HHS Public Access

Author manuscript

Zoonoses (Burlingt). Author manuscript; available in PMC 2024 November 21.

Published in final edited form as:

Zoonoses (Burlingt). 2024 January ; 4(1): . doi:10.15212/zoonoses-2024-0006.

OROPOUCHE VIRUS: MORE QUESTIONS THAN ANSWERS

Eduardo Jurado-Cobena, DVM, MSc, MPH[1,2]

[1]Department of Microbiology & Immunology, Graduate School of Biomedical Science

[2]Department of Biostatistics & Data Science, School of Public and Population Health University of Texas Medical Branch at Galveston, Galveston. TX, USA.

Abstract

Oropouche virus (genus *Orthobunyavirus*, family *Peribunyaviridae*) is an arthropod-borne virus that infects several species of animals and humans mostly in South America. Despite being described as a human pathogen over 60 years ago, little progress has been made towards the ecological and pathological aspects of this pathogen. However, with recent viral spread northward reaching Haiti and Cuba, it has been receiving more attention, evidenced by the growing number of relevant research articles. This commentary article provides the summary of the potential natural reservoirs and the expansion of endemic regions within the context of One Health. The clinical aspects of the human infection are revisited and discussed based on the latest evidence. The article briefly review research on the molecular virology and the pathology, highlighting unanswered questions crucial for comprehensive understanding of this viral disease, which imposes a significant burden on the affected populations.

Keywords

OROV; Orthobunyavirus; One-Health; vectors; Host-pathogen interactions; vertebrate hosts

1. INTRODUCTION

Oropouche virus (OROV) is the causative agent of Oropouche fever (ORO), a debilitating febrile illness that affects humans in South America [1–3] and North America [4,5] (Figure 1). The virus triggers "*explosive outbreaks of acute febrile illness*"[6] with a high percentage of convalescent individuals experiencing recurrence of symptoms [7] as well as circulate silently on human populations[3]. Although no fatalities attributed to ORO have been reported to date, the incapacitating febrile illness, occasionally accompanied by meningitis or meningoencephalitis, poses a significant public health concern in endemic countries. OROV is transmitted by arthropods such as biting midges (*Culicoides paraensis)* or mosquitoes. OROV belongs to the *Orthobunyavirus* genus, family *Peribunyaviridae*. Serologically, OROV is classified within the Simbu serogroup, which contains viruses of human and veterinary importance ([1] and references within). The tripartite negative-sense RNA genome comprises Small (S); Medium (M) and Large (L) segments. The L-segment encodes

CONFLICT OF INTEREST

The author declares no conflict of interest.

the RNA-dependent-RNA polymerase (L protein). The M-segment encodes a polyprotein containing two envelope glycoproteins Gn and Gc, as well as a nonstructural protein (NSm). The S-segment encodes the nucleocapsid (N) protein and a small nonstructural protein S (NSs), with both being within overlapping reading frames. In other Bunyavirales known to cause human diseases, the nonstructural NSs protein from the S segment has been identified as a major virulence factor. [8]

OROV infection was detected in patients' sera or in monocytes, lymphocytes, and dendritic cells within the human peripheral blood mononuclear cells (PBMCs). [9,10]. However, the mechanisms underlying the viral pathogenesis that triggers febrile illness or meningoencephalitis, and the mode of viral transmission in arthropod vectors remain unclear. There are no licensed antivirals or therapeutic interventions to support the recovery of ORO patients. Although OROV has not reached to the U.S., the geographical expansion of OROV into Haiti and Cuba [4,5], has raised concerns about potential viral spread into continental U.S. due to the presence of the vector midges in the Southern to Central U.S [11]. For a visual representation of the geographical distribution of *Culicoides paraensis* the review article from Files et al.[1], provides a compelling map.

1.a. Facilitating OROV surveillance through a One Health approach:

The initial human case of OROV was documented in 1955. The same study identified neutralizing antibodies in the sera of monkeys, including species such as cebus monkeys (*Cebus trinitatis*) and howler monkeys (*Alouatta seniculus*). [12] Twenty years later, reports from outbreaks in Brazil revealed not only several thousand infected humans but also the involvement of various other animal species. This included a rodent of the genus *Proechimys*, and intriguingly, various wild (including families *Cuculidae*, *Dendrocolaptidae*, *Formicariidae*, *Fringillidae*, *Pipridae*, *Thraupidae*, *Troglodytidae, Vireonidae* and *Tyrannidae*) and domestic (*Gallus gallus domesticus* and *Anas platyrhynchos domesticus*) birds[7]. It is worth noting that species within the families *Fringillidae, Tyrannidae* and *Troglodytidae* are also distributed throughout the Americas and other regions of the world [13]. OROV was first isolated from a three-toed sloth (*Bradypus tridactylus*) in Brazil in 1960. These animals are considered possible wild reservoirs for OROV across various geographical locations in North and South America. More recently, marmosets (*Callithrix spp.)* [2] have been implicated as potential host for OROV. Notably, in 1985, a reassortant containing an OROV-like S segment and a dissimilar M segment (referred to as Jatobal virus) was isolated from a South American coati (*Nasua nasua*). It was classified as belonging to the Simbu serogroup, similar to OROV. [14] Table 1 summarize the most recent reports (2009–2018) of OROV in animals. For previous years, the review from Romero-Alvarez & Escobar has a complete table.[2]

