Elsevier has created a Monkeypox Information Center in response to the declared public health emergency of international concern, with free information in English on the monkeypox virus. The Monkeypox Information Center is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its monkeypox related research that is available on the Monkeypox Information Center - including this research content - immediately available in publicly funded repositories, with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the Monkeypox Information Center remains active.

purposes of the present study, for which we thank them. We thank the nursing and laboratory staff for their crucial contributions in collecting and processing samples. This work was supported by the Italian Ministry of Health (Ricerca Corrente—line 1 and 2) and the European Commission Horizon 2020 (European-Virus-Archive-GLOBAL—871029). The INMI Monkeypox Study Group includes Isabella Abbate, Alessandro Agresta, Alessandra Amendola, Andrea Antinori, Francesco Baldini, Tommaso Ascoli Bartoli, Alessia Beccacece, Rita Bellagamba, Giulia Berno, Aurora Bettini, Nazario Bevilacqua, Licia Bordi, Marta Camici, Fabrizio Carletti, Angela Corpolongo, Stefania Cicalini, Francesca Colavita, Alessandra D'Abramo, Gabriella De Carli, Federico De Zottis, Lavinia Fabeni, Francesca Faraglia, Federica Forbici, Concetta Maria Fusco, Roberta Gagliardini, Anna Rosa Garbuglia, Saba Gebremeskel, Maria Letizia Giancola, Emanuela Giombini, Enrico Girardi, Giulia Gramigna, Elisabetta Grilli, Susanna Grisetti, Cesare Ernesto Maria Gruber, Eleonora Lalle, Simone Lanini, Daniele Lapa, Gaetano Maffongelli, Fabrizio Maggi, Alessandra Marani, Andrea Mariano, Ilaria Mastrorosa, Giulia Matusali, Silvia Meschi, Valentina Mazzotta, Claudia Minosse, Klizia Mizzoni, Martina Moccione, Annalisa Mondi, Vanessa Mondillo, Nicoletta Orchi, Sandrine Ottou, Carmela Pinnetti, Silvia Pittalis, Vincenzo Puro, Silvia Rosati, Gabriella Rozera, Martina Rueca, Laura Scorzolini, Eliana Specchiarello, Francesco Vaia, Francesco Vairo, Beatrice Valli, Alessandra Vergori, and Serena Vita.

*Daniele Lapa, Fabrizio Carletti, Valentina Mazzotta, Giulia Matusali, Carmela Pinnetti, Silvia Meschi, Roberta Gagliardini, *Francesca Colavita, Annalisa Mondi, Claudia Minosse, Laura Scorzolini, Stefania Cicalini, Gaetano Maffongelli, Eliana Specchiarello, Marta Camici, Aurora Bettini, Francesco Baldini, Massimo Francalancia, Klizia Mizzoni, Anna Rosa Garbuglia, Emanuele Nicastri, Enrico Girardi, Andrea Antinori, Francesco Vaia, Fabrizio Maggi, on behalf of the INMI Monkeypox Study Group*

francesca.colavita@inmi.it

Laboratory of Virology (DL, FCa, GMat, SM, FCo, CM, ES, AB, MF, KM, ARG, FM), Clinical and Research Department (VM, CP, RG, AM, LS, SC, GMaf, MC, FB, EN, AA), Scientific Direction (EG), and General Direction (FV), National Institute for Infectious Diseases 'Lazzaro Spallanzani' (IRCCS), Rome, Italy

1 Bunge EM, Hoet B, Chen L, et al. The changing epidemiology of human monkeypox-A potential threat? A systematic review. *PLoS Negl Trop Dis* 2022; **16:** e0010141.

2 Vaughan A, Aarons E, Astbury J, et al. Two cases of monkeypox imported to the United Kingdom, September 2018. *Euro Surveill* 2018; **23:** 1800509.

3 Reed KD, Melski JW, Graham MB, et al. The detection of monkeypox in humans in the western hemisphere. *N Engl J Med* 2004; **350:** 342–50.

