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Title: Global Expansion of Mpox: Addressing the Threat to Maternal Health and Healthcare Systems in Pakistan

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Clinical Question Box

Are vulnerable populations in Pakistan at risk of severe outcomes from current Mpox outbreaks?

Vulnerable groups in Pakistan, such as pregnant individuals and those in low-resource or flood-affected areas, face heightened risk due to limited immunity, scarce vaccines, and an already overburdened healthcare system. Preventive strategies like public awareness, targeted vaccination, and international support are essential to reduce morbidity and mortality and contain the outbreak effectively.

Abstract

Mpox, formerly known as monkeypox, is a zoonotic disease caused by the monkeypox virus (MPXV) of the Orthopoxvirus genus. Once confined to Central and West Africa, it has rapidly evolved into a global public health concern, with outbreaks reported in over 120 countries since 2022. The virus comprises two main clades: Clade I, associated with higher severity, increased complications, and poor maternal and fetal outcomes, and Clade II, particularly subclade IIb, which drove recent international transmission and is generally linked to milder disease. In August 2024, the World Health Organization re-declared mpox a Public Health Emergency of International Concern following the emergence of a new Clade Ib lineage in the Democratic Republic of Congo, which has demonstrated higher transmissibility and disproportionate effects on pediatric and pregnant populations. Pregnant individuals remain especially vulnerable, as Clade I infections carry heightened risks of miscarriage, intrauterine fetal demise, and vertical transmission, while data on Clade II remain limited. In resource-limited settings like Pakistan, the mpox threat is compounded by systemic healthcare challenges, including low health expenditure, inadequate infrastructure, and limited access to vaccines and antivirals. Addressing these challenges requires strengthened surveillance, equitable vaccine distribution, targeted maternal care strategies, and global collaboration to mitigate risks and safeguard maternal and neonatal health.

Keywords: Mpox, Maternal Health, Pakistan, Pandemic, Monkeypox

Virology and Global Spread of Mpox

Mpox, previously known as monkeypox, is a zoonotic viral disease caused by the monkeypox virus (MPXV), a member of the Orthopoxvirus genus.[1] Although the disease resembles smallpox in its rash presentation, it is typically less severe and less transmissible.[2] Mpox was first identified in monkeys in Denmark in 1958.[3] Historically, mpox was confined mainly to regions of Central and West Africa, but recent global outbreaks have prompted renewed attention.[4] In 2022, the World Health Organization officially renamed the disease "mpox" to eliminate geographic and animal-associated stigma.[5] However, the causative agent continues to be called Mpox until a new designation is provided by the International Committee on Taxonomy of Viruses. Mpx shares its genus with variola (smallpox) and vaccinia viruses. It exists in two primary clades: Clade I (formerly Central African or Congo Basin) and Clade II (formerly West African), with each clade containing additional subclades.[6] Clade I tends to be more virulent, while Clade II, including subclade IIb, was the dominant strain in the 2022 global outbreak. Genetic analyses indicate ongoing viral evolution, possibly due to human adaptation.[7] Clade I a primarily affects children in endemic rural areas, while Clade I b, associated with adult sexual transmission, has emerged in densely populated urban settings.[7,8]

Mpox is transmitted through multiple routes, involving both zoonotic and human-to-human mechanisms.[9] Animal-to-human transmission typically occurs through direct exposure to infected animals via bites, scratches, bodily fluids, or during the handling and preparation of bushmeat. Rodents are suspected to be the primary reservoirs. Human-to-human transmission primarily occurs through direct contact with skin lesions, body fluids, or contaminated objects (fomites), such as bedding or clothing. Although respiratory droplet transmission is possible, it is less common.[10] The 2022 outbreak highlighted sexual contact as a dominant transmission route,

particularly through close, intimate, skin-to-skin interactions, often resulting in lesions localized to the genital and perianal areas.[11] Vertical transmission from mother to fetus, as well as percutaneous transmission through needlestick injuries, has also been documented.[12] Viral DNA has been detected in semen, although its role in transmission remains uncertain.

