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**COMMENTARY | MONKEYPOX**

# Monkeypox in Pregnancy: Susceptibility, Maternal and Fetal Outcomes, and One Health Concept

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## ABSTRACT

An overlooked endemic zoonosis in Africa, monkeypox infection, which has spread to multiple non-endemic countries since early May 2022, was declared a Public Health Emergency of International Concern by the World Health Organization on July 23, 2022. As of August 8, 2022, over 28,000 confirmed and probable monkeypox cases were reported globally, including 6 deaths from the African continent and 4 deaths from the non-endemic regions. Although the current outbreak mostly belongs to the West African clade, which has a lower-case fatality ratio of <1%, there is limited data among immune-weakened individuals infected with monkeypox. It is still unknown if pregnant people are more susceptible to monkeypox. In addition, it is unclear whether having monkeypox increases the risk of birth defects. This commentary addresses reported cases of monkeypox infection in pregnancy and the possible maternal and fetal outcomes, including congenital monkeypox, miscarriage, or stillbirth. Factors behind the escalating global monkeypox outbreak, as well as the prevention and control of monkeypox via the One Health approach, are discussed to shed light on curbing the continuous emergence of monkeypox.

**Keywords**: • Monkeypox • Orthopoxvirus • Pregnancy • Mother-to-Child Transmission • Vertical Transmission • Zoonosis • One Health Concept • Prevention and Control



## 1. Introduction

Monkeypox is a viral zoonosis caused by the Monkeypox virus (MPXV), an orthopoxvirus that causes a disease with clinical presentations that resemble smallpox but is less severe and contagious.[1] Following the eradication of smallpox in 1980 and subsequent cessation of smallpox vaccination, monkeypox remains endemic to Central and Western Africa.[1] For decades, it has been neglected by the rest of the world.[2] Unexpectedly, since May 13, 2022, the monkeypox outbreak has been reported in several non-endemic countries without previously documented monkeypox transmissions, such as Spain, Germany, the United Kingdom, and France.[3] On July 23, 2022, the World Health Organization (WHO) declared the monkeypox outbreak a Public Health Emergency of International Concern (PHEIC) in light of the evolving outbreak with over 16,000 cases from more than 70 countries in 6 WHO regions, most of which are non-endemic and with no clear epidemiological links.[3] The WHO assesses the risk of monkeypox as "high" only in the European region and moderate globally and

in all other regions (the Americas, African, Eastern Mediterranean, and South-East Asia region).[3] However, the U.S. Centers for Disease Control and Prevention (CDC) claimed that cases are probably significantly underreported, and the actual number of cases is likely much higher than the reported totals.[4] In view of the unpredictable monkeypox situation worldwide, a holistic global action plan must be instituted to contain the disease by scaling up national response and surveillance, multisector collaboration, multilevel governance, and participation.

## 2. Epidemiological Trends and Transmission of Human Monkeypox

As of August 8, 2022, over 28,000 confirmed and probable monkeypox cases were reported globally, including 6 deaths from the African continent (5 deaths in Nigeria; 1 death in Ghana) and 4 deaths from the non-endemic regions (Spain – 2 deaths; Brazil – 1 death; and India – 1 death).[5] The recent monkeypox outbreak has raised concern as the majority of the cases were mostly associated with men who have sex with men (MSM) community.[3,6] In fact, the current magnitude of spread and expanded geographical range of monkeypox suggest possible undiscovered modes of transmission sustaining the current outbreak that requires more research to bridge the shortcomings.

Historically, the first human MPXV case was identified in the Democratic Republic of Congo (DRC) in 1970.[2] MPXV consists of two distinct genetic clades, namely the West African clade (WA) and the Central African or Congo Basin (CB) clade.[2] The CB clade is known to have a higher case fatality ratio (CFR) of 11% and is more infectious, contributing up to seven generations of inter-human transmission.[2,7,8] Currently, the ongoing 2022 monkeypox outbreak mostly belong to the less virulent WA clade that is associated with a lower CFR of <1%.[2,3,8] The geographical range of MPXV has increased due to the recent exploitations by animals from Ghana and travelers from Nigeria.[9,10] The first outbreak of MPXV that occurred in the United States (71 cases) in 2003 was associated with infected pet prairie dogs that were housed with Gambian pouched rats and dormice imported from Ghana.[9] In 2017, the largest West African monkeypox outbreak in Nigeria marked the start of the "exportation" of human monkeypox from the African continent to the non-endemic countries.[10] Monkeypox has been reported in travelers from Nigeria to Israel in September 2018, to the United Kingdom in September 2018, December 2019, May 2021, and May 2022, to Singapore in May 2019, and to the United States of America in July and November 2021.[8] Unfortunately, monkeypox has been spreading more widely since early May 2022.[8] Specifically, on May 4, 2022, a traveler who returned from Nigeria was confirmed as the first case in the United Kingdom.[11] Thereafter, other unrelated cases were detected to date in five continents, suggesting that there may have been multiple introductions from Africa.[11]

