MONTHLY SCIENTIFIC REVIEW ON OROPOUCHE VIRUS

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No. 1

The content of this document is subject to change as the health situation evolves. All informations comes from a valid and credible source.

Editors: Nathan Claveau, Emeline Simon, Tara Brosschot, Eric Rosenthal, Diana Molino, Douae Ammour, Mario Delgado-Ortega, Rachel Bellone, Dahlia Chebbah, Erica Telford, Sandrine Halfen, France Lert, Yoann Allier, Mathilde Certoux, Armelle Pasquet and Eric D'Ortenzio

ANRS Emerging Infectious Diseases - Paris, France
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General informations

This section details the history and latest developments of the outbreak, with significant events and updates on its current status.

The Oropouche virus (OROV) was first detected in 1955 in Trinidad and Tobago in the Caribbean near the Oropouche River. Since then, it has primarily affected South and Latin America, especially Brazil, Panama, Peru, Argentina, Bolivia, Colombia, Ecuador, and French Guiana. As of 2023, the virus has caused large outbreaks not only in historically endemic regions but also in new areas. By September 10, 2024, **the Americas reported 9,852 confirmed cases and 2 deaths** in six countries: Bolivia (356 cases), Brazil (7,931 cases and 2 deaths), Colombia (74 cases), Cuba (506 cases), Peru (930 cases), and recently the Dominican Republic (33 cases).

Cuba reported its first Oropouche outbreak in June 2024 with 500 confirmed cases and over 10,000 suspected cases, according to PAHO by September 23. While this outbreak did not lead to severe cases, it marked an unprecedented geographic expansion of the virus. In the Dominican Republic, 33 cases, including 3 deaths, have been confirmed to date, according to PAHO as of September 23.

As of September 13, 2024, 22 imported OROV disease cases have been detected from the US (21) and Canada (1). By August 20, 2024, 23 imported cases were reported by ECDC: 3 in Germany, 6 in Italy, 12 in Spain, 1 in the Netherlands, and 1 in France. Of these patients, 22 had returned from Cuba, and 1 from Brazil. **Vertical transmission of Oropouche virus** from mother to fetus had not been documented until five possible cases were identified in Brazil by July 30, 2024.

Scientific articles

This section presents relevant articles published on peer-reviewed scientific journals or pre-print platforms.

Replication-Competent Oropouche Virus in Semen of Traveler Returning to Italy from Cuba, 2024. Castilletti C, Huits R, Mantovani RP, Accordini S, Alladio F, Gobbi F.

Published in *Emerg Infect Dis* on 7 octobre 2024.
https://doi.org/10.3201/eid3012.241470

A febrile man in Italy who had traveled to Cuba in July 2024 was diagnosed with Oropouche fever. Reverse transcription PCR detected prolonged shedding of Oropouche virus RNA in whole blood, serum, urine, and semen. Sixteen days after symptom onset, replication-competent virus was detected in semen, suggesting risk for sexual transmission.

Human outbreaks of a novel reassortant Oropouche virus in the Brazilian Amazon region. Naveca FG, de Almeida TAP, Souza V, Nascimento V, Silva D, Nascimento F, Mejía M, de Oliveira YS, Rocha L, Xavier N, Lopes J, Maito R, Meneses C, Amorim T, Fé L, Camelo FS, de Aguiar Silva SC, de Melo AX, Fernandes LG, de Oliveira MAA, Arcanjo AR, Araújo G, André Júnior W, de Carvalho RLC, Rodrigues R, Albuquerque S, Mattos C, Silva C, Linhares A, Rodrigues T, Mariscal F, Morais MA, Presibella MM, Marques NFQ, Paiva A, Ribeiro K, Vieira D, da Silva Queiroz JA, Passos-Silva AM, Abdalla L, Santos JH, de Figueiredo RMP, Cruz ACR, Casseb LN, Chiang JO, Frutuoso LV, Rossi A, Freitas L, de Lima Campos T, Wallau GL, Moreira E, Lins Neto RD, Alexander LW, Sun Y, de Filippis AMB, Gräf T, Arantes I, Bento AI, Delatorre E, Bello G.

