



Editorial

Oropouche virus: A re-emerging arbovirus of clinical significance*



Introduction

Oropouche virus is a re-emerging arbovirus that has caused sporadic epidemics of febrile human disease in South America and the Caribbean. In the first six months of 2024, more than 8000 confirmed human cases of Oropouche virus disease (OVD) were reported in endemic regions in addition to Cuba, a country not previously reporting cases [1]. In parallel to the increase of cases in endemic regions, the European Centre for Disease Prevention and Control (ECDC) recently reported the first imported cases of OVD into Europe with 19 cases identified in Spain, Italy, and Germany related to recent travel to Cuba and Brazil, both areas currently experiencing outbreaks [2]. The US Centers for Disease Control and Prevention (CDC) have also reported 21 cases of OVD in the US among travellers returning from Cuba [3]. Newly involved geographical regions and the pace of these ongoing outbreaks have prompted efforts to better understand disease presentation and severity, transmission routes, and demographic distribution among susceptible individuals.

Oropouche virus

Oropouche virus (OROV), the causative agent of OVD, is a zoonotic arbovirus that belongs to the family *Peribunyaviridae*, genus *Orthobunyavirus* [4]. First isolated in Trinidad in 1955 from a forest worker, several large-scale outbreaks and epidemics have been reported in the Americas upon infection in humans since that time [5].

OROV has a tri-segmented genome prone to reassortment, potentially allowing for future viral emergence of novel viruses when co-infection with genetically similar viruses occurs. Three such OROV reassortants have previously been identified: Iquitos virus, Madre de Dios virus, and Perdões virus. Both Iquitos and Madre de Dios viruses have been associated with febrile illnesses in humans [6]; however, the importance of these emerging reassortant viruses has yet to be determined.

Viral transmission and geographic distribution

OROV is maintained by vector-borne transmission in a sylvatic cycle between susceptible reservoir hosts. This cycle can spillover into humans and establish urban transmission cycles in densely populated areas resulting in outbreaks in human populations. *Culicoides* midges, in particular *Culicoides paraensis*, are known to be competent vectors for transmission of OROV, and several species of mosquito including *Culex*

quillettidia venezuelensis, *Aedes serratus*, and *Culex quinquefasciatus* may contribute to the OROV transmission cycle; the urban cycle is thought to be driven by *Culicoides paraensis* and *Culex quinquefasciatus* [7]. Vector competence studies have demonstrated high infection and dissemination in midge species with limited competence in numerous mosquito species [8,9]. It is possible that viral polymorphisms are required to overcome either the mosquito midgut infection barrier or salivary gland infection barrier which could explain the sporadic nature of OVD outbreaks [7].

OROV has been identified in many countries in the Caribbean and Amazon Basin region of South America with the majority of reported cases located in Brazil and Peru. Since 2020, human cases have been identified in three countries not previously known to be endemic for OROV: French Guiana (2020), Ecuador (2020), and Cuba (2024) [4,10–12].

Culicoides paraensis is widely distributed from North America to Argentina. While this means the potential geographic distribution of OROV may extend beyond the currently perceived region, establishing endemicity would also require susceptible reservoir species to be present. Sloths are believed to be an important reservoir species, and the distribution of two- and three-fingered sloths aligns almost perfectly with the known area of endemicity for OROV. However, it has been hypothesised that non-human primates and some bird species may be reservoirs for the virus [6]. In regions where OROV is endemic, such as Brazil, antibodies have been detected in chickens and ducks, suggesting that wild and domestic birds might serve as amplifiers, although conclusive evidence is currently lacking [13]. In addition, neutralising antibodies to OROV have been detected in both domestic dogs and cattle [14].

The lack of knowledge on host reservoir species and the contribution of the different vectors in maintaining both sylvatic and urban transmission cycles make predicting the potential area of endemicity difficult. Surveillance is needed both in countries that border known endemic areas and in countries where imported cases are reported. As with other arboviruses, adoption of a One Health approach is needed in research, epidemiological, and ecological studies to assess impact and predict potential future issues.

Historically, OVD has been documented predominately during the rainy season in endemic areas, likely due to increased breeding of competent vectors [6]. Although many urban outbreaks have been identified, sustained urban transmission is not commonly reported and horizontal human-to-human transmission has not been described.

* This paper is being jointly published by International Journal of Infectious Diseases, IJID Regions and IJID One Health by Elsevier Inc. The articles are identical except for minor stylistic and spelling differences in keeping with each journal's style. Either citation can be used when citing this article.

