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Review

Oropouche fever, an emergent disease from the Americas

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Abstract

Oropouche virus is the aetiological agent of Oropouche fever, a zoonotic disease mainly transmitted by midges of the species *Culicoides paraensis*. Although the virus was discovered in 1955, more attention has been given recently to both the virus and the disease due to outbreaks of Oropouche fever in different areas of Brazil and Peru. Serological studies in human and wild mammals have also found Oropouche virus in Argentina, Bolivia, Colombia, and Ecuador. Several mammals act as reservoirs of the disease, although the sylvatic cycle of Oropouche virus remains to be assessed properly. Oropouche fever lacks key symptoms to be differentiated from other arboviral febrile illnesses from the Americas. Sporadic cases of aseptic meningitis have also been described with good prognosis. Habitat loss can increase the likelihood of Oropouche virus emergence in the short-term in South America.

Keywords: Oropouche virus; Oropouche fever; Arbovirus; Emergent disease; Outbreak

1. Introduction

Central and South America are considered hotspots of emergent zoonoses [1]. Just in the Amazon region of Brazil, 187 different species of viruses were isolated from 1954 to 1988 from mammals (including humans) and mosquitoes [2]. Indeed, South America has showed high diversity of arboviral pathogens in recent studies [3,4]. While novel viruses are not necessarily pathogenic, these numbers show the high viral richness in the Neotropic and its propensity for emergent arboviral diseases. In the early 2010's, at least four epidemics in the Americas were caused by arboviruses including epidemics of Dengue fever [5], Chikungunya [6], Zika [7], and outbreaks of Yellow fever [8].

Active epidemiological serosurveillance (i.e., samples collected from programmed surveys) has revealed circulation of at least five viruses of the Peribunyaviridae family in Brazil [2,9]; one of these is Oropouche, the aetiological agent of Oropouche fever. Oropouche fever is one of the most important feverish illnesses in Brazil and has been proposed as candidate disease for a next epidemic across the Americas, along with Venezuelan equine encephalitis and Mayaro fever [10−12]. In fact, in 2016 southern Peru reported a new epidemic of Oropouche fever [13].

Strikingly, there is a poor understanding of the natural history of this disease. A search of the keyword 'Oropouche' in Web of Science for data between 1950 and August 2017 retrieved 202 publications. From these, 189 were original articles, 21 abstract papers, and 13 review articles. The highest number of articles in a single year (i.e., 16) occurred in 2017, which suggests a recent increase of attention on Oropouche virus [14] (Fig. 1). Most publications were focused on the epidemiology of Oropouche virus, including its geographical distribution [15−17], medical entomology [16,18], clinical features [9,19], and molecular characterization [20,21]. Only a few publications focused on the natural history of the virus, e.g., pathogenesis of Oropouche virus [22−24] or its natural

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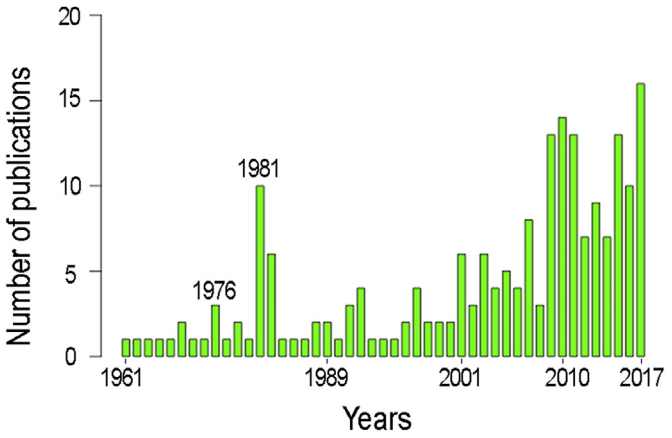

Fig. 1. **Publication effort of Oropouche virus.** Note that sixteen publications were found for 2017, the highest number of annual publications since the first report of the disease in 1961. Source: [14], data from Web of Science by August 2017.

reservoirs [25,26]. Thus, considering (i) the evident public health threat of arboviral diseases across the Americas, (ii) the raising concern of Oropouche fever as a plausible emergent infectious disease, and (iii) the limited understanding of the ecology of this disease, we aimed to provide an update of the research of Oropouche as a potential future epidemic.

2. History

Oropouche virus was first found in a symptomatic human from the village Vega de Oropouche, Trinidad, in 1955 [27]. This allowed the first virus isolation from a human case and a pool of *Coquilletidia venezuelensis* mosquitoes collected during the outbreak [27]. Oropouche virus is sometimes written as 'Oropuche,' which is particularly common and accepted in Spanish speaking countries. Oropouche virus is a negative-sense ribonucleic acid (RNA) virus belonging to the genus *Orthobunyavirus*, family Peribunyaviridae, which is one of the families with the largest number of viruses described, with at least 30 viruses recognized as causative agents of human disease including Oropouche virus, Ngari virus, and La Crosse virus [28,29].

Oropouche virus causes Oropouche fever, which is a dengue-like illness of sporadic outbreaks. The RNA viral genome of all *Orthobunyaviruses* is composed of three different molecules designated according to their relative number of nucleotides as S (small), M (medium), and L (large), which codify four structural proteins: the nucleocapside, two external glycoproteins, and the RNA polymerase, respectively [30] (Fig. 2). Considering the antigenic properties of *Orthobunyavirus*, Oropouche virus belongs to the Simbu serogroup, which includes at least seven species complexes and 22 recognized viruses [31].

The evolutionary history of Oropouche virus has not been reconstructed until recently, including the characterization of the whole genome [21,33]. By calculating the nucleotide substitution rate of N protein codified by the S sequence, it has been suggested that Oropouche virus emerged recently in the Brazilian Amazon [20]. Four lineages of Oropouche virus have been proposed to have dispersed from one monophyletic group around different areas. Genotype I occurs in Trinidad, genotype II in Peru, genotype III in Panama, and genotype IV in the Amazon region of Brazil and in an outbreak in Jujuy, northern Argentina. All Oropouche virus lineages have been found in Brazil [20,21,34,35], suggesting a plausible origin of the virus or high overlap in the distribution of vectors and virus reservoirs.