Regarding the vector, Table 2 summarizes the reports where arthropods has been pointed as OROV vectors. The main implicated vectors for urban infection are *Culicoides paraensis* and *Culex quinquefasciatus* [15]. Reinforcing this epidemiology-leaded entomological findings, another study reported the identification of OROV genetic material on *Culex quinquefasciatus* as well as human patients during one outbreak investigation in Brazil [16]. Interestingly, genomic material from OROV has been identified on male mosquitoes (*Culex*

quinquefasciatus-Gen Bank accession MT247713 *and Aedes aegypti- Gen Bank accession* MT247714) during a vertical transmission study of arboviruses in vector mosquitoes [17]. Rather if these findings may explain the lack of *C. paraensis* [18] on an Ecuadorian city where positive human cases of OROV infection were identified [19] remains to be proven. Also, *Culicoides sonorensis*, a North American midge, has shown high infection and dissemination rates for OROV under experimental conditions [20]. For a visual distribution of *Culex quinquefasciatus* vector in North America, the reader is directed to the article by Gorris et al.[21], caution is advised to interpret the species names since the "Pipiens Assemblage includes *Cx. pipiens, Cx. quinquefasciatus*"[22], adding an extra layer of biological complexity. For a visual distribution of *Culicoides sonorensis,* please see article by Shults et al.[23]

All these observations indicate that the natural cycle of OROV is likely a time-related evolution in terms of potential reservoir and vector species and adaptability to new ones, within the currently recognized transmission cycles (Figure 2). Such observations underscore the need of an integrated One Health approach for further identification of new reservoirs and the potential consequence for expanding its geographic range. Moreover, there is a need to monitor potential viral reassortment events [24] through active surveillance programs that incorporate wildlife. This is crucial because several OROV isolates encode the M-segment of unknown origins (M segment reassortant), such as Jatobal virus (Brazil), Iquitos virus (Peru), Perdões virus (Brazil), or Madre de Dios virus (Venezuela or Peru).

1.b. Gaps in understanding the pathogenesis of human Oropouche fever:

Cases of meningitis or meningoencephalitis following OROV infection have been reported in a small number of patients. Consequently, few studies have addressed the pathogenesis of OROV-induced meningoencephalitis in patients. One study revealed that OROV can infect microglia and neurons within human brain slice cultures, while astrocytes remain unaffected. Moreover, significant increase in TNF-α levels was detected in brain slice tissues infected with OROV, [25] suggesting that OROV infection within the central nervous system may induce proinflammatory reactions. Nevertheless, further characterization is required to fully elucidate the pathogenesis of OROV infection in the human brain. The "Trojan horse" mechanism has been proposed as the primary means of viral dissemination within OROV-infected humans, suggesting that the virus transverses the blood-brain barrier inside infected PBMCs. Nonetheless, the dynamics of viral dissemination, as well as the viral components facilitating the viral persistence within PBMCs, are still not fully understood, which warrants further investigation.

While limited pathological findings of OROV infections in humans exist, several animal models have been developed to characterize OROV infections *in vivo*. For instance, subcutaneous inoculation of the OROV BeAn19991 strain in three-week-old Syrian hamsters (*Mesocricetus auratus*) has been shown to induce meningoencephalitis, with viral antigens detected in neurons and hepatocytes [26]. The median lethal dose 50 (LD_{50}) was determined to be $10^{5.6}$ $TCID_{50}$/ml. Additionally, subcutaneous inoculation of the OROV BeAn19991 strain in one-day-old BALB/c mice could induce mild meningitis and viral infection in neurons, but not in hepatocytes [27]. These studies suggest that

OROV demonstrates potent neurotropism in rodent models, mirroring its infection pattern in humans. Furthermore, research has demonstrated that 6-week-old C57BL/6 mice exhibit resistance to OROV BeAn19991 strain infection via the subcutaneous route. In contrast, Ifnar−/− C57BL/6 mice inoculated with the OROV BeAn19991 strain uniformly succumbed to infection, with a mean survival time of 5 days [28]. Infected Ifnar−/− C57BL/6 mice displayed OROV-infected hepatocytes, focal hepatocytic necrosis, and infiltration of mononuclear cells. While there is limited evidence of hepatitis associated with OROV infection in humans, the study suggests that hepatocytes can serve as a potential viral target, influenced by the competency of innate immunity.

Hemorrhagic symptoms, including petechial rashes, epistaxis, gingival bleeding, and menorrhagia, have been documented during ORO outbreaks in Peru and Brazil [6,29,30]. In Brazil, up to 15.5% of patients reported hemorrhagic manifestations during an outbreak [6]. Additionally, two women infected in a laboratory setting experienced continued and profuse menses [30]. Chemokines are known to play a role in directing the migration of certain white blood cells from the bloodstream to infected tissue sites. A recent study demonstrated that patients experiencing acute OROV infection exhibit elevated levels of CCL2, CXCL8, CXCL10, IL-6, IL-10, IL-17A, TNF-α, and IFN-α [31]. However, whether cytokines and chemokines contribute to the hemorrhagic manifestations in OROV infection remains to be elucidated.

Furthermore, an early report highlighted miscarriages in two pregnant women who were in their second month of pregnancy, out of a total of nine pregnant patients [32]. Although the reported case numbers have been limited, viral tropism to placenta and fetus should be characterized in future studies.