MPXV can transmit from animal to human (via contact with infected animals or contaminated animal products) and human-to-human (via contact with infected people, contaminated objects, or mother to fetus), resulting from unprotected contact with respiratory droplets, lesions, body fluids, contaminated materials, and surfaces.[8] There is currently no conclusive proof of asymptomatic or long-distance airborne transmission of monkeypox.[12] Certainly, MPXV is more amenable to containment than SARS-CoV-2 due to its transmission via close contact and post-symptom onset. But the unprecedented surge in monkeypox cases implies disease control related to close or intimate physical contact transmission can be difficult.[12] A recent study of 528 cases from 16 countries discovered MPXV DNA in 29 out of 32 seminal fluid samples of individuals infected with MPXV, indicating that the virus may be transmitted sexually.[6] While the recent monkeypox cases have been reported predominantly among the MSM community,[6] being an MSM is not currently a known risk factor for MPXV transmission as close contact involves the direct transmission of bodily fluids not limited to sexual activity alone. Based on the available evidence, close physical contact with

infected persons remains the most significant risk factor for MPXV infection.[1]

## 3. Clinical Features and Disease Severity of Human Monkeypox

The incubation period of monkeypox averages 6 to 13 days but can range from 5 to 21 days.[1] Common presentations of monkeypox are fever, rash, and enlarged lymph nodes.[1] Monkeypox rashes usually manifest as papules, vesicles, or pustules that become firm, deep-seated, and umbilicated over time.[1] Additionally, monkeypox lesions can mimic those in other infections (e.g., chickenpox, measles, or sexually transmitted infections (STIs)) and require proper diagnostic testing to confirm the diagnosis, especially among individuals with epidemiologic risk factors for MPXV infection.[1,12] Monkeypox is typically a self-limited disease with symptoms lasting from 2 to 4 weeks.[8] Most infections during the ongoing outbreak are presented with milder clinical manifestations, which makes it more challenging to detect and stop transmission.[12] While the majority of patients are presented with rash, some cases exhibit fewer clinically apparent lesions.[12] Most recent infections also documented cases without experiencing prodromal symptoms such as fever or lethargy, which sets this outbreak different from the classic MPXV presentation and may delay diagnosis and isolation of those who are infected.[12]

The disease has a CFR ranging from 0 to 11 % among the general population in the monkeypox endemic regions but has been higher among young children.[8] Although the current monkeypox outbreak is mostly associated with the lower CFR WA clade, increased disease severity could occur among individuals with weakened immune systems.[13] The level of viral exposure, health status, and nature of complications are associated with the severity of the disease, which also explains why vulnerable populations, including the elderly, young children, and pregnant women, are more likely to experience more severe disease with complications and poor outcomes.[13] Even though the human-to-human transmission of MPXV is increasing, there is still little understanding of MPXV infection in pregnant women and the possible complications of mother-to-child transmission of MPXV during pregnancy.[14,15,16] Therefore, the knowledge of the MPXV infection during pregnancy is essential to determine the severity and implications of the infection in pregnant women as compared with non-pregnant women, as well as fetal outcomes.

## 4. Monkeypox in Pregnancy: Susceptibility, Maternal and Fetal Outcomes

According to the CDC, until July 2022, data regarding monkeypox infection in pregnancy are still limited.[15] It remains unknown if pregnant people are more susceptible to MPXV or if the infection is more severe in pregnancy.[15] Pregnant women with MPXV infection have similar signs and symptoms to those in non-pregnant individuals.[15] However, during pregnancy, just having a fever alone will be challenging to differentiate monkeypox from other pregnancy-related infections (e.g., chorioamnionitis – the inflammation of the membranes and chorion of the placenta) until the rash appears.[15] Rash in a pregnant woman with risk factors for MPXV infection needs to be distinguished from pregnancy-related dermatoses (e.g., pruritic urticarial papules and plaques of pregnancy), as well as common infections (chickenpox and STIs).[16] Owing to the complexity of differential diagnosis, more data are needed to assess the risk of maternal and perinatal morbidity and mortality resulting from delayed diagnosis and management of pregnant women with monkeypox.

