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non-pregnant people, the effects of this clade in pregnancy are unknown.

Here, we propose a clinical management algorithm for pregnant women with suspected monkeypox virus exposure (figure). Clinicians must maintain a high index of suspicion for monkeypox virus in any pregnant woman presenting with lymphadenopathy and vesiculopustular rash—including rash localised to the genital or perianal region—even if there are no apparent epidemiological links. Diagnosis is confirmed by nucleic acid amplification testing with real-time or conventional PCR for monkeypox virus from vesicles or genital lesions; additionally, we advise ruling out varicella, herpes simplex, and syphilis, as these might resemble monkeypox in pregnancy. Fetal ultrasound monitoring is required in cases of maternal monkeypox virus infection, and subsequent management should be based on the presence of ultrasound anomalies such as fetal hepatomegaly or hydrops. Monkeypox can have considerable risks to the fetus, so we also suggest testing asymptomatic pregnant women with significant monkeypox virus exposure to identify those who require fetal ultrasound follow-up. The sensitivity of molecular detection of monkeypox virus in the amniotic fluid is unknown. By analogy with cytomegalovirus, toxoplasmosis, and Zika virus infections, it is likely that monkeypox virus is shed in the amniotic fluid only once the fetal kidneys produce sufficient urine (ie, after 18–21 weeks' gestation).<sup>3</sup> At delivery, we recommend assessing viral load in umbilical cord blood and placenta and real-time PCR analysis of specimens obtained from the neonate.

For treatment, tecovirimat and vaccinia immune globulin can be considered for pregnant women who are severely ill. Tecovirimat is an inhibitor of the orthopoxvirus VP37 envelope wrapping protein. The European Medicines Agency has approved tecovirimat for monkeypox,

and tecovirimat can be used in the USA under an expanded access Investigational New Drug protocol for the empirical treatment of non-variola orthopoxvirus infections, including monkeypox. The US Food and Drug Administration (FDA) prescribing information for tecovirimat confirms that no embryotoxic and teratogenic effects have been detected in animal studies. Furthermore, the US Centers for Disease Control and Prevention<sup>4</sup> permits the emergency use of the live smallpox vaccine ACAM2000, which confers 85% cross-protective immunity against monkeypox, if high-risk exposure to monkeypox virus occurs in pregnancy. Patients must, however, be counselled on the rare risk of fetal vaccinia from ACAM2000, which can result in preterm delivery, stillbirth, neonatal death, and potential adverse maternal reactions. MVA-BN, a third-generation smallpox vaccine recently approved in the USA, Canada, and the EU, is possibly safer because it contains non-replicating virus and has not demonstrated adverse pregnancy outcomes.<sup>5</sup> Finally, we encourage the reporting of all cases of monkeypox virus in pregnancy to WHO and an international registry for emerging pathogens.<sup>6</sup>

These recommendations should be adapted to local guidelines and updated as more information arises.

We declare no competing interests.

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## Monkeypox genomic surveillance will challenge lessons learned from SARS-CoV-2

The emergence of a series of epidemiologically connected monkeypox virus infections around the world, with ongoing human-to-human transmission (as of June 15, 2022, 2103 confirmed cases, one probable case, and one death have been reported to WHO from 42 countries), raises concerns of a long-apprehended comeback of a human-adapted orthopoxvirus related to variola virus, the aetiological agent of smallpox. Since variola virus had no natural reservoir other than humans, the eradication of the virus by use of highly effective vaccines against orthopoxviruses was irreversible.<sup>1</sup> However, other orthopoxviruses have reservoirs in wildlife, such as cowpox virus (in voles), taterapox virus (in African gerbils), and monkeypox virus (in small mammals), do have the potential to spill into the human population and facilitate a restart of the genetic adaptation of the virus to



For WHO's monkeypox outbreak situation update see <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON393>

the human host, which once resulted in variola virus.<sup>2</sup> This adaptation is possible by the unique genomic make up of orthopoxviruses and their ability to jumpstart evolution by use of gene loss,<sup>3</sup> rather than by progressive mutation as seen in SARS-CoV-2.

Within orthopoxviruses, a genetic core of about 120 000 base pairs is highly conserved and thought to code for basic viral functions; however, towards the termini the orthopoxvirus genome is plastic, and large regions can be readily deleted (appendix). These regions contain genes related to host adaptation. Orthopoxviruses like variola virus that have adapted to a specific host species tend to lose many terminal host-restriction genes during adaptation (appendix), allowing them to spread more easily or cause more severe disease. This loss could optimise both the spread (eg, by droplet-related transmission) via enhanced systemic infection and disease severity.

Circulating monkeypox virus might be undergoing adaption for the human host, so we must keep its genetic changes under tight surveillance so as to be prepared when sudden epidemiological changes and prevent the emergence of a variola virus epigone. This surveillance, however, will require a conceptual shift from observing lone single nucleotide polymorphisms, as with SARS-CoV-2 variants, towards watching closely for the integrity and stability of the monkeypox virus genomic termini. Therefore, the constant sequencing of full monkeypox virus genomes is of utmost importance to detect not only single nucleotide polymorphisms but any intragenic frameshifts or premature stop codons, that might indicate initial signals of gene loss. This surveillance, however, requires the highest-quality genomic data and careful annotation. Currently many sequences from the ongoing outbreak are erroneous or do not have annotation, which makes it

difficult to establish useful genomic characterisation.

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## The monkeypox outbreak must amplify hidden voices in the global discourse

Tulio d Oliveira's Comment<sup>1</sup> on the global inattention to infectious disease science done in Africa is timely, as the largest outbreak of monkeypox outside of Africa continues.<sup>2</sup> As of June 15, 2022, 2103 laboratory-confirmed cases of monkeypox have been reported to WHO from 42 countries. The unexpected, unprecedented, and unusual nature of this outbreak in Europe and the Americas has spurred scientific, political, and media attention. Importantly, monkeypox has been known to cause human disease for over 50 years and is endemic in at least ten countries in west and central Africa with over a thousand incidences reported in the Democratic Republic of the Congo in the first 3 months of 2022 alone.<sup>3</sup> Specialists in these countries have decades of experience managing such outbreaks, often with little support, and have repeatedly warned of the potential for monkeypox's globalisation and the need for affordable tools and improved surveillance.

Despite the vast expertise of these specialists, their voices are notably

absent from the current discourse and many have struggled for years to raise awareness, publish their findings, or attract funding to study this disease.<sup>4</sup> As with the COVID-19 pandemic, monkeypox highlights inequities in access to vaccines, diagnostics, and treatments. High-resource nations, WHO, other global stakeholders, and government actors must meaningfully recognise the vast lived experience and repeated warnings of public health specialists in Africa. Equity in the global dialogue on pathogens with epidemic potential requires a priority seat at the table for those who have the most experience, despite them being pushed into the shadows for decades.

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See Online for appendix

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