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# Possibility of Invasion of *Oropouche* Virus (OROV) in Asia: A Real-Time Assessment is an Imperative Necessity

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## ABSTRACT

*Oropouche orthobunyavirus* (OROV), a viral pathogen from the Peribunyaviridae family, is emerging as a public health concern in South and Central America, particularly Brazil and Peru, since its identification in 1955 in South America. The virus is primarily transmitted by the midge *Culicoides paraensis*, though mosquitoes like *Culex quinquefasciatus*, *Aedes aegypti*, and *Aedes albopictus* might have the potential to play roles as complementary and/ or maintenance vectors. OROV has been reported to have infected more than half a million people to date and causes clinical symptoms viz. fever, headache, joint pain, and rash, similar to those of other endemic mosquito-borne diseases, thus presenting diagnostic dilemmas. The detection of OROV in the saliva and urine of infected individuals further highlights its complex transmission dynamics. The reports of sloths and primates serving as reservoir hosts in South America raise a warning bell regarding its potential adaptability to new hosts viz. rodents and bats if it gets introduced to Asia. Furthermore, the increasing global trade and travel threatens to enhance the possibility of the risk of OROV for cross-continental transmission, which has been clearly evidenced by the recent cases reported amongst travellers returning from South America to Europe and the United States. The diagnostic confusion with other endemic mosquito-borne diseases like dengue and chikungunya, complicates its detection and the ensuing control efforts. The eco-climatic similarities between South America and Southeast Asia strengthen the argument of the possible potential threat of OROV establishing in Asia, especially India, where the suspected vector species of OROV might support its transmission. There is, thus, an imperative need for enhancing surveillance and monitoring, strengthening public health preparedness, and undertaking research to alleviate the emerging threat of OROV in Asia.

**Keywords:** OROV, *Culicoides*, Mosquitoes, Surveillance

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## Introduction

*Oropouche orthobunyavirus* (OROV), an overlooked, neglected arbovirus from the Peribunyaviridae family, is gaining recognition as an important public health issue in South and Central America.[1] First identified in 1955 during an outbreak in Trinidad, West Indies, the virus has since led to recurrent epidemics in tropical areas, especially in Brazil and Peru. Over the past six decades, it has infected more than half a million people in documented outbreaks.[2–4] Though the Oropouche virus is primarily transmitted by the biting midge *Culicoides paraensis*, *Culex quinquefasciatus*, *Aedes aegypti* and *Aedes albopictus* species also play significant roles as secondary vectors.[5] The virus is primarily transmitted through urban and sylvatic cycles, with no evidence of direct human-to-human transmission.[6] Recent studies have detected OROV in the saliva and urine of infected patients, confirmed by sequencing, thus expanding the understanding of its transmission and natural history.[7,8] While OROV poses a significant health risk, its relatively low mortality rate and the absence of direct human transmission may lead to an underestimation of its impact, highlighting the need for increased awareness and research efforts. Ecological factors influencing the OROV outbreaks and transmission are not yet fully understood.[9,10] Dias et al. showed in their findings that dogs, horses and cattle sampled in populated cities of West-Central Brazil have been exposed to OROV.[11] This indicates a greater chance of urban transmission of OROV through other sylvatic cycles. In June and July of 2024, the European Union reported 19 cases of OROV fever which have a travel history to Brazil.[12] Furthermore globalisation, intercontinental travelling, etc. are increasing the possibility of the emergence of OROV in tropical zones like Southeast Asia especially India, where climatic and ecological conditions are similar to that of Latin America (the main region of OROV), for instance, other vector-borne viral diseases like Chikungunya, dengue, Japanese encephalitis etc. have been transmitted to Asian countries including India. Although the primary vector of OROV, *Culicoides paraensis*, is not found in India, other species of *Culicoides* are present in the country. Besides that, the secondary potential mosquito vectors of OROV are present in India as well as other Asian countries. Thus, the time has come to evaluate the possibilities of spreading of OROV in India as well as other Asian countries through profound sustained surveillance.