Published in *Nat Med* on 18 September 2024.
https://doi.org/10.1038/s41591-024-03300-3

In this study, the authors sequenced and analyzed 382 Oropouche virus (OROV) genomes from human samples collected in five Brazilian states, between August 2022 and February 2024, to uncover the origin and genetic evolution of OROV in the current outbreak. Genomic analyses revealed that the upsurge of OROV cases in the Brazilian Amazon coincides with spread of a novel reassortant lineage containing the M segment of viruses detected in the eastern Amazon region (2009-2018) and the L and S segments of viruses detected in Peru, Colombia, and Ecuador (2008-2021). The novel reassortant likely emerged in the Amazonas state between 2010 and 2014 and spread through long-range dispersion events during the second half of the 2010s. Phylodynamics reconstructions showed that the current OROV spread was mainly driven by short-range (< 2 km) movements consistent with the flight range of vectors. Nevertheless, a substantial proportion (22%) of long-range (> 10 km) OROV migrations were also detected, consistent with viral dispersion by humans. This data provides a view of the unprecedented spread and evolution of OROV in Brazilian western Amazon region.

Emergence of Oropouche fever in Latin America: a narrative review. Wesselmann KM, Postigo-Hidalgo I, Pezzi L, de Oliveira-Filho EF, Fischer C, de Lamballerie X, Drexler JF.

Published in *Lancet Infect Dis* on 17 September 2024.
https://doi.org/10.1128/jvi.00354-24

Oropouche fever has been suggested to be one of the most important vector-borne diseases in Latin America. However, both literature on OROV and genomic sequence availability are scarce, with few contributing laboratories worldwide. Due to unspecific symptoms, laboratory diagnostics are crucial. Several laboratory tests have been developed but robust commercial tests are hardly available. These potential non-human vertebrate reservoirs have not been systematically studied. Robust animal models to investigate pathogenesis and immune responses are not available. Epidemiology, pathogenesis, transmission cycle, cross-protection from infections with OROV reassortants, and the natural history of infection remain unclear. This Review identifies Oropouche fever as a neglected disease and offers recommendations to address existing knowledge gaps, enable risk assessments, and ensure effective public health responses.

Oropouche Fever, Cuba, May 2024. Benitez AJ, Alvarez M, Perez L, Gravier R, Serrano S, Hernandez DM, Perez MM, Gutierrez-Bugallo G, Martinez Y, Companioni A, Peña C, de Armas JR, Couto D, Betancourt I I, Sanchez MR, Resik S, Kouri V, Guzman MG.

Published in *Emerging Infectious Diseases* on 10 September 2024.
https://doi.org/10.3201/eid3010.240900

This study, conducted in Cuba in 2024, investigated 89 patients from Santiago de Cuba and Cienfuegos, most were negative for dengue, Zika, and chikungunya viruses. However, Oropouche virus (OROV) was detected in 83.1% of serum samples and 83.3% of urine samples through PCR analysis. Phylogenetic analysis revealed that the Oropouche virus strains in Cuba were closely related to those from Brazil. Further investigation into vectors identified the presence of OROV in *Culex quinquefasciatus* mosquitoes and biting midges (Ceratopogonidae), suggesting these insects could play a role in virus transmission. Vector control measures were implemented to curb the outbreak, with no severe or fatal cases reported.

Oropouche Virus (OROV) in Pregnancy: An Emerging Cause of Placental and Fetal Infection Associated with Stillbirth and Microcephaly following Vertical Transmission. Schwartz DA, Dashraath P, Baud D.

Published in *Viruses* on 9 September 2024.
https://doi.org/10.3390/v16091435

This review examines the biology, epidemiology, and clinical features of OROV, summarizes the 2023-2024 Oropouche virus epidemic, and describes the reported cases of vertical transmission and congenital infection, fetal death, and microcephaly in pregnant women with Oropouche fever, addresses experimental animal infections and potential placental pathology findings of OROV, and reviews other bunyavirus agents that can cause vertical transmission. Recommendations are made for pregnant women travelling to the regions affected by the epidemic.

Potential vertical transmission of Oropouche virus during the current outbreak. Samara A, Coutinho CM, Veal P, Osborne J, Duarte G, Ladhani S, Khalil A.

Published in *Lancet Infect Dis* on 9 September 2024.
https://doi.org/10.1016/s1473-3099(24)00571-1

Following the Oropouche virus RNA detection both in muliple tissues of a foetus that died at 30 weeks' gestation and in the post motem tissues of a 47-day-old baby with microencephalopathy, the authors alert clinicians for the risk of Oropouche infection in pregnant women with fever. They recommend pregnant women to discuss travel risks with their health-care provider, especially when travelling to areas with diseases such as Oropouche virus and Zika virus. They conclude that internationally, countries, including those that have not previously encountered Oropouche virus, need to enhance surveillance and develop effective testing for suspected cases, including in pregnant women.