Clinically, mpox typically begins with an incubation period of 5 to 13 days, though it can extend up to 21 days. Systemic symptoms such as fever, myalgia, headache, and lymphadenopathy often precede the rash.[13,14] The number of lesions can vary from a few to several hundred. Over the following weeks, lesions progress through distinct stages: macules, papules, vesicles, and pustules, each lasting 1-2 days. Lesions are characterized by hard, deeply rooted formations up to 10 mm in size.[15] However, during the 2022 outbreak, many patients lacked systemic symptoms and instead presented with localized lesions. The rash follows a predictable progression, from macules to papules, vesicles, pustules, and finally crusting. In endemic areas, the rash tends to be widespread, while in recent global outbreaks it has often been confined to the genital, anal, or oral regions, aligning with observed patterns of close-contact transmission.[16]

Human cases of mpox were first identified in the 1970s in the Democratic Republic of the Congo (DRC). After the global cessation of smallpox vaccination in 1980, the incidence of mpox increased, particularly across endemic regions of Africa.[17] The World Health Organization (WHO) reported over 60,000 suspected cases and nearly 1,800 suspected deaths between 2010 and 2023 in the DRC.[18] The 2022 outbreak was marked by unprecedented person-to-person transmission across multiple non-endemic countries. Initially reported in the UK, cases quickly spread across Europe, the Americas, and beyond, often linked to close physical or sexual contact, particularly among men who have sex with men.[19,20] A major outbreak began in the DRC in 2023 and expanded to neighboring nations, prompting the WHO to declare it a global public health emergency in

2024.[21] During 2022–2023, Pakistan also reported 11 confirmed cases.[15] The global mpox situation has escalated in 2024, with nearly 98,000 cases reported in approximately 120 countries.[22]

On 14 August 2024, the WHO re-declared mpox a Public Health Emergency of International Concern (PHEIC) following the emergence of a new Clade Ib lineage in the DRC (Table 1).[23] This decision was driven by the strain's sustained transmission, geographic spread to neighboring countries, and association with increased severity, particularly among children. In contrast to Clade II, which was responsible for the 2022–2023 global outbreak and is typically associated with milder disease and lower mortality, Clade I infections have historically carried higher fatality rates and more complications. While both clades remain susceptible to antivirals such as tecovirimat, resistance mutations have been more frequently reported in Clade I, underscoring the importance of ongoing surveillance and regulatory oversight. This background highlights the rationale for the WHO's 2024 PHEIC decision and provides critical context for global public health preparedness.

Treatment and Prevention

Clinical management of mpox is best guided by a risk-stratified framework that balances disease severity, patient vulnerability, and resource allocation. Antiviral therapy, particularly tecovirimat, should be prioritized for those at highest risk of complications. These include patients with severe or progressive disease, immunocompromised individuals, pregnant or breastfeeding persons, infants, and those with ocular, neurologic, or extensive mucocutaneous involvement.[24] In contrast, otherwise healthy patients with mild, self-limited illness are generally managed safely with supportive care alone, including analgesia, hydration, and treatment of secondary bacterial infections.[25] This approach preserves limited antiviral resources for populations most likely to benefit.

Antiviral resistance is an emerging concern. Resistance to tecovirimat is most often associated with mutations in the VP37 gene, which encodes its target protein. Such mutations have been documented in vitro and, in a small number of clinical cases, linked to reduced treatment effectiveness.[26] While resistance and treatment failures remain uncommon, these cases underscore the need for close clinical monitoring, particularly in patients with persistent or progressive disease. Genomic sequencing should be performed where feasible to detect resistance-associated mutations.[27] To mitigate resistance risk, antivirals should be reserved for clear clinical indications, adherence should be supported, and therapy should be combined with comprehensive supportive care. Ongoing surveillance and systematic reporting of resistance patterns are essential to guide stewardship.

Regulatory approvals for orthopoxvirus countermeasures add complexity to clinical decisions. For prevention, JYNNEOS (MVA-BN) is licensed in the United States for both smallpox and mpox, while ACAM2000 remains limited to smallpox, with safety concerns

restricting its use in certain populations.[28] Equity and access remain major challenges in the global mpox response. While vaccines and antivirals are more readily available in high-income countries, endemic regions in Central and West Africa continue to face critical shortages. Addressing these disparities requires coordinated international mechanisms to link surplus stockpiles from high-income settings with Africa CDC procurement and distribution channels, ensuring that countermeasures reach populations at highest risk.

