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Tegumentary leishmaniasis in the State of Amazonas: what have we learned and what do we need?

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ABSTRACT

This study evaluated the occurrence of American tegumentary leishmaniasis (ATL) in the State of Amazonas, Brazil, in the last 30 years with emphasis on the last 10 years (2001 to 2010). The disease was predominantly observed in males (76.2%), in the 21- to 30-year-old age group (26.6%) and in extractive workers (43.7%); 3.3% of the cases were the mucosal form. The endemic channel shows the disease seasonality, with a predominance of cases at the beginning and end of each year. The number of cases by municipality in the period of 2001-2010 shows the maintenance of the endemic in the localities where the highest numbers of cases have always been registered, namely, Manaus, Rio Preto da Eva, Itacoatiara and Presidente Figueiredo. The comparison of data from 2001 to 2005 and from 2006 to 2010 showed the emergence of this disease in municipalities that had been previously unaffected. In the last years, there has been a significant increase in the activities of control, diagnosis and treatment of leishmaniasis in the State of Amazonas. In conclusion, the historical series of ATL analyzed in this study suggests that the transmission foci remain and are even expanding, though without continuous transmission in the intra- or peridomicile settings. Moreover, the disease will persist in the Amazon while the factors associated with infection acquisition relative to forest exploitation continue to have economic appeal. There is a real expectation of wide variations in disease incidence that can be influenced by climate and economic aspects.

Keywords: Cutaneous leishmaniasis. Amazon. Epidemiology. Mucosal leishmaniasis.

INTRODUCTION

Tegumentary leishmaniasis is considered a neglected disease relevant to public health. Recently, the relevance of leishmaniasis, as estimated by the World Health Organization, was revised; the new estimate indicates that the worldwide incidence of cutaneous leishmaniasis varies from 0.7 to 1,200,000 new cases each year and that Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, Sudan, Costa Rica and Peru are responsible for 70 to 75% of those new cases. In the Americas, the estimated incidence varies from 187,200 to 307,800 cases, of which 38.9% occur in Brazil, although the official reporting does not exceed 30,000 cases annually in the country[1].

In Brazil, American tegumentary leishmaniasis (ATL) has a decreasing incidence. ATL coexists in a double epidemiological profile expressed by the maintenance of cases that originated from old foci or areas close to them and by the emergence of small outbreaks associated with the expansion of agricultural areas, the establishment of mineral extraction areas such as gold mining and oil prospecting, the construction of roads and the occupancy of new areas in the outskirts of cities[2].

The annual mean case numbers reported were 28,568 from 1985 to 1999, 31,204 cases from 2000 to 2005 and 22,985 cases from 2006 to 2010, with disease reported in all states. The Northern region had the highest raw number of cases, with 106,004 cases in the period from 2001 to 2010 and incidence rates per 100,000 inhabitants ranging from 114.8 to 163.5[3].

So far, seven different species of *Leishmania* have been described as etiologic agents of tegumentary leishmaniasis in the Brazilian Amazon: *Leishmania (Viannia) braziliensis,*

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*L*eishmania *(Viannia) guyanensis*, *L*eishmania *(L*eishmania*) amazonensis, L*eishmania *(Viannia) naiffi, L*eishmania *(Viannia) lainsoni, L*eishmania *(Viannia) shawi* and *L*eishmania *(Viannia) lindenbergi*[4]. Visceral leishmaniasis does not occur in the State of Amazonas.

ATL in the State of Amazonas is primarily a zoonosis[5], and its transmission cycle occurs among wild animals and sandflies. On most occasions, humans become infected via environmental changes when they interpose themselves in the sylvatic cycle by entering the animals' ecosystem[6].

Among the possible *L. (V.) guyanesis* wild reservoirs, the sloth (*Choloepus didactylus*) has been assigned as the main reservoir in regions of primary forest in the Brazilian Amazon and in some areas in French Guiana[7]. Also considered important wild reservoirs are *Tamandua tetradactyla* and, secondarily, *Proechimys* sp. (spiny rats) and *Didelphis marsupialis*. The latter exhibits infection rates exceeding 20% in the Manaus region[5][6][8]. The parasites can be found in the skin and viscera of these animals[9]. *D. marsupialis* is of great importance in forest areas altered by man because it feeds on domestic waste on the forest limits near houses[5], circulating constantly between the forest where it becomes infected and the human environment where it could be a source of infection for the sandflies present there, thus establishing a link between the sylvatic cycle and the peridomicile[10].

