Anthropogenic Dispersal of Leishmania (Viannia) braziliensis in the Americas: A Plausible Hypothesis

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There are several gaps in our knowledge on the origin and spread of Leishmania (Viannia) braziliensis, an etiological agent of cutaneous and mucocutaneous or American tegumentary leishmaniasis, to different biomes, hosts, and vectors, with important epidemiological implications, including the possible existence of an anthroponotic component. Historical, biological, and epidemiological evidence suggests that Leishmania (V.) braziliensis and its variants were preexistent in Amazonia with great genetic variability, where they dispersed with less variability to other regions (clonal expansion). During pre-Columbian times the parasite may have been transported by migrating humans and probably also their dogs, from western Amazonia to the high inter-Andean valleys and from there to other regions of South America. The same thing could have happened later, in the same way, when it spread to non-Amazonian regions of Brazil and other countries of South and Central America, between the late 19th and early 20th centuries, during the so-called Rubber Boom and construction of the Madeira-Mamoré Railway in the Brazilian Amazon, by migrant workers who later returned to their places of origin, transporting the agent. The parasite’s dispersal in genetic correlated clusters, involving unexpectedly distinct ecosystems in Brazil (Amazonian, Cerrado, Caatinga and Atlantic Forest biomes), has continued until the present through human displacement. The infection of certain species of domestic, synanthropic and even wild animals, could be secondary to anthropogenic introduction of L. (V.) braziliensis in new environments. We admit the same phenomena happening in the probable transference of Leishmania infantum (visceral leishmaniasis), and of Yersinia pestis (plague) from the Old world to the New world, generating domestic and wild enzotic cycles from these agents. These assumptions associated with human infections, chronicity and parasite persistence with possibility of recovery of Leishmania in peripheral blood, skin and scars of cured or asymptomatic patients, (that may provide an alternative blood meal), along with the sand flies’ adaptation to the peri-domicile and the high susceptibility of domestic dogs, horses, mules and cats to the parasite, can reinforce the evidence of anthropogenic spread of L. (V.) braziliensis.

Keywords: Leishmania (Viannia) braziliensis, mucocutaneous leishmaniasis, parasite persistence, human migrations, dogs, expansion in the Americas, anthroponosis, control
INTRODUCTION

Leishmania (Viannia) braziliensis is the most important etiological agent in Brazil and in the set of Andean countries that includes Amazonian areas, Venezuela, Colombia, Ecuador, Peru, and Bolivia, producing mucosal lesions, with predominantly rural and peri-domestic transmission (1).

In Brazil, L. (V.) braziliensis is distributed throughout the country, with numerous vector species involved in the transmission and an incidence of 11.9 cases per 100,000 inhabitants (2, 3). This parasite is considered the etiological agent of cutaneous and mucocutaneous leishmaniasis in approximately 55% of the cases occurring in the Brazilian Amazonia and 95% of those outside this region, with 3 to 5% of mucosal lesions in the country (4). The remaining 45% cases are caused by other dermotropic Leishmania species, such as L. (L.) amazonensis, L. (V.) guyanensis, L. (V.) naiffi, and in fewer cases L. (V.) lainsoni and L. (V.) shawi. In the western Amazonia, consisting of the Brazilian states of Amazonas, Acre, and Rondonia, bordering on Peru and Bolivia, the predominant species is L. (V.) braziliensis, although L. (V.) lainsoni and L. (V.) guyanensis have also been detected (5, 6).

L. (V.) braziliensis and its variants constitute a genetically related group, found both in different natural biomes and those modified by human action (5, 7) transmitted by various sandflies of the genus Lutzomyia, with rodents and marsupials considered reservoirs. Human infection by L. (V.) braziliensis is characterized by chronicity and latency, producing single or multiple ulcerated skin lesions that can self heal but with the possibility of local reactivation and late destructive metastatic involvement of the naso-oro-pharyngeal mucosa (8–10).

In Amazonia, where L. (V.) braziliensis appears to originate, in natural enzootic cycles, sylvatic sandflies like Lu. welcomei, Lu. davisi, Lu. complexa, and others have been incriminated as vectors, while sylvatic rodents of the genera Oryzomys, Akodon, Proechymys, Rhipidomys, the synanthropic Rattus rattus as well Didelphis marsupials are the suspected reservoirs, and humans are infected inadvertently (11).

