Chapter 6
Oropouche Fever: A Growing Threat in Latin America

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6.1 Introduction

Oropouche virus (OROV), which causes Oropouche fever (OROF), was originally isolated in 1955 from the blood of a feverish forest worker, who resided in a village called Vega de Oropouche in Trinidad and Tobago (Anderson et al. 1961). OROV is an arthropod-borne virus (or arbovirus) that is maintained in a transmission cycle involving midges as the arthropod vector and multiple vertebrates as potential wildlife hosts (Sakkas et al. 2018).

Following its isolation in Trinidad and Tobago, a large epidemic of OROV was reported in 1961 in Belem, Brazil, involving an estimated 11,000 people. In 1992, an outbreak of OROF was reported for the first time in the city of Iquitos, Peru (Aguilar et al. 2011; Travassos da Rosa et al. 2017). The virus has also been detected in Central America, where it was originally isolated in 1989 from febrile patients in

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Panama during a dengue monitoring program (Travassos da Rosa et al. 2017). Epidemiologic surveillance has also detected OROV circulation in several South American countries including Bolivia, Ecuador, Colombia, and Venezuela (Azevedo et al. 2007; Forshey et al. 2010; Gómez-Camargo et al. 2021; Navarro et al. 2016; Nunes et al. 2005; Wise et al. 2020). More recently, OROF cases have been recognized in the Caribbean country of Haiti in 2014 (Elbadry et al. 2021) and French Guiana in 2020 (Gaillet et al. 2021) highlighting the emerging potential and vast geographic distribution of OROV (Fig. 6.1). In 2024, an extensive outbreak has been reported in Cuba for the first time and then, 19 imported cases of Oropouche fever were reported for the first time in European Union countries: Spain, Italy, and Germany (www.ecdc.europa.eu/oropouche-cases-imported-europ). Eighteen of the cases had a travel history to Cuba and one to Brazil, but also 11 cases in Florida, ex Cuba, being then a warning about the importance of OROV as a growing global health problem, if the virus found competent vectors and hosts to develop a local

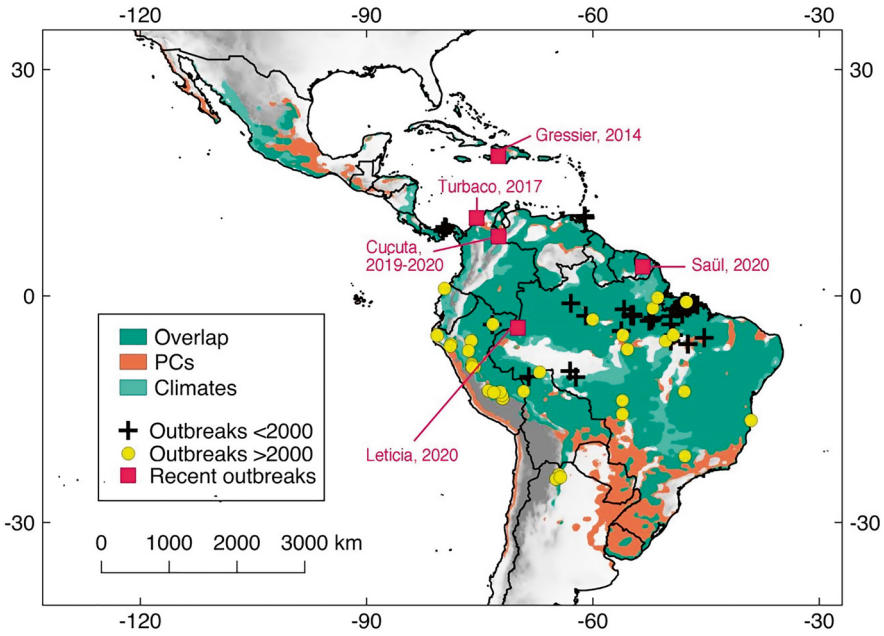

Fig. 6.1 Transmission risk of Oropouche virus (OROV) in the Americas. The transmission risk was estimated using species distribution models with hypervolumes based on one-class support vector machines (OC-SVM; Romero-Alvarez et al. 2023). Colors represent models created with climatic variables (light green), the components of a principal component analysis (PCs; orange) and the overlap between both models (green). Modeling details can be found in (Romero-Alvarez et al. 2023). Occurrences used for model development are depicted in yellow, while occurrences of Oropouche fever outbreaks before the 2000s are depicted with cruxes in black (notice the outbreaks in Panama). Finally, recent reports of Oropouche fever have identified the virus in French Guiana, Haiti, and Colombia and are shown here with red squares and arrows pointing to the locality and year of the outbreak

transmission cycle. Also for the first time since the discovery of OROV, two attributable deaths have been reported in Brazil (https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(24)00557-7/fulltext). Demographic information on these casualties is still scarce but include: non-pregnant females without known comorbidities less than 20 years old.