The ATL vectors in the region of Manaus are *Lutzomyia umbratilis* and *L. anduzei*. These vectors are considered respective primary and secondary vectors of *L. (V.) guyanensis*, the main species that causes ATL in the State of Amazonas[2].

In the Amazon, ATL has three different clinical forms: cutaneous, diffuse cutaneous and mucosal. Cutaneous leishmaniasis is the most predominant, especially in the Manaus region[11][12].

ATL IN THE STATE OF AMAZONAS AND IN THE METROPOLITAN REGION OF MANAUS

Since the 1970s, the consolidation of the Free Economic Zone of Manaus, which was associated with factors such as the flooding of major rivers of the Amazon Basin, resulted in constant migratory flow to the City of Manaus, with disorderly occupation of the city outskirts. This process coincided with the implementation of the Institute for Tropical Diseases of Manaus in 1974 – currently called the Tropical Medicine Foundation Dr. Heitor Vieira Dourado [*Fundação de Medicina Tropical Heitor Vieira Dourado* (FMT-HVD)] – that immediately began to play a key role both in the diagnosis and treatment of leishmaniasis cases and in the development of pioneering work on the periphery of the newly formed neighborhoods São José Operário and Cidade Nova, which increased the understanding of the essential aspects of leishmaniasis transmission in this new context[13].

In the historical series of ATL cases in the State of Amazonas from 1981 to 2010, there are large variations in the numbers of cases registered each year, with emphasis on the years 1985, 1992 and 2003, when the crude incidence was higher, and on the years 1994, 1996 and 1998, when the crude incidence was lower **(Figure 1)**.

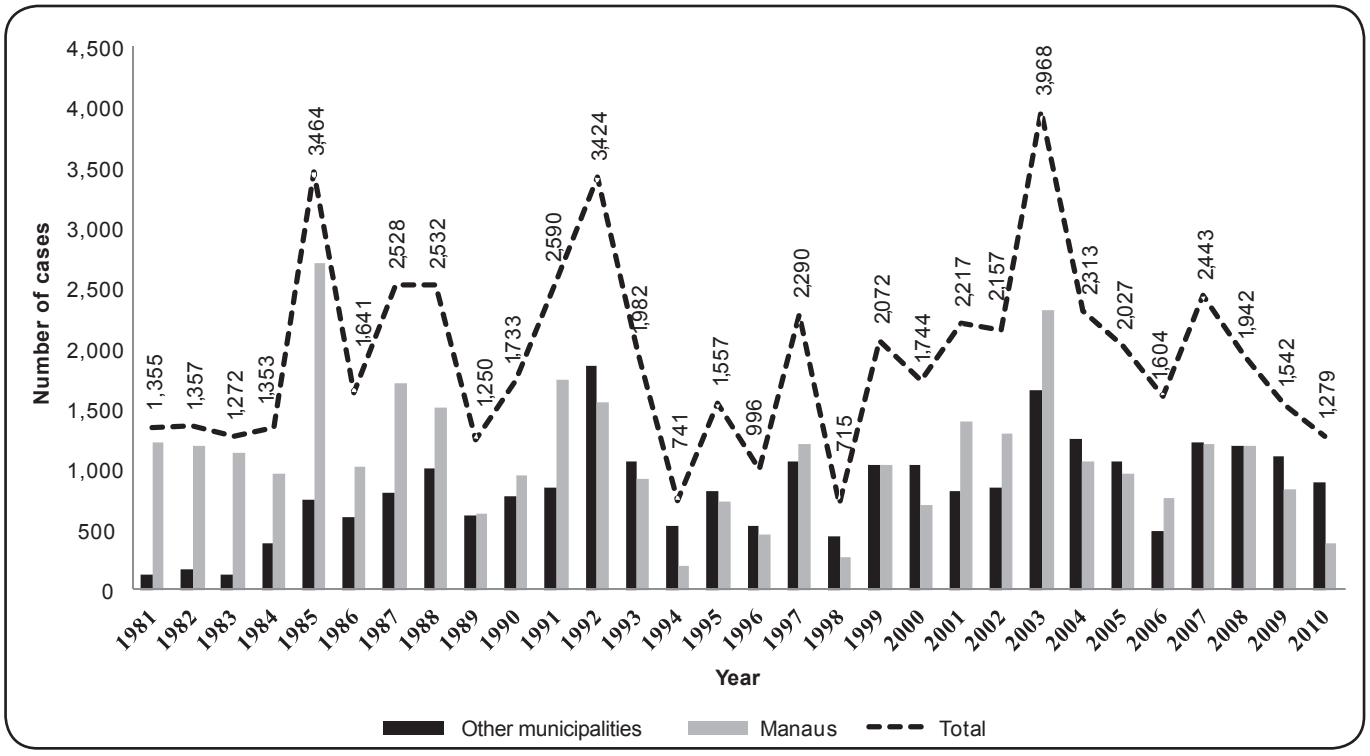


FIGURE 1 - Annual distribution of American tegumentary leishmaniasis cases in the State of Amazonas (1981 to 2010).