Outside the Amazonia, sylvatic cycles of L (V.) braziliensis in natural foci of occurrence have still not been defined (8, 12–14). However, this agent is found in altered environments in rural and peri-domestic cycles involving various sandfly species like Lu. intermedia, Lu. whitmani, Lu. migonei, and Lu. neivai, to the South, and the Verrucarum group in the Andean countries. Humans, domestic animals, and occasionally wild animals are also part of this lifecycle (15, 16).

This eclectic adaptation to various species of vectors and animal hosts, including domestic animals, in different modified environments, can explain the enormous capacity for dispersal of L. (V.) braziliensis, unlike the other dermotropic and sylvatic species in the Americas, more geographically limited. Thus, human infection can be acquired in the sylvatic or rural environment or near the domicile in the urban environment in Brazil, Argentina (17), and Andean countries neighboring on the Amazonia (18). Domestic dogs are highly susceptible to experimental infection and are frequently found naturally infected in Brazil, Argentina, Peru, Bolivia, Ecuador, Colombia, and Venezuela (1, 8, 19–21). In these animals, the lesions occur on hairless areas, which are more accessible to the insect vectors, like the snout, ears, and scrotum (8, 13, 19). In addition, L (V.) braziliensis has been detected by PCR associated with molecular hybridization in healthy skin fragments collected from naturally infected dogs from the state of Rio de Janeiro, Brazil (22).

Historically, there are no reports of mucosal lesions, characteristic of infection by this parasite, during the widespread deforestation that occurred in Brazil’s colonial period in the 16th, 17th, and 18th centuries in areas outside Amazonia that were much more densely populated. Much later, these same areas reported outbreaks of cutaneous lesions and the appearance of mutilating mucosal forms, like those reported in the late 19th and early 20th centuries and which continue to occur in these areas and in new areas of old colonization as isolated outbreaks.

The parasite’s persistence in the human host, evidence of humans and domestic animals acting as sources of infection, and historical evidence prior to and following the Iberian colonization highlight human migrations as the principal cause of this dispersal. In addition, we have currently observed a higher prevalence of mucosal lesions in the Southeast and South regions of Brazil, where the prevalence of cutaneous lesions is low. We believe this is due to a greater sensitivity of humans to the disease in areas where the endemic has arrived recently. We have interpreted this finding as a possible co-evolutionary adaptation of the parasite, with humans becoming an important secondary reservoir (4).

METHODOLOGY

We performed a non-systematic review of cutaneous and mucocutaneous leishmaniasis and L. (V.) braziliensis, involving studies on the following: (i) the incidence of this disease in countries of the Americas; (ii) genetic variability of L. (V.) braziliensis in different ecosystems; (iii) disturbed areas where peri-domiciliary transmission of leishmaniasis occurs; (iv) the clinical course of leishmaniasis and persistence of L. (V.) braziliensis in the skin, blood, and scars of cured or asymptomatic patients; (v) infection and susceptibility of the domestic dog to L. (V.) braziliensis; and (vi) historical records on occurrence of mucocutaneous leishmaniasis, related to human migration to and from the western Amazon. For this purpose, we used scientific and historical sources mostly published in scientific articles and some in specialized books from 1908 to 2021, in Brazil and in neighboring countries, in combination with our own experience and personal observations in over 40 years working in the field of leishmaniasis in different geographic areas of Brazil and other South American countries.

GENETIC VARIABILITY OF THE PARASITE

The enormous biodiversity of the Amazonia and the wide diversity of Leishmania species from sub-genus Viannia
suggest that this is the geographic origin of this sub-genus, and that species such as *L. (V.) braziliensis* have been circulating in the region for a long time, maybe since antiquity. *Leishmania* is assumed to have the capacity to spread through the hosts and vectors, interacting with situations in the different ecosystems and co-evolving with them (23).

