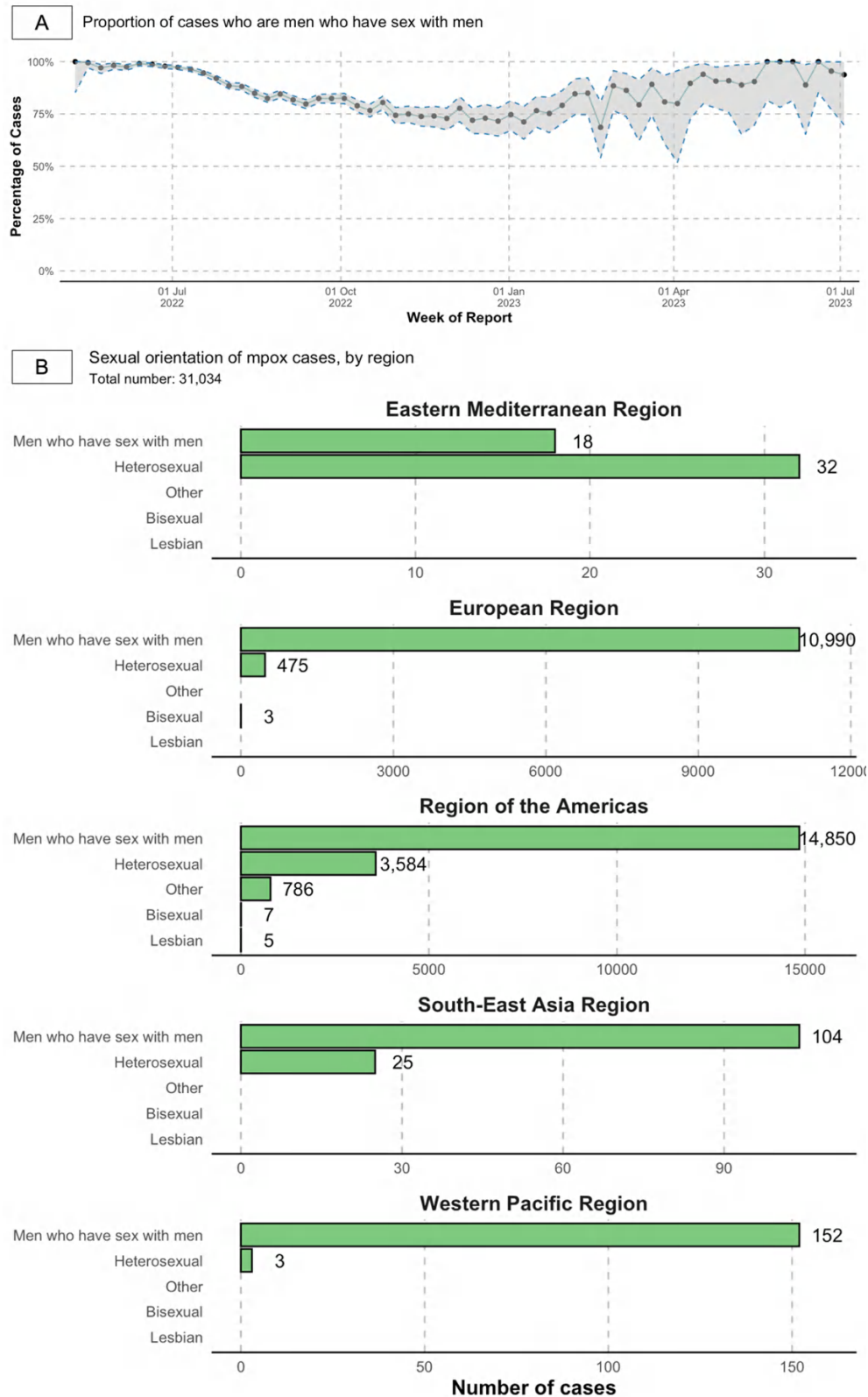


Figure 3. The proportion of cases of men who have sex with men (A) and sexual orientation by region (B) [8].