Viral virulence factors associated with OROV remain largely unknown. While NSs proteins from other bunyaviruses, including the families *Peribunyaviridae*, *Nairoviridae*, *Hantaviridae* and *Phenuiviridae*, have been shown to be a major virulence factor [8], the role of OROV NSs in pathogenicity remains incompletely characterized. It has been demonstrated that OROV NSs protein serves as a type-I IFN antagonist, as evidenced by experiments with recombinant OROV prototype Brazilian BeAn19991 strain and that lacking the NSs gene [33]. Another nonstructural protein, NSm, plays a crucial role in the assembly and morphogenesis of Bunyamwera virus [34], another member of the genus Orthobunyavirus. In the case of a Phlebovirus -Rift Valley Fever Virus (RVFV)-; it has been shown that NSm has implications on the arthropod vector infection cycle [35]. The NSm gene in OROV is situated between Gn and Gc and can undergo co-translational cleavage by signal peptidase [36]. However, limited information is available regarding the virological functions of the NSm protein in OROV despite the adapted evolution of this protein as evidenced on evolutionary studies[37].

Regarding the cellular receptor, Schwarz et al. reported that Lrp1 KO cell lines exhibited reduced, but not abolished OROV infection. Also upon intracranial (IC) inoculation with OROV BeAn19991 strain (100 PFU) with or without a purified domain from receptor-associated protein (RAP, which is a ligand for Lrp1), on female mice (3- to 4-wk-old C57BL/6J), animals inoculated with OROV+RAP purified domain showed 90% survival as opposite to the mice in the control group which succumbed, [38] suggesting that Lrp1 is

important in the context of neural infection on youth mice. In terms of host factors, the endosomal sorting complex required for transport (ESCRT) has been identified as a target during OROV replication using HeLa cells [39]. ESCRT is sequestered to Golgi membranes during OROV assembly, requiring specifically the interaction with charged multivesicular body protein 6 (CHMP6), which is part of the ESCRT III machinery complex as identified using recombinant expression of either the OROV M polyprotein or its components (Gn/Gc) transfected on either HeLa or HEK293 cells [40]. Importantly, the co-expression of OROV Gn and Gc proteins was necessary for them to progress into the Golgi.

2. DISCUSSION

During one of the initial outbreaks of Oropouche fever in Brazil [7], chickens and ducks were found to have antibodies against OROV. This led to suggestions that wild and domestic birds could act as amplifiers, but solid evidence to support this hypothesis is lacking ([2] and references within). However, this represents a significant knowledge gap, considering that many of the wild birds reported to harbor antibodies against OROV have geographic ranges covering the entire American continent from South to North. Furthermore, there is an increased risk that poultry farm workers may face if OROV can indeed be amplified in domestic birds. Regarding the vector; a recent review tried to pinpoint the geographical places where OROV has been identified and correlate them with the geographical places where known vectors has been reported, finding a “lack of significant relationships”[41]. This points out to the need to improve collaborations between epidemiologic and entomologic expertise under the One Health approach to clearly identify the vectors responsible for OROV transmission during outbreaks in light of the new evidence available .[16,17,19,20,42] Additionally, on a recent OROV outbreak on French Guyana, just one specimen of C. paraensis was identified, with the big percentage of arthropods being *Culex quinquefasciatus,* pointing to these as an important vector on urban/rural transmission.[43]

Characterizing the proinflammatory responses during OROV infection and understanding the molecular functions of OROV NSs and NSm proteins are crucial for gaining insight into OROV pathogenesis in humans. It is concerning that meningoencephalitis developed in human patients has not been thoroughly characterized, despite typically resolving without apparent sequelae. A recent study analyzing two different human biobanks reported that patients exposed to viruses causing encephalitis had a higher risk of developing neurodegenerative diseases, with the most significant association observed between viral encephalitis exposure and Alzheimer’s disease [44].

Although it is not lethal, hemorrhagic symptoms like petechial rashes, epistaxis, gingival bleeding, and menorrhagia are potential clinical concerns, which lack scientific understanding of the pathogenesis. As suggested in a previous study[29], a larger number of exposed and infected individuals increases the likelihood of symptoms, thereby making less common symptoms more apparent than in smaller outbreaks. An intriguing hypothesis proposed by the authors of the Peru outbreak[29] suggests that the absence of hemorrhagic manifestations and the “explosive outbreak” were not observed during another OROV outbreak in Iquitos, Peru, in 1992. They speculated that the prevalence of Dengue in that region might have overshadowed the effects of OROV on the population. This notion is

supported by a report from Brazil [6], which noted that all patients exhibiting hemorrhagic symptoms tested negative for Dengue IgM antibodies. Similarly, a report from Colombia indicated no occurrence of hemorrhagic symptoms despite identifying co-infections of OROV and dengue virus in ten patients residing in a hyperendemic dengue area during efforts to identify the causative agent of acute febrile illnesses [45]. Previous proof of concept study reported the protective effects of a non-related virus (Virus-like particles of polio virus) on SARS-CoV-2 and other respiratory viruses by means of innate immunity stimulation using mice [46], rather if this is the case on the context of OROV infection on Dengue endemic areas needs to be explored, especially since the human immune response to Dengue still is not fully understood. If this hypothesis holds true, it could be promising news for much of the endemic regions where OROV is silently circulating. However, it would be concerning for North America, potentially impacting the estimates of a recent study that employed spatial epidemiology models based on human outbreaks and concluded that up to 5 million people are at risk [47].