Clinical manifestations

Following an incubation period of 3-12 days, OVD presents as an acute febrile illness frequently associated with headache, myalgia, arthralgia, nausea, retro-orbital pain and photophobia [4,6]. Rare presentations include aseptic meningitis, haemorrhagic manifestations such as petechiae and epistaxis, anorexia, and rubella-like rash; no long-term sequelae have been identified [3,6,15]. In 2024, three patients with OVD were subsequently diagnosed with Guillain Barré Syndrome during their convalescence; all three patients recovered with no sequelae [16]. Fatal outcomes associated with OVD are extremely rare; however, two deaths in adults with no underlying medical conditions were reported in 2024 [17] in addition to two foetal deaths representing the first indication of potential vertical transmission [18].

Both the common symptoms and rare clinical manifestations are similar to numerous other (and more prevalent) arboviral diseases including dengue, yellow fever, Zika, chikungunya, and Mayaro, making clinical recognition difficult [19]. In addition, the challenges in diagnostics for arboviruses in endemic regions further complicate the ability to obtain robust comparative estimates of the burden of different arbovirus diseases [20]. These difficulties have likely resulted in an underestimation of the true burden of OVD and geographical distribution of OROV [4,6]. Unlike other arboviral illnesses, mild symptom recurrence following the initial febrile presentation has been reported in up to 60% of OVD patients [6].

Clinicians should consider OVD in patients reporting febrile illness with recent travel to Central America, South America, or the Caribbean. Due to recent reports of potential vertical transmission, additional vigilance is required in pregnant patients with compatible symptoms and recent travel to endemic regions.

Clinical diagnostics

Real-time PCR is the frontline diagnostic assay for detecting cases of OVD; however, this assay will only detect patients with ongoing viremia if serum samples are assessed which peaks approximately two days post onset of symptoms and rapidly wanes [21]. Similar limitations applying to genomic sequencing methodologies. Assessment of additional sample types such as saliva and urine may provide more reliable detection of viral RNA and should be considered in addition to serum samples for clinical diagnostics. OROV RNA has been detected in both urine and saliva five days post onset of symptoms [22]. Reactive antibodies will be detectable for a far longer period of time and at least one commercially available assay is available [23]; however, it is likely that these may take seven days or more to be detectable.

Additional tests that can be adopted include viral isolation and plaque reduction neutralisation assays. While these assays are expensive and time consuming to perform, they should be considered for probable cases, especially those involving pregnant travellers.

The US CDC have recently published interim guidance for testing and reporting of OVD cases which can be used as a foundation for countries lacking their own guidance [24].

Therapeutics and vaccines

At present, there are no specific therapies available for treatment of OVD; supportive care remains the mainstay for clinical management when cases are identified. The use of ribavirin, mycophenolic acid, and IFN- α has been described *in vitro* and *in vivo* in mouse models against OROV with variable results; similarly, there are limited data from animal models examining candidate vaccines [4]. The development of a vaccine for OROV presents a significant challenge due to potential for reassortment. At the present time, no vaccines for OROV have been licensed, although at least one is currently in development along with several more for closely related orthobunyaviruses [4,25]. For travellers or

those who reside in areas at risk, preventative control measures such as mosquito nets and insect repellents should continue to be emphasized.

Conclusions

The current OROV epidemic has reaffirmed the potential for neglected tropical diseases to re-emerge with significant impact to public health. It has been nearly 70 years since OROV was first isolated from a febrile patient, yet there is still a dearth of information regarding the enzootic viral cycle, the vector competence for key midge and mosquito species, host reservoir range, and reliable methods for clinical diagnosis. In addition, significant research is required to inform potential geographic expansion of OROV in the Americas, the potential for OROV to become established within susceptible reservoirs and vectors in other continents, the drivers of zoonotic spillover, and the potential impact of climate change.

While these questions may take many years to be answered, immediate attention is required to understand the current impact of OVD in endemic regions and potential public health control measures that can limit the burden of disease. In addition, clinicians in all countries should consider OVD in travellers from South America and the Caribbean presenting with fever (potentially with more severe clinical presentations) in addition to more common arboviral diseases associated with these regions. Particular attention should be paid to pregnant and immunocompromised patients with compatible symptoms and travel history due to the potential for vertical transmission and for more severe clinical outcomes.

Acknowledgements

The authors would like to acknowledge Professor Nick Beeching, Liverpool School of Tropical Medicine, for his contributions to the manuscript.

Disclosure statement

AD acknowledges support from the National Science Foundation (grant No. SES2200228). EP and KK acknowledges financial support for the PandemiX Center, from the Danish National Research Foundation (grant No. DNRF170). PJ and MK are part of the DURABLE consortium, co-funded under EU4Health programme under grant agreement 101102733.

