

Oropouche fever fatalities and vertical transmission in South America: implications of a potential new mode of transmission

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Oropouche fever, caused by the *Oropouche orthobunyavirus* (OROV), represents a significant yet often overlooked public health issue in South and Central America, particularly in northern Brazil.¹ The virus has been reported in Brazil, Bolivia, Colombia, Cuba, and Peru, totalling 9852 cases as of September 6, 2024, with Brazil accounting for over 80.5% (7931) of those cases (Fig. 1).² Up to September 7, 2024, the Ministry of Health of Brazil has reported 7931 cases of OROV infection, 3230 of them in the Amazonas state (40.72%), 1710 in Rondonia state (21.56%), and 886 in Bahia (11.17%).³ Furthermore, OROV belongs to the Simbu serogroup within the genus *Orthobunyavirus*, the largest genus of RNA viruses with over 170 named viruses across 18 serogroups and 48 species complexes. The Simbu serogroup includes 22 recognised viruses grouped into seven species complexes: Akabane, Manzanilla, Oropouche, Sathuperi, Simbu, Shamonda, and Shuni. Phylogenetic analysis of the S RNA, which encodes the nucleocapsid protein, has identified four major OROV genotypes (I-IV). Genotype I has been reported in Acre, Amazonas, Maranhão, and Pará in Brazil, as well as in French Guiana. Genotype II occurs

in Amapá, Brazil. Genotype III is present in Pará, Brazil, and Panama, while Genotype IV exists in Rondonia, Brazil. Genomic reassortment, where related viruses exchange genetic segments, plays a key role in *orthobunyavirus* biodiversity. Typically, the S and L segments (coding for nucleocapsid protein and RNA polymerase) are inherited together, while the M segment (coding for viral glycoproteins) mutates more easily under selective pressure.⁴

OROV has caused several outbreaks in the region, with clinical manifestations ranging from mild symptoms to rare neurological events closely resembling those of dengue and chikungunya, likely leading to underreporting of OROV infections in Brazil. The introduction of the chikungunya virus in Brazil in 2014 further complicated clinical diagnosis due to symptom similarity with OROV. Oropouche virus can present additional notable symptoms. These include rash, conjunctival injection, diarrhoea, severe abdominal pain, hemorrhagic symptoms, and petechiae. A retrospective study in Amapá from August 2014 to May 2015 noted that 10.24% of febrile patients had neutralising antibodies for OROV, indicating previous exposure.^{5,6} This makes Oropouche fever a neglected tropical disease in Brazil. Diagnostic confusion involving other arboviruses, Brazilian spotted fever, viral hantaviruses, and hepatitis poses ongoing public health challenges.

Transmission reaches its highest levels during the rainy season when the number of insect vectors increases. However, outbreaks can also happen during dry



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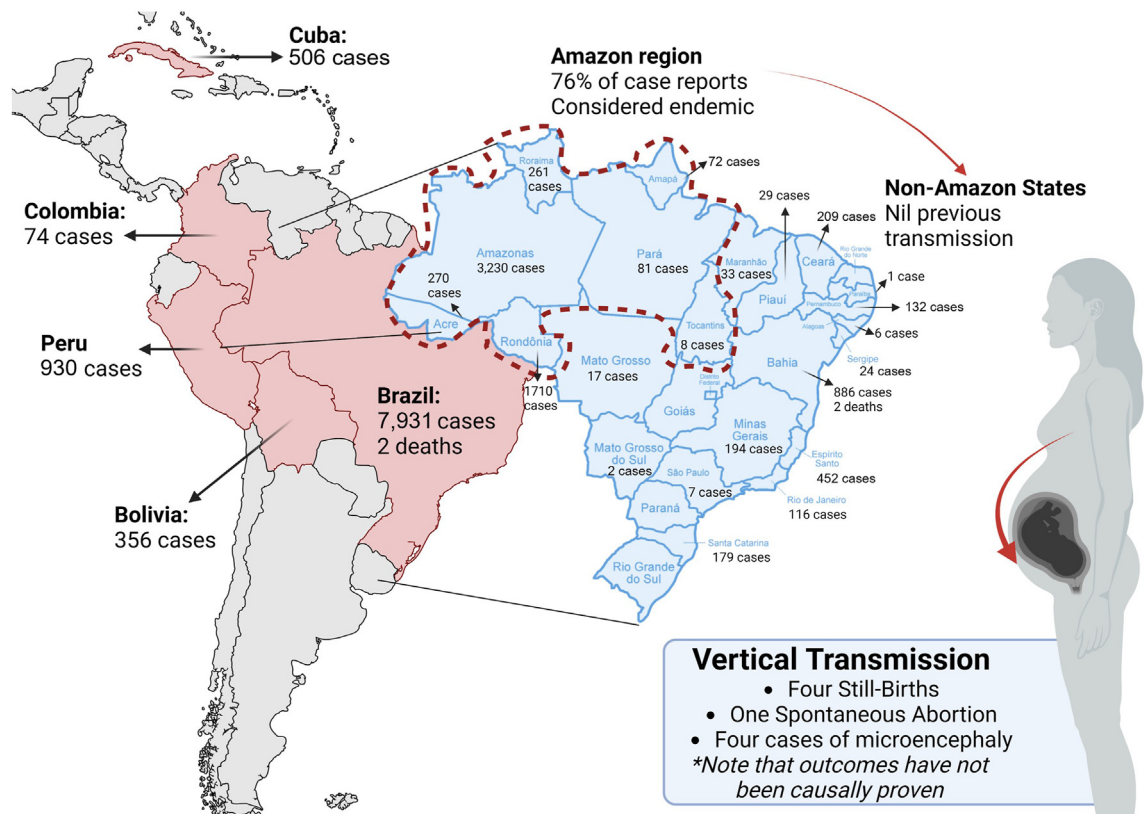