Pregnant women are among the various groups at increased risk for exposure to monkeypox due to the physiological changes in the immune system during pregnancy.[14] MPXV can be transmitted vertically from mother to fetus during pregnancy or to the newborn via close contact during and after delivery.[14] Currently, the frequency and risk factors for severity and adverse pregnancy outcomes are unclear.[15] The literature is still scarce, but there are previous cases reported that MPVX infection in pregnant women has contributed to more complications and adverse pregnancy outcomes, which include high chances of preterm delivery,

spontaneous abortion, and stillbirth.[14,16] Neonatal monkeypox infections have also been reported in cases of confirmed monkeypox during pregnancy.[15] In fact, infections of orthopoxvirus such as smallpox have been known to cause fetal death and are associated with an increased risk of mortality and morbidity in pregnant women as compared to non-pregnant women.[14]

A study with a cohort of 222 symptomatic individuals conducted in the Sankuru Province, DRC, between 2007 and 2011 reported fetal outcomes of four pregnancies with MPVX infection.[17] Of the four pregnancies, two had a first-trimester miscarriage (but in both cases, testing of pregnancy tissue was not performed), one was macerated stillbirth, and only one was an uncomplicated healthy baby.[17] For the case of fetal maceration upon intrauterine fetal death, the woman had a moderately severe MPXV infection at 18 weeks of gestation.[17] The macerated stillborn showed clinical features of monkeypox with diffuse cutaneous maculopapular skin lesions on the head, trunk, and extremities.[17] Virological, histological, and serological evidence suggested that the fetus died due to MPXV infection acquired via vertical transmission.[17] There was also hydrops fetalis, fetal hepatomegaly and peritoneal effusion resulting from induced cellular injury, but no congenital malformation was found.[17]

In another report presented in Zaire, a woman at 24 weeks of gestation with a probable monkeypox case delivered a premature infant.[18] Six weeks later, the infant developed a generalized skin rash that resembles MPXV and died from malnutrition.[18] Therefore, susceptible mothers and their fetuses should be carefully monitored to minimize the possible complications.[17,18] Adequate prevention and control measures are crucial to curb the spread of the disease, especially to vulnerable and high-risk groups.

Unfortunately, monkeypox has been largely neglected for decades, leading to data scarcity related to monkeypox in pregnancy. As the recent spread of monkeypox cases is alarming, effective surveillance played a crucial role in improving the availability and timeliness of data. For instance, amidst the ongoing monkeypox outbreak, the United States identified its first case of monkeypox in a pregnant woman in July 2022.[19] Both the mother and baby are fine. The baby was delivered safely and did not appear to have contracted the MPXV infection from the mother during the pregnancy.[19] The newborn was also given an intravenous infusion of immune globulin (an antibody treatment) authorized by the Food and Drug Administration (FDA) to deploy during monkeypox outbreaks.[19] In view of the inconsistent findings, this requires further investigation to explore the long-term outcomes of the current case.

## 5. Factors Behind the Continuing Emergence of Monkeypox

Factors such as climate change, agricultural activities, wildlife trade, travel, migration, and pathogen evolution, are interconnected to the emergence of MPXV.[20] Ecologic niche modeling (ENM) analysis also found that dense rainforest provides ideal environmental conditions and parameters for MPXV, contributing to its possible geographic range.[21] Multiple social and environmental factors are behind the continuing emergence of MPXV, which include the cessation of smallpox vaccination and factors that increase the frequency of contact between humans and the animal reservoir of MPXV.[22] Following the global eradication of smallpox in 1980, the smallpox immunization program stopped.[22,23] Since the smallpox vaccine confers significant cross-protective immunity (approximately 85% effectiveness) against monkeypox,[23] the halting of the smallpox vaccine may have contributed to the rise in monkeypox cases as people worldwide no longer have immunity to MPXV. Factors that expand humans' reach into animal habitats, such as deforestation, civil unrest, and poverty, have greatly increased their exposure to wild animals.[22] Poverty drives people to seek shelter in the rainforest and to participate in the illegal bushmeat trade and hunting.[22] Extreme weather and climate changes alter the environmental condition, causing wild animals to migrate to the peri-domestic secondary forest and human settlements, expanding the geographic range of some host species.[20,21] Worse still, an initial zoonosis further spreads from human-

to-human via travel and migration, speeding up outbreaks in new places.[20]

## 6. One Health Concept in Infection Prevention and Control (IPC) for Monkeypox

Taking into consideration that most emerging infectious diseases reported globally (especially those declared as PHEIC) are zoonotic diseases, prevention should target breaking the transmission chain both from animal-to-human and human-to-human.[12,24,25,26] Therefore, the collaboration between health and veterinary professionals, along with the environmental or ecological professionals, is crucial in infection prevention and control (IPC) for zoonoses.[27] The cooperation between human, animal, and ecological sectors is called the One Health concept. The goal of One Health is to improve population health by recognizing that human and animal health are interdependent and tied to the ecosystem.[27]

