

Oropouche virus: critical research priorities for this re-emerging pathogen

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DOAJ: [b92d56f4e0e94891aa9403e5072dcbb6](https://doi.org/10.48107/CMJ.2025.03.005)

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Introduction

Oropouche virus (OROV), is a zoonotic arbovirus whose public health relevance has recently increased. A member of the *Peribunyaviridae* family, genus *Orthobunyaviridae*, it was first identified in 1955 in workers within the Melajo forest of Trinidad. Since then, it has caused periodic outbreaks across Central and South America.^{1,2} Clinical disease results in an acute febrile illness termed "Oropouche Fever", associated with gastrointestinal, musculoskeletal and in a few cases, neurological symptoms that may resemble meningitis or encephalitis.²

The disease burden of OROV was previously unknown, partly due to underreporting with silent transmission across remote populations.³ Moreover, since well-known arboviruses such as Dengue, Chikungunya and Zika shared similar symptoms, misdiagnosis was likely. However, in January 2024, an unprecedented surge in OROV cases was observed across several South American countries with over 10,000 cases identified.^{3,4} Concerningly, was the spread to non-endemic regions such as Cuba, Southern Eastern USA and multiple European countries.^{5,6} This re-emergence of OROV, now underscores the critical need to identify knowledge gaps that can serve as the basis for potential research priorities to strengthen epidemic preparedness.

Understanding the reassortment strain

It is well known that novel strains of viruses can emerge via reassortment of their genetic material. This occurs when two or more related viruses infect the same cell, resulting in the exchange of their gene segments to produce a new lineage. OROV's single stranded RNA genome has this capacity for reassortment with other members of the *Peribunyaviridae* family, producing variants that can have enhanced virulence.⁷ In the recent outbreak, a new reassortment strain, OROV 2015-2024 was identified.⁸ This lineage carried small (S) and large (L) segments of the Iquito virus, a related species, while retaining the medium (M) segment of the parental OROV strain.^{3,8} The result was a highly pathogenic variant with efficient replication capacity, plaque formation and ability to escape previous humoral responses.³ It has been suggested that these features may have contributed to its sustained transmission and expansion to non-endemic area.³ Consequent upon that, it is essential for predictive models based on newly acquired genomic and epidemiological data to be created to assess the reassortment potential and evolving pathogenic

mechanisms within the *Peribunyaviridae* family. This can aid in anticipating when and where new strains may emerge. Moreover, with its increased virulence, genomic analysis of this reassortment strain is needed to identify suitable targets and conserved sequences that can guide vaccine and therapeutic development.

Understanding changes in vector competence

The primary vector responsible for OROV transmission is the *Culicoides parenesis*, a biting midge, that thrives in humid and tropical climates. Spread occurs via a sylvatic cycle involving non-human primates, rodents or sloths and an urban cycle driven by zoonotic spillover to humans.² Part of this knowledge comes from older vector competence studies that evaluated how well a vector transmitted the OROV virus to its host. While *Culicoides* efficiently acquired and transmitted the virus with infectivity rates of > 20%, mosquitoes, specifically *Aedes* and *Culex* species, were inefficient vectors.^{9,10} However, with the recent surge in cases and expansion to non-endemic regions, there are concerns of changes in these vector dynamics. It has been suggested that mutational alterations in the novel viral strain may have enhanced infectivity within *Culicoides* midges or allowed mosquitoes to become highly efficient vectors.^{3,8,10} The latter is based on the theory that this new strain can bypass the mosquito midgut.¹⁰ As a result, there is a need for updated vector competence studies that explores how viral evolution enhances acquisition by the vector. Understanding this will allow for targeted vector control strategies that can either lower the efficiency of a known vector to transmit the virus or limit the spread to new vector species.

Socioeconomic drivers of the re-emergence: the need for social based research

While viral and vector dynamics were crucial drivers of this re-emergence, social factors were also involved. In Brazil, the outbreak epicentre, reports have cited environmental mismanagement due to rapid urbanisation as a precipitating factor.¹¹ Over the last four years, the deforestation rate within the Amazon Basin has more than tripled, with a surge of urban centres in once previously forested areas.¹¹ This has likely led to increased interactions between humans and zoonotic vectors, allowing for enhanced transmission. Additionally, the initial outbreaks occurred in Brazilian states with a lower human development index, which may reflect a combination of reduced health seeking behaviours, limited access to rapid diagnostics and treatment facilities.^{12,13} Together, these deficiencies may have

sustained the spread once established.

To address this, there is a need for social based research that explores two main themes: the impact of urban development on OROV disease epidemiology and community-based interventions to prevent and limit outbreaks. Such research can increase our understanding of the local knowledge and perceptions surrounding vector control, water use practices and health seeking behaviour that can serve as the basis for health education campaigns. Moreover, assessment of variations in attitudes and practices across urban versus rural regions can allow for a useful comparative analysis. By combining such findings with existing epidemiological data, urban planners and public health officials can map out high risk zones for outbreaks and create tailored behavioural interventions based on contextual gaps identified.

Conclusion

The unprecedented surge in OROV has re-established this pathogen as a critical public health threat. It's silent dispersion over the years with sudden re-emergence is a testament to the need to advocate for continuous research that can aid in timely identification and control. Key elements to support this must focus on exploring the virologic, vectorial and human dependent drivers. The prediction of new reassortments with amplified virulence and correlation with disease presentation can aid in our understanding of its evolving pathogenic mechanisms. In addition, the gaps in vector competence studies, once addressed, can refine the aims of entomological surveillance and support targeted vector control strategies. Finally, with rapid expansion of the global population, the future body of research must collate climatic, land use and socio-economic data. This will ultimately aid in creating a comprehensive strategy to balance urban growth with the need to maintain environmental homeostasis and limit further zoonotic spillover.

Ethical approval statement: Not applicable.

Financial disclosure or funding: The author received no funding for this work.

Conflict of interest: The author declares no conflicts of interest.

Informed consent: Not applicable

Author contributions: Dr. Nadine Louis is the sole author of this editorial.

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