Fig. 1: Oropouche virus in Latin America has led to reported cases, including two deaths in Brazil. Vertical transmission has been observed, with one fetal death, one miscarriage, and four instances of microcephaly in newborns, although no causal link has been confirmed. This remains to be confirmed. Additionally, there are three more fetal deaths in Pernambuco state, with two cases still under investigation. These instances of vertical transmission complicate the understanding of new infection routes, potentially contributing to emerging epidemic patterns, and suggest further research into their implications for maternal and neonatal health.

seasons if the density of vectors stays high. Understanding these patterns of transmission is essential for implementing successful public health interventions. Transmission of OROV by the biting midge *Culicoides paraensis* involves biological transmission to susceptible hosts after feeding on viremic individuals, with infection rates reaching up to 80% and transmission rates 25–83%. OROV assembly and budding occur at Golgi cisternae, attracting the endosomal sorting complex required for transport (ESCRT) proteins necessary for viral morphogenesis and egress. This highlights a unique host cell hijacking mechanism for efficient viral particle production.⁷

The ongoing outbreak includes 10 Brazilian non-Amazonian states where no autochthonous transmission has been reported in 2024. The first two fatal cases linked to OROV infection were also reported from Brazil.⁸ The first case involved a 24-year-old woman from Valença, Bahia, who developed severe symptoms on 23 March 2024, sought medical care multiple times, and died four days later. RT-PCR

confirmed OROV, with other arboviruses testing negative.⁹ The second case was a 21-year-old woman from Camamú, Bahia, who exhibited severe symptoms, including fever, rash, bleeding, and vomiting, and died three days later on 9 May 2024. RT-PCR confirmed OROV in serum samples collected on 10 May 2024, with negative results for other arboviruses (Dengue, Zika, Chikungunya, and Mayaro).⁹

Perhaps the emerging hypothesis of vertical transmission and foetal effects is the most problematic of the current outbreak. The presence of OROV in placenta samples was confirmed in at least one case, and the potential vertical transmission and unfavourable foetal outcomes were recently reported on July 25, 2024, in Brazil.⁹ Additionally, spontaneous abortion was observed in 2 of 9 pregnant women with a serological diagnosis of OROV infection during the second month of gestation in an investigation in the 1980s.^{9–11} More studies are needed, but this question should be promptly addressed and cases in pregnancy managed in a cautionary way. Recent cases in Brazil included one

fetal death and one miscarriage, both in Pernambuco state, as well as four cases of microcephaly in newborns in Acre and Pará states. Additionally, there were three more fetal deaths in Pernambuco state, with two of these cases still under investigation for vertical transmission (Fig. 1). These vertical transmissions add to the complexity of potential new routes of infection, could contribute to the development of new epidemic patterns, and highlight the importance of further research into its implications for maternal and neonatal health.¹²

Case studies from Colombia and French Guiana illustrate the emergence of Oropouche fever in new regions with significant attack rates and a range of symptoms. In French Guiana, an outbreak in Saül in 2020 had an attack rate of 43.2% among residents, with persistent tiredness reported by 73.2% of patients. In Colombia, a study from 2019 to 2022 found OROV to be an emerging cause of acute febrile illness, with 10.9% of cases testing positive for OROV by RT-qPCR.^{13,14}

The nonspecific symptoms of Oropouche fever can be like those of other arbovirus infections, making it difficult to diagnose and predict using clinical models. The disease ranks as the second most prevalent arboviral infection in Brazil, following Dengue, and has a significant capacity for causing epidemics.¹⁵ The absence of targeted antiviral therapies or a vaccine highlights the importance of employing vector control tactics and implementing personal protection measures.¹⁶ The potential for vertical transmission, indicating the silent propagation of the virus within mosquito populations, complicates outbreak control and epidemiological understanding. Increased surveillance and research are essential to determine the actual burden of Oropouche fever and develop effective public health strategies.¹¹

Contributors

RS, SS, RM drafted the first version, SRK, SK, PS, AM contributed with literature review, CF, CL, AJRM reviewed regional and national epidemiological data, JF, and VA developed the figure. All authors contributed with subsequent versions of the manuscript. All authors approved the final version of the manuscript submitted.

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Declaration of interests

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