4 WHO. 2022 monkeypox outbreak: global trends. July 28, 2022. https://worldhealthorg.shinyapps.io/mpx_global/ (accessed July 28, 2022).

5 European Centre for Disease Prevention and Control. Risk assessment: monkeypox multi-country outbreak. May 23, 2022. https://www.ecdc.europa.eu/en/publications-data/risk-assessment-monkeypox-multi-country-outbreak (accessed July 22, 2022)

6 Heskin J, Belfield A, Milne C, et al. Transmission of monkeypox virus through sexual contact—a novel route of infection. *J Infect* 2022; published online June 1. https://doi.org/10.1016/j.jinf.2022.05.028.

7 Antinori A, Mazzotta V, Vita S, et al. Epidemiological, clinical and virological characteristics of four cases of monkeypox support transmission through sexual contact, Italy, May 2022. *Euro Surveill* 2022; **27:** 2200421.

8 Noe S, Zange S, Seilmaier M, et al. Clinical and virological features of first human monkeypox cases in Germany. *Infection* 2022; published online July 11. https://doi.org/10.1007/s15010-022-01874-z.

9 Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox virus infection in humans across 16 countries—April–June 2022. *N Engl J Med* 2022; published online July 21. https://doi.org/ 10.1056/NEJMoa2207323.

10 Le Tortorec A, Matusali G, Mahé D, et al. From ancient to emerging infections: the odyssey of viruses in the male genital tract. *Physiol Rev* 2020; **100:** 1349–414.

Monkeypox: how will we know if the treatments work?

Published **Online** August 2, 2022 https://doi.org/10.1016/S1473-3099(22)00514-X

See **Online** for appendix

Clinical trials of treatments are a priority for emerging infectious disease outbreaks. When we design trials, fit-for-purpose endpoints are crucial, as these will inform decisions on case management, regulatory approval, and priority for public health funding and interventions.

Monkeypox highlights the difficulties in designing primary endpoints for emerging diseases. Globally, we have a limited understanding of what typical monkeypox is—the common and most severe symptoms, the symptoms that cause most distress to patients, the duration of infectivity, and potential complications. Furthermore, patterns of disease might vary, both between individuals and between different clades of virus. Descriptions of clade I disease emphasise disseminated rash and describe a mortality of around 10%.[1] Experience of clade IIb or III disease outside Africa suggests a predominance of genitourinary and perianal lesions,[2] with new complications (such as proctitis),[2] and there have been no deaths caused by these clades in the current outbreak. Although case ascertainment bias cannot be excluded, causes for milder disease need to be established and might be linked to the way the virus is being transmitted. Our primary motivations for treating monkeypox vary depending on severity and risk of transmission and, therefore, might shift focus between symptom relief, preventing complications, shortening the duration of patient isolation, or preventing spread of disease.

Our understanding of a disease grows with the number of cases and, in the field of emerging infections, by use of standardised clinical characterisation and biological sampling protocols.[3] However, waiting for optimal clinical understanding before starting a trial is impractical—many outbreaks are short-lived (especially when working within the geographical borders of regulatory agencies) and we perpetually risk being too late, with the outbreak being declared over before the trial recruits.[4]

The challenging work to find primary outcomes that reflect the diversity of disease and meet the needs of patients, regulators, and public health officials is underway. It is uncertain whether one primary outcome will be feasible across trials to facilitate data sharing and synthesis through meta-analysis, or whether a range of trials with different outcomes might better meet these needs.