The historical distribution of OROV outbreaks has been documented elsewhere (Romero-Alvarez and Escobar 2018). In this chapter, we expanded upon those observations and included an estimated map of the transmission risk in the Americas using species distribution models with hypervolumes based on support vector machines (Romero-Alvarez et al. 2023). While the majority of reported cases continue to occur in Brazil (with approximately 30 OROV documented outbreaks) and Peru (Sakkas et al. 2018), it is likely that the true public health impact of OROV in these and other countries remains unknown due to limited diagnostic capacity and the similarity of OROF clinical presentation to other arboviruses, such as dengue, Zika, chikungunya, or yellow fever. As a consequence, the incidence and disease burden of OROV are likely underestimated. Current OROV surveillance efforts are limited with the bulk of methods focusing on serological testing in humans and animals (Aguilar et al. 2011; Azevedo et al. 2007; Baisley et al. 1998; Castro et al. 2013; da Costa et al. 2017; Mattar and Gonzalez 2015; Navarro et al. 2016; Pinheiro et al. 1981; Rodríguez-Morales et al. 2017; Romero-Alvarez and Escobar 2018; Sakkas et al. 2018; Travassos da Rosa et al. 2017; Vasconcelos et al. 2011).

6.2 Genome Organization and Replication of OROV

Oropouche virus (OROV) is an enveloped virus and a member of the order *Bunyavirales*, family *Peribunyaviridae*, genus *Orthobunyavirus.* As other members of this genus, OROV has the typical tripartite, negative-sense RNA genome structure consisting of the large (L), medium (M), and small (S) segments, named based on their molecular sizes (Elliott 2014). The L segment is 6846 nucleotides long and contains an open reading frame (ORF) of 2250 amino acids encoding the RNA-dependent RNA polymerase (Aquino et al. 2003). The M segment encodes a single ORF, which is processed after or during translation, yielding the NSm protein and the two glycoproteins Gn and Gc. Finally, the S segment encodes the nucleocapsid protein (N) and the nonstructural protein NSs in two overlapping ORFs (Travassos da Rosa et al. 2017).

6.2.1 OROV Replication Cycle

Early events in its replication cycle involve the attachment of the viral glycoproteins to the host cell receptor. Due to the broad cell tropism and the multiple species that are susceptible to OROV infection (Dias et al. 2022; Sciancalepore et al. 2022), it is

likely that several receptors or, alternatively, highly conserved receptors across species mediate OROV entry to the host cell. Recently, the host protein low-density lipoprotein-related protein 1 (Lrp1) was identified as a host factor mediating OROV cell entry (Schwarz et al. 2022). Knockdown of Lrp1 dramatically decreased viral replication, consistent with a reduction in viral entry (Schwarz et al. 2022). However, OROV replication was not completely abolished in this experiment, suggesting the involvement of other host factors in OROV entry.

Entry of OROV into host cells in association with clathrin-coated pits requires low pH for viral membrane fusion and release of the nucleocapsid into the cytosol (Santos et al. 2008). Although many aspects of OROV replication cycle remain poorly understood, it likely occurs in the cytoplasm in a similar process as those described for other bunyaviruses. It is believed that after uncoating of the viral genome, transcription of negative-sense vRNA to complementary mRNA occurs mediated by the viral ribonucleoprotein and the three viral RNA templates by using an endonuclease associated with the polymerase complex to "steal" 5'cap structures from host cell mRNA (Schmaljohn and Nichol 2007; Patterson et al. 1984). Replication of the genome requires a switch from mRNA synthesis to synthesis of cRNA templates and then vRNA in a process that still has not been well defined (Jin and Elliott 1993). Following transcription, translation of the L and S segments occurs on free ribosomes in the cytosol, whereas translation of the M segment-associated glycoproteins occurs on the endoplasmic reticulum (ER)-bound ribosomes.