In some cases, various manifestations occur both vertically and horizontally. Figure 5 shows the horizontal course of the MPX infection at each location (anal, genital, and skin). Lesions caused by MPX virus appear within 1-3 days of systemic symptoms. They are generally clustered, as shown on the left side (anal lesions), or isolated on the middle side (genital lesions) and right side (skin lesions). These lesions are accompanied by papules protruding from the skin and a generally itchy, serous fluid discharge in the central umbilication. In the span of a few days, the umbilication center widens until the lesion opens, and scabs form approximately two weeks after the onset of symptoms. Lesions can heal on their own, but HIV-positive people and those with STIs have a longer healing time and need medical treatment as a result of a lower immune system than normal people. The clinical manifestations of anal, genital, and skin lesions in MPX-infected individuals with HIV coinfection and STIs are shown in Figure 5 [24].

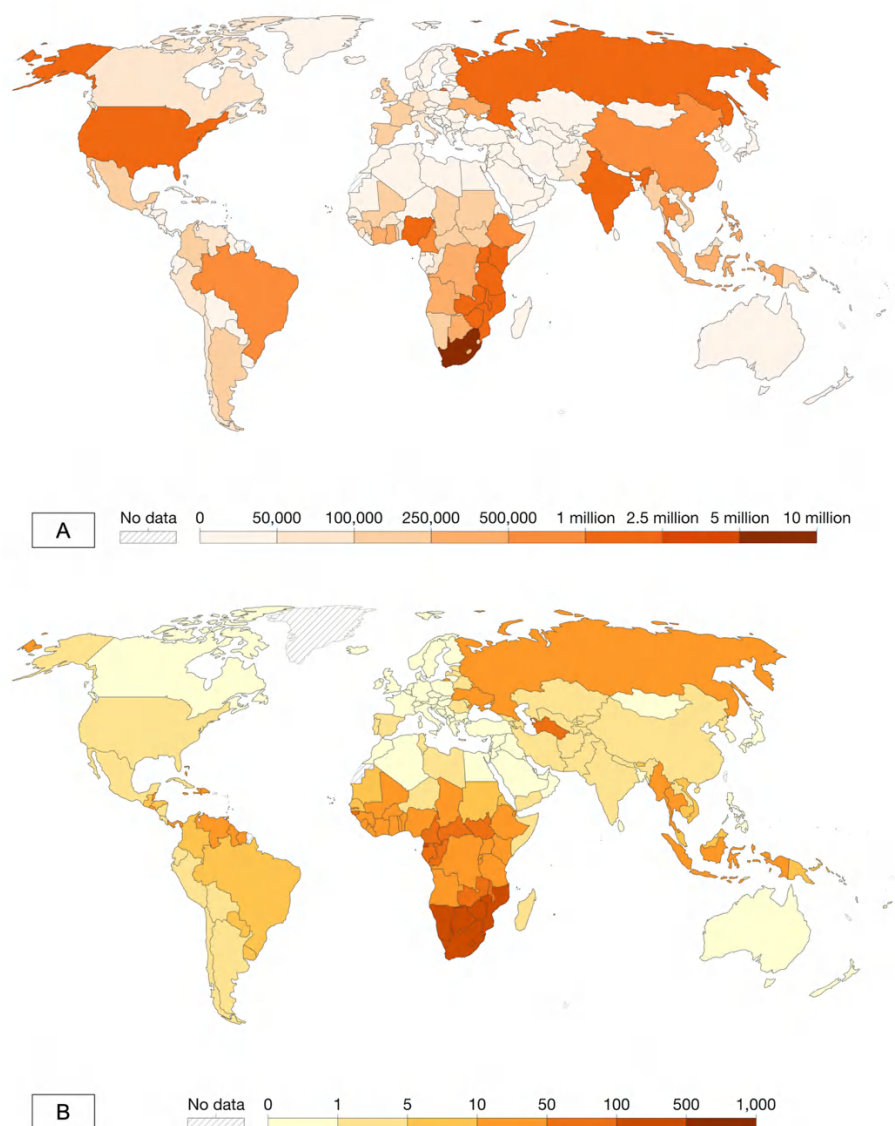


Figure 4. Map of the distribution of HIV cases (A) and deaths (B) worldwide from 1990 – 2022 [21].

In the case of same-sex sexual activity, the risk of HIV transmission may already be elevated owing to various factors. Anal intercourse carries a higher risk of HIV transmission than vaginal intercourse [25]. The delicate nature of anal tissues, combined with the potential for microtears and trauma during intercourse, can increase susceptibility to HIV infection [26]. Engaging in unprotected receptive anal sex, particularly in HIV-positive individuals, significantly increases this risk. In marginalized populations, people with MPX and coinfection with HIV or STIs often live close to one another, increasing the risk of transmission through person-to-person contact [5,27].