Regulatory pathways for tecovirimat differ across regions and require clear delineation between prevention and treatment indications. At present, tecovirimat is not approved for prophylactic use in any jurisdiction; its regulatory authorizations apply exclusively to treatment. In the United States, the FDA has approved tecovirimat solely for the treatment of smallpox, while access for mpox is limited to the Expanded Access Investigational New Drug (EA-IND) protocol.[29] By contrast, the European Medicines Agency has authorized tecovirimat specifically for mpox, while in Japan the drug has recently been approved for orthopoxvirus infections more broadly.[30,31] Real-world outcomes reported through the U.S. EA-IND program have yielded mixed observational evidence, reflecting both the practical need to deploy therapy during outbreaks and the inherent limitations of non-randomized data.[32] These findings underscore the importance of ongoing randomized controlled trials, which remain critical to defining the magnitude and consistency of treatment benefit in mpox.

The clinical algorithms for managing mpox exposure and symptoms are shown in Figure 1. If there are no symptoms, vaccination with JYNNEOS is recommended within 4 days of exposure, may reduce severity if given up to 14 days post-exposure, and is considered on a case-by-case basis thereafter; infants under 6 months may receive VIGIV after public health consultation. If symptoms are present, patients should be evaluated for mpox, with severe cases,

such as those involving ocular, central nervous system, or airway involvement, severe pain, or rapid progression, referred for hospitalization and treated with tecovirimat, escalating to brincidofovir or cidofovir ± vaccinia immune globulin intravenous (VIGIV) if necessary. For mild cases, treatment is guided by risk factors including immunosuppression, pregnancy, infancy, or significant skin disease: high-risk patients may receive antivirals alongside supportive care, while others typically require supportive care alone. Worsening symptoms should prompt reevaluation, and stable patients should remain in home isolation until all lesions are fully healed.

158 **Concerning Pregnancy**

159 Mpox can cross the placenta and may lead to adverse outcomes in up to 50% of cases.[33]
160 Data from Clade I infections indicate a high risk of miscarriage, intrauterine fetal demise, and
161 vertical transmission. For example, among eight pregnancies reported in the DRC between 2023
162 and 2024, four resulted in fetal loss.[34] Historical cases have also documented in utero infection,
163 including severe fetal complications such as hydrops fetalis and widespread fetal skin lesions.[35]
164 Among 222 symptomatic patients hospitalized with Mpox in the DRC between 2007 and 2011,
165 four were pregnant; three of these women experienced stillbirths.[36] While Clade II infections may
166 be associated with less severe pregnancy outcomes, data remain limited. In one 2022 outbreak
167 report involving 10 cases, no vertical transmission was identified. However, another report
168 described three pregnancy losses among nine cases, along with two liveborn infants who
169 developed rashes and tested positive for Mpox shortly after birth.[37]

170 Pregnant or lactating individuals diagnosed with or exposed to mpox should be managed
171 in consultation with an infectious diseases specialist whenever feasible. Clinical decision-making
172 should account for the specific risks to the pregnant person, fetus, and newborn. Clinical
173 manifestations of mpox in pregnant individuals are generally similar to those observed in non-
174 pregnant populations. Although mpox was historically thought to cause more severe disease during
175 pregnancy, recent evidence from the global outbreak beginning in May 2022 involving Clade II
176 virus does not support increased disease severity in this group.[38] However, adverse fetal outcomes
177 have primarily occurred during the first or early second trimester, indicating a period of heightened
178 vulnerability in early gestation.[22]

179 Vaccination is a critical component in the prevention and post-exposure management of
180 mpox during pregnancy and the postpartum period.[39] Pregnant individuals with significant

exposure should be evaluated for post-exposure prophylaxis with the Modified Vaccinia Ankara vaccine, such as JYNNEOS, when indicated.[28] Although mpox-specific vaccines are not currently FDA-approved for use in pregnancy, animal studies and limited human data, including findings from a study involving 300 pregnant women, suggest a favorable safety profile.[40] JYNNEOS is also considered safe during lactation due to its non-replicating nature. LC16 is another vaccine option with minimal replication potential.[41] Conversely, ACAM2000 has recently been authorized for use against mpox in high-risk individuals; however, it is a live, replication-competent Vaccinia virus with contraindications in immunocompromised persons and carries risks of myocarditis and other adverse effects.[42] It should also be avoided in pregnant and breastfeeding individuals due to insufficient safety data.[43]

