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News & Views

Why to be serious about re-emergence of an obscure animal virus

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INTRODUCTION

Virus from forest to human nearest

Almost unknown or very little known, an obscure insect-borne animal virus named Oropouche virus (OROV), suddenly appeared in an explosive manner across Brazil during 2024. Oropouche fever is a neglected tropical disease. Long back in 1955, Oropouche virus (strain TRVL 9760) was first isolated from the blood of a febrile forest worker in the village of Vega de Oropouche, near the Oropouche River in Trinidad and Tobago, West Indies. Subsequently on 18th October 1960, another strain of OROV (TRVL 35111) was isolated from a pool of 177 mosquitoes (*Coquillettidia venezuelensis*) collected in bush forest, Nariva Swamp, Trinidad. This second strain (TRVL 35111) was antigenically closely related to the earlier detected strain TRVL 9760 (prototype strain) by complement fixation (CF) and virus neutralization (NT) tests (Anderson et al., 1961). OROV causes acute febrile symptoms with common clinical symptoms like that of dengue fever. Symptoms are typically biphasic with an acute phase of 2–4 days, followed by a remission and a resurgence of symptoms. It is a self-limiting disease. So, patients recover without sequel. However, persistent myalgia and asthenia may continue up to1 month (Gaillet et al., 2021). In 1960, the OROV was detected from a three toed sloth (*Bradypus tridactylus*) captured near a forest area of eastern Brazil and from a pool of *Ochlerotatus serratus* mosquitoes captured nearby area. Both mammal and insect were found to be positive for Oropouche virus. In the same time, nearly 11,000 human cases from Belem city of Brazil were detected as suspicious of Oropouche fever (Pinheiro et al., 1962). All these indicated the involvement of animal species and zoonotic importance of this virus. During 2008, while carrying out an active epidemiological sero surveillance and prospective study of acute febrile cases in northern Brazil, it had shown the evidence of circulation of at least five viruses of the *Peribunyaviridae* family in Brazil, one of these was Oropouche virus. Findings of that study confirmed the re-emergence of the virus (Vasconcelos et al., 2009). During May 2024, Cuba reported its first case of OROV. Certainly, the virus has remained endemic in the Amazon Basin, but now its portrait has expanded beyond the rainforest. It is apprehending for an epidemic for Brazil (Moutinho, 2024a). More detail about the migratory path of OROV from Brazil to Italy then Europe, America and Canada has been described in a recent review (Salvato, 2025).

Animal large or small virus detected in all

In February 2000, the OROV strain BeAN 626998 was isolated from a sylvatic monkey (genus *Callithrix*) from Grande Sertão Veredas National Park of Brazil. When mice were injected intracerebrally with the OROV strain BeAN 626998 and BeAn 626990, all of them showed signs of the disease (Nunes et al., 2005). As per laboratory findings, animal models of OROV infection are restricted to rodent models. As of now hamster and mouse models have been reported as susceptible host for OROV infection but these models do not support to amplify genetically reassorted variants. Similarly, OROV causes systemic disease analogous to humans, as well as liver injury and severe neurological symptoms in immunocompetent Syrian golden hamster (Rodrigues et al., 2011). Therefore, it is a subject of concern to animal scientist as because this virus circulates among birds, sloths, and non-human primates. The virus is transmitted to human due to biting of one kind of mosquito species known as *Culicoides paraensis*.

Virus once unknown now well grown

OROV (*Orthobunyavirus oropoucheense*) is an arthropod-borne RNA virus classified within the order *Bunyavirales*, family *Peribunyaviridae* and genus *Orthobunyavirus* (International Committee on Taxonomy of Viruses [ICTV], 2025). In brief, OROV genome consists of tri partite, single-stranded, negative-sense RNAs, named: S (small, ~ 0.7 kb), M (medium, ~ 4.4 kb), and L (large, ~ 6.9 kb) segments (Elliott, 2014). The S segment encodes the nucleocapsid and a non-structural protein (NSs); the