Genital and anal lesions, which can be caused by a range of genital skin diseases, including herpes, syphilis, opportunistic infections, and human papillomavirus (HPV), are also common among MSM [28,29]. These lesions can increase the risk of HIV transmission and other infections and can be challenging to diagnose and treat. Several cases in the United States of America, Africa, Brazil, Germany, and the United Kingdom reported that people who engaged in risky MSM two weeks to one month earlier were found to have genital and perianal lesions accompanied by genital skin diseases and sexually transmitted diseases, such as syphilis and herpes, and were diagnosed as HIV-positive [16,18,20,23,30]. Thus, infection with these three diseases is hazardous for MSM, including those with poor health and poor sexual behavior. The triple burden of MPX, HIV, and genital skin disease presents a significant epidemiological challenge. Co-occurrence of these infections can lead to increased transmission rates and more severe health outcomes. Additionally, treating these infections can be challenging because some treatments for one infection can interfere with the treatment of another.

MPX, HIV, and genital skin diseases can hinder treatment in immunocompromised populations because they impair the immune system, making people more susceptible to opportunistic infections [14,15]. HIV-positive individuals may experience more severe cases of infection and are at a greater risk of developing complications from genital skin diseases, which can result in higher rates of morbidity and mortality. As these three diseases share the same risk factors, namely, unprotected sexual activity and a compromised immune system, identifying risk factors that predispose directly and indirectly will be challenging and result in overlapping outcomes [13,14]. This condition heightens the dangers and difficulties faced by medical professionals when diagnosing and treating patients. Concurrent diagnosis of multiple diseases can be difficult because their symptoms may overlap, resulting in potential diagnostic delays. These delays can impede the treatment and management of the condition in an expedient manner, thereby potentially deteriorating health outcomes. Moreover, the interactions and comorbidities between diseases can influence the progression and severity of other diseases. This makes it difficult to treat MPX and genital skin diseases, particularly in HIV-positive individuals with compromised immune systems [3,19].

These interactions can result in complex clinical scenarios, necessitating individualized treatment approaches. Controlling MPX, HIV, and genital skin diseases in endemic and sporadic regions is complicated by social, economic, cultural, and healthcare factors. One of the greatest obstacles is the lack of access to health services in many endemic regions, particularly in low-income and middle-income countries. This can make diagnosing and treating these infections difficult, increase transmission, and worsen health outcomes. Triple-burden disease necessitates an exhaustive public health response. These include fortifying disease surveillance systems to detect cases promptly, ensuring that healthcare providers are well informed about interactions between these diseases, and implementing effective communication strategies to educate the public on disease prevention and early detection [29].

Furthermore, limited resources may be available to implement prevention and control measures, such as education and awareness campaigns, access to testing and treatment, and the development of effective vaccines [27]. This can make it difficult to reach marginalized populations, such as MSM and other vulnerable groups [24]. This community faces new threats in the form of health disparities. Threefold burden diseases can have a disproportionate impact on vulnerable populations with limited access to health services, resulting in additional health disparities. It is essential to address these disparities to ensure that everyone receives adequate and timely care [31–33]. In many regions, the availability of qualified health personnel is an obstacle to effective treatment. A multidisciplinary approach involving infectious disease specialists, dermatologists, and HIV care teams is required to manage patients with triple-stage disease. Coordinating treatment and care for these people can be difficult and require a large number of resources that have a thorough understanding of the prevention, treatment, and coping strategies for each of the sufferers' characteristics [34–36].

The stigma and discrimination associated with these infections also make it difficult to engage with affected communities and implement effective prevention and control measures [29]. In some instances, stigma and discrimination can prevent people from pursuing testing and

treatment, resulting in increased transmission and worse health outcomes [4,29]. Moreover, the co-occurrence of these infections can result in more severe health outcomes, further complicating their treatment and administration. This emphasizes the need for prevention and control strategies considering the interconnected nature of these infections. Control of MPX, HIV, and genital skin diseases in endemic regions requires a comprehensive, multifaceted approach that considers social, economic, and health-related factors. This may involve improving access to healthcare services, implementing effective prevention and control measures, addressing stigma and discrimination, promoting integrated approaches to prevention and control, and strengthening infectious disease surveillance systems to detect cases promptly with a case-by-case, person-by-person, and region-by-region approach to accelerate disease prevention and early detection.