The assembly of OROV requires the processing and maturation of the Gc and Gn through the secretory pathway. After the OROV glycoproteins are translated in the endoplasmic reticulum as a nascent polypeptide, they are proteolytically processed to generate Gn and Gc, glycosylated, and transported to the Golgi apparatus as heterodimeric protein complexes for virus assembly (Walter and Barr 2011). In the Golgi apparatus, the glycoproteins interact with ribonucleoprotein genome segments, and virus assembly and budding occur at the Golgi membranes within the lumen of Golgi-derived vesicles, which are then secreted from the cell. This process requires the recruitment of the cellular endosomal sorting complexes required for transport (ESCRT) machinery for virus particle production. The cellular ATPase that stimulates the disassembly of assembled ESCRT-III filaments at the neck of the vesicles promoting membrane scission was shown to play a role in OROV release (Barbosa et al. 2023). Further investigations revealed that the ESCRT-III component CHMP6, which physically interacts with the OROV glycoproteins, enhances glycoprotein secretion (Barbosa et al. 2023, 2018). It would be interesting to determine whether all OROV species, including reassortant viruses, use a similar mechanism for virus entry, assembly, and release.

6.3 Evolution and Phylogeny of OROV

Bunyaviruses in general undergo genetic reassortment with related RNA viruses, forming novel viruses with different disease potential (Briese et al. 2013; Palacios et al. 2011). It is believed that genetic reassortment is a driving force in OROV evolution, as has been suggested for other bunyaviruses (Briese et al. 2013).

In recent years, an increasing number of OROV reassortants have been identified via genetic and antigenic analyses (Aguilar et al. 2011; Ladner et al. 2014; Saeed et al. 2001; Tilston-Lunel et al. 2015). Jatobal virus (JATV) was the first recognized reassortant. The prototype strain BeAn 423380 was isolated in 1985 from a carnivore (*Nasua nasua*) in Pará, Brazil, and was classified as a member of the Simbu serogroup based on neutralization tests (Figueiredo and Da Rosa 1988). Subsequent molecular studies revealed the S segment was ~83.4% identical at the nucleotide level to OROV; however, the M segment sequence had low sequence identity with <66% similarity to OROV (Ladner et al. 2014). Neutralization assays confirmed that the viruses lack cross-reactivity, and in vivo studies in hamsters confirmed differences in pathogenicity when compared to OROV (Saeed et al. 2001).

A second reassortant was identified in Peru from patients suffering from acute undifferentiated febrile illness (Aguilar et al. 2011). The prototype strain IQT9924 was isolated in 1999 from a 13-year-old boy who had symptoms that included fever, headache, eye pain, body pain, arthralgias, diarrhea, and chills. The virus was responsible for subsequent outbreaks of "OROV" detected through passive surveillance studies in Peru (Aguilar et al. 2011). Clinical data confirmed that IQT9924 caused many of the same clinical manifestations as OROV; however, 38% of the patients infected with IQT9924 had respiratory complaints (i.e., cough) that were not commonly reported in OROV-infected patients (Aguilar et al. 2011). Genetic analyses revealed that IQT9924 shares S and L segments of OROV. However, the M segment was distinct from OROV and JATV, and therefore the name Iquitos virus (IQTV) was proposed for this new virus.

In an attempt to better understand the phylogenetic relationship between Simbu serogroup viruses, Ladner et al. (2014) conducted genetic characterization of orthobunyaviruses and observed that the strain FMD1303 isolated in Madre de Dios, Peru, from a patient with febrile illness that was initially (tentatively) classified as OROV had the S and L segments genetically related to OROV. However, the investigators noted that the range of sequence diversity fell outside those observed with other OROV strains. Notably, the M segment sequence was genetically related to the M segment of IQTV. Given its genetic uniqueness, the investigators proposed the name Madre de Dios virus (MDDV) to classify this new variant (Ladner et al. 2014).

Genetic analyses of OROV strains from Brazil identified an additional reassortant virus isolated from two marmosets in Minas Gerais state in Brazil in 2012 (strains BeAn 790177 and BeAn 789726) (Tilston-Lunel et al. 2015). The reassortant virus had a unique M segment and a S segment lacking 11 residues at the 3′ untranslated region. Based on the genetic analysis, the investigators proposed the name Perdões virus (Tilston-Lunel et al. 2015).

In recent years, the International Committee on Taxonomy of Viruses has established new criteria for species demarcation within the genus *Orthobunyaviruses* and considered new species viruses with less than 96% identity in the complete amino acid sequence of the L protein (https://talk.ictvonline.org/ictv-reports/ictv_online_report/negative-sense-rna-viruses/bunyavirales/w/peribunyaviridae/1238/genus-orthobunyavirus). Based on these new classification criteria, OROV, IQTV, MDDV, and Perdões virus are now considered members of the *Orthobunyavirus oropoucheense* species, which also includes Pintupo virus. Given the lack of sequence information, the genetic relationship between OROV with Pintupo virus remains unknown.