3. Geographical distribution

Orthobunyaviruses have horizontal genetic transfer [29]; at least three virus populations have been identified as reassortments of Oropouche virus, including the Iquitos virus in northeast Peru [36], the Madre de Dios virus isolated from southeast Peru and northeast Venezuela [37,38], and the Perdões virus isolated in southeast Brazil [21]. Both Iquitos and Madre de Dios virus populations have caused human outbreaks [36,38].

The current knowledge of the distribution of Oropouche virus has been based on passive epidemiological surveillance (i.e., surveys after cases are noted but not during epidemiological silence) from samples collected after outbreaks in Trinidad, Brazil, Panama, and Peru [9,19,34,39–41]. On the otehr hand, active surveillance has revealed unnoticed virus circulation: up to 2% of people living in non-endemic areas showed antibodies against Oropouche virus [42]. Recent efforts to track Oropouche virus distribution via passive or active epidemiological surveillance in wild mammals and humans showed virus circulation in Argentina, Bolivia, Colombia, Ecuador, and Venezuela [3,34,37,43–45] (Table 1; Fig. 3).

3.1. Oropouche fever in South America

In 1960, a three-toed sloth (*Bradypus tridactylus*) and a pool of *Aedes (Ochlerotatus) serratus* mosquitoes were found positive to Oropouche virus in eastern Brazil. At the same time, the Belém–Brasília highway was in construction in the area and was proposed as a causative factor for the epidemic of Belém City in the state of Pará in 1961 where around 11,000 human cases were reported as suspicious of Oropouche fever [40]. Since then, several explosive Oropouche fever outbreaks in urban settlements have been reported in Brazil. It has been estimated that >100,000 people were infected between 1980 and 1981 in the states of Pará and Amazonas, Brazil [15].

In the period between 1961 and 2000, >30 Oropouche fever epidemics were recorded across Brazil, in regions including Acre, Amapá, Amazonas, Goiás, Maranhão, Pará, Rondônia, and Tocantins [15,26,41,42] (Table 1, Fig. 3). In 2000, Oropouche virus genotype III was detected in southeastern Brazil in a wild primate (*Callithrix penicillata*) [26]. Later, in 2003 and 2004 Oropouche fever was again detected in new regions of Pará (i.e., Parauapebas and Porto de Moz) [17]. By 2004, only one case of Oropouche fever was reported in Acrelândia in the northwest of Brazil (Acre state), supporting the idea of

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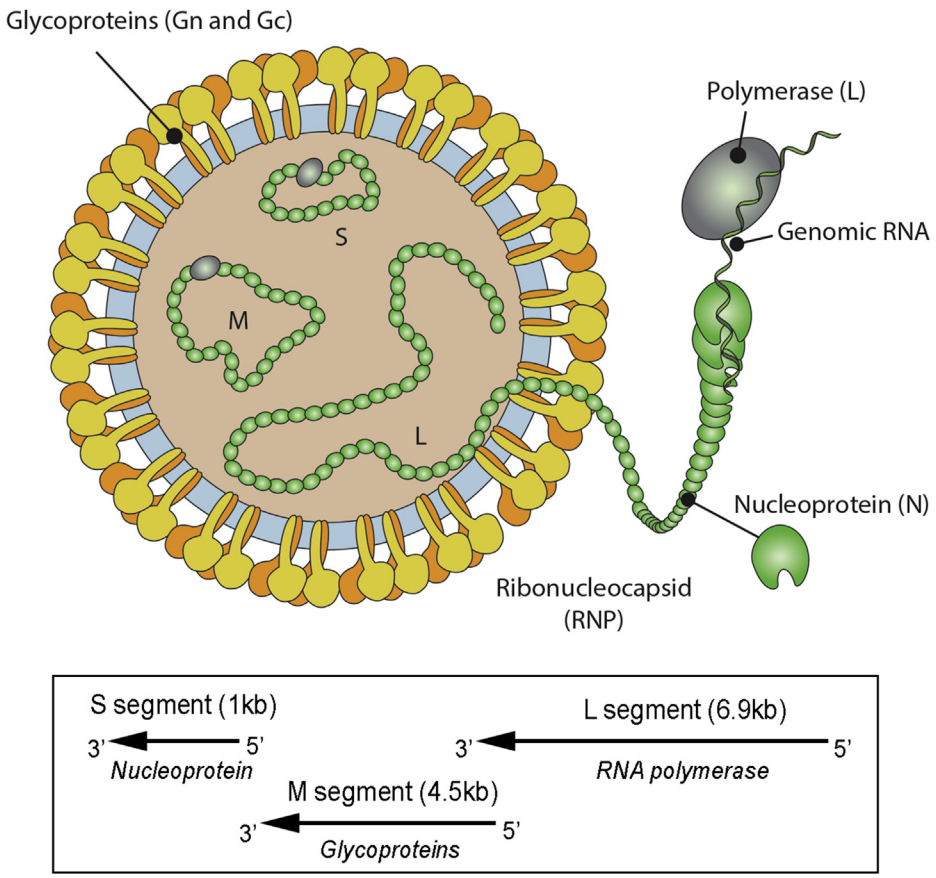

Fig. 2. **Schematic representation of the genus *Orthobunyavirus*.** Oropouche virus belongs to the genus *Orthobunyavirus*. The virion of Bunyamwera virus is the prototype for this genus. Evidence suggests that all the members of *Orthobunyavirus* share similar structural characteristics: average virion size (80–120 nm) and average genome size for the three fragmented RNA segments (inset box, kb = kilobase) [29]. Arrows in the inset box represent the reading frame 3′–5′ for each RNA segment; the corresponding codified proteins are in italics. Image credit: Philip Le Mercier. Modified from ViralZone (www.expasy.ch/viralzone), Swiss Institute of Bioinformatics [32].

an endemic circulation of Oropouche virus in northwestern Brazil [46]. However, by 2006 an Oropouche fever outbreak affected ~18,000 people in northern Brazil after a long period (>25 years) of epidemiological silence [9]. More recently, between 2007 and 2008, new outbreaks were reported in Pará state at Trairão and Novo Progresso [47], and at Manaus city in the Amazonas state [48], which was previously affected (Fig. 3). Between 2011 and 2012, new outbreaks occurred in several municipalities of Mato Grosso [49]. In 2016, Oropouche virus was detected in a febrile person in the coastal region of Brazil for the first time and, more importantly, the case occurred close to the most populated cities of the country [50]. Additionally, a recent report showed that nine of 306 serum samples (3%), negative for Dengue, Zika, and Chikungunya, were positive to Oropouche virus in at least 20 municipalities of the Amazon state from 2011 to 2016 [51].