Oropouche Virus Disease Among U.S. Travelers — United States, 2024. Morrison A, White JL, Hughes HR, Guagliardo SAJ, Velez JO, Fitzpatrick KA, Davis EH, Stanek D, Kopp E, Dumoulin P, Locksmith T, Heberlein L, Zimler R, Lassen J, Bestard C, Rico E, Mejia-Echeverri A, Edwards-Taylor KA, Holt D, Halphen D, Peters K, Adams C, Nichols AM, Ciota AT, Dupuis AP 2nd, Backenson PB, Lehman JA, Lyons S, Padda H, Connelly RC, Tong VT, Martin SW, Lambert AJ, Brault AC, Blackmore C, Staples JE, Gould CV.

Published in *CDC* on 5 September 2024.
https://doi.org/10.15585/mmwr.mm7335e1

Following the Oropouche virus RNA detection both in muliple tissues of a foetus that died at 30 weeks' gestation and in the post motem tissues of a 47-day-old baby with microencephalopathy, the authors alert clinicians for the risk of Oropouche infection in pregnant women with fever. They recommend pregnant women to discuss travel risks with their health-care provider, especially when travelling to areas with diseases such as Oropouche virus and Zika virus. They conclude that internationally, countries, including those that have not previously encountered Oropouche virus, need to enhance surveillance and develop effective testing for suspected cases, including in pregnant women.

Oropouche virus genomic surveillance in Brazil. Moreira FRR, Dutra JVR, de Carvalho AHB, Reis CR, Rios JSH, Ribeiro MO, Arruda MB, Alvarez P, Souza RP, Voloch C, Zauli DAG, Aguiar RS.

Published in *Lancet Infect Dis* on 26 August 2024.
https://doi.org/10.1016/s1473-3099(24)00558-9

In this correspondance paper, the authors conducted a rapid nationwide survey using molecular diagnosis and whole-genome sequencing to investigate the emergence and spread of Oropuche virus (ORPV) across Brazil. They screened 30 clinical samples and identified six positive cases. They conducted a series of bioinformatic analyses, which show that these viruses clustered with high statistical support in two monophyletic clades dated between late 2023 and early 2024. Clade 1 comprises four sequences dated between November 2023 and February 2024; clade 2 comprises two sequences dated between December 2023 and April 2024. These clades cluster with sequences from the lineage that circulated in the epidemic in north Brazil. This analysis confirmed the previously reported reassortment pattern. Phylogenetic methods also support the emergence of diverse non-synonymous substitutions. Although limited by sample size, these results suggest multiple exports of OROV from north Brazil to other regions between 2023 and 2024, leading to autochthonous chains of transmission and the accumulation of mutations with potential phenotypic effects.

Oropouche fever: reports of vertical transmission and deaths in Brazil. Martins-Filho PR, Carvalho TA, Dos Santos CA.

Published in *Lancet Infect Dis* on 22 August 2024.
https://doi.org/10.1016/s1473-3099(24)00557-7

This communication examines the biology, epidemiology, and clinical features of OROV, summarizes the 2023–2024 Oropouche virus epidemic, and describes the reported cases of vertical transmission and congenital infection, fetal death, and microcephaly in pregnant women with Oropouche fever, addresses experimental animal infections and potential placental pathology findings of OROV, and reviews other bunyavirus agents that can cause vertical transmission. Recommendations are made for pregnant women travelling to the regions affected by the epidemic.

Oropouche fever outbreak in Brazil: an emerging concern in Latin America. Sah R, Srivastava S, Kumar S, Golmei P, Rahaman SA, Mehta R, Ferraz C, Apostolopoulos V, Rodriguez-Morales AJ.

Published *Lancet Microbe* on 3 July 2024.
https://doi.org/10.1016/s2666-5247(24)00136-8

Since 2023, a sharp rise in cases has been reported, with over 5,000 cases in Brazil alone in 2024. Factors such as urbanization, deforestation, and climate change exacerbate the spread of the disease. Preventive measures like insect repellents, protective clothing, and early medical attention are recommended for those in endemic regions. Increased awareness, prevention, and surveillance are vital to managing the outbreak.

The search for an antiviral lead molecule to combat the neglected emerging Oropouche virus. Peinado RDS, Saivish MV, Menezes GL, Fulco UL, da Silva RA, Korostov K, Eberle RJ, Melo PA, Nogueira ML, Pacca CC, Arni RK, Coronado MA.