6.4 Eco Epidemiology: Vectors, Hosts, and Transmission Cycle

OROV persists in nature via two transmission cycles: an urban cycle and a sylvatic cycle. The urban cycle, which is commonly connected with illness outbreaks, is thought to be mainly driven by the biting midge *Culicoides paraensis* (Pinheiro et al. 1981; Romero-Alvarez and Escobar 2018; Travassos da Rosa et al. 2017; Walsh et al. 2021). Furthermore, OROF epidemics in Brazil have a seasonal pattern and have primarily occurred during the rainy season, which coincides with the highest density of *C. paraensis* populations (Azevedo et al. 2007; Vasconcelos et al. 2011). Humans are thought to be the sole vertebrate hosts in the urban cycle because OROV infection has not been detected in domestic animals, with the exception of birds (Sakkas et al. 2018).

Members of the families *Ceratopogonidae* and *Culicidae* (Arthropoda: Hexapoda) have been frequently implicated in the transmission of OROV. Within these families, the genera *Culicoides* (Ceratopogonidae), *Culex*, *Aedes*, and *Coquillettidia* (Culicidae) have been referenced in publications since 1981 (Cardoso et al. 2015; Romero-Alvarez and Escobar 2018; Walsh et al. 2021).

The genus *Culicoides* contains approximately 1400 species distributed worldwide with the exception of the polar areas and New Zealand. *Culicoides* spp. also contain species that serve as vectors for other arboviruses with significant human and veterinary health risks. Around the world, more than 50 distinct viruses, many of them of significant veterinary interest, have been isolated from *Culicoides* midges (Mellor et al. 2000).

Although it is uncertain what animals *Culicoides* midges feed on, data suggests that they are generally mammalophilic and/or ornithophilic, preying on a variety of mammals and birds depending on the availability of these hosts (Lassen et al. 2012). The host preference and feeding behavior of *Culicoides* midges have been examined utilizing observational studies based on the capture of adult female midges using light, sticky, or animal-baited traps or by direct aspiration from animals, with the latter being the most reliable study method (Augot et al. 2017; Sick et al. 2019; Walsh et al. 2021).

The ability of *C. paraensis* to thrive and reproduce in semi-urban settings near densely populated areas is suggested to explain its large geographic range. *C. paraensis* is abundant during the hot and wet months of the year (Aybar et al. 2012; Mellor et al. 2000; Mercer et al. 2003; Walsh et al. 2021). *C. paraensis* larvae grow in a variety of environments that can stay moist and support larval nutrition during dry seasons, including rainforests, damp soil, tree holes, riverbanks, and phytotelmata such as rotting banana and plantain stalks, stumps, and cacao husks, which facilitate its presence in the human landscape and its preference for biting during mild to heavy rains, as well as indoors during the day and night (Aybar et al. 2012; Mellor et al. 2000; Mercer et al. 2003; Walsh et al. 2021).

Furthermore, OROV is found in areas where the hematophagous mosquito species *Culex quinquefasciatus*, *Coquillettidia venezuelensis*, and *Aedes* (*Ochlerotatus*) *serratus* can breed and perhaps become infected with the virus (Anderson et al. 1961; Cardoso et al. 2015; Travassos da Rosa et al. 2017). The mosquito species *Cq. venezuelensis* and *Ae. serratus*, found in Trinidad and the Amazonian region of Brazil, were suggested as the sources of OROV isolation in 1960 (Pinheiro et al. 1981; Travassos da Rosa et al. 2017). Both species are common in sylvatic habitats and are potentially secondary viral vectors (Alfonzo et al. 2005; Mendez et al. 2001). Further study is necessary, though, to better understand their function as capable vectors and their involvement in epidemics.

The main vertebrate hosts participating in the sylvatic cycle are unknown. However, there is evidence that wild birds, the three-toed sloth (*Bradypus tridactylus*), and certain New World non-human primates (NHP)—primarily capuchin and howler monkeys—are involved. Further evidence of the spread of OROV was its isolation in 2003 from a small primate, a marmoset (*Callithrix*), in the state of Minas Gerais in southeast Brazil, far from the Amazon region (Nunes et al. 2005; Pinheiro et al. 1981) and also the isolation in a *Cebus olivaceus* in the Orinoco river basin in Venezuela (Navarro et al. 2016). HI antibodies against OROV have been found in wild birds belonging to the families Formicariidae, Troglodytidae, Cuculidae, Fringillidae, Dendrocolaptidae, Tyrannidae, Vireonidae, Thraupidae, and Pipridae (Pinheiro et al. 1976). HI antibodies against OROV have also been identified in domestic chickens and one duck. During five epidemics in Brazil, various domestic vertebrates were examined for OROV antibodies. There were no OROV-specific antibodies found in cats, dogs, or pigs (Files et al. 2022; Pinheiro et al. 1981).

