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Evolutionary implications of human transmission of monkeypox: the importance of sequencing multiple lesions

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The international outbreak of monkeypox that was recognised in May, 2022 represents a new transmission route for monkeypox virus. Since it was first recognised as a zoonotic pathogen in the 1970s, this virus has frequently jumped from its rodent reservoir hosts into people, predominantly in the Democratic Republic of the Congo. Such zoonotic events are estimated at several thousand per year, but are characterised by low human-to-human transmission.[1,2] In the Democratic Republic of the Congo, zoonosis is predominantly seen in school-age boys in rural areas, who engage in hunting small game.[3] By contrast, the outbreak that began in Nigeria in 2017 predominantly involved men aged 25–40 years in urban or periurban areas, with no obvious connection to suspected animal reservoirs.[4]

The presentation of monkeypox in the current outbreak is also new. Traditionally, human monkeypox presents as a generalised monomorphic pustular rash, and genital lesions are rare.[5–7] In the current international outbreak, including in Nigeria, an ulcerating genital rash develops in the majority of cases. For clinical presentations outside Africa, the genital rash precedes the generalised pustular rash, which is often minor.[4,8–12] This presentation suggests that the genital area is a site of primary infection, giving rise to a localised rash, which is then sometimes followed by a secondary disseminated infection. Interestingly, reports from Nigeria up to 2020 and the USA in 2003 describe most patients as having monomorphic lesions, whereas in the current outbreak clinicians in the UK anecdotally report predominantly pleiomorphic lesions at different stages of eruption at the same time.

In the current outbreak, monkeypox virus seems to be transmitting via a primary localised rash (appendix). Transmission via primary rash (primary transmission) removes the requirement for the virus to establish a general disseminated infection, and this could facilitate the evolution of variants. Such a transmission route could also facilitate the co-transmission of multiple variants, as primary lesions avoid the bottleneck of secondary dissemination. If monkeypox virus is adapting to human transmission by this novel route, the adaptations should most readily be seen in genomes that are sequenced from primary rash lesions.

Although transmission outside central Africa might be predominantly via primary rash, secondary disseminated rashes are still observed. If multiple genomes are transmitted via the primary rash, then the current situation could involve the co-transmission of two syndromes—a localised or primary monkeypox and a generalised or secondary monkeypox—that have different in-host selection pressures and pose different transmission hazards. Although both syndromes are initially caused by the same virus, primary monkeypox is expected to favour variants that are adapted for primary transmission, whereas generalised monkeypox would favour variants that are capable of disseminated infection.

Importantly, primary transmission chains are likely to be accelerated relative to transmissions via secondary rash. Also, if the current international spread reflects, or facilitates, adaptation for primary transmission, the incidence of disseminated infections might reduce over time. A reduction in disseminated infections would reduce the risk of transmission by fomites or droplets, but might also lead to a higher proportion of unrecognised infections, increasing the difficulty of breaking the transmission chain. Additionally, if primary transmission facilitates variants that are better adapted to this transmission route, we might expect further evolution as adaptation to humans is refined by natural selection. Monitoring by health authorities for the emergence of variants that are adapted for primary transmission is therefore important.

In generalised rashes caused by *Orthopoxvirus* species, each lesion is thought to be clonal.[13,14] As such, a genome sequence taken from a single lesion might not be representative of the population within the patient, although this might not be the case for lesions that represent a primary focus of infection. If viruses closer to the zoonotic parent are more fit for disseminated infection, then we will expect to see more of these parental sequences recovered from secondary rash lesions, and a higher proportion of adaptive mutations in genomes recovered from primary rash lesions. To gain a full understanding of the evolution and adaptation of monkeypox virus in this international

See Online for appendix

outbreak, sequencing genomes from multiple lesions from both the primary and secondary rash of individual patients is of crucial importance. In practical terms, and particularly in the current outbreaks in Europe, this approach could mean sampling genital and perianal lesions in addition to lesions elsewhere on the body. Studies such as the ISARIC–WHO Clinical Characterisation Protocol for Severe Emerging Infections,[15] which was recently adapted for monkeypox, provide opportunities to obtain longitudinal samples from multiple sites and compartments for virus characterisation. Such an approach enables the comparison of longitudinal virology results with respective exposure histories and clinical descriptions of the rash illness, to explore hypotheses about primary and secondary transmission.

We declare no competing interests.

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