Several studies in Brazil, Peru, and Bolivia have demonstrated great genetic variability in *L. (V.) braziliensis* in the Amazon region and less variability in other regions (5, 24–26), leading to the supposition of active transportation of sub-populations of this *Leishmania* to new sites. Interestingly, major similarity has been demonstrated among isolates from Brazilian Amazonia (Pará state), the South of Brazil (Paraná state), and the Andean countries (Peru) (27). *L. (V.) braziliensis*, grouped by different phenotyping and genotyping methods in Brazil, displays major similarities between the samples from the North, namely the rainforest (Amazonian Biome) and the Northeast, or semiarid scrub forest (Caatinga), thus characterizing a cluster, while the similarities between samples from the Central West, with a dry savannah climate (Cerrado) and the Southeast and South, with a wet climate (Atlantic Forest), characterize another cluster, both with similarities to the reference (M2903) of Amazonian origin (28).

Such findings suggest that the clonal dispersal of the same genetically correlated strain over continental distances must depend more on the migration of the human host with the capacity to travel great distances than that of other possible animal reservoirs or insect vectors, restricted to given ecosystems. Likewise, the observed clusters (28) coincide with the human migratory routes both from the past (North-Northeast) and more recent periods (Central West-Southeast and South) in Brazil.

In order to prove the hypothesis of clonal dispersion of *L. (V.) braziliensis*, future evaluations of samples with different origins using more discriminatory methods such as multilocus sequence typing and multilocus microsatellite typing could be performed to evaluate the intra and inter-specific genetic diversity of isolates from different Brazilian regions and other countries (29, 30). Currently, Leishmania RNA viruses are being studied extensively because they may be related to severity of the disease, including metastatic progression and worsening of lesions, for example (31). However, this must be an ancient phenomenon, and we believe, as our study proposes, that it has not contributed to changes in the parasite’s pathogenic profile since prehistoric times.

**PARASITE PERSISTENCE**

*Leishmania* has been found in scars from healed lesions several years after treatment (32–36), on healthy skin before treatment (36), and in peripheral blood in the absence of an active lesion (36–39). The whole parasite has been detected by culture and in situ immunohistochemistry (40) as well as its DNA by using polymerase chain reaction (PCR) (35). These findings could explain the reactivation of old lesions and the induction of reactivation as well as the occurrence of new lesions following trauma or immunosuppression and metastasis to mucosae causing destructive lesions. Thus, demonstration of the parasite in extra-lesional tissues shows that *L. (Viannia)* parasites circulate systemically during disease activity and after resolution of the lesions (36). The parasite’s viability (in culture), infectivity (in laboratory animals), and PCR reactivity in blood have also been observed. The parasite can also be detected by PCR in the blood of individuals with subclinical or inapparent infections observed in both endemic and non-endemic areas. The individuals remain infected indefinitely and present a cell-mediated immune response, as evidenced by the Montenegro skin test (delayed-type hypersensitivity test - DTH) to *Leishmania* antigens or by the presence of *L. (V.) braziliensis* in the blood, detectable by PCR (37, 38, 41, 42).

Attempts to isolate other dermotropic species in human peripheral blood have been unsuccessful (43).

Parasite presence or persistence for many years both in chronic lesions and in inapparent or cured infections make human hosts a potential source of infection for vectors in the new regions where they settle (8).

**HUMANS AND DOMESTIC ANIMALS AS POSSIBLE SOURCES OF INFECTION**

Most authors still assume the obligatory existence of a natural sylvatic cycle for *L. (V.) braziliensis*, outside the Amazonia, probably by analogy with the enzootic cycles of the new species of *Leishmania*, described since the 1950s in Mexico, *L. (L.) mexicana* (44), and in the Amazonia, *L. (V.) guyanensis* (45), reinforced by findings of *Leishmania* spp. in wild animals (46–48). Few admit the possibility of a sylvatic or synanthropic cycle being secondary to the anthropic introduction of *L. (V.) braziliensis* in environments with potential vectors. Thus, the possible participation of humans and domestic animals in the transmission cycle in certain environments is masked by the forest landscape, where the prior existence of sylvatic sources of infection is sometimes erroneously presupposed.