The views expressed are those of the authors and do not necessarily represent those of their organisations. The funders had no role in analysis, decision to publish, or preparation of the manuscript.

Angel N. Desai[#]

Division of Infectious Diseases, University of California Davis Health, Sacramento, CA, 95817

Ashley Otter

Emerging Pathogen Serology group, Vaccine Development and Evaluation Centre, UK Health Security Agency, Porton Down, Salisbury, UK
NIHR Health Protection Research Unit in Emerging Zoonotic Infections, UK

Marion Koopmans

Viroscience Department, Pandemic and Disaster Preparedness Centre, ErasmusMC, Rotterdam, The Netherlands

Guido Granata

Systemic and Immune Depression-Associated Infection Unit, Clinical and Research Department, National Institute for Infectious Diseases "L. Spallanzani", IRCCS, 00149, Rome, Italy

Martin P. Grobusch

Center of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Amsterdam University Medical Centers, location University of

Amsterdam, Amsterdam Infection & Immunity, Amsterdam Public Health – Global Health, University of Amsterdam, Amsterdam, The Netherlands

Varol Tunali

Faculty of Medicine, Department of Microbiology, Izmir University of Economics, Turkey

Roberta Astorri

Infectious Diseases Unit, Department of Mental Health and Public Medicine, University of Campania "Luigi Vanvitelli", 80131 Naples, Italy

Pikka Jokelainen

Infectious Disease Preparedness and One Health, Statens Serum Institut, Copenhagen, Denmark

Gilbert Greub

Institute of Microbiology, University of Lausanne and University Hospital Center (CHUV), 1005, Lausanne, Switzerland

Service of Infectious Diseases, University Hospital Center (CHUV), Lausanne, Switzerland

Önder Ergönül

Koç University İşbank Center for Infectious Diseases, Istanbul, Türkiye

Department of Infectious Diseases and Clinical Microbiology, Koç University School of Medicine, Istanbul, Türkiye

Sofia R. Valdoleiros

Infectious Diseases Department, Centro Hospitalar Universitário de São João, Porto, Portugal

Faculty of Medicine, University of Porto, Porto, Portugal

Chantal P. Rovers

Department of Internal Medicine, Division of Infectious Diseases, and Radboudumc Community of Infectious Diseases, Radboud University Medical Center, Nijmegen, the Netherlands

Antonino Di Caro

Unicamillus - International University of Medical Science, 00131, Rome, Italy

Infectious Diseases and Tropical Medicine Department, IRCCS Sacro Cuore Don Calabria Hospital, 37024, Negrar di Valpolicella (Verona), Italy

Raffaella Pisapia

Emerging and highly contagious infectious diseases Unit. "D. Cotugno" Hospital, Azienda Ospedaliera dei Colli, Naples, Italy

Francesco Maria Fusco

Systemic infection and infections of immunocompromised host "D. Cotugno" Hospital, Azienda Ospedaliera dei Colli, Naples, Italy

Ana Pereira do Vale

Veterinary Sciences Centre, University College Dublin, Belfield, Dublin 4, Ireland

Karen A. Krogfelt, Eskild Petersen

Department of Science and Environment, PandemiXcenter, Roskilde University, Denmark

Barry Atkinson

NIHR Health Protection Research Unit in Emerging Zoonotic Infections, UK Diagnostics and Pathogen Characterisation, UK Health Security Agency, Porton Down, Salisbury, UK

