Mpox: Why the classic rash is no longer the only sign

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The widespread monkeypox virus (MPXV) outbreak in 2022 presented new challenges for global public health systems, with over 86,000 people infected. This outbreak raised concerns about MPXV becoming endemic outside its original geographical areas, leading to repeated human spillover infections or sustained person-to-person spread.1 While classical public health measures and vaccination efforts have blunted the virus's spread, cases persist in numerous countries, necessitating a re-evaluation of diagnostic paradigms.1

KEY TAKEAWAYS

- The Pivot: Mpox presentations are evolving beyond the classic vesicular rash, demanding a broader diagnostic consideration among clinicians.
- The Data: Mpox cases continue to be reported in 28 countries as of March 2023, underscoring ongoing transmission risks.1
- The Action: Clinicians should maintain a high index of suspicion for mpox, particularly in at-risk populations, even in the absence of typical skin lesions, and ensure robust diagnostic and surveillance capacity.

The 2022 mpox outbreak, which saw more than 86,000 individuals infected, highlighted the urgent need for continued surveillance, effective vaccines, and accessible therapeutics.1 This global health event showed the potential for MPXV to establish itself outside its historically endemic regions, posing a persistent threat of human spillover and sustained community transmission. Public health responses, including isolation, contact tracing, quarantine, and vaccination, did mitigate the initial surge.1 But the continued reporting of cases in 28 countries as of March 2023 indicates that the virus remains a significant concern, requiring clinicians to adapt their diagnostic approaches.

The traditional understanding of mpox, often associated with a characteristic vesicular or pustular rash, is increasingly insufficient for current clinical practice. The evolving epidemiology of the virus, coupled with varied patient populations and potential viral adaptations, means that presentations can be subtle or atypical. This shift necessitates a heightened awareness among healthcare providers, especially those in primary care and infectious disease specialties, to consider mpox in patients presenting with less conventional symptoms. The Roper et al. paper in Vaccine emphasizes that while classical public health interventions have been valuable, the ongoing transmission demands a more comprehensive strategy that includes improved diagnostic capabilities.1

The Evolving Clinical Picture

Mpox, caused by the monkeypox virus, has historically been characterized by a prodromal phase of fever, headache, muscle aches, and lymphadenopathy, followed by the development of a widespread rash that progresses through macular, papular, vesicular, pustular, and scab stages. This classic presentation, often starting on the face and extremities, guided initial diagnostic efforts during the 2022 outbreak. But as the outbreak progressed, clinicians encountered cases that

deviated significantly from this textbook description. These atypical presentations included solitary lesions, lesions confined to the genital or perianal area, or even presentations mimicking sexually transmitted infections without the systemic symptoms or widespread rash. Such variations complicate early diagnosis and can lead to delayed treatment and continued transmission, particularly within high-risk communities.

The virus's capacity for evolution and expansion beyond previously identified risk groups remains a key concern.1 This means that clinicians cannot rely solely on historical epidemiological patterns or classic symptomology. The paper by Roper and colleagues highlights the need for increased diagnostic and surveillance capacity to identify areas and populations where the virus is present and may seed resurgence.1 This includes developing and deploying more sensitive and rapid diagnostic tests that can detect MPXV in diverse clinical samples, not just from typical skin lesions. For instance, a patient presenting with proctitis or pharyngitis, without any visible skin lesions, could still be infected, requiring a broader differential diagnosis and targeted testing.

Understanding Transmission and Risk

Mpox transmission primarily occurs through close contact with an infected person or animal, or with contaminated materials like bedding. During the 2022 outbreak, sexual contact, particularly among men who have sex with men, was a significant transmission route, leading to many cases presenting with anogenital lesions. This specific mode of transmission often resulted in localized rashes that could be mistaken for herpes simplex, syphilis, or other sexually transmitted infections, delaying accurate diagnosis. The virus can also spread through respiratory droplets during prolonged face-to-face contact, though this is less common than direct contact with lesions or bodily fluids. Understanding these diverse transmission pathways is essential for identifying at-risk individuals and implementing effective public health interventions.

Certain populations face a higher risk of severe outcomes from mpox infection. These include immunocompromised individuals, those with untreated HIV, pregnant women, and patients with inflammatory skin conditions.1 These groups require particular attention, not only for early diagnosis but also for proactive protection from community transmission. Clinicians must be vigilant in informing these high-risk patients about the potential for infection and the importance of preventive measures. This also means that when these patients present with any unusual symptoms, even if not classically mpox-like, a thorough evaluation including mpox testing should be considered. The challenges in diagnosing emerging viral threats are well-documented, and mpox is no exception.

Vaccines and Therapeutics: Efficacy Gaps

Several vaccines and drugs are available for the prevention and treatment of MPXV infections. These include smallpox vaccines, which offer cross-protection against mpox, and antiviral agents like tecovirimat. But the efficacy of these interventions against mpox in the context of the 2022 outbreak remains largely unknown in human populations.1 While animal models have established their efficacy, real-world data on human outcomes are still being gathered. This gap in evidence shows a critical priority: more data on the efficacy of vaccines and drugs in infected humans must be collected.1 This includes observational studies, real-world evidence analyses, and potentially randomized controlled trials where feasible.