It was reported that LD_{50} of the OROV MD023 strain is 45 PFU in 3–4-week-old hamsters [48], which indicates it is more pathogenic than BeAn19991 strain (LD_{50} of $10^{5.6}$ $TCID_{50}$/ml). Although both BeAn19991 strain and MD023 strain are similarly pathogenic to humans, hamsters showed a distinct susceptibility to these two OROV strains. However, the pathological changes induced by the MD023 strain have not been analyzed in comparison to those caused by the BeAn19991 strain. This comparative model will be valuable for elucidating host and viral factors that may influence the outcome of OROV infection as well as potentially be useful to test antiviral treatments.

CONCLUSIONS

The questions about the vectors on the different viral transmission cycles, the lack of consistent results between vector presence and outbreaks on recent reports, the poor understanding of the natural reservoirs, the incomplete understanding of OROV pathogenic factors linked to the pathogenesis in humans and the human susceptibility to develop hemorrhagic symptoms as well as the replication compartments within the human body and if viral tropism to placenta and fetus exists remains to be elucidated. The characterization of certain viral strains on animal models and its use on the search for identifying host factors affected and potential treatments is in slow development. The recent reports from outbreaks across several Latin-American countries and the recent detection on Cuba are clear indicators of the geographical expansion of this neglected tropical disease which has some potential fatalities under investigation as the number of susceptible individuals increased.[49]

ACKNOWLEDGEMENTS

The author receives support from the Sealy Institute for Vaccine Sciences and Institute for Human Infections & Immunity (IHII), Emerging and Tropical Infectious Diseases Training Program Grant; Pre-Doctoral Fellowship NIAID T32AI007526-23 (Dr. Lynn Soong). The author deeply thanks Drs. T. Ikegami and C. Alkan (UTMB) for their proofreading and valuable feedback.

REFERENCES

1. Files MA, Hansen CA, Herrera VC, et al. Baseline mapping of Oropouche virology, epidemiology, therapeutics, and vaccine research and development. npj Vaccines. 2022;7(1):38. doi:10.1038/s41541-022-00456-2 [PubMed: 35301331]
2. Romero-Alvarez D, Escobar LE. Oropouche fever, an emergent disease from the Americas. Microbes and Infection. 2018;20(3):135–146. doi:10.1016/j.micinf.2017.11.013 [PubMed: 29247710]
3. Sakkas H, Bozidis P, Franks A, Papadopoulou C. Oropouche Fever: A Review. Viruses. 2018;10(4):175. doi:10.3390/v10040175 [PubMed: 29617280]
4. MINSAP R Nota informativa del Ministerio de Salud Pública. Sitio oficial de gobierno del Ministerio de Salud Pública en Cuba. Published May 27, 2024. Accessed June 17, 2024. https://salud.msp.gob.cu/nota-informativa-del-ministerio-de-salud-publica-8/
5. Elbadry MA, Durães-Carvalho R, Blohm GM, et al. Orthobunyaviruses in the Caribbean: Melao and Oropouche virus infections in school children in Haiti in 2014. PLOS Neglected Tropical Diseases. 2021;15(6):e0009494. doi:10.1371/journal.pntd.0009494
6. Mourão MPG, Bastos MS, Gimaque JBL, et al. Oropouche Fever Outbreak, Manaus, Brazil, 2007–2008 - Volume 15, Number 12—December 2009 - Emerging Infectious Diseases journal - CDC. doi:10.3201/eid1512.090917
7. Pinheiro FP, Travassos da Rosa AP, Travassos da Rosa JF, Bensabath G. An outbreak of Oropouche virus diease in the vicinity of santarem, para, barzil. Tropenmed Parasitol. 1976;27(2):213–223. [PubMed: 941251]
8. Leventhal SS, Wilson D, Feldmann H, Hawman DW. A Look into Bunyavirales Genomes: Functions of Non-Structural (NS) Proteins. Viruses. 2021;13(2):314. doi:10.3390/v13020314 [PubMed: 33670641]
9. Ribeiro Amorim M, Cornejo Pontelli M, Fabiano de Souza G, et al. Oropouche Virus Infects, Persists and Induces IFN Response in Human Peripheral Blood Mononuclear Cells as Identified by RNA PrimeFlow™ and qRT-PCR Assays. Viruses. 2020;12(7):785. doi:10.3390/v12070785 [PubMed: 32708342]
10. de Souza Luna LK, Rodrigues AH, Santos RIM, et al. Oropouche virus is detected in peripheral blood leukocytes from patients. Journal of Medical Virology. 2017;89(6):1108–1111. doi:10.1002/jmv.24722 [PubMed: 27787907]
11. Borkent A, William L. Grogan J. Catalog of the New World Biting Midges North of Mexico (Diptera: Ceratopogonidae). Zootaxa. 2009;2273(1):1–48. doi:10.11646/zootaxa.2273.1.1
12. Downs WG, Aitken THG, Anderson CR, Spence L. Oropouche Virus: a New Human Disease Agent from Trinidad, West Indies *. The American Journal of Tropical Medicine and Hygiene. 1961;10(4):574–578. doi:10.4269/ajtmh.1961.10.574 [PubMed: 13683183]
13. Birds of the World - Comprehensive life histories for all bird species and families. Published January 19, 2024. Accessed January 20, 2024. https://birdsoftheworld.org/bow/home
14. Saeed MF, Wang H, Suderman M, et al. Jatobal virus is a reassortant containing the small RNA of Oropouche virus. Virus Research. 2001;77(1):25–30. doi:10.1016/S0168-1702(01)00262-3 [PubMed: 11451484]
15. Roberts DR, Hoch AL, Dixon KE, Llewellyn CH. Oropouche Virus: III. Entomological Observations from Three Epidemics in Pará, Brazil, 1975. The American Journal of Tropical Medicine and Hygiene. 1981;30(1):165–171. doi:10.4269/ajtmh.1981.30.165 [PubMed: 7212163]
16. Cardoso BF, Serra OP, Heinen LB da S, et al. Detection of Oropouche virus segment S in patients and in Culex quinquefasciatus in the state of Mato Grosso, Brazil. Mem Inst Oswaldo Cruz. 2015;110:745–754. doi:10.1590/0074-02760150123 [PubMed: 26517653]
17. da Silva Ferreira R, de Toni Aquino da Cruz LC, de Souza VJ, et al. Insect-specific viruses and arboviruses in adult male culicids from Midwestern Brazil. Infection, Genetics and Evolution. 2020;85:104561. doi:10.1016/j.meegid.2020.104561
18. Mosquera JD, Zapata S, Spinelli G, Gualapuro M, León R, Augot D. An updated list of the Culicoides (Diptera, Ceratopogonidae) fauna from Ecuador. Parasite. 29:63. doi:10.1051/parasite/2022061

