

Dear Editor,

We believe our manuscript “Early underdetected dissemination across countries followed by extensive local transmission propelled the 2022 mpox epidemic” is an excellent candidate for publication in *Cell* due to the journal’s sustained commitment to publishing impactful research on epidemic preparedness, mpox, and phylodynamics.

In 2022, mpox (previously known as monkeypox) evaded early detection and sparked a public health emergency of international concern, resulting in over more than 88,000 recorded cases worldwide in already marginalized and vulnerable communities. While cases after summer 2022 have declined, mpox outbreaks continue to be reported worldwide. Due to social stigmas around case reporting and sub-clinical disease manifestation, surveillance data alone can only provide limited insights into mpox transmission dynamics. Understanding how mpox spread across the world and which interventions were effective at curbing transmission is critical to prevent recurring mpox epidemic waves and to anticipate infectious diseases threats. In the present manuscript, we tackle these pivotal questions through the joint analysis of genomic, mobility and epidemiological data.

Employing phylogeographic and phylodynamic inference models, we characterize mpox spread between five global regions. We find extensive community transmission prior to detection by public health surveillance. Through the development of novel methods to estimate mpox transmission intensity that account for changes in case-detection, we challenge prior estimates of mpox transmission rate and allow for more accurate evaluation of the impact of population-wide interventions. Our analyses show that after initial seeding, viral introductions played a negligible role in prolonging regional epidemics. As such, we estimate that a complete travel ban after initial seeding would have only prevented less than 10% of all cases. Finally, in contrast to widespread belief, we show that the North American epidemic began to decline before even 10% of the population at high risk for mpox in the US had any vaccine-induced immunity, suggesting that behavioral modifications among men who have sex with men, not vaccination campaigns, had a dominant impact in stopping early transmission.

Our work underlines the disappointing performance of global public health surveillance in response to the mpox epidemic. Despite the general advocacy for improved surveillance following the COVID-19 pandemic, we uncover cryptic local transmission and numerous introductions of mpox in the Americas and three European subregions prior to detection of the first mpox case. These conclusions should constitute a warning signal for public health jurisdictions to swiftly build and improve broad pathogen surveillance infrastructures in order to prepare for future outbreaks. Our work shows that rapid pathogen detection and subsequent behavioral change could be sufficient to curb epidemic spread, potentially impacting future global health policy.

Our findings are highly relevant for policymakers and scientists across a wide range of disciplines (including virology, epidemiology, evolutionary biology, and bioinformatics) in promoting broader routine specimen screening as a core tenant of pandemic preparedness. We believe our work to constitute a critical contribution to answering some of the outstanding questions regarding mpox transmission and control that were outlined in *Cell* by Rothenburg et al. [\(1\)](#). This would also greatly contribute to *Cell*’s commitment to understanding global and regional infectious disease spread through new methods in genomic epidemiology [\(such as in references 2–5\)](#).

Given the significance of this work for the global public health and scientific community, and the marginalized populations impacted by mpox, we thank you for your consideration.

Yours sincerely,

Miguel Paredes and Trevor Bedford, on behalf of all authors.

## References

1. Rothenburg S, Yang Z, Beard P, Sawyer SL, Titanji B, Gonsalves G, et al. Monkeypox emergency: Urgent questions and perspectives. Cell. 2022 Sep 1;185(18):3279–81.
2. Tegally H, Wilkinson E, Tsui JLH, Moir M, Martin D, Brito AF, et al. Dispersal patterns and influence of air travel during the global expansion of SARS-CoV-2 variants of concern. Cell. 2023 Jul 20;186(15):3277-3290.e16.
3. Siddle KJ, Krasilnikova LA, Moreno GK, Schaffner SF, Vostok J, Fitzgerald NA, et al. Transmission from vaccinated individuals in a large SARS-CoV-2 Delta variant outbreak. Cell. 2022 Feb 3;185(3):485-492.e10.
4. Fauver JR, Petrone ME, Hodcroft EB, Shioda K, Ehrlich HY, Watts AG, et al. Coast-to-Coast Spread of SARS-CoV-2 during the Early Epidemic in the United States. Cell. 2020 May 28;181(5):990-996.e5.
5. Grubaugh ND, Saraf S, Gangavarapu K, Watts A, Tan AL, Oidtman RJ, et al. Travel Surveillance and Genomics Uncover a Hidden Zika Outbreak during the Waning Epidemic. Cell. 2019 Aug 22;178(5):1057-1071.e11.