In 1985, a large ATL outbreak occurred due to the construction of a housing complex in the North Zone of Manaus (*Cidade Nova*), reaching an alarming incidence of 3,464 cases. This outbreak constituted an increase in incidence of 174% compared to the average of 1,334 cases in the previous four years (1981 to 1984), and 78.4% of these cases were autochthonous to the municipality of Manaus. It is believed that climatic factors and the maintenance of a large number of human settlements in the periphery of Manaus contributed to the increased number of cases in 1992[13] [14] [15].

In 2003, the increase in the number of cases was attributed to climatic factors because rainfall remained high and constant in Manaus, favoring vector maintenance and proliferation throughout that year. This scenario may have occurred in the entire North Region because the highest numbers of cases of the last years for this region were recorded in 2003 (14,099 cases) and 2004 (13,726 cases)[3].

Some hypotheses have been raised to explain the decreased numbers of cases in 1994, 1996 and 1998. In those years, there was an increase in the average temperature, which was associated with low rainfall most likely due to increased deforestation. More recently, from 2006 to 2010, there was a decrease in the number of cases, which was likely a result of reduced deforestation due to control by federal agencies such as the Brazilian Institute of Environment and Renewable Natural Resources [*Instituto Brasileiro do Meio Ambiente e dos Recursos Naturais Renováveis* (IBAMA)][16].

The municipality of Manaus accounts for 54.2% of the reported cases of ATL in the last 30 years in the State of Amazonas. The vast majority of reported cases in the state originate mainly from municipalities that comprise the so-called Metropolitan Region of Manaus and from municipalities situated along two roads – AM 010 and BR 174[13] [14] [17] [18]. Another activity that contributes a significant number of ATL causes is the annual training conducted by military organizations in the jungle because Manaus is a strategic region that borders four countries[19].

The most common occurrence of the disease is in the form of outbreaks. The level of exposure of affected individuals is directly related to planned agricultural settlements or, more frequently, to the municipality's periphery occupation, with infections of the latter occurring in a disordered way in most cases[10] [13] [14] [15]. As a result, the population is exposed to vectors because most of the houses in the recent settlements are built too close to the edge of the forest; thus, the population can be reached by the vectors' radius of action. The vectors go to houses because they are attracted by several factors, including light and the presence of synanthropic animals, such as *Didelphis marsupialis* and domestic animals like dogs[20].

It is likely that transmission also occurs in the intra- and peridomiciles in Manaus, first by the proximity of humans to forest areas because most of the houses in the recent settlements are built less than 100m from the forest edge and also because the vector's source of blood, the wildlife, becomes more scarce due to the human presence[10]. Nevertheless, transmission in these areas seems to be transient because it is interrupted once urbanization is completed something that does not occur in dense forest areas, where the exposure to vectors is constant.

CLINICAL CHARACTERISTICS, DIAGNOSIS AND TREATMENT

Most cases reported in the State of Amazonas correspond to the cutaneous form of ATL, whose presentation varies from localized to disseminated lesions[2] [10] [17]. The clinical manifestations of the localized form in Manaus, in which infection by *L. (V.) guyanensis* is predominant, differ from the localized form observed in regions in which infection by *L. (V.) braziliensis* is predominant. The localized lesions observed in patients in Manaus are more numerous and smaller, and the diagnosis is easier due to the abundance of parasites in the lesions[21]. *Leishmania (V.) guyanensis* has a lower response to the antimonials compared to *L. (V.) braziliensis*[22]. More recently, co-infection with human immunodeficiency virus (HIV) has been described, with some peculiarities in its clinical characteristics and therapeutic response[23].

One of the largest issues of the disease in the Americas is the occurrence of mucosal leishmaniasis (ML), which is mainly associated with infection by *L. (V.) braziliensis*. In the Amazon, the individuals affected by mucosal leishmaniasis usually work in primary forest areas and are involved with activities related to the extraction of forest products. Therefore, these individuals often do not have access to timely diagnosis and treatment[12].

Regarding the ML etiology in the Amazon, Guerra et al.[12] published 46 autochthonous cases diagnosed at the FMT-HVD, of which 30 cases were caused by *L. (V.) braziliensis* and 16 were caused by *L. (V.) guyanensis*. These data illustrate the importance of *L. (V.) guyanensis* in the disease etiology in the Amazon.