In Peru, it has been suggested that Oropouche virus reached the country by spreading across the riverbanks of the Amazonas River, facilitated by human mobilization [19]. The disease was first detected in Iquitos, Department of Loreto, in 1992 from a serosurvey after a Dengue outbreak [52]. Since then, cases of Oropouche fever have been detected continuously in Iquitos region [19,53,54]. In the town of Santa Clara, 10 km from Iquitos, a study found that visiting forest areas was a risk factor for Oropouche virus exposure [53]. Endemicity of Oropouche in Peru has been proposed, mainly due to the increased propensity of local residents to have antibodies compared to immigrants [53]. Since 1994, Oropouche fever outbreaks have been reported in Puerto Maldonado of the Madre de Dios Department in southeastern Peru, with more recent outbreaks in 2015 and 2016 [39,54,55]. Oropouche fever has also been detected in northern Peru, specifically in San Martín and Cajamarca Departments in 2010 and 2011 respectively [19,56], and at least ten localities in the southern Cusco Department in 2016 [13] (Table 1, Fig. 3).

A multinational survey for the diagnosis of cases of acute febrile illnesses of unknown origin confirmed Oropouche virus in human cases from Ecuador (Guayaquil) and Bolivia (Cochabamba), although the time frame of the sampling (from 2000 to 2007) and the passive surveillance design complicated the identification of the origin of cases [3]. At the same time (i.e., 2000–2004), Ecuador reported the detection of Oropouche virus in health centers of the Amazonian province of Puyo [43]. In Colombia, Oropouche virus has been detected in non-human primates across different regions, although human cases remain to be reported [34,44,45]. In Argentina, febrile

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Table 1
Localities of Oropouche virus detections from 1955 to 2017. Georeferenciation of localities was performed using geographic coordinates directly collected from references or geolocated using GEOnet Names Server (http://geonames.nga.mil/gns/html/) and Google Earth. * = High uncertainty due to the nature of the correspondent research (retrospective serosurveys); thus, localities should be treated with care due to difficulties to declare cases as autochthonous.

Country	Province/State	Locality	Latitude	Longitude	Years of detection	References
Argentina	Jujuy	Jujuy*	−24.186061	−65.302525	2005	[34]
Bolivia	Cochabamba	Cochabamba*	−17.4173	−66.1661	2005–2007	[3]
Brazil	Acre	Acrelândia	−10.076392	−67.058698	2004	[46]
Brazil	Acre	Xapuri	−10.651986	−68.497411	1996	[26]
Brazil	Amapá	Mazagão	−0.115827	−51.286247	1980, 2009	[15,21,65]
Brazil	Amazonas	Manaus	−3.119028	−60.021731	1981, 2007–2008	[15,26,48]
Brazil	Amazonas	Barcelos	−0.975355	−62.924509	1980	[26]
Brazil	Bahía	Porto Seguro	−16.444354	−39.065366	2016	[50]
Brazil	Maranhão	Barra do Corda	−5.501892	−45.2465	1993	[17]
Brazil	Maranhão	Porto Franco	−6.339769	−47.397914	1988	[41]
Brazil	Mato Grosso	Várzea Grande	−15.648968	−56.131384	2011–2012	[49]
Brazil	Mato Grosso	Nova Mutum	−13.824482	−56.080166	2011–2012	[49]
Brazil	Mato Grosso	Cuiabá	−15.601411	−56.097892	2011–2012	[49]
Brazil	Pará	Abaetetuba	−1.722189	−48.87927	1960–1981	[82]
Brazil	Pará	Altamira	−3.198666	−52.210401	1996	[26]
Brazil	Pará	Alter do Chão	−2.504264	−54.954642	1975	[15,42]
Brazil	Pará	Ananindeua	−1.364272	−48.374721	1960–1981	[82]
Brazil	Pará	Augusto Corrêa	−1.022803	−46.639357	1960–1981	[82]
Brazil	Pará	Baião	−2.683333	−49.683333	1972	[15,42]
Brazil	Pará	Belém	−1.437281	−48.470614	1961, 1968–69, 1979–80, 2008	[26,40–42]
Brazil	Pará	Belterra	−2.638659	−54.934831	1975	[15,42]
Brazil	Pará	Benfica	−1.304496	−48.302002	1960–1981	[82]
Brazil	Pará	Bragança	−1.061619	−46.783011	1967, 1979–80	[15,42]
Brazil	Pará	Brasil Novo	−3.305523	−52.539236	1996	[17]
Brazil	Pará	Capanema	−1.2061	−47.177344	1960–1981	[82]
Brazil	Pará	Caraparu	−1.373728	−48.152162	1960–1981	[82]
Brazil	Pará	Caratateua	−0.994943	−46.72265	1967	[15,42]
Brazil	Pará	Castanhal	−1.298329	−47.917162	1960–1981	[82]
Brazil	Pará	Curuçá	−0.730009	−47.855826	1960–1981	[82]
Brazil	Pará	Igarapé Açu (Bragantina)	−1.136496	−47.617826	1980, 2006	[9]
Brazil	Pará	Itupiranga	−5.134735	−49.327687	1975	[15,42]
Brazil	Pará	Magalhães Barata (Bragantina)	−0.798955	−47.601977	1980, 2006	[9]
Brazil	Pará	Maracanã (Bragantina)	−0.7661347	−47.45371	1980, 2006	[9]
Brazil	Pará	Mojuí dos Compos	−2.682202	−54.642484	1974–75	[15,42]
Brazil	Pará	Novo Progresso	−7.038894	−55.415717	2008	[47]
Brazil	Pará	Oriximiná	−1.761832	−55.863813	1996	[26]
Brazil	Pará	Palhal	−4.616667	−56.233333	1975	[15,42]
Brazil	Pará	Parauapebas	−6.066667	−49.9	2003	[17,26]
Brazil	Pará	Porto de Moz	−1.75	−52.233333	2004	[17,26]
Brazil	Pará	Quatro Bocas	−2.412811	−48.039450	1978	[59]
Brazil	Pará	Santa Izabel do Pará	−1.298205	−48.157043	1992	[44]
Brazil	Pará	Santarém	−2.450629	−54.700923	1974–75	[15,42]
Brazil	Pará	Serra Pelada	−5.933335	−49.670714	1994	[44]
Brazil	Pará	Tomé-Açu	−2.418394	−48.154522	1960–1981	[82]
Brazil	Pará	Trairão	−5.179103	−56.024998	2008	[47]
Brazil	Pará	Tucuruí	−3.766076	−49.67777	1988	[26]
Brazil	Pará	Vigia	−0.856936	−48.137939	1960–1981	[82]
Brazil	Pará	Viseu	−1.201705	−46.138706	1960–1981	[82]
Brazil	Pará	Vitória do Xingu	−2.887456	−52.013096	1996	[9]
Brazil	Rondônia	Ariquemes	−9.906703	−63.02916	1991	[15]
Brazil	Rondônia	Ouro Preto do Oeste	−10.719278	−62.259273	1991	[15]
Brazil	Tocantins	Paranã	−12.620142	−47.876062	2002	[17]
Brazil	Tocantins	Porto Franco	−6.34106	−47.395395	1988	[41]
Brazil	Tocantins	Tocantinópolis	−6.326137	−47.423087	1988	[41]
Ecuador	Guayas	Guayaquil*	−2.170931	−79.922258	2003–2007	[3]
Ecuador	Pastaza	Puyo*	−1.492393	−78.002413	2001–2004	[43]
Ecuador	Pastaza	Shell*	−1.49983	−78.06234	2001–2004	[43]
Panama	Panama	San Miguelito	9.050321	−79.470679	1990	[15,34]
Panama	Panama	Chilibre	9.149731	−79.619052	1990	[15,34]
Panama	Panama Oeste	Bejuco	8.606157	−79.888482	1989	[15,34]
Peru	Cajamarca	Casa Blanca	−6.050427	−78.826681	2011	[56]