Antiviral treatment protocols for mpox in pregnant individuals align closely with those for the general population, with modifications for fetal monitoring.[44] The U.S. CDC recommends tecovirimat as the first-line antiviral for use during pregnancy and lactation.[45] In the setting of acute maternal infection, fetal surveillance through nonstress testing or biophysical profiles is advised, particularly if findings could alter clinical management. Additionally, serial ultrasound monitoring until delivery may be prudent due to the limited understanding of mpox's effects on fetal development.[46]

Obstetric care should proceed according to standard guidelines, although cesarean delivery may be considered when genital lesions are present to reduce the risk of intrapartum transmission.[47] The efficacy of cesarean section in preventing neonatal infection remains uncertain due to the possibility of antepartum transmission. Postnatally, infection control measures should include isolating uninfected neonates from infected parents and other newborns until the parent is no longer infectious. Infected individuals should refrain from breastfeeding unless no safe

alternative is available, as the risk of transmission via breast milk or close contact is not fully understood. The WHO recommends isolating neonates from infected mothers until full maternal recovery, confirmed by two negative polymerase chain reaction (PCR) tests.[48] Lesion swabs are the preferred specimens for mpox diagnosis, with PCR targeting conserved regions such as F3L and G2R remaining the gold standard. Clade or lineage testing is mainly useful for surveillance and atypical cases. Commercial assays, including the Alinity m MPXV, are authorized but may be affected by clade diversity, highlighting the need for ongoing validation.[49]

Preventive strategies for mpox in pregnant individuals generally mirror those for non-pregnant populations but require additional consideration. Smallpox vaccines, which confer approximately 85% protection against mpox, may be considered in this population despite limited pregnancy-specific data. Prophylaxis with non-replicating or minimally replicating vaccines such as JYNNEOS and LC16 is preferred.[50] Ongoing research is needed to better characterize vaccine safety, antiviral efficacy, and optimal management strategies in pregnant and postpartum individuals affected by mpox.

Challenges for Pakistan's Healthcare System

In Pakistan, the healthcare system is already overwhelmed by existing dengue and malaria outbreaks, with an estimated direct cost of PKR 35,823 (US$358) per case.[51] Additionally, in 2022, malaria cases surged to 3.4 million, further complicated by historic floods that caused over $15 billion in damages.[52] These compounded health crises have significantly strained the healthcare system, making it highly vulnerable to the additional burden of an Mpox outbreak.[53] With healthcare expenditure in Pakistan at just 2.95% of GDP, significantly below the WHO recommended threshold of 5% for low-income countries, the country's health infrastructure is critically underfunded.[54] The shortage of healthcare professionals is stark, with only one doctor per 1,300 people, and even fewer nurses and paramedical staff.[55] Pakistan faces significant challenges in dealing with Mpox outbreaks due to insufficient healthcare infrastructure. These challenges include inadequate resources: a lack of separate healthcare beds for infectious patients, and limited access to necessary medical supplies such as personal protective equipment (PPE), vaccines, and antiviral medications. An Mpox outbreak in such a context could overwhelm the already underfunded and overburdened health sector.

Mitigating the potential economic and health impacts of an Mpox outbreak requires several strategies. First, there is an urgent need for robust preventive measures, including widespread health education to raise awareness about the disease and its transmission. Vaccination programs, particularly with proven vaccines like JYNNEOS, should be expanded and made accessible to vulnerable populations. Second, international collaboration is crucial. Pakistan will require significant financial support and resources from the global community to bolster its healthcare infrastructure.[56] This includes improving access to essential medical supplies, such as PPE and

241 medication. Ultimately, establishing a global surveillance system is crucial for monitoring
242 emerging infectious diseases, such as Mpox.

243

Conclusion

Mpox has transitioned from a regional zoonotic disease to a global health concern, driven by changes in transmission patterns, waning immunity, and increased human-to-human spread. The resurgence of Clade I and the global spread of Clade IIb highlight the virus's evolving threat. Pregnant individuals face risks, requiring tailored prevention and care. In countries like Pakistan, where healthcare systems are already overburdened, an Mpox outbreak could be especially damaging. Strengthening surveillance, expanding vaccine access, improving public awareness, and fostering international support are critical to controlling current outbreaks and preventing future ones.