In addition to demonstrating the permanence of *Leishmania* in the blood and tissues of healthy individuals, there is empirical evidence that humans can act as a reservoir due to the positivity to xenodiagnosis with sandflies on the lesion’s edges (36, 49, 50). Epidemiological evidence suggests that a high proportion of infected individuals play an important role in *L. (Viannia)* species transmission, when associated with high population density and the anthropophilia of sandflies adapted to areas altered by human action in Brazil, Bolivia, and Peru (36, 51).

In a neighborhood with households displaying human cases, DTH reactivity is more exacerbated, and risk of the disease is 7.5 times greater (52). The most important risk factor for the disease in children is the presence of a family member with a history of cutaneous leishmaniasis (53). The same is true for familial clustering of cases of mucosal lesions, where environmental factors appear to be more determinant than genetic origin (54). Likewise, the importance of domestic dogs in the
increased risk of human infection in Peru and Brazil has been demonstrated (20, 55–57).

In addition, various studies on sandfly feeding preference highlight humans and dogs (both associated with major migrations) as secondary food sources (58). Thus, dogs play a proven role in the peri-domiciliary transmission of *L. (V.) braziliensis* in Brazil (55) and *L. (Viannia)* in Peru (20). Horses, mules, and domestic cats have also been found infected with *L. (V.) braziliensis* (59–62).

**HISTORY AND DISPERSAL OF LEISHMANIA (V.) BRAZILIENSIS**

There are few historical records on the occurrence and dispersal of mucocutaneous leishmaniasis in the Brazilian literature or that of other Latin American countries. However, there are consistent reports by 16th and 17th-century chroniclers on the occurrence of cutaneous and nasal mucosal lesions related to insect bites, among the sparse population in the navigable regions of the Amazonia and the pre-Andean regions, where such lesions still occur (12, 63). The mucosal form is also depicted in pottery (Huacos) from the pre-Incan Moche and Chimú eras, found in Peru and Ecuador and dated to 400–900 AD, representing facial deformations suggestive of mucocutaneous leishmaniasis (64). Paleopathological material from prehistoric skulls studied in Peru, close to modern-day Lima (65) and in the Atacama Desert in Chile, from 500 to 1,000 years ago, show lesions in the facial bone structure that are consistent with the mucosal form, proven by the detection of *Leishmania* DNA (66, 67).

Historical, archeological, and epidemiological evidence suggests the occurrence of the destructive mucosal form of leishmaniasis, typical of *L. (V.) braziliensis*, in pre-Columbian Andean populations that journeyed into the Amazon and returned to the altiplano, producing new cases of the cutaneous form (uta) and mucosal form (espundia) in the inter-Andean valleys and as far as the western coast of Peru (12, 68). In addition, due to the great susceptibility of dogs to *L. (V.) braziliensis* and its variants, we believe that contact with these animals, including the mystical Peruvian hairless dog, of pre-Hispanic origin, may have contributed to the dispersal of *L. (V.) braziliensis*. The absence of hair on these animals, offering a larger body surface for the sandfly’s blood meal, would tend to increase its potential for infection and transmission to humans.

**THE BRAZILIAN CASE**

Various hypotheses have been raised to explain the origin of genus *Leishmania* and the occurrence of mucocutaneous leishmaniasis in Brazil (69–71). The theory of the “Mediterranean origin” of the disease in Bahia, proposed by Juliano Moreira in 1908 and Aguiar Pupo in 1912 (70), refers to its purported introduction into Northeast Brazil by the Phoenicians (Syrians) in antiquity. The theory of the “Andean origin”, proposed by Rabello in 1925, contends that the disease originated in the highlands of Bolivia and Peru, spreading from there across the Andean countries to Argentina and Amazonia. Rabello previously reported that the disease was being spread by workers from the rubber groves in Amazonia returning to their home states, especially Ceará and Bahia, then migrating again to both forest areas and urbanized areas, as observed in the city of Rio de Janeiro in the 1920s (70).

The “Amazonian” theory that we proposed in 1994 considers the possibility that the disease originated in the western Amazonia, which includes Brazil, Peru, and Bolivia, principally south of the Marañón-Solimões-Amazon rivers, where *L. (V.) braziliensis* predominates, expanding from there until the present day through to the Central, East, and South regions of Brazil (8, 12, 72).