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M segment encodes the two glycoproteins Gc and Gn, and a non-structural protein (NSm); and the L segment encodes the RNA-dependent RNA polymerase. Sequencing N gene (SRNA) of 28 different OROV strains indicated the presence of 3 genotypes, designated I, II, and III, as described in an earlier report (Saeed et al., 2000). Due to reassortment in viral genome, three distinct lineages; Iquitos virus (IQTV), Madre de Dios virus (MDDV), and Perdões virus (PDEV) are in circulation. Out of these, MDDV and IQTV have been associated with human diseases (Usuga et al., 2024). Genetic analyses of OROV isolated from Iquitos (capital city of Peru), was found to be a novel reassortment containing the S and L segments of OROV and the M segment of a novel Simbu sero group virus. This new virus was designated as IQT first isolated during 1999 from city Iquitos and subsequently was responsible for outbreaks of "Oropouche fever" during 2005 and 2006 in Iquitos (Aguilar et al., 2011). During the current outbreak, more than 10,000 laboratory-confirmed cases have been reported from Brazil alone. Why the virus exploded so intensely with re-emergence during 2023-24 remained indeterminate until exploratory *in vitro* data published in 2025 suggest that the increased incidence might be related to viral factors underlying the 2024 outbreak. Substantial evidence has directed towards appearance of a new revised version of the virus that replicates faster and to higher titres in mammalian cells within 24 hours after infection. New incarnation of this virus has shown better fitness than the prototype BeAn 19991 strain as previous immunity is too frail to neutralise the new variant generated due to genetic reassortment. Unlike most of the insect-borne viruses having single segment RNA, the genome of Oropouche virus harbouring three-segment RNA genome that makes it vulnerable for swapping RNA segments resulting creation of new variants. Due to genetic reassortment, new variant gained immune evasion property and amplify rapidly resulting in high infectivity among human population (The Lancet, 2024). Within an infected host, when a host cell is co-infected by multiple viruses, exchange of gene segments takes place resulting releases of progeny viruses with new genome combinations, thereby, mutants and variants remain in circulation (Schwartz, 2025). These mutants are amalgamation of S and L segments of different OROV strains. Sequencing data and phylogenetic analysis of the 2023-24 epidemic isolate (AM0088) with the historical prototype strain BeAn19991 indicated genetic reassortment of its RNA genome (Scachetti et al., 2025). As per research finding, mouse anti-sera against IQTV can sparsely neutralise OROV, indicating past infection with OROV does not protect against disease with IQT9924 (IQT) virus, signifying prevalence of distinct serotypes, without reciprocal protecting effect (Aguilar et al., 2011).

Disease status from adult to foetus

Affected human being exhibit mild symptoms with fever and headache, muscle and joint pain, dizziness, nausea, and vomiting. However, neurological damage such as meningoencephalitis is observed in severe cases that may ends with fatality. Similarly, pregnancy complications like stillbirths and congenital disabilities are commonly observed with this virus. Since 1982, Pan American Health Organization (PAHO) has alerted with the report of miscarriages in two pregnant women infected with Oropouche virus (Quaglia, 2024). On 12th July 2024, the Brazilian Ministry of Health reported four cases of microcephaly in newborns of infected mothers and one foetal death that might be associated with the OROV. On 17th July 2024, PAHO has asked other countries to remain vigilant for similar cases as a precautionary measure to curtail the spread of the disease (Moutinho, 2024b). As per report published in *Lancet*, the OROV IgM was detected in six of 68 newborns with microcephaly of unknown cause. RNA fragment of OROV was detected in pleural fluid, CSF, brain, heart, liver, lung, and kidney in one of the infants born in 2024 and died on day 47 of its birth. These data suggested the possibility of vertical transmission of Oropouche virus in pregnant mother (das Neves Martins et al., 2025). Presence of OROV specific antibodies in the blood and cerebrospinal fluid of babies born with microcephaly provide evidence either vertical transmission of virus from mother to foetus or passive transfer of maternal antibody to offspring. Simultaneously detection of viral RNA from OROV in the umbilical cord as well from the brain, liver, kidneys, lungs, heart, and spleen of a still born at 30 weeks of gestation provide substantial evidence of viral transmission to cross the placental barrier of mother to reach the developing foetus (Moutinho, 2024b).

Virus reservoir source of spillover

Mammals and wild birds act as natural reservoirs for Oropouche virus in its sylvatic cycle. Potential reservoirs for this virus include sloths, non-human primates (*Sapajus paella*, *Alouatta caraya*), and rodents (Proechimys species). OROV specific antibodies in birds, have been found in members of the *Formicariidae*, *Fringillidae*, *Thaurapidae*, and