(*continued on next page*)

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Table 1 (*continued*)

Country	Province/State	Locality	Latitude	Longitude	Years of detection	References
Peru	Cusco	Cusco*	−13.53195	−71.967463	2000–2007	[3]
Peru	Cusco	Echarate	−12.735741	−72.614288	2016	[13]
Peru	Cusco	Kimbiri	−12.618733	−73.787498	2016	[13]
Peru	Cusco	Lares	−13.105302	−72.044594	2016	[13]
Peru	Cusco	Palma Real	−12.626443	−72.69288	2016	[13]
Peru	Cusco	Pichari	−12.520314	−73.827843	2016	[13]
Peru	Cusco	Quebrada Honda	−12.681124	−72.279309	2016	[13]
Peru	Cusco	Quellouno	−12.635893	−72.555899	2016	[13]
Peru	Cusco	Yuveni	−12.75572	−73.134699	2016	[13]
Peru	Loreto	Iquitos	−3.743673	−73.251633	1992, 1998, 2000–2007	[3,52,54]
Peru	Loreto	Santa Clara	−3.784884	−73.339184	1998	[53]
Peru	Madre de Dios	Puerto Maldonado	−12.590908	−69.196314	1994, 1998, 2000–2007, 2016	[3,39,54,55]
Peru	San Martín	Bagazán	−7.228056	−76.491111	2010	[19]
Trinidad	Sangre Grande	Vega de Oropouche	10.604593	−61.095406	1954	[27]

cases were reported in Jujuy as positive for Oropouche virus in 2005 [34].

3.2. Oropouche fever in Central America

Oropouche fever in Central America has been, in general, neglected. The virus is barely considered during epidemiological surveillance even in areas of febrile cases of unknown aetiology [57]. However, the circulation of the virus occurs in the southern Central America region. For example, in 1989, Panama reported an Oropouche fever outbreak in Bejuco, Chilibre, and San Miguelito [15,34]. It is necessary to consider Oropouche virus as a candidate agent causing outbreaks of febrile symptomatology in Central American countries, especially in regions of Panama and southern Costa Rica.

4. Natural history

Mammals and wild birds act as natural reservoirs for Oropouche virus in its sylvatic cycle (Table 2; Fig. 4). In birds, antibodies have been found in members of the Formicariidae, Fringillidae, Thaurapidae, and Columbidae families; thus the role of these and other birds in the perpetuation and dispersal of the virus needs more exploration [25,34,58,59]. Considering the broad distribution and movement potential of birds acting as plausible reservoirs, outbreaks should be expected even in remote regions if vectors and susceptible hosts coexist under suitable densities [60].

Potential mammal reservoirs include sloths, non-human primates (*Ca. penicillata*, *Sapajus apella, Alouatta caraya*), and rodents (*Proechimys* sp.). The role of wild mammals in the cycle of the virus has been explored mainly in Brazil [21,26,40,61,62], but more biogeographic regions should be explored to assess if the ecological and spatial patterns of Oropouche virus found in Brazil are consistent throughout the continent (Table 2). In terms of plausible vectors in the sylvatic cycle, mosquito species known to maintain the virus are limited (i.e., *Coquilletidia venezuelensis* and *Ae. serratus*, see below). Vector competence of these and other mosquito species have been poorly explored in the sylvatic context. Apparently, humans get infected in the forest and act as "bridges" translocating the virus from natural areas to urban settlements [63]. In the urban and suburban cycle, the midge *Culicoides paraensis* is implicated in the effective spread and maintenance of Oropouche virus resulting in dramatic epidemics once the virus is translocated to populated areas, affecting thousands of people (e.g., >10,000 cases in Brazilian outbreaks [15]). In various epidemics reported in Brazil, the phenomena of 'epidemic sweep' was proposed to describe the movement of infected people among villages facilitating the spread of Oropouche fever through multiple (~10) towns [15,17,34,42]. Considering the small home range of *Cu. paraensis* [64], epidemic sweep may help to explain outbreaks between distant regions.

Apparently, the virus circulates at low levels in humans and wildlife reservoirs. However, once a disturbance in the community occurs (e.g., habitat loss), Oropouche fever outbreaks may emerge [13,19,42,47,56]. During outbreaks of Oropouche fever, domestic animals such as chickens have been suggested as amplifiers (i.e., host species facilitating the increase in prevalence). However, quantitative evidence is still necessary to support this hypothesis, which may be of high relevance to control and prevent epidemics [25,34].