19. Wise EL, Pullan ST, Márquez S, et al. Isolation of Oropouche Virus from Febrile Patient, Ecuador. Emerg Infect Dis. 2018;24(5):935–937. doi:10.3201/eid2405.171569 [PubMed: 29664378]
20. McGregor BL, Connelly CR, Kenney JL. Infection, Dissemination, and Transmission Potential of North American Culex quinquefasciatus, Culex tarsalis, and Culicoides sonorensis for Oropouche Virus. Viruses. 2021;13(2):226. doi:10.3390/v13020226 [PubMed: 33540546]
21. Gorris ME, Bartlow AW, Temple SD, et al. Updated distribution maps of predominant Culex mosquitoes across the Americas. Parasites & Vectors. 2021;14(1):547. doi:10.1186/s13071-021-05051-3 [PubMed: 34688314]
22. Harbach RE. Culex pipiens: Species Versus Species Complex – Taxonomic History and Perspective. moco. 2012;28(4s):10–23. doi:10.2987/8756-971X-28.4.10
23. Shults P, Hopken M, Eyer PA, et al. Species delimitation and mitonuclear discordance within a species complex of biting midges. Sci Rep. 2022;12(1):1730. doi:10.1038/s41598-022-05856-x [PubMed: 35110675]
24. Ladner JT, Savji N, Lofts L, et al. Genomic and phylogenetic characterization of viruses included in the Manzanilla and Oropouche species complexes of the genus Orthobunyavirus, family Bunyaviridae. Journal of General Virology. 2014;95(5):1055–1066. doi:10.1099/vir.0.061309-0 [PubMed: 24558222]
25. Almeida GM, Souza JP, Mendes ND, et al. Neural Infection by Oropouche Virus in Adult Human Brain Slices Induces an Inflammatory and Toxic Response. Frontiers in Neuroscience. 2021;15. Accessed March 27, 2023. https://www.frontiersin.org/articles/10.3389/fnins.2021.674576
26. Rodrigues AH, Santos RI, Arisi GM, et al. Oropouche virus experimental infection in the golden hamster (Mesocrisetus auratus). Virus Research. 2011;155(1):35–41. doi:10.1016/j.virusres.2010.08.009 [PubMed: 20727376]
27. Santos RI, Almeida MFP, Paula FE, et al. Experimental infection of suckling mice by subcutaneous inoculation with Oropouche virus. Virus Research. 2012;170(1):25–33. doi:10.1016/j.virusres.2012.07.006 [PubMed: 22877689]
28. Proenca-Modena JL, Sesti-Costa R, Pinto AK, et al. Oropouche Virus Infection and Pathogenesis Are Restricted by MAVS, IRF-3, IRF-7, and Type I Interferon Signaling Pathways in Nonmyeloid Cells. Doms RW, ed. J Virol. 2015;89(9):4720–4737. doi:10.1128/JVI.00077-15 [PubMed: 25717109]
29. Alvarez-Falconi PP, Ruiz BAR. Brote de Fiebre de Oropuche en Bagazán, San Martín - Perú: Evaluación Epidemiológica, Manifestaciones Gastrointestinales y Hemorrágicas. Revista de Gastroenterología del Perú. Published online 2010:334–340. doi:10.47892/rgp.2010.304.421
30. Pinheiro FP, Rosa da APAT, Rosa da JFST, et al. Oropouche Virus: I. A Review of Clinical, Epidemiological, and Ecological Findings. The American Journal of Tropical Medicine and Hygiene. 1981;30(1):149–160. doi:10.4269/ajtmh.1981.30.149 [PubMed: 6782898]
31. de Oliveira E, Azevedo R do SS, Coelho-dos-Reis JG, et al. IFN-α as a time-sensitive biomarker during Oropouche virus infection in early and late seroconverters. Sci Rep. 2019;9(1):17924. doi:10.1038/s41598-019-54223-w [PubMed: 31784575]
32. Borborema CAT, Pinheiro FP, Albuquerque BC, Rosa da APAT, Dourado HV. Description of the first outbreaks of Oropouche fever recognized in the State of Amazonas. Brazil. Revista do Instituto de Medicina Tropical de São Paulo. 1982;24(3):132–139. [PubMed: 6818662]
33. Tilston-Lunel NL, Acrani GO, Randall RE, Elliott RM. Generation of Recombinant Oropouche Viruses Lacking the Nonstructural Protein NSm or NSs. Williams B, ed. J Virol. 2016;90(5):2616–2627. doi:10.1128/JVI.02849-15
34. Shi X, Kohl A, Léonard VHJ, Li P, McLees A, Elliott RM. Requirement of the N-Terminal Region of Orthobunyavirus Nonstructural Protein NSm for Virus Assembly and Morphogenesis. Journal of Virology. 2006;80(16):8089–8099. doi:10.1128/jvi.00579-06 [PubMed: 16873265]
35. Kreher F, Tamietti C, Gommet C, et al. The Rift Valley fever accessory proteins NSm and P78/NSm-GN are distinct determinants of virus propagation in vertebrate and invertebrate hosts. Emerg Microbes Infect. 2014;3(10):e71. doi:10.1038/emi.2014.71 [PubMed: 26038497]
36. Shi X, Botting CH, Li P, et al. Bunyamwera orthobunyavirus glycoprotein precursor is processed by cellular signal peptidase and signal peptide peptidase. Proceedings of the National Academy of Sciences. 2016;113(31):8825–8830. doi:10.1073/pnas.1603364113

