# Interim Guidance on Monkeypox Exposure for Pregnant People

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**Original:** June 3rd, 2022
**Revised:** June 9th, 2022
**Reaffirmed:** November 2nd, 2022

## Recommendations

1. Smallpox vaccine should be recommended as post-exposure prophylaxis (PEP) to pregnant women who are exposed to monkeypox in accordance with jurisdictional-specific direction on categories of exposures that qualify for PEP.

2. Pregnant individuals with suspected monkeypox should be managed by an interdisciplinary team as there is a paucity of data on monkeypox in pregnancy, but signals of profound morbidity for the pregnancy exist.

## Epidemiology

Monkeypox virus belongs to the *Orthopoxvirus* genus in the family Poxviridae. The *Orthopoxvirus* genus also includes variola virus (causes smallpox), vaccinia virus (used in the smallpox vaccine) and cowpox. Monkeys, rodents and non-human primates can harbour the virus and infect people.[1]

Monkeypox cases in humans have been increasing since its discovery in the 1950s, especially in the Democratic Republic of Congo (DRC), where it is now considered endemic. The age of infection has increased over time from young children to now more predominantly young adults and those of reproductive age.[2] While most cases occur in central Africa, cases outside of Africa have been reported periodically. The last outbreak in North America was reported in several American states in 2003 when community transmission resulted from contact with infected prairie dogs that had been housed with rodents imported from Ghana.[3] This outbreak was effectively contained with extensive education, laboratory testing and use of smallpox vaccines and treatments.[4]

## Natural History

The incubation period of monkeypox is usually 7-14 days, but can range from 5-21 days. The prodromal illness begins with generalized symptoms including fever, headache, myalgias, backache, lymphadenopathy (as a point of distinction from smallpox and varicella which do not cause lymphadenopathy), drenching sweats, chills and fatigue. Within 1-10 days, the patient develops a rash. The rash typically progresses from macules to papules, to vesicles, then to pustules that finally crust. The rash may start on the face and then spread to other parts of the body. In general, the illness lasts 2-4 weeks. The Central African clade can cause death in 1 in 10 persons, but the West African Clade is much less severe. The reported cases in the recent outbreak are of the West African Clade (milder disease).[5, 6]

*The WHO classifies severity of monkeypox based on number of skin lesions:*

- Mild <25 skin lesions
- Moderate 25-99 skin lesions
- Severe 100-250 skin lesions
- Grave >250 skin lesions

**Investigation**

The differential diagnoses for presentations of fever, rash and lymphadenopathy in pregnancy are broad, and include human immunodeficiency virus, syphilis, varicella, cytomegalovirus and parvovirus B19. Given the potential impact of these conditions on the fetus, they must be considered in the initial investigations for a suspected case of monkeypox in pregnancy. In addition, coxsackie virus (the pathogen causing hand, foot and mouth disease) can cause mouth, palmar and plantar vesicular lesions, but does not cause specific maternal/fetal morbidity.

To identify monkeypox, polymerase chain reaction (PCR) testing can be performed on oral secretions or a skin biopsy during the prodromal phase with early macular rash. There are high amounts of virus in the vesicular lesions that can be deroofed and the fluid swabbed for PCR testing during the vesicular phase. Nasopharyngeal swabs can also be sent for PCR and, depending on the clinical presentation, other specimens may be indicated. At present, testing is only occurring at reference laboratories and an epidemiological link to a known case is required for testing. Consultation with local medical microbiology experts is recommended.