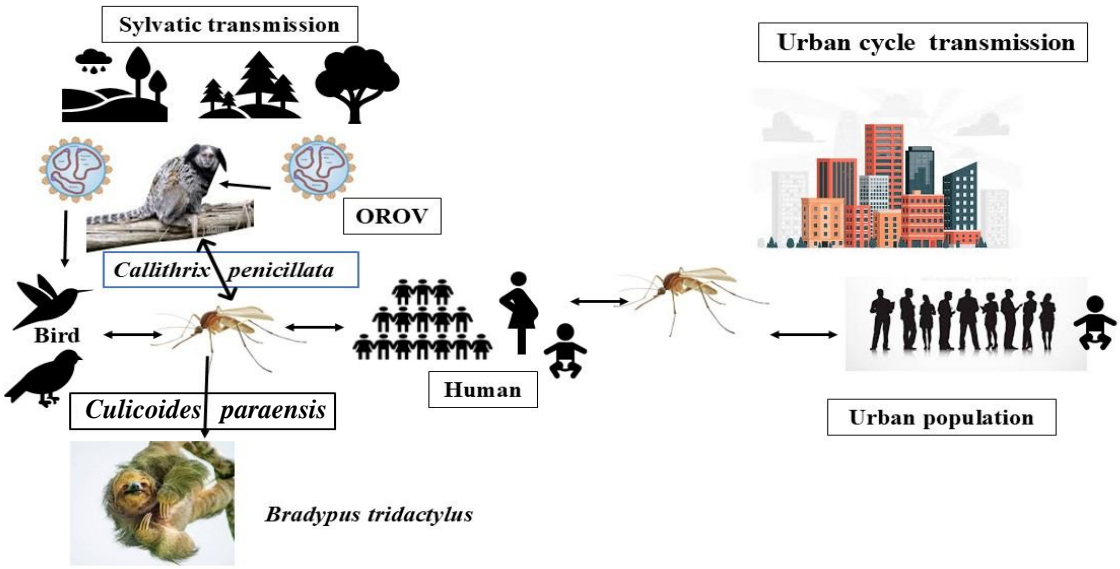

Fig. 1. Transmission cycle of Oropouche virus from animal to man

Columbidae families; nevertheless, more explanation is awaiting to prove these species as prime suspect for viral dissemination (Romero-Alvarez & Escobar, 2018). As per published literature, antibodies against OROV were detected in Pigeons, Duck, monkeys, rodents, chickens, and wild and domestic birds (Pinheiro et al., 1981). Detection of virus-neutralizing antibodies against OROV in cattle and dogs, have suggested a previous exposure of these domestic animals to OROV and might be playing role in the virus enzootic cycle (Dias et al., 2024). Once vectors and susceptible hosts coexist at certain densities there is ample chance of virus spread to other susceptible hosts including human population (Couto-Lima et al., 2017). OROV is probably maintained through a sylvatic and an urban cycle. Interestingly humans are the suspected link between the sylvatic and urban transmission cycles as the vector *C. paraensis* is present both urban and rural location (Fig.1). Humans are the major vertebrate hosts in the urban cycle of OROV. It is not clear whether the virus spread occurs with the movement of human or animal. Whether insect vector is prime cause of virus spread has been less discussed. Under laboratory situation using hamster-human infection have shown biting midge (*C. paraensis*) as major vector for this virus. Experimental transmission of Oropouche virus from man to hamster was achieved 6 to 12 days after *C. paraensis* had sucked the infective blood meal. Contrary to it, field survey has shown low probability to victimised *C. paraensis* (Diptera: *Ceratopogonidae*) for disease transmission as near about thousands of midges (1:12,500) are required for virus isolation (Pinheiro et al., 1982).

Diagnosis and prognosis

Prognosis of the disease ends with recovery but may cause meningoencephalitis in neonatal. Preferably conventional test like HI, complement fixation test, and ELISA is performed to detect OROV specific IgM and IgG, whereas for virus isolation, newborn mice and cell culture provide high success rate. Several cell cultures such as C6/36, Vero, BHK-21, MA III, LCM-MK2, and primary chicken embryo fibroblasts, support replication of OROV causing cell destruction of monolayers as characteristic cytopathic effect (Pinheiro et al., 1981). Presently RT-PCR and Real time PCR is more sensitive and specific too. As of now no vaccine is available to control the virus in endemic area.

Conclusion

Prepare and care

Till 25th November 2024, cumulative data collected and published by WHO on 5th December 2024, a total of 11,634 confirmed Oropouche cases, including two deaths, have been reported in the American regions, across ten countries and one territory (World Health Organization [WHO], 2024). Currently the spread of this virus has been subsided and no new case has been reported since early September 2024 (Quaglia, 2024). Geographically, India is located far away from Brazil. Hence, we may expect that there is a remote chance of migration of infected animal or vector carrying OROV to spread the disease in Indian soil. With this reasoning, we may think India will remain safe from OROV but absolute freedom from this virus is an unrealistic thought. Factors such as migration, trade, tourism, and

transportation networks are major driving force allowing the virus to establish itself in geographically distant and ecologically diverse regions as predicted in a recent report (Naveca et al., 2024). In modern world, infectious virus movement in a pandemic speed through flight mode transport is unarguably true that we have already experienced during COVID-19 period. Keeping this in mind, on 17th July 2024 PAHO has already warned; countries those are not yet under the grip of OROV to remain watchful as a precautionary measure to limit the spread of this virus. No evidence of human-to-human transmission of this virus has been confirmed yet. There is no specific antiviral treatment or vaccine available for Oropouche virus. Based on the current information WHO advises travel or trade restrictions to the affected counties for the time being as a precautionary measure, but we must remain vigilant to block the unusual nature of the virus spread.

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