37. Gutierrez B, Wise EL, Pullan ST, et al. Evolutionary Dynamics of Oropouche Virus in South America. Parrish CR, ed. J Virol. 2020;94(5). doi:10.1128/JVI.01127-19
38. Schwarz MM, Price DA, Ganaie SS, et al. Oropouche orthobunyavirus infection is mediated by the cellular host factor Lrp1. Proceedings of the National Academy of Sciences. 2022;119(33):e2204706119. doi:10.1073/pnas.2204706119
39. Barbosa NS, Mendonça LR, Dias MVS, et al. ESCRT machinery components are required for Orthobunyavirus particle production in Golgi compartments. PLOS Pathogens. 2018;14(5):e1007047. doi:10.1371/journal.ppat.1007047
40. Barbosa NS, Concha JO, daSilva LLP, Crump CM, Graham SC. Oropouche Virus Glycoprotein Topology and Cellular Requirements for Glycoprotein Secretion. Journal of Virology. 2022;97(1):e01331–22. doi:10.1128/jvi.01331-22 [PubMed: 36475765]
41. Walsh CES, Robert MA, Christofferson RC. Observational Characterization of the Ecological and Environmental Features Associated with the Presence of Oropouche Virus and the Primary Vector Culicoides paraensis: Data Synthesis and Systematic Review. Tropical Medicine and Infectious Disease. 2021;6(3):143. doi:10.3390/tropicalmed6030143 [PubMed: 34449725]
42. Pereira-Silva JW, Ríos-Velásquez CM, Lima GR de, et al. Distribution and diversity of mosquitoes and Oropouche-like virus infection rates in an Amazonian rural settlement. PLOS ONE. 2021;16(2):e0246932. doi:10.1371/journal.pone.0246932
43. Gaillet M, Pichard C, Restrepo J, et al. Outbreak of Oropouche Virus in French Guiana - Volume 27, Number 10—October 2021 - Emerging Infectious Diseases journal - CDC. doi:10.3201/eid2710.204760
44. Levine KS, Leonard HL, Blauwendraat C, et al. Virus exposure and neurodegenerative disease risk across national biobanks. Neuron. 2023;111(7):1086–1093.e2. doi:10.1016/j.neuron.2022.12.029 [PubMed: 36669485]
45. Ciuoderis KA, Berg MG, Perez LJ, et al. Oropouche virus as an emerging cause of acute febrile illness in Colombia. Emerging Microbes & Infections. 2022;11(1):2645–2657. doi:10.1080/22221751.2022.2136536 [PubMed: 36239235]
46. Xiao Y, Lidsky PV, Shirogane Y, et al. A defective viral genome strategy elicits broad protective immunity against respiratory viruses. Cell. 2021;0(0). doi:10.1016/j.cell.2021.11.023
47. Romero-Alvarez D, Escobar LE, Auguste AJ, Del Valle SY, Manore CA. Transmission risk of Oropouche fever across the Americas. Infectious Diseases of Poverty. 2023;12(1):47. doi:10.1186/s40249-023-01091-2 [PubMed: 37149619]
48. Aguilar PV, Barrett AD, Saeed MF, et al. Iquitos Virus: A Novel Reassortant Orthobunyavirus Associated with Human Illness in Peru. Turell MJ, ed. PLoS Negl Trop Dis. 2011;5(9):e1315. doi:10.1371/journal.pntd.0001315 [PubMed: 21949892]
49. Moutinho S Little-known virus is on the rise in South America. Science. 2024;384(6700):1052–1053. doi:10.1126/science.adq8852 [PubMed: 38843341]
50. Wesselmann KM, Postigo-Hidalgo I, Pezzi L, et al. Emergence of Oropouche fever in Latin America: a narrative review. The Lancet Infectious Diseases. 2024;0(0). doi:10.1016/S1473-3099(23)00740-5
51. Pauvolid-Corrêa A, Campos Z, Soares R, Nogueira RMR, Komar N. Neutralizing antibodies for orthobunyaviruses in Pantanal, Brazil. Aguilar PV, ed. PLoS Negl Trop Dis. 2017;11(11):e0006014. doi:10.1371/journal.pntd.0006014
52. Casseb AR, Silva SP, Casseb LMN, Chiang JO, Martins LC, Vasconcelos PFC. PREVALÊNCIA DE ANTICORPOS CONTRA ARBOVÍRUS DA FAMÍLIA Bunyaviridae EM BÚFALOS DE ÁGUA. Ciênc anim bras. 2015;16:428–436. doi:10.1590/1089-6891v16i327208
53. Dias H, Familiar-Macedo D, Pauvolid-Corrêa A, Barreto Dos Santos F. Exposure of domestic animals to Mayaro and Oropouche viruses in West-central Brazil, 2016–2017. In: ; 2022. Accessed June 25, 2024. https://www.researchgate.net/publication/376750657_Exposure_of_domestic_animals_to_Mayaro_and_Oropouche_viruses_in_West-central_Brazil_2016-2017
54. Anderson CR, Aitken THG, Downs WG, Spence L. Oropouche Virus: a New Human Disease Agent from Trinidad, West Indies *. The American Journal of Tropical Medicine and Hygiene. 1961;10(4):574–578. doi:10.4269/ajtmh.1961.10.574 [PubMed: 13683183]