**Transmission**

The virus enters the body through broken skin, the respiratory tract or mucous membranes. Animal-to-human transmission can be through a bite, scratch, bush meat preparation, direct contact with a lesion or body fluids or indirect contact with body fluids such as bedding. Human-to-human contact is principally through large droplet transmission (prolonged face-to-face contact is required), as well as, direct contact with a lesion or body fluids or indirect contact with body fluids such as bedding. A more recent epidemiologic analysis from the DRC has raised questions about mode of transmission because, among the cohort studied, it was not clear whether all current cases had contact with an infected person.[7, 8]

There is limited information regarding asymptomatic shedding but the current research indicates viral shedding coincides with the onset of symptoms. Asymptomatic carriage and viral shedding prior to the onset of symptoms has not been reported.[7] Current recommendations from the Public Health Agency of Canada include airborne, droplet and contact precautions to be employed for suspected, probable and confirmed cases of monkeypox.[9]

**Prevention**

Smallpox vaccine has been reported to reduce the risk of monkeypox by 85% among previously vaccinated persons in Africa. Exposed persons should be vaccinated within 4 days of exposure if possible. Vaccination after 4 days, but before 14 days may not prevent infection but may attenuate symptoms.[3, 5]

**Treatment**

There is no proven treatment for monkeypox at present. To control outbreaks, smallpox vaccine, antivirals (e.g., cidofovir and tecovirimat) and vaccinia immune globulin (VIG) can be used.[9] Cidofovir is classified as category C by the FDA because in animal studies embryotoxicity and teratogenicity were noted, including reduced fetal weight and increased incidence of fetal external, soft tissue and skeletal abnormalities. There is no available safety data for tecovirimat in pregnancy. While no studies of the vaccinia immunoglobulin are known, other immunoglobulins have been used extensively in pregnancy and felt to be safe. There are no contraindications to the use of the smallpox vaccine in emergency and exposure situations.

**Monkeypox and pregnancy[3, 5]**

We know that other orthopoxvirus infections, such as variola virus (smallpox) result in worse outcomes in pregnant compared to non-pregnant women (i.e., higher rate of hemorrhagic smallpox that carries a case-fatality rate of 70% for unvaccinated pregnant women). In addition, smallpox infection in pregnancy is associated with spontaneous abortion, stillbirth and preterm delivery. However, it is not known whether this holds true with monkeypox.

There are a limited number of reports from which to inform ourselves about monkeypox in pregnant women. As detailed below, of the 5 cases reported in the formal literature, 1 resulted in a live birth, 2 in miscarriages and 1 stillbirth and 1 neonatal death:

- In the DRC (formerly Zaire), there was a case of a woman who was 24 weeks pregnant when she developed monkeypox (culture-proven) and she delivered a 1,500 g female infant 6 weeks later (at 30 weeks) with a generalized skin rash resembling monkeypox. This infant died of malnutrition at 6 weeks of age.[3]
- A case series by Mbala et al.[5] reported fetal outcomes for four pregnant women in the DRC. These four women were the only pregnant patients among 222 patients symptomatic from monkeypox. Of these four women, by WHO classification, one had mild disease, two had moderate disease and one had severe disease. The *only* live birth was from the woman with mild disease, who was infected in the early 2$^{nd}$ trimester, while the other three patients had either miscarriages (2/4) or fetal demise (1/4). Monkeypox was detected on the fetal tissue of the 18 week fetal demise case along with visible skin lesions on the infant.[5]

If monkeypox is diagnosed in a pregnant patient, a multidisciplinary team including maternal-fetal medicine and infectious diseases or reproductive infectious diseases should be assembled.

**Smallpox vaccine in pregnancy**

There has been an evolution of the smallpox vaccine over time with an attenuation of viral replication potential. The first- and second-generations (e.g., ACAM 2000®) of vaccines are live-attenuated vaccines with replication potential, but the third-generation vaccine (e.g., Imvamune®) uses non-replicating virus which *de facto* cannot cause vaccinia in the recipient.