Figure 5. Clinical manifestations of anal, genital, and skin lesions in monkeypox-infected individuals with HIV coinfection and STIs. This image is courtesy of Antinori et al. [24]

Lessons learned from an epidemiological perspective

The lessons learned from the cases of MPX, HIV, and genital skin disease from an epidemiological perspective include the following: (1) Importance of surveillance: All three diseases have demonstrated the importance of surveillance in detecting outbreaks and monitoring disease trends. Effective surveillance systems can help identify outbreaks early, allowing timely intervention to prevent further spread of the disease [37]; (2) Role of risk factors: Understanding the risk factors associated with these diseases is critical for preventing their spread. For example, HIV is primarily transmitted through unprotected sex, and the sharing of contaminated needles and targeted interventions can reduce the risk of transmission [38]. (3) The impact of social determinants of health socioeconomic factors, such as poverty, discrimination, and limited access to healthcare can contribute to the spread of these diseases. Addressing these underlying factors can help to reduce the burden of these diseases [11,36]. (4) The importance of prevention strategies: Preventive measures such as vaccination, condom use, and safe injection practices can help reduce the transmission risks of these diseases. Implementing these strategies on a large scale can significantly affect disease transmission [39,40]. (5) The need for effective treatments: Treatment options for these diseases can help reduce morbidity and mortality, and improve the quality of life of those affected. The development of effective treatments should be a priority for controlling and managing these diseases. (6) The importance of public health messaging: Public health messaging plays a critical role in raising awareness about these diseases and promoting behaviors that can reduce the risk of transmission. Effective messaging should be tailored to specific at-risk populations and delivered through multiple channels to ensure broad reach [40–42].

The triple burden of MPX, HIV infection, and genital skin disease necessitates a comprehensive and individualized strategy that considers person-, time-, and place-specific factors [37,43]. Controls that consider person, time, and location, such as *Person*: Interventions should be targeted at populations at the highest risk, such as those who engage in high-risk sexual behavior or people who inject drugs. Tailored interventions that consider the specific needs of these populations might be more effective. *Time*: Monitoring disease trends and detecting outbreaks early can be critical for controlling the spread of these diseases. Effective surveillance systems should be in place to identify and respond quickly to outbreaks. *Place*: Geographic factors such as population density and access to healthcare can impact disease transmission. Interventions should consider a specific geographic context and be tailored to the local context. For example, interventions that work in urban settings may be ineffective in rural areas.

CONCLUSIONS

Co-infection with MPX, HIV, and genital skin disease results in a triple burden. Currently, triple burden disease has increased significantly in weekly cases, reaching 104.9% globally. This phenomenon is commonly associated with MSMs who engage in sexual intercourse without condoms and do not undergo PrEP. Co-infection with MPX, HIV, and genital skin disease caused 90.9% of deaths. Triple-burden disease conditions pose threats and challenges in reducing morbidity and mortality in the community, such as increasing the burden of coinfection in the coming months, which have more severe health consequences, high mortality, and more complex treatment management; increasing immunocompromised populations at high risk of infection with new diseases that trigger increased mortality and morbidity; increased overlapping risk factors leading to a slowdown in disease identification and management; and the existence of diagnosing challenges that require high precision, speed, and accuracy to minimize mortality and high interaction and comorbidity requires health care preparedness and presents better treatment challenges. Addressing these threats requires a coordinated effort involving healthcare systems, policymakers, and communities to improve prevention, diagnosis, and management strategies and reduce the burden of these diseases on affected people and populations. Approaches based on people, time, and place combined with One Health in Complex Settings (OHICS) and epidemiological modeling can be leveraged to control these three diseases in the future.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, Data curation, formal analysis, visualization, and supervision: IMDM. Resources; Investigation, Validation: DSE, SM, KI, LNA. Writing–original draft: IMDM, TPU; writing–review and editing: SM, KI, ZVC.

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ETHICS STATEMENT

The need for ethics approval was waived for this study because no patient data were reported.

ABBREVIATIONS

HIV, Human immunodeficiency virus; HPV, Human papilloma virus; MPXV, Monkeypox Virus; MSM, Men Who Have Sex with Men; OHICS, One Health in Complex Settings, PrEP, preexposure prophylaxis; and STI, sexually transmitted infection.

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