The first descriptions of cases of cutaneous and mucosal lesions suggestive of leishmaniasis in the Western Amazonia occurred in Bolivia in 1876 and again in 1903, during the war between Bolivia, Brazil, and Peru, involving a land dispute for the Acre region (18, 73).

In Brazil, outside of Amazonia, from the 16th to the late 19th centuries, when extensive deforestations occurred for crop farming and cattle-raising, there is no record of outbreaks of skin ulcerations or destructive mucosal diseases, the latter of which were unlikely to have gone unnoticed.

In the last two decades of the 19th century and the first two decades of the 20th century, there were various waves of migrants from Northeast Brazil (mainly from the state of Ceará, with 54,875 migrants) to western Amazonia, due to the Great Drought and a smallpox epidemic in the Northeast (1877–1880). The migrants were attracted by the Rubber Boom (1868-1913) and returned to the Northeast with the mucosal form of the disease (74). The rubber-tapping areas were predominantly along the tributaries on the right side of the Solimões and Amazon rivers.

Another important magnet, although for a short period of time, was the construction of the Madeira-Mamoré Railway (1907-1912) linking Porto Velho to Guajará-Mirim in the western Amazonia, aimed at transporting rubber and other products from Bolivia and Brazil to ports on the Atlantic, but interrupted by the collapse of international rubber prices (75).

The railway construction project had attracted some 21,810 workers, including South and Central Americans. In particular there were workers from the British colonies in Central America and the Caribbean with experience in construction of railways and the Panama Canal, who had returned to their places of origin (75).

In Southeast Brazil, in the late 19th and early 20th centuries, European and Asian immigrants and especially workers from Northeast Brazil came from areas in Amazonia to clear forests and build the Northwest Railway linking Bauru in the state of São Paulo to Corumbá in Mato Grosso. Major outbreaks of “ferida bravá” (‘wild sore’) or “Baurú ulcer” occurred, beginning in 1905, with the disease remaining endemic until the 1940s, accompanying the expansion of coffee cultivation. It was not until 1909 that the etiological agent of the disease was identified...
as *Leishmania* by Lindenberg, Carini, and Paranhos, and termed *Leishmania braziliensis* by Gaspar Vianna in 1911 (later emended to *L. braziliensis* (apud Vianna 1912)).

However, in areas contiguous to the previously cleared Atlantic Forest, during the long slaveholding period (1530–1888), there were no records of the mucosal disease until 1879, and no report among the Kaingang Indians, native to the region.

In the late 19th century, various medical reports attributing the etiology to syphilis suggest the occurrence of cases of mucosal leishmaniasis in: the Uberaba region of Minas Gerais state, in 1879 by Carneiro da Cunha; Rio de Janeiro state, based on museum specimens from the School of Medicine, since 1882; São Paulo state, based on diagnoses performed in Italy by Breda among returning immigrants, in 1884; Bahia state, in 1895 by Juliano Moreira; and in the Brazilian Amazonia, in 1910, by Matta (70). However, the first parasitologically confirmed cases of mucosal lesions were reported in São Paulo by Splendore in 1910 (70). Meanwhile, the first records of the cutaneous form in Paraguay and Argentina occurred in 1913 and 1915, respectively, and a great epidemic occurred in Paraguay during the Chaco War in 1934 (76).

Cutaneous forms and to a lesser degree the mucosal forms were reported in nearly all the states of Brazil by the late 1940s. In the 1950s and 60s, when organochlorine pesticides with heavy residual action were used indiscriminately in farming areas in Southeast and Northeast Brazil (coffee, cotton, cacao), the disease virtually disappeared from these areas (8, 77).

Since the 1960s, Brazil witnessed a process of accelerated urbanization that contributed to the reproduction of a rural living pattern on the periphery of large cities, especially in the Southeast and South. In addition to this event, various others coincided with the resurgence of mucocutaneous leishmaniasis in Brazil, beginning in the 1970s and 80s and persisting to the present (78–80). Suspension of organochlorine use in the control of malaria and Chagas disease; a ban on these pesticides for agricultural use; the reappearance of anthropophilic sandfly species in environments with plant cover; the renewed intense migratory movement associated with social exclusion and climate changes (81), the expansion of the distribution of sandflies in the intertropical range associated with global warming, besides the highway construction and mining of gold and other minerals in Amazonia, as well as the construction of hydroelectric plants such as Itaipu, on the border with Paraguay (8, 82).