Importantly, this third-generation vaccine only became licensed in 2019-2020 and therefore most data that we have related to the use of smallpox vaccine in pregnancy is based on first- and second-generation technology that uses a live-attenuated vaccinia virus *with* replicating potential. Badell *et al* conducted a systematic review that included 37 articles dating back into the 19th century.[10] No adverse maternal outcomes were described for those vaccinated. This systematic review focused on three primary outcomes:

- **Spontaneous abortion**: no association was found between the use of the smallpox vaccine and spontaneous abortion even when analysis was restricted to studies considering first trimester exposure (RR 1.03, 95% CI 0.76-1.41)
- **Congenital defects:** no increased risk of congenital anomaly for fetuses exposed to the smallpox vaccine (RR 1.25 95% CI 0.99-1.56). Of five studies restricted to first trimester exposure, four demonstrated no increased risk of congenital anomalies and one demonstrated an increased risk with no specific pattern of congenital anomaly associated with the smallpox vaccination.
- **Fetal vaccinia:** Of the 37 articles, 18 articles included fetal outcomes of 12,201 pregnant women vaccinated against smallpox and no cases of fetal vaccinia were reported. In 19 articles, 21 cases of fetal vaccinia were described between 1809 to present.

The vaccine that is available for use in the current outbreak in Canada is a third-generation vaccine (Imvamune®) that is non-replicating. No clinical trials have been conducted in pregnant individuals, although approximately 300 pregnancies have been reported to the manufacturer with no safety issues identified. Similarly, the available developmental and reproductive toxicity (DART) data has not identified safety issues in animal studies. No data is available to determine whether Imvamune® is excreted in breastmilk, but given that it is non-replicating, it is unlikely. Therefore, there is no biological concern with using this vaccine in pregnancy.

Based on a small number of case reports and our experience with other viruses from the same family in pregnancy (i.e., smallpox), we believe that the risk of monkeypox to the pregnant woman and fetus could be significant. While data specific to the use of Imvamune in pregnancy are limited, the experience of using less-attenuated smallpox vaccines during pregnancy from 1809 to present is reassuring. Further, the rare risk of fetal vaccinia infection is felt to be completely obviated by use of a third-generation live-attenuated, non-replicating vaccine such as Imvamune®. **Hence, the smallpox vaccine should be recommended as post-exposure prophylaxis (PEP) to pregnant women, who are exposed to monkeypox, in accordance with jurisdictional-specific direction on categories of exposures that qualify for PEP.**

**Maternal-to-Child-transmission**

Based on the few cases of monkeypox in pregnancy that have been reported, vertical transmission appears possible. In the five cases reported by Jameison[3] and Mbala,[5] two had supportive evidence of in utero transmission. The rate and gestational age at which it occurs is unclear and the fetal consequences are yet to be delineated. Almost nothing is known about genital tract shedding and perinatal monkeypox transmission.

**Mode of Delivery**

For antenatal monkeypox resolved by the time of delivery, mode of delivery should be determined based on obstetrical factors exclusively. There is no evidence that cesarean delivery will prevent neonatal monkeypox in the context of maternal monkeypox infection. In the context of active isolated genital lesions, cesarean delivery could be considered.

Peripartum Considerations

Infant and newborn monkeybox disease appears to have serious morbidity. Horizontal transmission in the newborn period is of concern. It is advised to engage a multidisciplinary team including infection prevention and control experts, as well as, pediatric infectious diseases specialists to make decisions with respect to co-habitation of a newborn and mother who is actively infected with monkeypox. Where an infant appears uninfected at birth, strong consideration should be given to temporary separation of mother and infant in an attempt to prevent newborn infection. The length of time of separation will depend on individual factors (e.g stage of disease at delivery) and should be decided in consultation with a multidisciplinary team.

**Breastfeeding**

It is unknown whether monkeypox can be transmitted through breast-feeding or breastmilk. With active maternal disease, avoidance of breastfeeding until resolution of symptoms may be considered. Multidisciplinary discussions should guide management of individualized cases.[11]

**Precautions for patient interactions**

For anyone presenting with unexplained fever, rash or prominent lymphadenopathy, monkeypox should be considered on the differential diagnosis, and appropriate contact, droplet and airborne precautions should be used. Testing, treatment and public health notification should be carried out in accordance with jurisdiction-specific protocols.

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