6.5 Geography and Ecological Risk Variables for Oropouche Virus (OROV) Outbreaks

The geography and epidemiology of OROV is in constant evolution and expansion. As of 2023, OROV has been identified in new areas, including regions where human cases were not previously reported such as French Guiana, Haiti, Colombia, and Ecuador.

The first report of OROF in Ecuador in 2016 prompted a follow-up study demonstrating that the standard primers used for detection of OROV failed to accurately detect positive samples, negatively impacting the detection of OROV in Esmeraldas, in northern Ecuador (Wise et al. 2018, 2020). Similarly, although evidence of OROV circulation in mosquitoes and humans in Colombia dates back to the 1960s (Groot 1964), it was only through the use of unbiased molecular approaches (i.e., next-generation sequencing) that evidence of OROV as a cause of acute undifferentiated febrile illness was obtained in samples collected from Turbaco, Bolívar, in northern Colombia (Gómez-Camargo et al. 2021). Additional OROF cases were detected through the implementation of targeted real-time PCR (qPCR) in samples collected from febrile patients residing in Cucuta and Leticia Departments (Ciuoderis et al. 2022), and serological studies across the Cauca Department have also confirmed exposure to OROV in that region (Gil-Mora et al. 2022).

Currently, the extensive serological evidence of OROV circulation in South America suggests a widespread distribution of OROV, which is likely under- or misdiagnosed, obscured by other febrile diseases (Forshey et al. 2010). For instance, an outbreak of OROV was reported in French Guiana in 2020 with 23 human cases detected by PCR and microneutralization tests, which represents the first detection of the virus in this country (Gaillet et al. 2021). In Haiti, a human case was identified in 2019 in a study analyzing school-children exposure to arthropod-borne viruses, demonstrating the presence of OROV in Hispaniola Island (Elbadry et al. 2021).

Usually, acute undifferentiated febrile illness is treated with supporting clinical measures (i.e., hydration, fever control) due to its self-limited nature; thus, there are scarce incentives to relate febrile syndromes with their causing pathogen. In South America, around 40–60% of febrile illnesses are not confirmed by laboratory tests (Carabali et al. 2021). Recent OROV reports and the wide distribution of the urban cycle vector *C. paraensis* suggest a wide—yet undetected—distribution of OROF in the Americas with potentially five million people at risk of OROV infection (Romero-Alvarez et al. 2023). These reports also suggest that OROV outbreaks may be related with recent habitat alteration, specifically vegetation loss (Romero-Alvarez and Escobar 2017; Romero-Alvarez et al. 2023) (Fig. 6.1).

As a zoonotic disease, the sylvatic cycle of OROV requires a human-wildlife interface for the emergence of outbreaks and epidemics (Romero-Alvarez and Escobar 2017). Traditionally, wildlife species recognized as OROV reservoirs include the sloth *Bradypus tridactylus*; non-human primates such as *Alouatta caraya*, *Sapajus apella*, and *Callithrix penicillata*; and multiple families of wild birds (Files et al. 2022; Romero-Alvarez and Escobar 2017; Sakkas et al. 2018; Travassos da Rosa et al. 2017). Such studies, however, are limited, and the available information on wildlife reservoirs does not allow determining patterns of viral circulation clearly related to the role of wildlife ecology on the prevalence of the virus. For instance, the distributional range of *B. tridactylus* barely overlaps with known OROF outbreaks. Actually, OROF outbreaks overlap with the geographic distribution of the primate *S. apella*, a species for which little information exists regarding OROV transmission (Fig. 6.2). *Sapajus apella has* been proposed as a potential reservoir based on the presence of antibodies against OROV in Brazil (Batista et al.

