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## The 2022 monkeypox outbreak: the need for clinical curiosity



In the UK, the 2022 monkeypox outbreak was heralded by an imported case on May 7, 2022, with a typical history and presentation for imported monkeypox, including a widespread vesiculopustular rash and relevant travel history.<sup>1</sup> Shortly afterwards, and perhaps due to public notification and increased awareness following this case, a cluster of cases was identified among gay, bisexual, and other men who have sex with men with no travel history and no epidemiological link to the index case.<sup>1</sup> Since then, more than 60 000 laboratory confirmed cases have been identified in 105 countries and territories.<sup>2</sup>

What is striking about this outbreak, as highlighted in the study by Kristina Angelo and colleagues in *The Lancet Infectious Diseases*,<sup>3</sup> is how the outbreak has confounded what was previously known (or thought to be known) about the epidemiology, transmission, and clinical features of monkeypox. The wide geographical reach Angelo and colleagues' study provides a truly global picture of the current outbreak and increases our understanding of how this outbreak is behaving differently from what was previously assumed of the disease. Historically, monkeypox has been considered for patients presenting with compatible lesions usually in the same stage of development, a febrile prodrome, and history of travel to an endemic country or contact with a diagnosed case. However, in this cross-sectional study, travel was not a risk factor, and a sizeable minority of cases (>40%) had lesions at multiple stages of development: previously this would have been considered relatively unusual for monkeypox and might have prevented diagnostic testing. The authors also found that although patients with HIV were more likely to have a higher rash burden, there was no association between HIV status and severe illness.

This leads to questions about how long monkeypox has been circulating, unrecognised, in its present form, and whether lessons can be learned for identifying other emerging infectious diseases. Patients presenting with unusual or unexplained symptoms are by no means unusual. Very often, such illnesses are self-resolving and aetiological identification, although satisfying, might be clinically unnecessary. However, the 2022

monkeypox outbreak demonstrates that although identifying the cause of a resolving illness might have minimal impact at the individual patient level, it might be of great importance at the population level if the illness is an emerging or evolving infectious disease of public health consequence. Clinicians should remain alert for the unusual, and remain unsatisfied by the unexplained. Without clinical curiosity and heightened awareness resulting in identification of the early native UK clusters, and the initial notification to WHO, the monkeypox outbreak might have gone unrecognised for much longer, both in the UK and globally. Delayed identification risks ongoing public and health-care worker exposure to a disease with significant morbidity, if not mortality.

This outbreak, and early experience from the SARS-CoV-2 pandemic, illustrates why narrow case definitions and restricted access to testing might impede public health responses. For this reason, the UK case definition for a so-called possible case is deliberately broad, allowing clinicians with a reasonable suspicion of monkeypox to refer patients for testing.<sup>4</sup> However, offering such broad testing has only been possible with rapid upscaling of laboratory testing capacity, with an increase in throughput from 1–2 samples monthly to more than 1500 samples weekly. This increased capacity has allowed comprehensive testing and instils confidence that the reported epidemiology is a true reflection of the epidemic with minimal ascertainment bias.

A similarly broad approach was needed during the last large outbreak of monkeypox in a non-endemic country. In the 2003 US outbreak, the suspicion of monkeypox was raised when lesions from patients with no epidemiological risk factors, and negative on tests for conventional infectious aetiologies were investigated by electron microscopy, a relatively non-specific diagnostic method. Identification of pox-like viruses on lesion tissue resulted in comprehensive public health investigations, which ultimately identified the connection between human cases and imported exotic animals housed in the same animal facility as prairie dogs later sold as pets to most of the human cases.<sup>5</sup>



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It is therefore important that clinicians remain curious when faced with patients with undiagnosed diseases that do not necessarily fit accepted case descriptions. Consideration might need to be given to the possibility of occult importations or atypical transmission events for patients with no relevant epidemiology but whose symptoms fit diseases traditionally considered only in recent travellers. Agnostic testing through metagenomics or evolving serological approaches might provide a route for earlier identification of unusual infections in the future, but at present, we encourage clinicians with puzzling cases to discuss with national experts and reference laboratories, who similarly need to be open minded and, where practically possible, generous in offering testing for unusual illnesses that do not fit rigid case definitions.

We declare no competing interests.

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- 1 UK Health Security Agency. Monkeypox cases confirmed in England—latest updates. <https://www.gov.uk/government/news/monkeypox-cases-confirmed-in-england-latest-updates?UNLID=454048141202210404910> (accessed Oct 4, 2022).
- 2 WHO. Multi-country outbreak of monkeypox, External situation report #6–21 September 2022. <https://www.who.int/publications/m/item/multi-country-outbreak-of-monkeypox--external-situation-report--6---21-september-2022> (accessed Sept 29, 2022).
- 3 Angelo KM, Smith T, Camprubi-Ferrer D, et al. Epidemiological and clinical characteristics of patients with monkeypox in the GeoSentinel Network: a cross-sectional study. *Lancet Infect Dis* 2022; published online Oct 7. [https://doi.org/10.1016/S1473-3099\(22\)00651-X](https://doi.org/10.1016/S1473-3099(22)00651-X).
- 4 UK Health Security Agency. Monkeypox: case definitions. <https://www.gov.uk/guidance/monkeypox-case-definitions> (accessed Sept 22, 2022).
- 5 Melski J, Reed K, Stratman E, et al. Multistate outbreak of monkeypox—Illinois, Indiana, and Wisconsin, 2003. *MMWR Morb Mortal Wkly Rep* 2003; 52: 537–40.