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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 *Peribunyaviridiae*, 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 *Coquillettidia 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].

OVD 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.

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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.

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