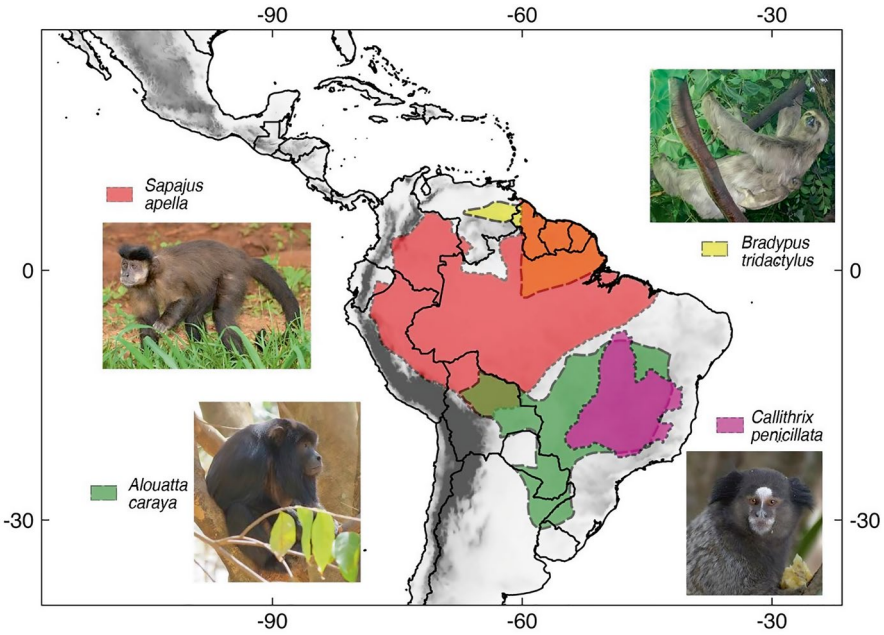

Fig. 6.2 Potential wildlife reservoirs of the sylvatic life cycle of Oropouche virus (OROV). The figure depicts the accepted distribution of one sloth species (*Bradypus tridactylus*) and three non-human primates (*Sapajus apella*, *Alouatta caraya*, and *Callithrix penicillata*), which have been incriminated as reservoirs of OROV. Geographic distributions obtained from the International Union for Conservation of Nature (IUCN) species ranges as of August 2023. Notice that even if considering all the ranges together, multiple OROV outbreaks are outside these ranges, suggesting that other reservoirs might be sustaining OROV in the wild. (The pictures are taken from Wikipedia accordingly: *C. penicillata* and *S. apella*: Dario Sanches (https://commons.wikimedia.org/wiki/File:Sagui_Tufos_Pretos_(Callithrix_penicillata).jpg, https://commons.wikimedia.org/wiki/File:Macaco-prego_(Cebus_apella).jpg), *A. caraya*: Miguelrangeljr (https://commons.wikimedia.org/wiki/File:Alouatta_caraya_male.JPG), *B. tridactylus*: G.dallorto (https://species.wikimedia.org/wiki/Bradypus_tridactylus#/media/File:9092_-_Milano_-_Museo_storia_naturale_-_Diorama_-_Bradypus_trydactilus_-_Foto_Giovanni_Dall'Orto_22-Apr-2007.jpg))

2012). In Brazil, OROV antibodies have also been detected in two *A. caraya* primates from urban areas in the city of Goiânia, state of Goiás (Gibrail et al. 2016), while the primate *C. penicillata* was incriminated as reservoir host after virus detection in Perdões, state of Mina Gerais (Tilston-Lunel et al. 2015). The geographic distribution of these potential reservoirs overlaps only partially with the geographic distribution of OROF outbreaks, reported in Peru, Ecuador, and Colombia (Fig. 6.1 versus Fig. 6.2), suggesting a likely role of all of these species on sustaining viral circulation in the wild and viral spillover to humans. Future research directions in the ecology of OROV could include filling knowledge gaps on the sylvatic reservoirs and vectors to better understand drivers that facilitate cross species transmission and rises in prevalence to anticipate human outbreaks.

6.6 Final Remarks

Currently, the true public health impact of OROV remains poorly understood. The limited resources available for surveillance and diagnostics negatively impacts the recognition of cases and outbreaks caused by OROV. The continuous recognition of novel OROV reassortants highlights the need to keep monitoring for their emergence, which might have increased pathogenicity in humans or enhanced transmission potential in arthropod vectors.

A sustained monitoring and diagnostics in samples collected from wildlife and patients with undifferentiated febrile illnesses are warranted. Given the recognition of OROV in new geographic areas, it is also critical to include OROF as a potential clinical entity for diagnosis and to expand efforts for vector surveillance to recognize and incriminate vectors that can be contributing to the emergence and expansion of OROV in the Americas.

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