Published *Current Research in Microbial Sciences* on 24 April 2024.
https://doi.org/10.1016/j.crmicr.2024.100238

This study focuses on the research of natural molecules as potential antiviral compounds against Oropouche virus (OROV), a member of the Peribunyaviridae family and the causative agent of a dengue-like febrile illness transmitted by mosquitoes. Wedelolactone (WDL), a coumestan derived from Eclipta prostrata (Asteraceae), has been demonstrated to inhibit some viral proteins (HIV integrase and HCV RNA dependent RNA polymerase), and virus replication (HCMV), making it useful to target a wide range of viruses. Authors report the in silico effects of WDL on the OROV N-terminal polymerase and its potential inhibitory effects on several steps of viral infection in mammalian cells in vitro, which revealed that WDL indeed acts as a potential inhibitor molecule against OROV infection.

This section provides a digested list of a more extensive content accessible in Excel format here.

Relevant news

This section presents official reports from health agencies, manufacturers and press releases with reliable sources.

Mysterious Oropouche virus is spreading: what you should know

Published by *Nature* on 30 September 2024.
https://www-nature-com.proxy.insermbiblio.inist.fr/articles/d41586-024-02746-2

The virus is endemic to the Amazon but is now spreading outside the region — and has been linked to human deaths for the first time.

WHO launches global strategic plan to fight rising dengue and other Aedes-borne arboviral diseases

Published by WHO on 3 October 2024.
https://www.who.int/news/item/03-10-2024-who-launches-global-strategic-plan-to-fight-rising-dengue-and-other-aedes-borne-arboviral-diseases

The WHO has launched a Global Strategic Plan to combat rising dengue and other Aedes-borne arboviral diseases, emphasizing the need for enhanced surveillance and vector control. This one-year plan requires $55 million to address these threats, focusing on vulnerable populations in endemic regions. The initiative highlights the importance of community engagement and collaborative efforts, essential for controlling both dengue and Oropouche virus outbreaks.

Mysterious Oropouche virus is spreading: what you should know

Published by Nature on 30 September 2024.
https://www-nature-com.proxy.insermbiblio.inist.fr/articles/d41586-024-02746-2

The virus is endemic to the Amazon but is now spreading outside the region — and has been linked to human deaths for the first time.

Imported Oropouche virus cases continue steady US rise

Published by CIDRAP on 18 September 2024.
https://www.cidrap.umn.edu/oropouche-virus/imported-oropouche-virus-cases-continue-steady-us-rise

The CDC reported a total of 74 imported Oropouche virus cases in the U.S., primarily in Florida and linked to travel to Cuba, while raising concerns about severe fetal outcomes associated with the virus.

Oropouche cases in Americas near 10,000

Published by CIDRAP on 9 September 2024.
https://www.cidrap.umn.edu/oropouche-virus/oropouche-cases-americas-near-10000

PAHO reported 1,774 new Oropouche virus cases in the Americas, mostly from Brazil, Peru, and Cuba, with the Dominican Republic now affected and severe fetal outcomes reported, including 11 fetal deaths in Brazil.

PAHO publishes update on Oropouche fever in the Americas

Published by PAHO on 10 September 2024.
http://www.paho.org/en/news/10-9-2024-paho-publishes-update-oropouche-fever-americas

PAHO's latest update reports 9,852 confirmed Oropouche virus cases in the Americas, with Brazil accounting for the majority. The report emphasizes increasing surveillance and prevention efforts, especially for pregnant women, as cases of fetal death and congenital anomalies have been linked to the virus. The update highlights the urgent need for vector control measures due to the virus's spread to previously unaffected areas.

PAHO upgrades Oropouche virus risk, probes more fetal deaths

Published by CIDRAP on 5 August 2024.
https://www.cidrap.umn.edu/oropouche-virus/paho-upgrades-oropouche-virus-risk-probes-more-fetal-deaths

PAHO has upgraded the risk level for Oropouche virus due to a rise in fetal deaths in Brazil, emphasizing the need for improved surveillance and health responses in affected regions.

PAHO urges countries to strengthen prevention, surveillance and diagnosis of the Oropouche virus following its geographic spread and recent clinical findings

Published by PAHO on 2 August 2024.
https://www.paho.org/en/news/2-8-2024-paho-urges-countries-strengthen-prevention-surveillance-and-diagnosis-oropouche-virus

PAHO has urged countries to enhance prevention, surveillance, and diagnosis of the Oropouche virus, stressing the need for improved laboratory capacities and timely reporting of cases. It also highlights the importance of training healthcare providers to identify the virus effectively and implementing robust vector control strategies to mitigate its spread.

Virus spreading in Latin America may cause stillbirths and birth defects

Published by Science on 20 July 2024.
https://www.science.org/content/article/virus-spreading-in-latin-america-may-cause-stillbirths-and-birth-defects

Oropouche virus could be linked to brain malformation and stillbirths, Brazilian health officials say.

