Title: Monkeypox: how will we know if the drugs work?

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Monkeypox: how will we know if the drugs work?

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

Monkeypox highlights the difficulties of 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 may vary, both between individuals and between different clades of virus. Descriptions of clade I disease emphasise disseminated rash and describe a mortality around 10%.[1] Experience of clade IIb/III disease outside Africa suggests a predominance of genito-urinary and perianal lesions[2], with new complications (such as proctitis)[2] and there have been no deaths. While 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 missing the boat with an outbreak being declared over before the trial recruits.[4]

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

There are a variety of outcomes currently up for debate (see table 1). The PALM 007 randomized controlled trial of tecovirimat in the Democratic Republic of the Congo (DRC) 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 DRC with clade I disease[5] and is appropriate for that context but may be difficult to extrapolate to emerging disease phenotypes. In terms of pharmaceutical action, resolution of *active* (presumed infectious) lesions is a precise measure but may not be representative for what is increasingly a polymorphic disease with other organ manifestations. Even so, when a lesion is no longer active is not agreed - for example, whether a scab needs to be merely present, or have fallen off, or whether underlying skin/mucosa must be fully healed. Complete lesion resolution is a more meaningful outcome for patients – but prolonged lesion presence may represent bacterial superinfection for which an antiviral will not have a direct effect. Lesion assessment is likely prone to variation between clinicians reviewing patients.

Time to resolution of viral presence in blood or swab or throat samples is particularly informative for infection control planning, but there is a paucity of longitudinal biological sampling to inform use of these. Ordinal scale outcomes for disease severity might be

possible but lack precision if most cases are mild. For an affected individual, the fact that lesions have healed may be of little consequence if they are troubled by a persistent ulcer. Some studies include exploratory outcomes to capture this phenomenon but including resolution of such ulcerating lesions as a primary outcome may 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 safely needed to commence recruitment in trials. These require the scientific community to achieve consensus over important definitions helping to shape future research (such as what constitutes an *active* lesion, or a *severe* case, or a *complication*). These should harmonise where possible, but also facilitate exploration of the diversity of disease being seen 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 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.

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

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Table 1: Options for **primary** outcomes for clinical trials evaluating treatment safety and efficacy for Monkeypox.

Proposed outcome	Possible variations	Best suited to	Pros	Cons
Time to lesion resolution	• Time to resolution of *active* lesions • Time to *complete resolution* of all lesions • Proportion of (*active)* lesions resolved	Typical disease in patients without complications	• 'Time-to' analysis • Patient focused outcome. • Possibly the best clinical proxy of infectiousness	• Fails to capture patients without lesions • Fails to capture other manifestations (e.g. proctitis) • Healing time impacted by bacterial super-infection or surgical intervention • Inter-rater reliability of defining lesion not known. • No agreed definition of an *active* lesion or *completely resolved* lesion • Difficult to assess mucosal and genital lesions
Viral kinetics	• Variation in site – throat, blood, lesion that sample collected • Time to negative sample vs more detailed kinetics • PCR vs viral culture	Inpatients	• 'Time to' analysis • More direct correlation with antiviral effect.	• Difficulty obtaining samples in isolating patients • Pain or inconvenience of sampling for patients • Lack of longitudinal biologic sampling available in literature to inform design • Detection by PCR may not represent detection of live virus
Composite ordinal scale e.g. a) All active lesions resolved b) Active lesions c) Hospitalised with complicated monkeypox d) Death	Many possible	• Severe disease • Diverse disease presentation	• Patient focused outcome • Ordinal scale analysis	• Difficulty with ensuring mutual exclusivity of elements of the scale • No agreed definition on *severe* or *complicated* monkeypox • Fails when there is a narrow spectrum of disease severity
Lesion-based ordinal scale e.g. (a) All lesions completely resolved b) All active lesions resolved c) Active lesions but no new lesions d) New lesions occurring	Many possible	Non-hospitalised patients with low risk of death.	• Patient focused outcome • Ordinal scale analysis	• Fails to capture patients without lesions • Fails to capture other manifestations (e.g. proctitis) • Healing time impacted by bacterial super-infection or surgical intervention • Inter-rater reliability of defining lesion not known. • No agreed definition of an *active* lesion or *completely resolved* lesion • Difficult to assess mucosal and genital lesions