55. Pinheiro FF, Pinheiro M, Bensabath G, Causey O, Shope R. Epidemia de vírus Oropouche em Belém. Revista de Servico Especial de Saude Publica. 1962;12:15–23.

56. Pinheiro FP, Travassos da Rosa AP, Travassos da Rosa JF, Bensabath G. An outbreak of Oropouche virus diease in the vicinity of santarem, para, barzil. Tropenmed Parasitol. 1976;27(2):213–223. [PubMed: 941251]

57. Pinheiro FP, Travassos Da Rosa APA, Gomes MLC, LeDuc JW, Hoch AL. Transmission of Oropouche Virus from Man to Hamster by the Midge Culicoides paraensis. Science. 1982;215(4537):1251–1253. doi:10.1126/science.6800036 [PubMed: 6800036]

58. Hoch AL, Pinheiro F, Roberts DR, Gomes MLC. Laboratory Transmission of Oropouche Virus by Culex Quinquefasciatus Say. PAHO; 1987:55–61. https://iris.paho.org/bitstream/handle/10665.2/27854/ev21n1p55.pdf?sequence=1

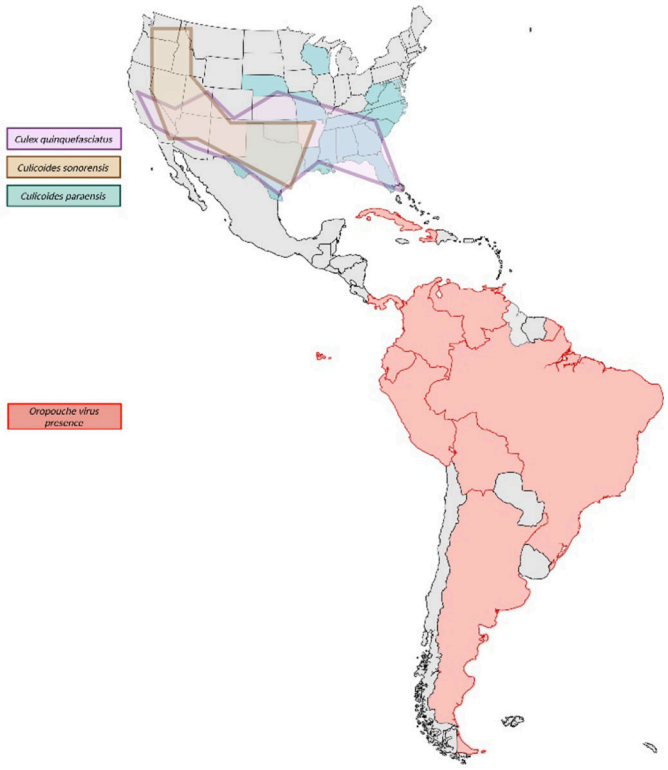

Figure 1:

Countries on which Oropouche virus has been identified (red) and vectors distribution (USA)

Vector distribution in USA adapted from Gorris et al.[21], Shults et al.[23], and Files et al.[1]; Countries on which Oropouche virus has been identified (red) on vertebrates (including humans), adapted from Wesselmann et al.[50] as well as recent report from Cuba [4]