### EPIDEMIOLOGICAL IMPLICATIONS

In Amazonia, *L. (V.) braziliensis* continues to predominate in the southern watershed of the Amazon Basin.

Several factors favor the emergence of transmission foci for leishmaniasis by *L. (V.) braziliensis*. These include an increase in the sandfly population in the primary peri-forest environment, soon after deforestation, probably due to the decrease in natural predators and increase in feeding sources: loss of the “edge effect” (8, 83) or the fitness of certain vector species to rural and peri-urban environments that have already been altered for years, and the possible sources of infection already existing there or recently introduced (8). Sources of infection can also include humans with subclinical infection or with the untreated disease, or those that respond poorly to treatment, including cases of co-infection with HIV (84). The low efficiency of vector transmission and the long incubation period before the appearance of new secondary clinical or subclinical cases all mask the evidence of possible introduction of *L. (V.) braziliensis* by humans and/or dogs and subsequent involvement of synanthropic animals such as rodents (85) and marsupials.

Meanwhile, in many wooded areas of the Atlantic Forest subject to extensive deforestation in the 1980s, in the Southeast of Brazil (Rio-Santos Highway), no cases were reported initially. Peridomiciliary cases began to appear a decade later, reinforcing the assumption that the arrival of humans and their dogs, symptomatic or asymptomatic carriers of *L. (V.) braziliensis*, could explain the origin of the endemic.

**Figure 1** shows a map with archeological, paleopathological, and clinical/historical findings and possible dispersal routes for *L. (V.) braziliensis* in the Americas.

### FINAL REMARKS

In endemic areas, the high proportion of individuals with nonsymptomatic infection, even those considered treated and cured, but at risk of reactivation, in addition to the growing importance of domestic transmission, suggest convincing circumstantial evidence of the anthroponotic transmission of *Leishmania* (*Viana*) (32).

Parasite persistence and the narrower genetic diversity of *L. (V.) braziliensis* isolates, found in humans (86–88) and with a wide geographic distribution (5), reinforce the evidence that the parasite was initially introduced and continues to be spread by the human host in environments that have been altered for a long time, as well as in recently deforested environments with high vector density.

This situation, in addition to sylvatic transmission, gives rise to new foci of the endemic, producing various transmission patterns: peri-sylvatic, rural, peri-urban and urban, aggravated by the peri-domiciliary presence of dogs, equids, and/or synanthropic animals (89). In both peri-domiciliary and domiciliary transmission, it is common for younger persons and women to be affected (8).

Thus far, samples from blood and skin fragments of *R. rattus*, captured in an endemic area in the state of Minas Gerais, were found positive for *L. (V.) braziliensis* in PCR-hybridization experiments (85). *R. rattus*, with eclectic habits, introduced into the Americas by European colonists, and synanthropic marsupials whose population grows with anthropic activities in the peri-domicile, could be a link between the sylvatic and peri-domiciliary environments. These animals could take the opposite route, carrying the *Leishmania* introduced by humans or dogs from the peri-domiciliary cycle to the sylvatic environment in a process similar to the introduction of the bubonic plague in the Americas, associated with *R. rattus*, establishing a secondary
sylvatic cycle. In addition, *L. (L.) infantum* was introduced into the Americas during the colonization periods and nowadays such specie is found in domiciliary, peri-domiciliary, and sylvatic cycles infecting dogs, marsupials, rodents, and foxes, respectively (90).

In short, beginning with its Amazonian origin, the parasite’s dispersal across various biomes due to human migrations associated with high rates of subclinical infections, as well as the chronicity of the disease and parasite persistence in infected or treated humans, linked to the presence of sandflies and the high susceptibility of domestic dogs, are the facts that point to the anthropogenic spread of *L. (V.) braziliensis* in the Americas.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article-supplementary material. Further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

MM conceived the idea of the study, designed the methodology and wrote the first draft of the manuscript. KM, AF, AOS, LM, and RP
contributed to investigation, analyze, data interpretation and review of the manuscript. MM and AOS got research funding. All authors contributed to the article and approved the submitted version.

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