Regarding ATL treatment, the state of Amazonas is one of the pioneers in the use of pentamidine, which has been used routinely for at least 28 years following the trials by Pradinaud and Talhari[24] [25]. Clinical trials were performed and revealed that the clinical efficacy of pentamidine was similar or even superior to that of antimonials in the treatment of the cutaneous and mucosal forms of ATL[26]. More recently, trials with miltefosine performed at FMT-HVD demonstrated that this compound had an efficacy of 71.4% in the treatment of *L. (V.) guyanensis*[27].

The implementation of new diagnostic tests, such as polymerase chain reaction (PCR), for ATL diagnosis at FMT-HVD has created the opportunity for this reference unit to enhance their role in the species-specific detection of the parasite and to improve the current knowledge about the disease behavior in the region[28].

The use of nasofibroscopy and imaging testing in patients with ML, in addition to establishing referral routes with local otorhinolaryngology services, has allowed the production of new knowledge to improve the management of patients with the most severe form of the disease.

ANALYSIS OF THE HISTORICAL CASE SERIES REPORTED FROM 2001 TO 2010

The behavior of ATL cases reported in the State of Amazonas from 2001 to 2010 was evaluated. The data were obtained from

the database of the Foundation for Health Surveillance of the State of Amazonas [*Fundação de Vigilância em Saúde* (FVS)]. In total, 21,492 cases were analyzed, of which 16,372 (76.2%) were males and with the majority of cases (5,711; 26.6%) corresponding to the 21- to 30-year-old age group **(Figure 2)**. This age group and male gender are predominately affected due to their greater exposure, which is associated with occupational factors. Among the professional occupations, 9,394 (43.7%) cases were recorded in individuals who work with extractive activities **(Table 1)**.

The cases reported in the period mentioned above are distributed in 60 (96.8%) of the 62 municipalities in the state. Regarding the clinical forms of ATL, the cutaneous form was predominant, accounting for 20,752 (96.6%) cases, and the mucosal form was present in 740 (3.3%) cases. During the rainy season, from October to May, when there is an increase in the vector density, higher numbers of human cases are recorded. The ATL endemic channel in the state of Amazonas clearly illustrates the disease seasonality, with a predominance of cases in the beginning and end of each year, corresponding to the period of greater rainfall in the region, a trend demonstrated even in the epidemic year of 2003 **(Figure 3)**.

In the State of Amazonas, the geographic distribution of the endemic from 2001 to 2010 was maintained in localities where the highest numbers of cases have always been recorded, namely, Manaus, Rio Preto da Eva, Itacoatiara and Presidente Figueiredo **(Figure 4)**. A comparison of the periods of 2001 to 2005 and 2006 to 2010 illustrated the emergence of the disease in previously unaffected municipalities[29].

Regarding the affected municipalities, the data show a pattern of greater severity in the border regions of the state, particularly in the east, west and south in the municipalities of Apuí, Boca do Acre, Envira, Humaitá, Lábrea, Presidente Figueiredo, Rio Preto da Eva and especially Coari and Carauari in the central region. The factors that contribute to a higher occurrence of the disease in these localities are certainly associated with the impacts of socioeconomic and environmental processes that influence the disease transmission dynamic, such as the expansion of agricultural areas and plant and mineral extractive activities. In the south of the state, the municipalities Lábrea, Humaitá, Boca do Acre and Apuí have the highest deforestation rates due to strong expansions of agricultural and livestock activities in the midwest region and to the plant and mineral extractive activities in those areas[29].

The discovery of new mining areas between the municipalities of Novo Aripuanã, Apuí and Humaitá resulted in intense migration to these sites, with consequent deforestation. In addition, the nut-gathering activities in the municipality of Lábrea and the activities along the roads interconnecting these municipalities to the state of Rondônia are factors to be considered regarding the transmission and generation of ATL in this region [16] [29].