4.1. Vectors of Oropouche virus

Laboratory (e.g., hamster-human infection) and field research (e.g., positivity to Oropouche virus during outbreaks) have incriminated the biting midge *Cu. paraensis* (Diptera: Ceratopogonidae) (Fig. 5) as a main vector of Oropouche virus [16,41,59,65,66]. However, field surveys have shown low probabilities of detection of Oropouche virus in this vector species, and thousands of midges are necessary to achieve virus isolation (ratio of 1:12,500) [16].

Midges, including *Cu. paraensis*, are small arthropods (~2.5 mm) of blood-sucking females from the Diptera order. Midges are active during the morning with a peak of activity in early and late afternoon both inside and outside human dwellings, facilitating human–midge interactions at crepuscular periods [18,59,66]. In the forest, *Cu. paraensis* thrive in tree-holes, leaf debris, and damp soil [67,68]. In man-modified landscapes the species finds suitable crop lands, using banana

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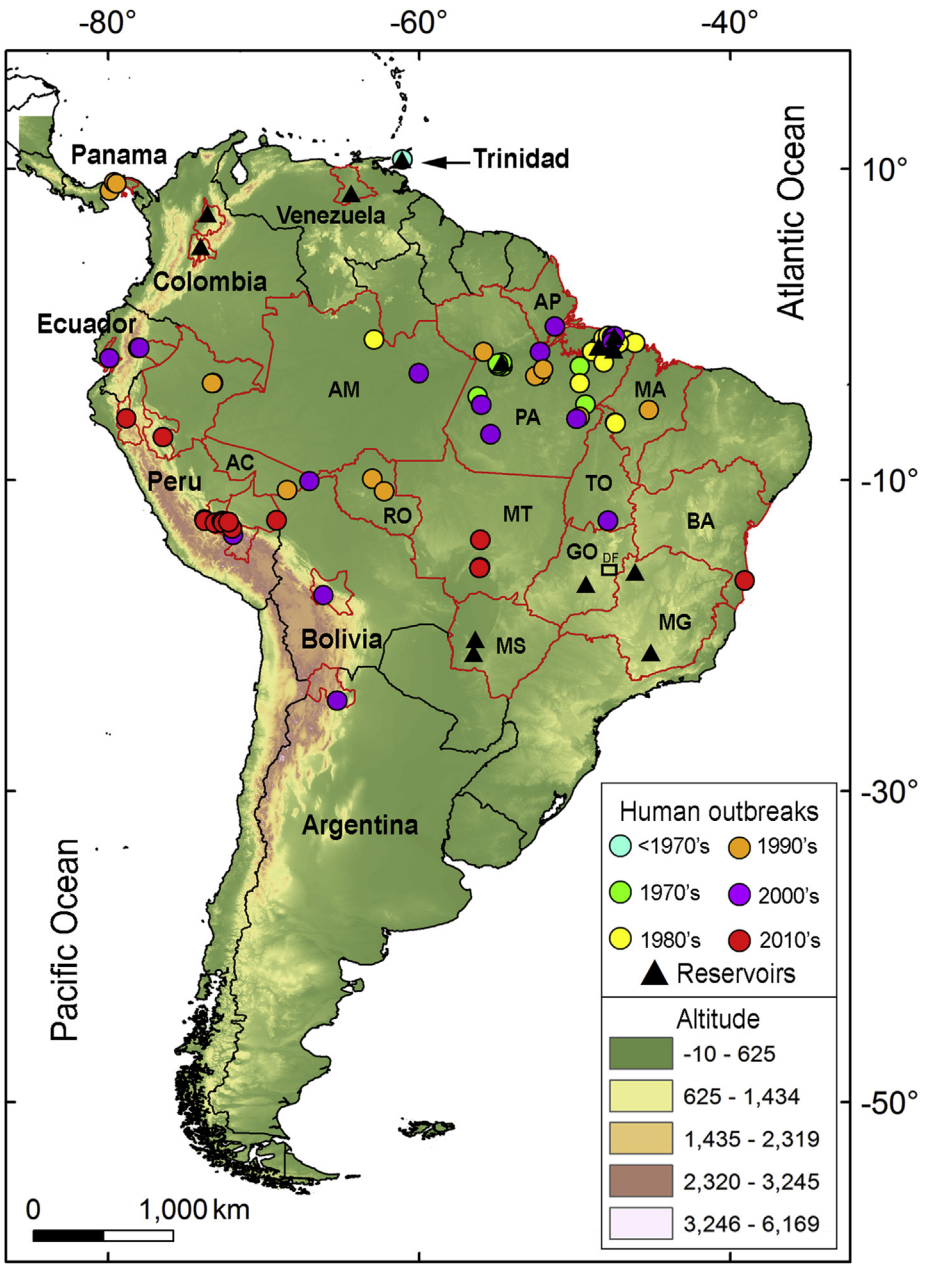

Fig. 3. **Geographic distribution of Oropouche virus in Central and South America.** Distribution of outbreaks (points) and reservoirs (black triangles) from active and passive surveillance. Outbreaks are categorized based on its most recent detection: before 1970's (turquoise; Trinidad), 1970's (green), 1980's (yellow), 1990's (orange), 2000's (purple), 2010's (red). Red lines denote administrative areas documenting Oropouche. Oropouche virus has been isolated from non-human primates in Colombia but specific information regarding locality of the cases was not available (see Table 2). DF = Distrito Federal, AC = Acre, AP = Amapá, AM = Amazonas, BA = Bahía, GO = Goiás, MA = Maranhão, MT = Mato Grosso, MS = Mato Grosso do Sul, MG = Minas Gerais, PA = Pará, RO = Rondônia, and TO = Tocantins.

and cocoa remains as breeding sites possibly due to their high content of organic matter and high humidity [69]. In terms of its geographic distribution, Cu. paraensis populations have been identified throughout tropical and subtropical areas across the Americas. This high plasticity to climates and broad range suggests a potential of Cu. paraensis for the spread of Oropouche fever in the coming years, facilitated by the rise of human movement [68,70–72].