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437 Table 1. Key Characteristics of Mpox Clades and Rationale for WHO PHEIC

Feature	Clade I (Central Africa)	Clade II (West Africa)	Notes / WHO 2024 PHEIC Context
Lineages	Clade Ia, Clade Ib (emergent in 2024, DRC)	Clade IIa, Clade IIb	Clade Ib prompted the re-declaration
Epidemiology	Historically endemic in Central Africa; higher transmission potential	Responsible for 2022–2023 global outbreak; more urban spread	Clade Ib spread across DRC and neighboring countries
Clinical Severity	Higher case fatality rate (up to 10%), more complications	Lower case fatality (<1% in 2022 outbreak); milder disease course	Pediatric cases disproportionately affected in 2024 outbreak
Antiviral Response	Susceptible to tecovirimat, but resistance mutations documented	Susceptible to tecovirimat; fewer resistance cases reported	Reinforced need for monitoring under EA-IND and EU approvals
WHO Decision (2024)	Declared PHEIC on 14 August 2024due to Clade Ib's severity and cross-border spread	—	Emphasized urgency for global coordination, vaccine access, and equity

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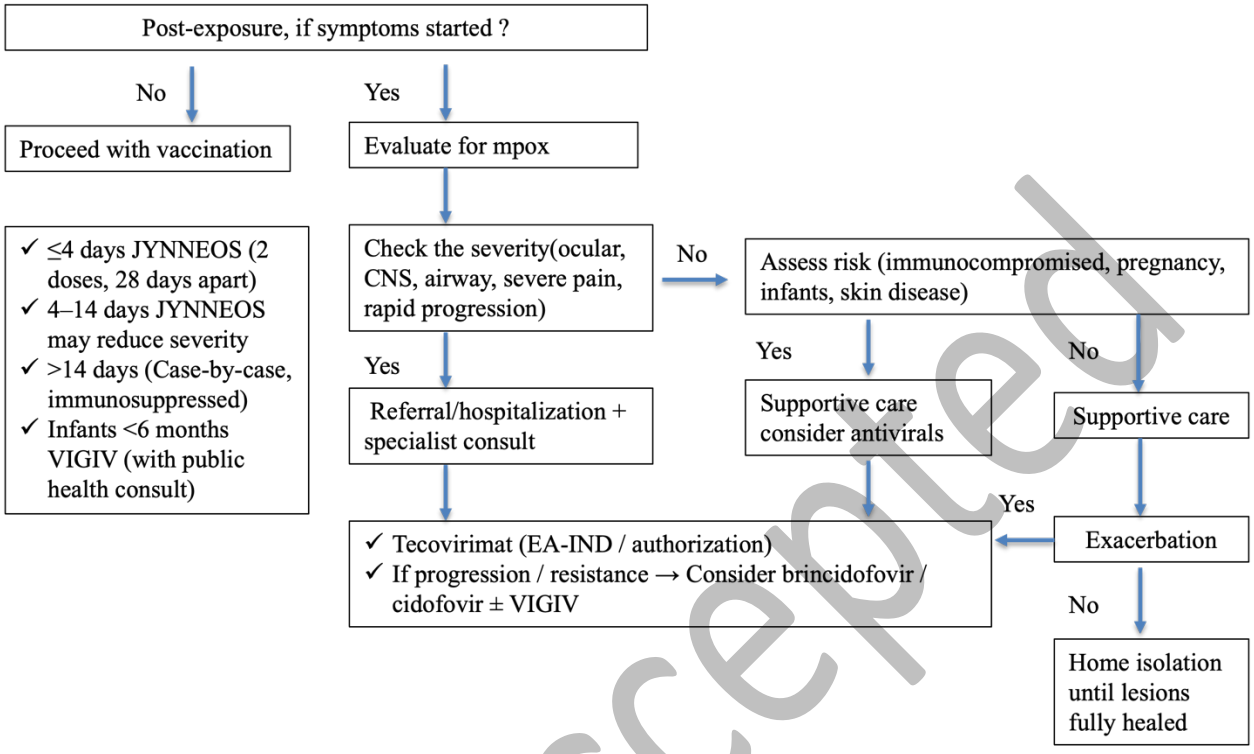
439 Figure 1: Clinical Algorithms Following Mpox Exposure



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441 CNS: central nervous system; EA-IND: expanded access – investigational new drug; VIGIV:

442 vaccinia immune globulin intravenous