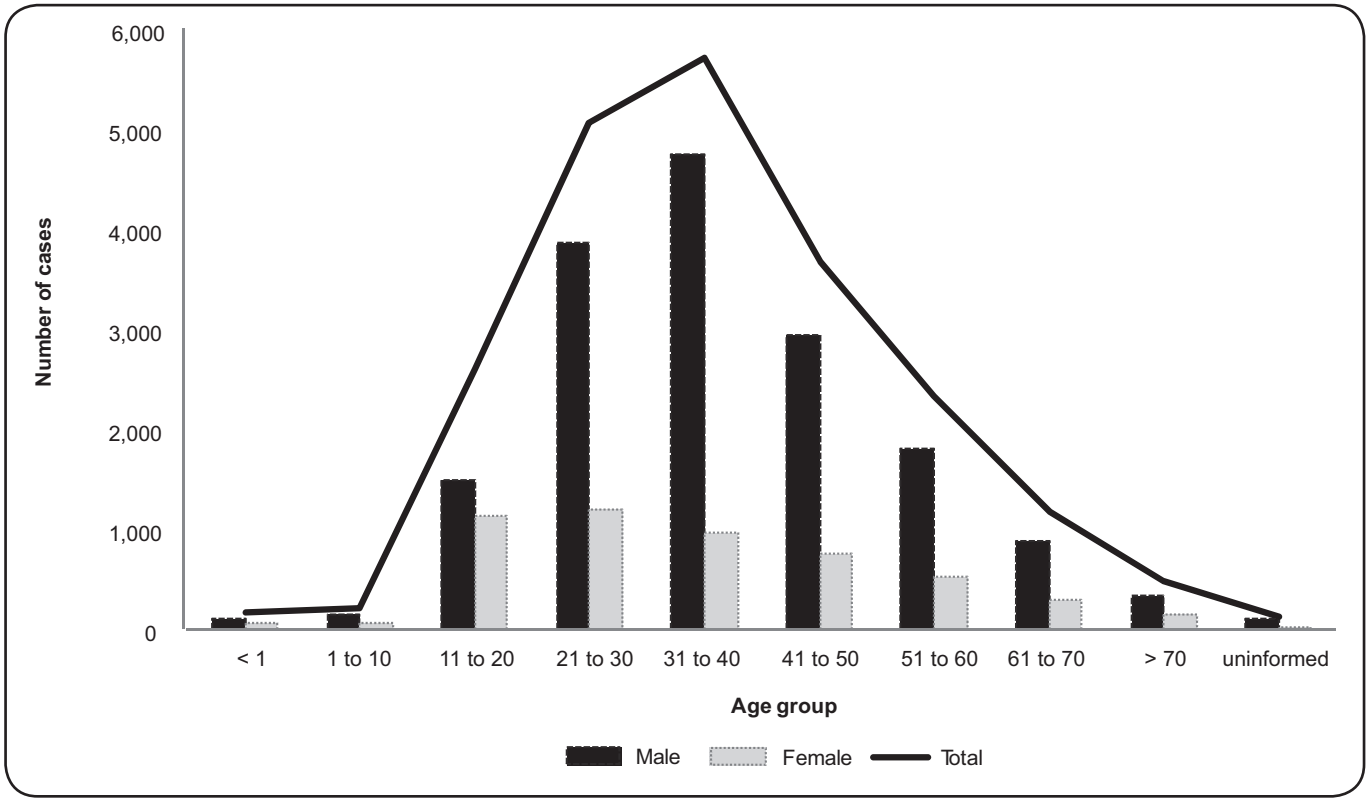


FIGURE 2 – Distribution of American tegumentary leishmaniasis cases in the State of Amazonas according to gender and age group (2001 to 2010).

TABLE 1- Distribution of ATL cases in the State of Amazonas according to professional occupation (2001 to 2010).

Professional occupation*	Number	Percentage
Agricultural, forestry, hunting and fisheries workers	9,394	43.7
No information in the database	3,263	15.2
Students	2,121	9.9
Domestic and trade workers	1,994	9.3
Minors	1,566	7.3
Workers in good production and industrial services	960	4.5
Other occupations not well defined	804	3.7
Administrative workers	606	2.8
Military, police and military fireman	306	1.4
Science and arts professionals	259	1.2
Repair and maintenance workers	188	0.9
Middle-level technicians	31	0.1
Total	21,492	100.0

*According to the Brazilian Institute of Geography and Statistics [*Instituto Brasileiro de Geografia e Estatística* (IBGE)], 2010. **ATL:** American tegumentary leishmaniasis.