## Vector Ecology and Transmission Potential of OROV in Relation to the Emergence Probability in Asia (Especially India)

The Oropouche virus is primarily transmitted by the biting midge *Culicoides paraensis*, a vector found in tropical climates. The virus can also be carried by mosquitoes and other midge species under the genus *Culicoides*. McGregor et al. demonstrated in their study that *Culex quinquefasciatus* exhibit higher infection rates of 9.71% and 19.3% at 10 and 14 DPI (days post infection), respectively[13] and some potential for dissemination (2.91% and 1.23%) along with low transmission potential (0.97% and 0.82%) whereas *Culicoides sonorensis* has a significantly high infection rate of 86.63% and an impressive dissemination rate of 83.14% with a transmission potential of 19.77% at 14 DPI. De Mendonça et al. evaluated the ability of OROV to infect, replicate, and be transmitted by three anthropophilic and urban species of mosquitoes, *Aedes aegypti*, *Aedes albopictus*, and *Culex quinquefasciatus*.[5] Their study demonstrates that OROV is constrained by the midgut barrier in three primary urban mosquito species. However, if this barrier is bypassed, the virus can be transmitted to vertebrate hosts with high efficiency. This presents a significant threat of establishing persistent urban transmission cycles and facilitating the geographic spread of OROV to other continents. Several species of *Culicoides* midges are widespread in Asia, particularly in rural areas where stagnant water bodies provide breeding grounds,[14,15] with some already implicated in the transmission of other arboviruses like bluetongue virus in livestock.[16] The presence of these midges in India and Southeast Asia increases the likelihood of OROV vectors establishing themselves if the virus is introduced. Similarly, *Culex* mosquitoes, which are abundant in Asia, are known vectors of other diseases like Japanese encephalitis and West Nile virus and have been reported to have the potential to transmit OROV as well.[5,17]

The ecological conditions across India and much of Southeast Asia have warm, humid climates and extensive rice paddies and irrigation systems which create ideal conditions for the breeding of *Culicoides* and *Culex* mosquitoes[18,19] and their proliferation.[20–23] As OROV vectors already thrive in such environments in South America, similar ecological settings in Asia could support the establishment and spread of the virus. Reservoir hosts for the virus include sloths and primates, which sustain the sylvatic cycle of transmission. However, humans participate in an urban transmission cycle, which becomes particularly dangerous during outbreaks in densely populated areas.

## Zoonotic Potential and Reservoir Hosts

OROV has zoonotic potential, meaning it can cycle between animals and humans.[24] In South America, sloths and primates act as reservoir hosts for the virus.[25] While these animals are not native to Asia, several mammalian species, including rodents, bats, and monkeys, could potentially serve as new reservoirs for the virus if introduced. As discussed before, Dias et al. showed in their findings that dogs, horses and cattle sampled in populated cities of West-Central Brazil have been exposed to OROV.[11] Thus the adaptability of OROV to different hosts and vectors raises concerns that the virus could establish new sylvatic cycles in Asia, creating long-term reservoirs of infection that would be difficult to control.

## Globalisation and Cross-Continental Transmission

Increasing numbers of tourists and workers moving between South America and Asia raise the risk of OROV being imported. Travel-associated outbreaks are becoming a recognised pattern for arboviruses, for example, dengue, chikungunya and Zika etc. were transmitted to Asia through travellers and now have become a threat to public health.[26] OROV has been reported recently from other continents too. As of August 16, 2024, a total of 21 *Oropouche* virus disease cases among US travellers returning from Cuba have been reported.[27] In June and July of 2024, the European Union reported 19 cases of *Oropouche* virus fever which have a travel history to Brazil.[12] However, no outbreak happened in these areas, maybe due to the unavailability of the vector species as well as the environmental factors required for viral transmission.

## Diagnostic Confusion and Limited Awareness

One of the problems that still exists is the potential for OROV to be misdiagnosed since the symptoms of *Oropouche* fever are similar to those of dengue and chikungunya, including fever, headache, joint pain, and rash. In places where medical facilities are already overcrowded, patients who display these symptoms are likely to get symptomatic therapy without a formal diagnosis.[24,25] Even while RT-PCR and serological tests can reliably identify OROV, these techniques are frequently unavailable in low-resource settings.[28]

Bernandes-Terzian et al. also reported sporadic and clinically silent infection of OROV disease from Acre, Brazil.[29] Similar scenarios may occur in India as well as other countries of tropical Asia. Thus, proper clinical and serological surveillance of travellers from South American countries is essential in India as well as other Asian countries to reduce the risk of OROV entry.

## Discussion

In order to analyse the possible emergence of arbovirus like OROV in Asia especially India, we must understand the epidemiology of other arboviral diseases that already have been transmitted from other continents to Asia including India for instance, chikungunya, West Nile fever, Japanese encephalitis etc.