The key principle of One Health is to improve the coordination between public health, veterinary, and environmental services.[27] For example, an application of One Health in monkeypox control is when epidemiologists and veterinarians collaborate in an outbreak investigation, identifying the animal reservoir of monkeypox, and ecologists explore the ecological change or conditions favorable to the emergence of monkeypox. In short, cooperation under one health principle is essential to advance knowledge and capacity in the prevention, detection, and response to emerging diseases.[27]

## 7. Vaccines and Therapeutics

Currently, there is no specific treatment approved for monkeypox virus infection.[28] However, antiviral medications such as tecovirimat (TPOXX), cidofovir (Vistide), and brincidofovir (Tembexa) used for smallpox treatment may help the patient with MPXV infection.[28] Thus, research on therapeutic agents and newer smallpox vaccines should be scaled up to be ready for the current and future re-emergence of MPXV.

Smallpox vaccine is particularly important for pregnant women as MPXV infection in newborns can be reduced by maternally acquired antibodies if the infection occurs before delivery.[29] JYNNEOS and ACAM20000 are the two vaccines against orthopox infection that the FDA has approved.[30] ACAM2000 is a live replicating vaccine approved for smallpox prevention but may be used against monkeypox.[30] ACAM2000 is associated with a higher risk of certain serious adverse reactions compared to JYNNEOS.[30] The only FDA-licensed vaccine in the United States that is approved for the prevention of monkeypox disease is JYNNEOS.[31] It is a subcutaneous, two-dose non-replicating vaccine.[31] Thus, based on available data, JYNNEOS has been demonstrated to be safe for use in immune weakened or compromised individuals.[31]

## 8. Conclusion and Global Health Implications

The WHO has declared a PHEIC six times since the International Health Regulations (IHR) were revised in 2005 following the SARS outbreak: for H1N1 influenza, polio, Zika, COVID-19, and twice for Ebola.[12] Currently, WHO has three active PHEIC globally, namely COVID-19, polio, and monkeypox.[24]

The multi-country outbreak of monkeypox meets all the three criteria defining a PHEIC under the International Health Regulations— (i) being an extraordinary event (since nontravel-related cases have never been identified outside endemic regions of Central or Western Africa), (ii) a public health risk to other States (MPXV has spread to more than 70 countries in 6 WHO regions), and (iii) a potential need to require a coordinated international response (MPXV cases are escalating globally).[24] Declaration of PHEIC further places a significant burden on the healthcare system, leading to health disparities and inequalities.

In conclusion, Monkeypox is a high-threat pathogen that causes significant disease to public health. Therefore, it is crucial to focus on building surveillance capacities that will provide valuable information for designing appropriate prevention,

preparedness, and response activities. Some specific recommendations are noteworthy:

1) Collaboration with researchers from endemic countries with vast experience and data on the disease will ensure that scientific knowledge advances more quickly.
2) Commission expedited studies to better understand the disease epidemiology, its clinical complications during pregnancy, long-term outcomes, possible birth defects and the role of various modes of transmission is essential.
3) Conceptualize a comprehensive One Health approach involving collaboration between public health, veterinary and environmental professionals to better understand animal-to-human transmission, acquiring knowledge and capacity to detect and respond to an emerging disease.
4) Accelerate clinical research into vaccination, therapeutics, and diagnostic tools, especially Artificial Intelligence and improve their effectiveness and comprehend how to apply them in future outbreaks.
5) Implement a coordinated response and holistic public health measures to curb transmission and protect people (especially the vulnerable groups) from the virus.
    a. For instance, enhanced disease surveillance, contact tracing, isolation of cases, strengthening of clinical management and IPC in hospitals and clinics, document control and treatment practices, timely and transparent data transmission, communication of scientific findings, and optimized care of people with the virus.
    b. Communicate prevention information and engage communities in affected areas. Optimize digital health literacy to increase awareness and enable people to understand and manage their health. Introduce awareness-raising programs to healthcare workers and the general population, especially high-risk groups.

## Compliance with Ethical Standards

***Conflicts of Interest:*** *The authors declare no conflict of interest.* ***Financial Disclosure****: None declared.* ***Funding/Support****: None declared.* ***Ethics Approval:*** *This study was based on existing literature.* ***Acknowledgments:*** *None.* ***Disclaimer:*** *None*

### Key Messages

- Over 28,000 cases of monkeypox were reported globally, most of which were from non-endemic countries as of August 8, 2022.
- Limited and inconsistent findings regarding monkeypox infection require further investigation to explore the long-term outcomes.
- Early diagnosis, isolation, effective contact tracing, risk communication, community engagement efforts, and vaccination strategies are key to the effective control of this outbreak.
- The use of the One Health approach multi-disciplinary collaboration will help to address research about monkeypox and preparedness for outbreaks.

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