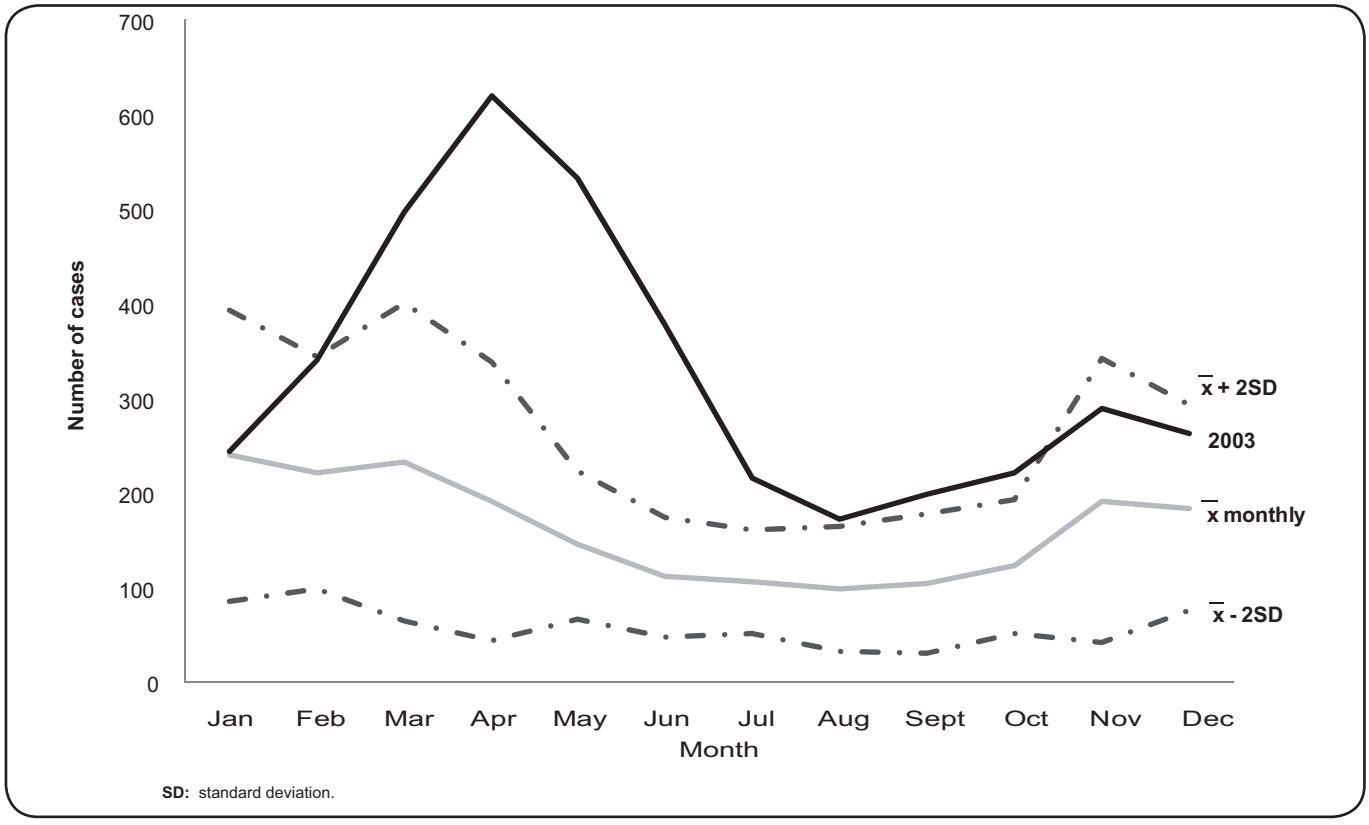
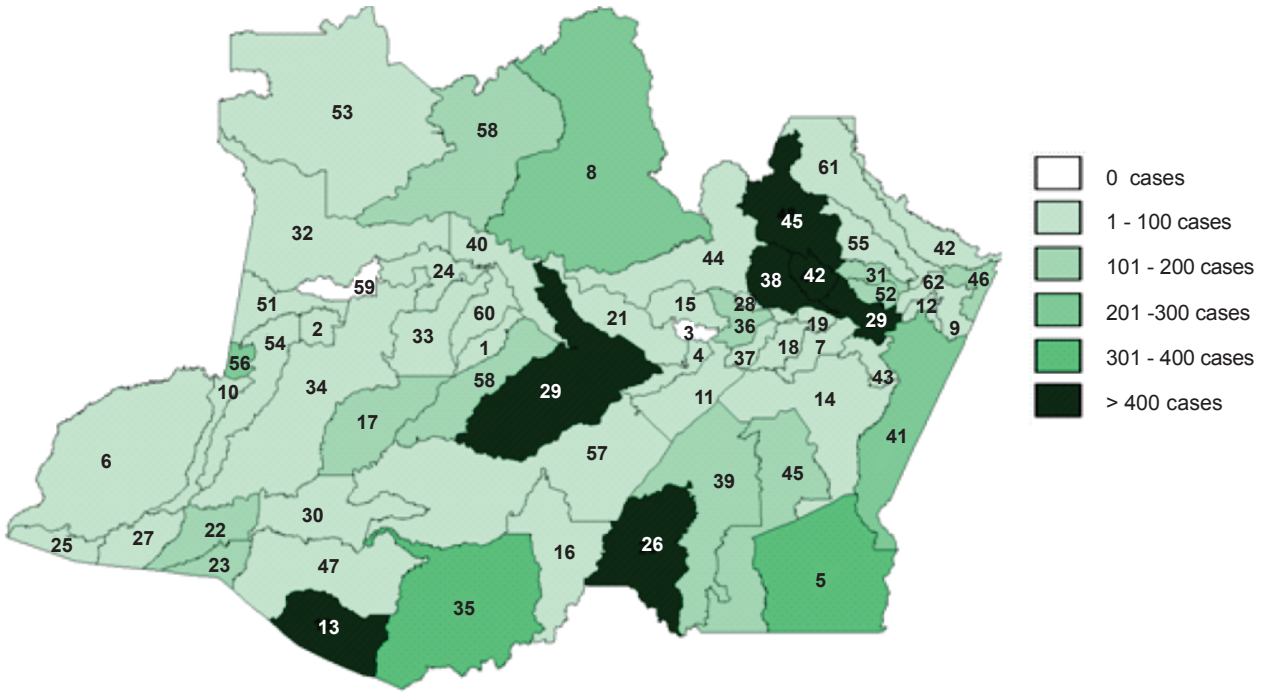