The availability of treatments and vaccines, especially in historically endemic and enzootic areas, is another pressing concern. Global collaborations are necessary to ensure that government authorities work with the private sector in

both developed and low and middle-income countries to provide equitable access.1 This is not merely a humanitarian issue; it is a global health security imperative, as uncontrolled outbreaks in any region can quickly become a global threat. The logistical challenges of vaccine distribution and therapeutic access, particularly in resource-limited settings, present significant hurdles that require coordinated international efforts. The lessons learned from other infectious disease outbreaks, such as the recent diarrhea parasite outbreak across Europe, highlight the importance of rapid, equitable access to countermeasures.

Public Health Engagement and Preparedness

Effective public health responses depend heavily on community engagement, particularly with the hardest-hit populations. This engagement must be non-stigmatizing to increase understanding and acceptance of public health measures.1 Stigma can drive infections underground, making contact tracing and surveillance efforts far less effective. Open communication, culturally sensitive messaging, and involving community leaders are essential components of a successful public health strategy. This approach fosters trust and encourages individuals to seek testing and care without fear of discrimination.

The mpox outbreak serves as a stark warning that pandemic preparedness plans require additional coordination and resources.1 This includes establishing repositories of mpox clinical samples, such as blood, fluids, tissues, and lesion material, for researchers.1 These repositories are invaluable for understanding viral evolution, developing new diagnostics, and evaluating the effectiveness of vaccines and therapeutics. The ongoing opportunity for transmission means that preparation for continuing transmission, resurgence, and repeated spillovers of MPXV is not optional, but essential. Clinicians, therefore, need to be equipped with the latest knowledge and tools, perhaps even a comprehensive reference like the Oxford Handbook of Infectious Diseases and Microbiology, to navigate these evolving threats.

The challenge of mpox extends beyond immediate crisis management. It demands a sustained, proactive approach to infectious disease surveillance and response. This includes investing in public health infrastructure, training healthcare workers in recognizing atypical presentations, and fostering international cooperation to monitor and control outbreaks. The global interconnectedness means that a localized outbreak can rapidly escalate, showing the need for robust early warning systems and rapid response capabilities. The experience with mpox reinforces the idea that infectious disease threats are dynamic and require continuous adaptation of clinical and public health strategies.

The Imperative for Enhanced Diagnostics

The core issue remains the need for enhanced diagnostic capabilities. Relying on the classic presentation of mpox is no longer sufficient. Clinicians must consider mpox in a broader range of differential diagnoses, especially in patients presenting with unexplained rashes, mucocutaneous lesions, or even systemic symptoms without overt dermatological manifestations. This requires access to rapid, reliable PCR testing, which remains the gold standard for MPXV detection. The ability to test diverse sample types, including swabs from oral lesions, rectal swabs, or even pharyngeal swabs, is essential for detecting atypical cases.

But the availability and accessibility of such testing vary significantly across regions. In many settings, diagnostic capacity is limited, leading to delays in diagnosis and potential onward transmission. This disparity highlights the need for global efforts to strengthen laboratory infrastructure and ensure equitable access to diagnostic tools. Without robust diagnostic networks, surveillance efforts will remain incomplete, hindering the ability to track viral spread and

identify emerging hotspots. The ongoing reporting of cases in multiple countries, even after the initial peak, underscores this persistent diagnostic challenge. The broader implications of diagnostic gaps in infectious disease management are profound, affecting everything from individual patient outcomes to global pandemic preparedness.

Addressing Vulnerable Populations

Protecting vulnerable populations from mpox infection and severe outcomes is a paramount concern. Immunocompromised individuals, including those with HIV, are at higher risk of prolonged illness and more severe disease. Pregnant women represent another high-risk group, given the potential for vertical transmission and adverse pregnancy outcomes. Patients with inflammatory skin conditions, such as eczema, may experience more extensive or severe rashes, complicating diagnosis and management. These groups require targeted public health messaging, priority access to vaccines, and heightened clinical vigilance. The non-stigmatizing engagement with communities is particularly important here, ensuring that individuals feel safe seeking care and adhering to public health advice. This proactive approach is essential to prevent severe morbidity and mortality in those most susceptible.

> **CLINICAL IMPLICATIONS**
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> The persistent reporting of mpox cases, even after the initial global alarm, means clinicians cannot afford to drop their guard. The virus is not confined to its classic presentation, and relying on the textbook vesicular rash will lead to missed diagnoses and continued transmission. We must broaden our differential to include mpox in patients with atypical mucocutaneous lesions or even unexplained systemic symptoms, particularly in at-risk populations.
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> Diagnostic capacity needs a serious upgrade. If we are to truly blunt the spread, clinicians need rapid, accessible PCR testing for MPXV, capable of analyzing diverse sample types. The current reliance on animal model data for vaccine and therapeutic efficacy in humans is insufficient; real-world evidence is desperately needed to guide treatment decisions and public health strategies.
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> The focus on vulnerable populations, immunocompromised individuals, pregnant women, and those with inflammatory skin conditions, is non-negotiable. These groups face higher risks of severe outcomes, demanding targeted protection and heightened clinical suspicion. Ignoring the social determinants of health and failing to engage communities in a non-stigmatizing way will only perpetuate outbreaks, making future control efforts more challenging.
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> This ongoing mpox situation is a clear signal that our pandemic preparedness plans are still lacking. We need better global coordination, more resources for surveillance, and a commitment to establishing clinical sample repositories. The virus is evolving, and our response must evolve faster, or we will continue to chase outbreaks rather than prevent them.

REFERENCES

1. 1. Roper RL, Garzino-Demo A, Del Rio C. Monkeypox (Mpox) requires continued surveillance, vaccines, therapeutics and mitigating strategies. Vaccine. 2023;41(19):3091-3095. doi:10.1016/j.vaccine.2023.04.013

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