Culex quinquefasciatus was proposed as a candidate competent vector of Oropouche fever during an outbreak in Brazil [40], later confirmed under laboratory conditions by infecting healthy hamsters from mosquitoes exposed to infected hamsters with Oropouche virus [73]. During a Dengue outbreak in Brazil in 2011–2012 [49], the segment S of Oropouche virus RNA was detected in eight of 287 pools (2.79%) of *Cx. quinquefasciatus* captured in the outbreak area. Additionally, five human cases were confirmed infected with Oropouche virus [49]. Considering the potential role of *Cx. quinquefasciatus* in the epidemiology of Oropouche virus and the broad potential range of the species [74], Oropouche could

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Table 2
Localities of Oropouche virus from detections in reservoirs from 1955 to 2017. Animal species incriminated as reservoirs of Oropouche virus are presented. Georeference was performed using coordinates or geolocation of metadata using GEOnet Names Server (http://geonames.nga.mil/gns/html/) and Google Earth. * = High uncertainty in location. Detailed information of Colombian reservoirs is not available from published literature.

Country	Province/State	Locality	Latitude	Longitude	Species	Years of detection	References
Brazil	Goiás	Goiânia city	−16.686882	−49.264788	*Alouatta caraya*	2011–2013	[62]
Brazil	Mato Grosso do Sul	Bonito	−21.129816	−56.492635	*Sapajus apella*	2010	[83]
Brazil	Mato Grosso do Sul	Miranda	−20.239965	−56.377257	*Sapajus* spp.	2013	[61]
Brazil	Minas Gerais	Arinos	−15.915423	−46.111764	*Callithrix* spp.	2000	[26]
Brazil	Minas Gerais	Perdões	−21.096459	−45.087905	*Callithrix penicillata*	2012	[21]
Brazil	Pará	Belém	−1.437281	−48.470614	*Columbina talpacoti*	1961	[58]
Brazil	Pará	Maracanã	−0.7661347	−47.45371	*Bradypus tridactylus*	1971	[17]
Brazil	Pará	Quatro Bocas	−2.412811	−48.039450	Fringillidae, Thaurapidae	1981	[59]
Brazil	Pará	Santa Maria	−1.35054	−47.57653	*Bradypus tridactylus*	1960	[40]
Brazil	Pará	Santárem	−2.450629	−54.700923	Domestic birds	1976	[25]
Brazil	Pará	Santárem	−2.450629	−54.700923	*Proechimys* sp.	1976	[25]
Brazil	Pará	São Miguel	−1.616811	−47.482144	*Bradypus tridactylus*	1971	[17]
Colombia*	Cundinamarca	No data*	5.026003	−74.030012	Non-human primates	2000–2001	[45]
Colombia*	Santander	La Lizama	7.121112	−73.595772	Non-human primates	1964, 2000–2001	[45]
Trinidad	Sangre Grande	Vega de Oropouche (Nariva swamp)	10.391107	−61.039270	*Cebus* spp. *Alouatta* spp.	1955	[27]
Venezuela	Anzoátegui	Atapirire	8.433523	−64.370597	*Cebus olivaceus*	2010	[37]

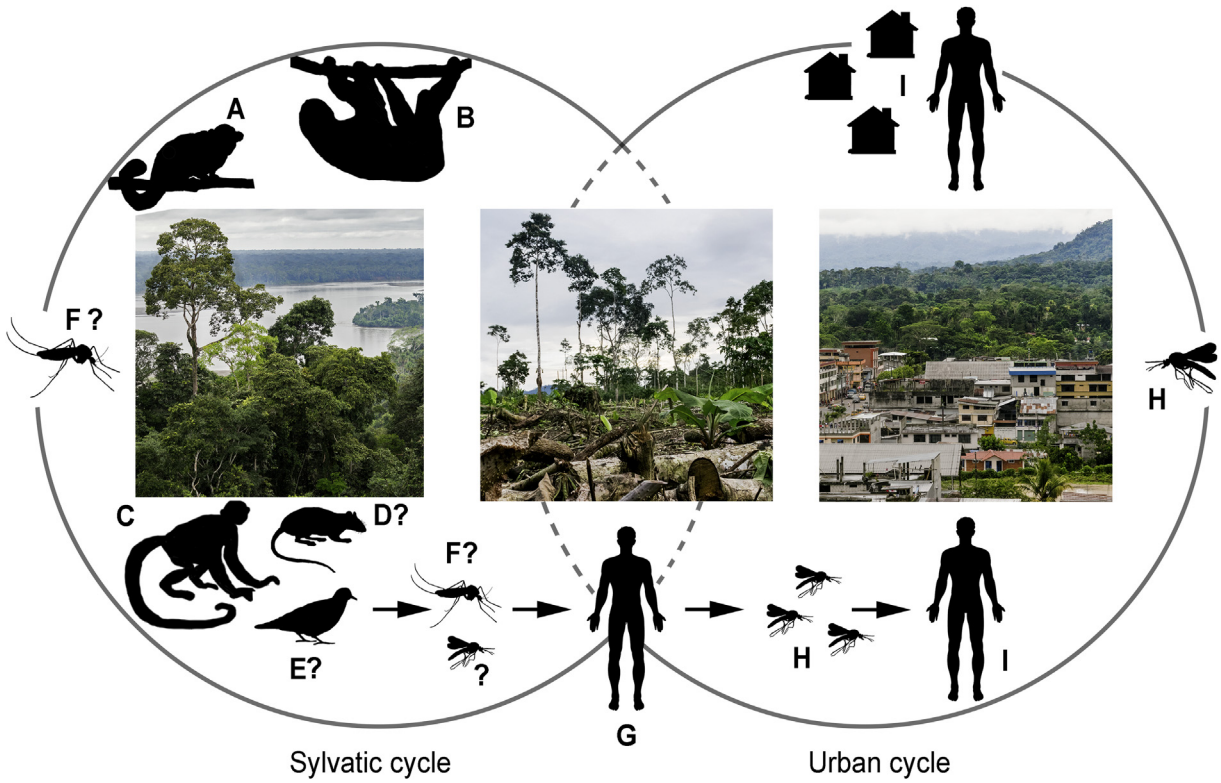

Fig. 4. **Life cycle of Oropouche virus in the wild and domestic interface.** Sylvatic Oropouche virus cycle includes wild mammals such as *Callithrix penicillata* (A), *Bradypus tridactylus* (B), *Sapajus alloata* (C), *Allouatta caraya*, and the plausible role of *Proechimys* sp. (D). Oropouche virus also has been isolated from wild birds (E). Mosquito species incriminated in the maintenance of Oropouche virus has been suggested (*Coquillettidia venezuelensis* and *Aedes serratus*, (F). Anthropogenic disturbance of natural areas may facilitate Oropouche virus spillover to humans (G), generating outbreaks in urban settlements (I). The urban cycle is apparently maintained by *Culicoides paraensis* (H). *Culex quinquefasciatus* has also been implicated in Oropouche virus circulation. The role of *Cu. paraensis* and *Cx. quinquefasciatus* in the sylvatic life cycle is still unclear (F).

also be dispersed by *Cx. quinquefasciatus* into new geographic areas including Africa, Australia, or southeast Asia.