Fact sheets

This section provides a short overview of of the epidemiology, virology, clinical features and risk assessment related with the disease.

Oropouche disease is an arboviral disease caused by the Oropouche virus (OROV), a single-stranded RNA virus belonging to the *Orthobunyavirus* genus of the *Peribunyaviridae* family. This virus is endemic in several regions of Central and South America, as well as the Caribbean, where it actively circulates. Human transmission primarily occurs through the bite of small midges of the *Culicoides* genus (*Culicoides paraensis*), which inhabit forested and humid areas.

After OROV infection, **the incubation period ranges from 3 to 10 days**. Symptoms are often non-specific and can easily be confused with other arboviruses like Dengue, Chikungunya, or Zika. Patients may experience fever, headaches, nausea, joint and muscle pain, conjunctivitis, and abdominal pain. However, about **80% of infected individuals remain asymptomatic**. Recovery typically takes about a week, though it may extend for several weeks in some cases. Around 4**% of symptomatic cases may develop severe, neuroinvasive forms**, including meningitis and encephalitis. **Vertical transmission** of the virus, from mother to child during pregnancy, is still being studied.

Diagnosis of Oropouche disease relies on several methods. Virus detection via RT-PCR is possible between days 1 and 7 after symptom onset. Serological tests like ELISA can detect IgM and IgG antibodies, which appear from day 1 to two weeks after illness onset. Biological samples used for these tests include serum, saliva, and urine. In patients with signs of neuroinvasive disease, cerebrospinal fluid analysis can also be performed.

Treatment is primarily symptomatic, focusing on hydration, pain relief, and antipyretics. **No specific antiviral treatment** is currently available. As with Dengue, the use of aspirin and nonsteroidal anti-inflammatory drugs is discouraged to reduce the risk of bleeding. Although several antiviral candidates have been tested against OROV, none have proven effective. Ribavirin, tested in vitro on mice, showed no antiviral activity against OROV, though it was effective against other *Orthobunyaviruses* like Tacaiuma and Guama viruses. Favipiravir has not yet been tested against OROV but has shown efficacy against other viruses in the *Peribunyaviridae* family.

There is **currently no vaccine for Oropouche**. A preclinical study evaluated a vaccine candidate based on vesicular stomatitis virus (VSV) expressing OROV glycoproteins. This study demonstrated protection in mice, with reduced viral loads after exposure to the virus.

Diagnosis and care

This section offers a short overview of currently available countermeasures and recommendations for diagnosis, prevention and care.

Currently, Oropouche is an underdiagnosed disease because its clinical symptoms overlap with those of other arboviruses like Dengue, Chikungunya, and Zika, requiring laboratory confirmation, which delays diagnosis. Developing rapid diagnostic tests for OROV would enable early virus detection.

Moreover, no specific antiviral treatment is currently available, and very few clinical trials have been conducted in humans. Ribavirin, mycophenolic acid, and IFN-α have been tested for OROV. In vitro studies showed that ribavirin and mycophenolic acid lacked antiviral activity against OROV, unlike for two other *orthobunyaviruses*, Tacaiuma virus and Guama virus. IFN-α showed limited in vitro activity, dependent on dose and timing of treatment. Favipiravir has not yet been tested for OROV but shows promising activity against several related *Peribunyaviridae* viruses.

Developing an effective vaccine is also a priority, though studies are still scarce. Immunoassays have identified several epitopes for potential vaccine candidates, particularly T and B cell epitopes from the OROV polyprotein. Recently, a candidate vaccine based on vesicular stomatitis virus expressing OROV glycoproteins protected mice from viral challenge by reducing viral load. Cross-protection with existing vaccines against other viruses should also be explored.

Guidelines and practical information

This section lists official manuals of recommendations for clinical practice or public health policy published by leading health organizations.

20 September 2024	Updated Interim Guidance for Health Departments on Testing and Reporting for Oropouche Virus Disease (CDC)
10 September 2024	Interim Guidance for Evaluating and Managing Infants Born to Pregnant People with Confirmed or Probable Oropouche Virus Disease (CDC)
9 August 2024	Threat Assessment Brief - Oropouche virus disease cases imported into the European Union (ECDC)
3 August 2024	Public Health Risk Assessment related to Oropouche Virus (OROV) in the Region of the Americas. (PAHO)
17 July 2024	Recommendations for the Detection and Surveillance of Oropouche in possible cases of vertical infection, congenital malformation, or fetal death. (PAHO)