FIGURE 3 - Seasonality of American tegumentary leishmaniasis cases in the State of Amazonas according to the cumulative sum for each month (2001 to 2010).



1. Alvares (8 cases), **2**. Amaturá (1 case), **3.** Anamã (0 cases), **4.** Anori (1 case), **5.** Apuí (375 cases), **6.** Atalaia do Norte (58 cases), **7.** Autazes (55 cases), **8.** Barcelos (224 cases), **9.** Barreirinha (12 cases), **10.** Benjamin Constant (5 cases), **11.** Beruri (9 cases), **12.** Boa Vista do Ramos (15 cases), **13.** Boca do Acre (411 cases), **14.** Borba (67 cases), **15.** Caapiranga (27 cases), **16.** Canutama (30 cases), **17**. Carauari (127 cases), **18.** Careiro (21 cases), **19.** Careiro da Várzea (2 cases), **20**. Coari (447 cases), **21.** Codajás (21 cases), **22**. Eirunepé (194 cases), **23.** Envira (151 cases), **24.** Fonte Boa (8 cases), **25.** Guajará (14 cases), **26.** Humaitá (404 cases), **27.** Ipixuna (85 cases), **28.** Iranduba (12 cases), **29.** Itacoatiara (991 cases), **30**. Itamarati (16 cases), **31.** Itapiranga (108 cases), **32.** Japurá (9 cases), **33.** Juruá (9 cases), **34.** Jutaí (2 cases), **35.** Lábrea (319 cases), **36.** Manacapuru (199 cases), **37**. Manaquiri (1 case), **38.** Manaus (10,879 cases), **39**. Manicoré (167 cases), **40.** Maraã (6 cases), **41**. Maués (268 cases), **42.** Nhamundá (49 cases), **43**. Nova Olinda do Norte (51 cases), **44.** Novo Airão (64 cases), **45.** Novo Aripuanã (120 cases), **46.** Parintins (122 cases), **47.** Pauini (83 cases), **48.** Presidente Figueiredo (1,730 cases), **49.** Rio Preto da Eva (2,621 cases), **50.** Santa Izabel do Rio Negro (101 cases), **51.** Santo Antônio do Içá (8 cases), **52**. Silves (60 cases), **53.** São Gabriel da Cachoeira (146 cases), **54**. São Paulo de Olivença (9 cases), **55.** São Sebastião do Uatumã (24 cases), **56.** Tabatinga (202 cases), **57.** Tapauá (90 cases), **58.** Tefé (182 cases), **59.** Tonantins (0 cases), **60.** Uarini (22 cases), 61. Urucará (36 cases), **62.** Urucurituba (14 cases).

FIGURE 4 - American tegumentary leishmaniasis mapping according to the absolute number of cases per municipality in the State of Amazonas - 2001 to 2010. **Municipalities of the State of Amazonas (absolute number of cases in parenthesis).**

The natural gas and petroleum extraction activities and the construction of the Coari-Manaus oil pipeline through primary forest areas and crossing the municipalities of Coari, Codajás, Anori, Anamã, Caapiranga, Manacapuru and Iranduba explain the increased number of cases in the central region of the state, particularly in Coari. This increase is due to the construction and maintenance of the oil pipeline, which involves several activities inside primary forest areas, such as seismic records of the petroleum extraction areas, inspections of pipelines in strategic sites, deforestation and the opening of forest clearings for the installation and maintenance of the pipeline[29] [30].