The mosquito species *Co. venezuelensis* and *Ae. serratus* were proposed as vectors of the sylvatic cycle of Oropouche virus in Trinidad and Brazil respectively [27,40]. However, their role as competent vectors and their participation in outbreaks require further research [31,34]. Similarly, *Cu. paraensis* and *Cx. quinquefasciatus* may also have a role in the sylvatic cycle of Oropouche fever and more research on this topic is warranted.

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Fig. 5. ***Culicoides paraensis*, main vector of Oropouche virus.** *Culicoides paraensis* are midges that maintain the urban cycle of Oropouche virus. Female midges are among the smallest blood-sucking arthropods (~2.5 mm), making difficult their detection, capture, and preservation. Oropouche virus has only been identified in *Cu. paraensis* from Brazil, while attempts to identify the virus in *Cu. paraensis* from Peru have remained unsuccessful. Image credit: Maria Luiza Felippe-Bauer, Instituto Oswaldo Cruz, Rio de Janeiro, RJ, Brazil.

5. Epidemiology and clinical features

Oropouche fever is a neglected human pathogen, affecting >500,000 humans in Brazil [31,34]. Number of cases and distribution of the disease, however, may be underestimated [13,34]. The effect of host gender on the prevalence of Oropouche fever has been contradictory, with some studies suggesting higher prevalence in men [41] and others in women [17]. Similarly, age groups affected do not have a clear pattern, with reports suggesting higher prevalence in younger populations [9] and others in older populations [53].

Oropouche fever outbreaks apparently have a seasonal pattern, with most events occurring during the rainy seasons [34]. The virus is transmitted primarily via vectors [16,65], but accidental air-borne infection has been reported in laboratory conditions [42]. The incubation period ranges between four and eight days [34]. After this period, symptoms and high viremia are manifested. During the viremic period, infected people can serve as source of the virus for *Cu. paraensis* during three to four days [16,34]. The acute phase of the disease usually lasts from two to seven days [34]. Around sixty percent of patients develop an array of symptoms resembling those of classical arbovirus infections. A considerable number of Oropouche fever outbreaks have been detected retrospectively during serological surveys for undifferentiated febrile illnesses in Brazil, Peru, and Argentina [34,51,55]. Thus, Oropouche fever should be included as candidate when assessing febrile syndromes in Central and South America considering the co-circulation of multiple arboviruses, the range of vectors, and the similarity of symptoms.

Oropouche fever symptoms include fever (~39 °C), headache, myalgia, arthralgia, chills, photophobia, dizziness, nausea and vomiting. Less frequently, patients experience rash, anorexia, retro-orbital pain, and general malaise [9,19,41,48,56] (Fig. 6). Hemorrhagic phenomena such as epistaxis, gingival bleeding, or petechiae have also been described [48]. The association of specific symptoms with certain virus lineages is still unknown. Indeed, the association between the severity of symptoms with specific virus lineages also remains to be explored [19,34]. Rare symptoms described in published literature include menorrhagia and miscarriage which has been suggested for Oropouche fever and other members of the antigenic Simbu group [15,34,42]. Most symptomatic patients recover spontaneously after ~7 days, although some patients have experienced symptoms such as myalgia and asthenia as long as one month [15,34]. Almost 60% of cases show relapses within the next two weeks after recovery with a similar symptomatic picture as the first illness, but sometimes described as more severe [34,41,44]. While this pattern may be an increase of the virus circulation in the infected person, it can also represent re-infections in areas with constant circulation of infected vectors. Thus, the drivers of relapses in symptoms need to be clarified.

Oropouche virus infections with extremely painful headaches anticipate aseptic meningitis [75]. These patients also experience neck stiffness, dizziness, nausea, vomiting, lethargy, diplopia, and nystagmus that could last up to two weeks [75,76]. Aseptic meningitis usually follows a good prognosis without sequels [31,76].

6. Diagnoses and treatment

Clinical diagnosis of Oropouche fever is challenging [43]. Laboratory analyses have shown marked leukopenia reaching as low as 2,000 leucocytes per ml, but in general, common blood tests such as the basic metabolic panel are inconclusive [34]. The virus has been successfully isolated from the cerebrospinal fluid of individuals with aseptic meningitis showing normal levels of glucose, increased white blood cells (i.e., pleocytosis), and increased protein density [75,76].

Diagnosis confirmation relies mainly on commercially unavailable serological assays [31]. The combination of compatible symptoms plus one positive serum sample of IgM detected with enzyme-linked immunosorbent assay (ELISA) should be considered positive for an acute Oropouche fever case until virus detection can be established. Immunological diagnosis, however, depends on a timely collected serum sample—within a time-window of five days after the onset of symptoms, to detect antibodies during highest viremic levels [34]. Other immunological tests include ELISA IgG seroconversion, immunofluorescence, hemagglutination inhibition, neutralizing, and complement fixation tests [9,31,34]. Diagnosis can also be established from virus isolation in cell cultures [17,34] and from molecular detection of RNA segments S or M (Fig. 2) via reverse transcription polymerase chain reaction (RT-PCR). Segment M is specific for Oropouche virus