There are various proposed outcomes being considered for clinical trials evaluating treatment safety and efficacy for monkeypox (appendix p 1). The PALM 007 randomised controlled trial of tecovirimat in the Democratic Republic of the Congo will use time to monkeypox lesion resolution as its primary outcome. This outcome was determined by analysis of several years' worth of clinical data from patients in the Democratic Republic of the Congo with clade I disease[5] and is appropriate for that context, but might be difficult to extrapolate to emerging disease phenotypes. In terms of pharmaceutical action, resolution of active (presumed infectious) lesions is a precise measure, but might not be representative for what is increasingly a polymorphic disease with other organ manifestations. Even so, there is no consensus on when a lesion is resolved—for example, whether a scab needs to be merely present, or have fallen off, or whether the underlying skin or mucosa must be fully healed. Complete lesion resolution is a more meaningful outcome for patients, but prolonged lesion presence might represent bacterial superinfection for which an antiviral treatment will not have a direct effect. Lesion assessment is likely to be prone to variation between clinicians reviewing patients.

Time to resolution of viral presence in blood, swab, or throat samples is particularly informative for infection control planning, but there is a paucity of longitudinal biological sampling to inform the use of these. Ordinal scale outcomes for disease severity might be possible, but these might not be precise if most cases are mild. For an affected individual, lesions having healed might be of little consequence if they have symptoms from a persistent ulcer. Some studies include exploratory outcomes to capture this phenomenon, but including resolution of such ulcerating lesions as a primary outcome might be more appropriate in some instances.

The way forward should be two-pronged. There are urgent deliberations at present (including those led by WHO) to focus on what is needed to safely commence recruitment in trials. These require the scientific community to reach a consensus over important definitions that will help to shape future research (such as what constitutes an active lesion, or a severe case, or a complication). Deliberations should harmonise where possible, but also facilitate exploration of the diversity of disease being observed and adapt with our growing understanding. We advocate that these are consolidated in the longer-term using strategies employed for other diseases (such as cutaneous leishmaniasis, which shares with monkeypox the issues of heterogenous skin lesions and definitions of resolution)[6] that do due process to considerations such as patients' preferences for outcomes,[7] and make use of further natural history and biological sampling evidence as it accrues.

All authors are investigators on the MOSAIC cohort study for monkeypox and the Expanded Access Programme of tecovirimat in the Central African Republic. JD is an investigator on the PALM 007 trial.

*Amanda Rojek, Jake Dunning, Piero Olliaro
amanda.rojek@ndm.ox.ac.uk

International Severe Acute Respiratory and Emerging Infections Consortium, Pandemic Sciences Institute, University of Oxford, Oxford OX3 7DQ, UK (AR, JD, PO); Emergency Department, Royal Melbourne Hospital, Melbourne, VIC, Australia (AR); Department of Infectious Diseases, Royal Free London NHS Foundation Trust, London, UK (JD)

1 Bunge EM, Hoet B, Chen L, et al. The changing epidemiology of human monkeypox—a potential threat? A systematic review. *PLoS Negl Trop Dis* 2022; **16:** e0010141.
2 Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox virus infection in humans across 16 countries—April–June 2022. *N Engl J Med* 2022; published online July 21. https://doi.org/10.1111/NEJMoa2207323.
3 Abbas A, Abdukahil SA, Abdulkadir NN, et al. The value of open-source clinical science in pandemic response: lessons from ISARIC. *Lancet Infect Dis* 2021; **21:** 1623–24.
4 Rojek AM, Martin GE, Horby PW. Compassionate drug (mis)use during pandemics: lessons for COVID-19 from 2009. *BMC Med* 2020; **18:** 265.
5 Pittman P, Martin J, Kingebeni P, et al. Clinical characterization of human monkeypox infections in the Democratic Republic of the Congo. *medRxiv* 2022; published online May 29. https://doi.org/10.1101/2022.05.26.22273379 (preprint).
6 Olliaro P, Grogl M, Boni M, et al. Harmonized clinical trial methodologies for localized cutaneous leishmaniasis and potential for extensive network with capacities for clinical evaluation. *PLoS Negl Trop Dis* 2018; **12:** e0006141.
7 Erber AC, Arana B, Ben Salah A, et al. Patients' preferences of cutaneous leishmaniasis treatment outcomes: findings from an international qualitative study. *PLoS Negl Trop Dis* 2020; **14:** e0007996.