Similarly, as already mentioned, this study was based on secondary data analysis, and data on occupation were not available from the database utilized herein. For the same reason, there exists the possibility that cases imputed to a certain municipality could have originated from another location. In this sense, the municipality of Manaus, as the center of most reported cases, should be overestimated regarding both overall numbers and specifically in relation to indigenous cases. However, it is estimated that approximately 10,000 indigenous people live in the city of Manaus. In addition, indigenous families who have migrated from their original habitations are now living on the margins of roadsides and around the City of Manaus (in disordered settlements near the forest), high-risk areas for ATL.

In recent years, there has been a significant increase in the control, diagnosis and treatment of leishmaniasis in the State of Amazonas, which has been associated with factors such as the improved quality of services provided and the expansion of academic and research activities. This is especially true in agencies such as FMT-HVD, the Alfredo da Matta Foundation (*Fundação Alfredo da Matta*), the National Institute of Amazonian Research [*Instituto Nacional de Pesquisas da Amazônia* (INPA), *Universidade Federal do Amazonas* (UFAM) and *Universidade do Estado do Amazonas* (UEA)], with new undergraduate, medical residency, master and doctoral programs that could influence the number of reported cases.

Regarding ATL diagnosis, most cases were diagnosed by lesion scrapings that were stained using the Giemsa or Panoptic

methods. The Montenegro skin test can also be used, mainly for the diagnosis of suspected ML cases. Other tests, such as parasite culture and histopathological tests, are performed in Manaus in large health centers, namely, FMT-HVD, the Dermatology and Venereology Foundation *Dr. Alfredo da Matta* [*Fundação de Dermatologia e Venereologia Dr. Alfredo da Matta* (FUAM)] and UFAM, or by survey, such as in the case of INPA. More recently, the use of polymerase chain reaction (PCR) in diagnosis, especially at the species level, has allowed advances in the management and knowledge of the case distribution in the state[12] [26] [27].

The information system has worked well, allowing the processing of case data. Nevertheless, this system still has many problems with case closure rates due to the failure of patients to attend return appointments because they consider the wounds to be healed, a factor that is explained by the distances between their homes and the health centers.

Over the years, initiatives have been developed, mainly by FVS and FMT-HVD, in an attempt to decentralize case diagnosis and treatment by offering training courses in different municipalities and for different healthcare professionals, such as physicians, pharmaceuticals/biochemists, dentists, nurses, laboratory technicians and health surveillance and endemic agents. However, the majority of the patients in Manaus end up going to FMT-HVD and FUAM as their first choice institutions, mainly because of the efficiency of these centers: in most cases, the patient leaves with an established diagnosis and a defined treatment plan in a single appointment.

FINAL CONSIDERATIONS

Over the years, some facts concerning ATL have become clear. The disease has expanded over the state of Amazonas, despite the decreased number of reported cases in determined periods, especially after 2006, which indicates that the population might be less exposed but that the transmission foci still remain and might even be expanding.

Transmission remains associated with human penetration of the vectors' biotope, where individuals become infected and/or are reached by the vectors' radius of action in sites or houses built near the forest. This scenario results in the infection of older age groups, women, children and even pets such as dogs. However, continuous transmission in the intra- or peridomicile settings does not occur.

Considering the transmission profile in the region, the low or zero ATL vulnerability to the application of control measures directed towards vectors or reservoirs in the Amazon region demands the need to maintain a healthcare structure that allows for the timely diagnosis and treatment of ATL cases.

Therefore, the development of highly accurate, reliable diagnostic tests that are easy to handle and that can be used in primary healthcare centers becomes essential. Similarly, the conduction of clinical trials with new antileishmanial drugs is strategic for improving the treatment of tegumentary forms of leishmaniasis. The development of topical formulations for the treatment of the localized cutaneous form of ATL should be a goal in the medium term, and FMT-HVD presents itself as qualified to perform these tests.

In conclusion, the historical series of ATL analyzed in this study suggests that the disease will persist in the Amazon region while the factors relative to forest exploitation that are associated with infection acquisition continue to have economic appeal. There is a real expectation of wide variations in disease incidence that can be influenced by climatic and economic aspects. In this context, the constant presence of reference units such as FMT-HVD will remain a strategy for the continuing education of healthcare professionals responsible for the diagnosis, treatment and monitoring of infected patients. These units will aim to increase the knowledge base regarding the disease, consequently improving its control.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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