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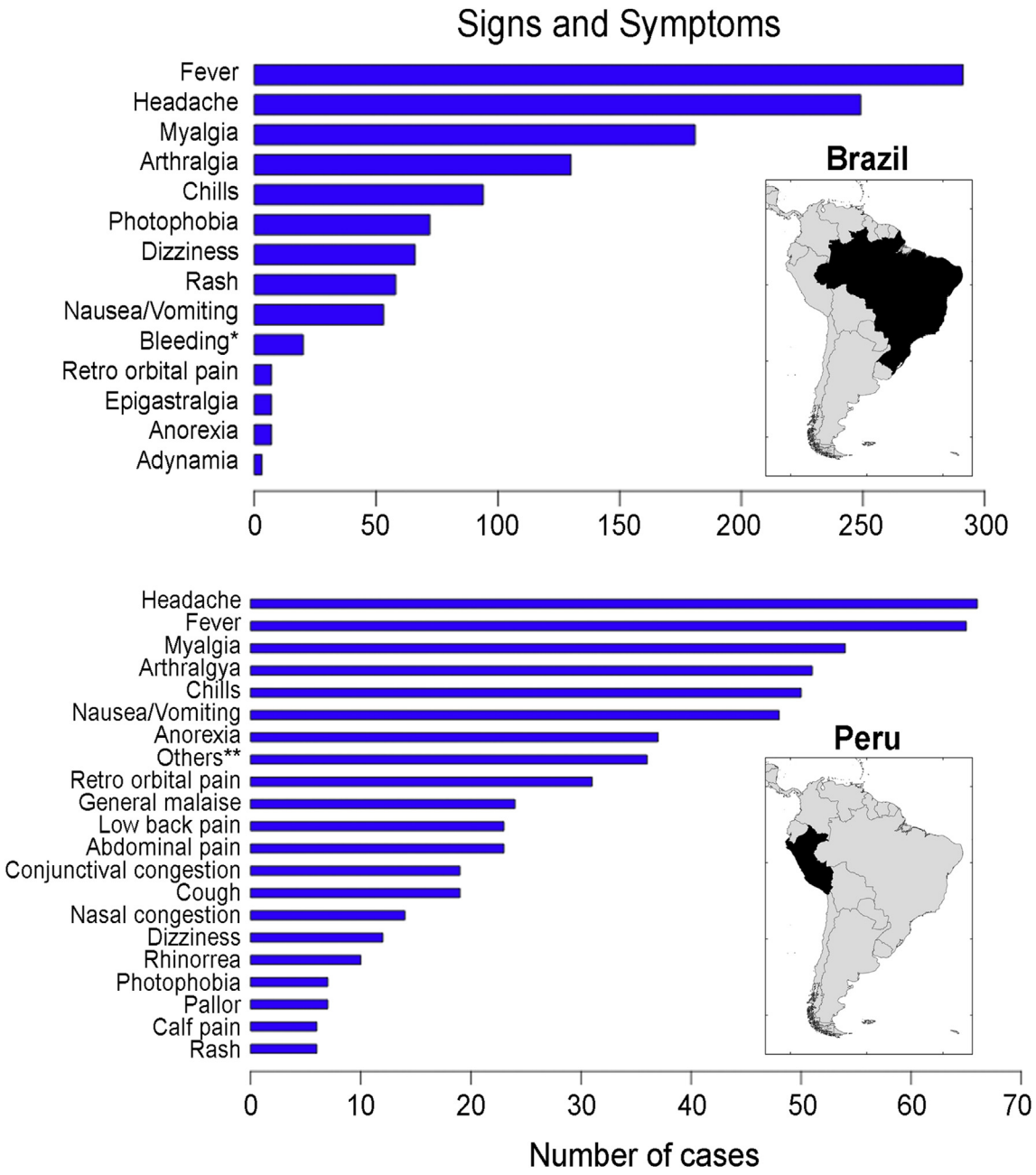

Fig. 6. **Reported clinical features of Oropouche fever.** Symptomatology of Oropouche fever resembles those of other arbovirus febrile illnesses. Symptoms and signs have been published for Brazil (top panel) and Peru (bottom panel). *Bleeding: Hemorrhagic phenomena have been described in Brazilian patients and include epistaxis, gingival bleeding, and petechiae. **Others: Symptoms reported with less frequency include diarrhea, lymphadenopathy and hypothermia, pruritus, dehydration, hypotension, sore throat and chest pain, lipothymia, petechiae, odynophagia, skin spots, tachycardia, altered mental status, and cold limbs. Source: [9,39,46] for Brazil, and [19,54] for Peru.

disregarding reassortments [31,49]. Recently, de Souza Luna et al. (2016) have used immunofluorescence to detect Oropouche virus from peripheral blood leucocytes with promising results [50].

Treatment is focused on fever management and pain relief as in acute Dengue fever; however, Oropouche fever treatment should be repeated during relapse episodes. Usually, Oropouche fever follows good prognosis, even among hospitalized patients. No fatalities have been attributed to Oropouche fever since the first epidemic in 1960 [19,34,76].

7. Potential emergence of Oropouche fever

With more attention being directed to Oropouche fever by formal and informal academic literature (Fig. 1), international health agencies, and local news [39,51,55,77], Oropouche and other arthropod-borne diseases are going to be reported with increased frequency. This phenomenon evidently shows our limited knowledge on the diversity of Neotropical pathogens with anthropophilic potential [4]. The accelerated anthropogenic land cover changes facilitate spillover events and the

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Fig. 7. **Human–wildlife interface in anthropogenic disturbed regions.** Globalization and demographic expansion usually bring deforestation and the invasion of natural areas. This land use change takes sylvatic diseases in close association with naïve populations. In the case of Oropouche virus, sloths were found positive to the virus in Brazil just before the first epidemic in this country in 1961. Image of a rural house in a village of Ecuador where sloths are used as bush meat and pets, which may facilitate Oropouche fever outbreaks. Credits: Daniel Romero–Alvarez.

emergence of diseases [78] (Fig. 7). Vasconcelos et al. (2001) identified several environmental anthropogenic disturbances driving the emergence of viral pathogens in Brazil, including deforestation for agricultural purposes, highway and dam construction, urbanization and colonization of novel areas, and landscape overuse [2]. Unsurprisingly, these factors are common throughout the world and surely will increase considering the environmental, political, and behavioral needs of an inexorable growing human population [79]. More quantitative research is needed to assess the consequences of landscape change in the emergence of these pathogens, which could be an straightforward approach considering the availability of new strategies including satellite-derived data and digital epidemiological surveillance [80]. For example, in a recent outbreak of Oropouche fever in southeast Peru, vegetation loss was identified in outbreak localities [13]. Finally, climate change will influence Oropouche virus distribution, as has been demonstrated for other infectious diseases where vectors increase or diminish their distribution according to environmental suitability, bringing their own pathogens with them [81]. This scenario coupled with the global connectivity through air flight implies a dramatic capacity of pathogens to be translocated [6] and should be considered while studying the distributions of infectious diseases worldwide.

Conflicts of interest

None declared.

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