References

- [1] WHO Oropouche virus disease - Region of the Americas; 2024 <https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON530> (accessed Sept 8, 2024).
- [2] ECDC. Threat assessment brief: Oropouche virus disease cases imported to the European Union. 2024. <https://www.ecdc.europa.eu/en/publications-data/threat-assessment-brief-ropouche-virus-disease-cases-imported-european-union> (accessed Sept 8, 2024).
- [3] Morrison A, White JL, Hughes HR, et al. Oropouche Virus Disease Among U.S. Travellers — United States, 2024. *MMWR Morb Mortal Wkly Rep* 2024;73:769–73.
- [4] Files MA, Hansen CA, Herrera VC, et al. Baseline mapping of Oropouche virology, epidemiology, therapeutics, and vaccine research and development. *NPJ Vaccines* 2022;7:38.
- [5] Anderson CR, Spence L, Downs WG, Aitken TH. Oropouche virus: a new human disease agent from Trinidad, West Indies. *Am J Trop Med Hyg* 1961;10:574–8.
- [6] Travassos da Rosa JF, de Souza WM, Pinheiro F de P, et al. Oropouche Virus: Clinical, Epidemiological, and Molecular Aspects of a Neglected Orthobunyavirus. *Am J Trop Med Hyg* 2017;96:1019–30.
- [7] de Mendonça SF, Rocha MN, Ferreira FV, et al. Evaluation of Aedes aegypti, Aedes albopictus, and Culex quinquefasciatus Mosquitoes Competence to Oropouche virus Infection. *Viruses* 2021;13. doi:10.3390/v131050755.
- [8] Carpenter S, Groschup MH, Garros C, Felipe-Bauer ML, Purse BV. Culicoides biting midges, arboviruses and public health in Europe. *Antiviral Res* 2013;100:102–13.
- [9] McGregor BL, Connally CR, Kenney JL. Infection, Dissemination, and Transmission Potential of North American Culex quinquefasciatus, Culex tarsalis, and Culicoides sonorensis for Oropouche Virus. *Viruses* 2021;13:226.
- [10] Wise EL, Márquez S, Mellors J, et al. Oropouche virus cases identified in Ecuador using an optimised qRT-PCR informed by metagenomic sequencing. *PLoS Negl Trop Dis* 2020;14:e0007897.
- [11] Gaillet M, Richard C, Restrepo J, et al. Outbreak of Oropouche Virus in French Guiana. *Emerg Infect Dis* 2021;27:2711–14.
- [12] Toledo ME, Monteagudo Diaz S, Montenegro Calderón T, Kreppel K, Van Damme E, Vanlerberghe V. Preparedness for emerging epidemic threats: detection of Oropouche circulation in Cuba. *Lancet Infect Dis* 2024;24:e484.
- [13] Pinheiro FP, Travassos da Rosa AP, Travassos da Rosa JF, Bensabath G. An outbreak of Oropouche virus disease in the vicinity of santarem, para, barzil. *Tropenmed Parasitol* 1976;27:213–23.
- [14] Dias HG, Familiar-Macedo D, Garrido IO, dos Santos FB, Pauvolid-Corrêa A. Exposure of domestic animals to Mayaro and Oropouche viruses in urban and peri-urban areas of West-Central Brazil. *One Health Outlook* 2024;6:12.
- [15] Moura MPG, Bastos MS, Gimma JBL, et al. Oropouche fever outbreak, Manaus, Brazil, 2007–2008. *Emerg Infect Dis* 2009;15:2063–4.
- [16] de Armas Fernández JR, Peña García CE, Acosta Herrera B, et al. Report of an unusual association of Oropouche Fever with Guillain-Barré syndrome in Cuba, 2024. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol* 2024 published online Sept 14. doi:10.1007/s10096-024-04941-5.
- [17] Bandeira AC, Pereira FM, Leal A, et al. Fatal Oropouche Virus Infections in Nonendemic Region, Brazil, 2024. 2024; 30. DOI:10.3201/eid3011.241132.
- [18] Lenharo M. Mysterious Oropouche virus is spreading: what you should know. *Nature* 2024 published online Aug 26. doi:10.1038/d41586-024-02746-2.
- [19] Eckerle I, Briciu VT, Ergönül O, et al. Emerging souvenirs-clinical presentation of the returning traveller with imported arbovirus infections in Europe. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2018;24:240–5.
- [20] Kasbergen LMR, Nieuwenhuijse DF, de Bruin E, Sikkema RS, Koopmans MPG. The increasing complexity of arbovirus serology: An in-depth systematic review on cross-reactivity. *PLoS Negl Trop Dis* 2023;17:e0011651.
- [21] Ciudoderis KA, Berg MG, Perez LJ, et al. Oropouche virus as an emerging cause of acute febrile illness in Colombia. *Emerg Microbes Infect* 2022;11:2645–57.
- [22] do Nascimento VA, Santos JHA, Monteiro DC, da S, et al. Oropouche virus detection in saliva and urine. *Mem Inst Oswaldo Cruz* 2020;115:e190338.
- [23] EUROIMMUN. EUROIMMUN introduces Anti-Oropouche Virus ELISAs - Clinical Laboratory int. 2024; published online March 14. <https://clintabint.com/euroimmun-introduces-anti-ropouche-virus-elisas/> (accessed Sept 8, 2024).
- [24] CDC. Interim Guidance for Health Departments on Testing and Reporting for Oropouche Virus Disease. Oropouche. 2024; published online Aug 27. <https://www.cdc.gov/ropouche/php/reporting/index.html> (accessed Sept 8, 2024).
- [25] Stubbs SH, Cornejo Pontelli M, Mishra N, et al. Vesicular Stomatitis Virus Chimeras Expressing the Oropouche Virus Glycoproteins Elicit Protective Immune Responses in Mice. *mBio* 2021;12:e0046321.

#Corresponding author.

E-mail address: andesai@ucdavis.edu (A.N. Desai)