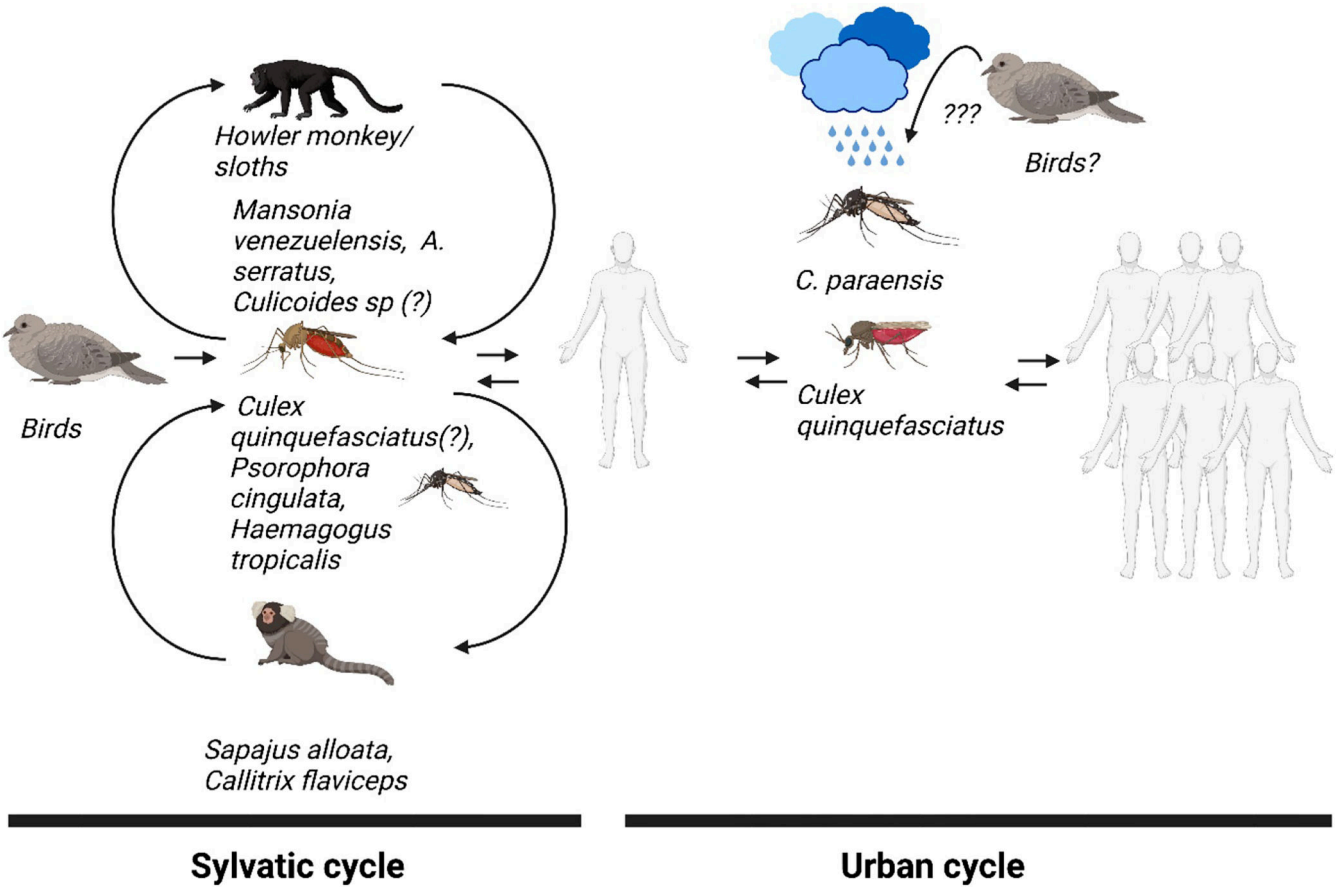

Figure 2:
Oropouche virus transmission cycles

Table 1:

Recent evidence of Oropouche virus infection in vertebrates.

Animal identified	Type of viral identification	Viral transmission cycle	Year of report	Reference
Horse (Equus caballus)	Antibody ($PRNT_{90}$)	Sylvatic/rural	2009–2011	[51]
Sheep (Ovis aries)	Antibody ($PRNT_{90}$)	Sylvatic/rural	2009–2011	[51]
Water buffalo (Bubalus bubalis)	Antibody (HI)	Rural/urban	2009	[52]
Dog (Canis lupus familiaris)	Antibody ($PRNT_{90}$)	Rural/urban	2016–2018	[53]
Cattle (Bos taurus/Bos indicus)	Antibody ($PRNT_{90}$)	Rural/urban	2016–2018	[53]

$PRNT_{90}$ = 90% Plaque Reduction Neutralization Test; HI = Hemagglutination Inhibition test

Table 2:

Oropouche virus vectors reported on the literature.

Arthropod identified	Type of viral identification	Viral transmission cycle	Year of report	Reference
Mansonia venezuelensis (Theobald)	Viral isolation	Sylvatic	1960	54
Aedes scapularis	Experimental (viral isolation)	Sylvatic	1960	54
Aedes serratus	Experimental (viral isolation)	Sylvatic	1960	54
Culex fatigans	Experimental (viral isolation)	Sylvatic	1960	54
Psorophora ferox	Experimental (viral isolation)	Sylvatic	1960	54
Aedes (Ochlerotatus) serratus	Viral isolation	Sylvatic	1960	55
Culex quinquefasciatus	Viral isolation	Urban	1967/1968	56
Culicoides paraensis	Viral isolation	Urban	1975	56
Culicoides paraensis	Experimental (viremic man to hamster)	Urban	1982	57
Culex quinquefasciatus	Experimental (viremic hamster to hamster)	n/a	1987	58
Culex quinquefasciatus	S segment	Urban *	2013	16
Psorophora cingulata	S segment (RT-qPCR)	Sylvatic	2016	42
Haemagogus tropicalis	S segment (RT-qPCR)	Sylvatic	2016	42
Aedes (Ochlerotatus) serratus	S segment (RT-qPCR)	Sylvatic	2016	42
Culex quinquefasciatus **	S segment	Urban	2017/2018	17
Aedes aegypti **	S segment	Urban	2017/2018	17
Culicoides sonorensis	Experimental	Urban	2021	20

* In this report, *C. paraensis* was not present on the surrounding areas using the collection methods described within the article.

** Male mosquitoes