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*Uncovering the impact of infection routes on within-host MPXV dynamics: insights from a mathematical modeling study*

The unprecedented mpox outbreak in non-endemic regions during 2022-2023, which has seen a recent resurgence in late 2023-2024, poses a significant public health threat. Despite its global spread, the viral dynamics of mpox infection and the specific characteristics driving these outbreaks remain insufficiently explored. We propose mathematical models to examine the interactions between host immune responses and the virus across three distinct infection routes (intravenous, intradermal, and intrarectal). The models are calibrated using viral load data from macaques infected through each of these three infection routes. Subsequently, we calculate the infectiousness of each infected macaque, finding that the proportion of presymptomatic infectiousness is highest in those infected via sexual contact, followed by skin-to-skin contact. These observations demonstrate that close contact during sexual activity is a significant route of viral transmission, with presymptomatic spread playing a crucial role in the 2022-2023 multi-country outbreak and potentially also in the 2023-2024 multi-source outbreak. Leveraging model predictions and infectiousness data, we assess the impact of antiviral drugs on interventions against mpox infection. The results suggest that early administration of antiviral drugs can reduce peak viral loads, even in individuals with compromised immunity.