The most significant human arboviral disease, dengue virus (DENV), most likely started in non-human primates (sylvatic cycle) in Africa.[30] During colonial expansion, the first epidemics were documented in 1779–1780 and spread throughout Asia, Africa, and North America because of international shipping.[31] The primary DENV vector, the *Aedes aegypti* mosquito, was brought to Asia via trade from Africa, which contributed to the spread of dengue in the region.[32] With significant outbreaks in the Philippines, Thailand, and Vietnam, Southeast Asia emerged as the epicentre of dengue epidemics in the 1950s and 1960s.[33] All four dengue virus serotypes (DENV-1 to DENV-4) were discovered at this time, indicating that several strains were circulating concurrently, which increased the intensity and complexity of dengue outbreaks.[34] Dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS), the fatal forms of dengue were first reported in the 1950s in Southeast Asia, in the Philippines and Thailand. DHF is believed to be caused due to secondary infections with a different serotype of the dengue virus, leading to a hyperimmune response in individuals who had previously been infected with a different serotype. In 1963 and 1964, the city of Calcutta, India, experienced severe epidemics of dengue haemorrhagic fever.[35] That means DENV took more than 150 years to transform into a fatal form. Similarly, OROV fever is not fatal at present but the disease is spreading at a high rate in the South America region, which in near future can get mutated to different serotypes as well and can cause critical conditions in humans, for example, a novel strain of the OROV (AM0088) from the 2023–24 outbreak in Brazil was shown to be more virulent than the preceding strain (BeAn1991), with a considerably higher replication in mammalian cells at 12 and 24 hours after infection.[36]

First discovered in Africa in 1952, chikungunya made its way to Asia in the 1950s and 1960s, causing outbreaks in Thailand, Sri Lanka, and India.[37] The virus resurfaced in the 2000s after a period of dormancy, resulting in devastating epidemics.[38] The main mosquito vector, *Aedes aegypti*, and *Aedes albopictus* (a viral mutation that boosted *Aedes albopictus* transmission) were crucial to its spread.[39] Chikungunya is still endemic in Asia today, posing a constant threat to public health.[40] Thus, chikungunya is a perfect example that arboviral disease transmission can be accelerated through globalisation as well as mutation of the virus (led to a choice of a new vector other than the principal vector). Similarly, the OROV virus could be transmitted through new vectors like other species of *Culicoides* or different mosquito species as discussed before.

Yellow fever virus is known to spread and infect mosquitoes and primates of new regions (spillback event), creating a new enzootic cycle that closely mirrors the original sylvatic transmission cycle, despite the taxonomic differences between hosts and vectors in the old and new regions.[40] Zika virus infections have also been identified in New World primates, indicating that a persistent enzootic cycle may develop.[41] Bhattacharya & Basu assessed a wide variety of reservoir hosts for the Japanese encephalitis virus, suggesting the potential for multiple animal hosts.[42]

Therefore, there appears to be a significant risk that tropical arthropod vectors, along with a wide range of wild and peridomestic animals in Asia, may create a suitable ecological niche for new animal reservoirs of OROV and its subsequent enzootic transmission.

Additionally, the symptomatic similarities with other endemic arboviruses, the diagnostic dilemma and the relatively mild symptoms associated with OROV pose a considerable risk of its going undetected, despite its possible prevalence in densely populated regions of Asia, including India. In such a situation, this may facilitate the virus to evolve and mutate while simultaneously also selecting suspected vectors which are endemic to Asia for establishing itself in previously naive regions. The possibility of an outbreak of the OROV in Asia, including India cannot be thus ruled out. Hence, the need of the hour to establish a sound surveillance system, enhance monitoring and public health preparedness, and undertake research to mitigate the emerging threat of OROV in Asia.

## Conclusion

*Oropouche* orthobunyavirus, OROV, is undoubtedly an emerging public health threat in Asia, particularly in India, where environmental conditions and the presence of vector species provide ideal conditions for its transmission. Increasing globalisation coupled with extensive travel potentiates the possibility of the introduction of OROV to newer areas. These factors coupled with the clinical similarities with other endemic mosquito-borne viral diseases and the associated diagnostic challenges threaten to spiral OROV into a public health challenge in hitherto unaffected areas. It is thus pertinent to establish a sound surveillance system, strengthen public health preparedness and undertake research for the effective mitigation of the looming threat of OROV in Asia.

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