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ORIGINAL ARTICLE

EVOLUTION OF AMERICAN TEGUMENTARY LEISHMANIASIS CASES REPORTED IN *PARANÁ* STATE, BRAZIL

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SUMMARY

Leishmaniases are infectious diseases caused by protozoa of the genus *Leishmania*. They are widely distributed worldwide and endemic in 88 countries in four continents. The present study analyzed the reported cases of American Tegumentary Leishmaniasis (ATL) in *Paraná* State (Brazil) from January 2007 to December 2013. The data were grouped according to Regional Health (RH) districts and macroregions, which allowed visualization of the reality in each region in the state. A total of 2,879 ATL cases were reported and distributed among the 22 RH districts, with an average detection rate of 3.9 cases per 100,000 inhabitants. The northwestern region accounted for 50.1% of the total cases, and the northern region accounted for 26.0-76.1% of the reported cases. The 6th RH district did not report any cases. The 7th, 9th, and 18th RH districts had a higher cure rate (> 80%), and lower cure rates were found in the 1st, 4th, and 12th RH districts. Reported unfavorable outcomes included treatment abandonment and death. Overall cure rates are based on the entire country, and unfavorable outcomes require greater attention of managers and health professionals to meet the goals of the Brazilian Ministry of Health.

KEYWORDS: *Leishmania* sp.; Cutaneous leishmaniasis; Notifiable diseases; Epidemiology; Epidemiological monitoring.

INTRODUCTION

Leishmaniases are infectious diseases caused by protozoa of the genus *Leishmania* that affect the skin, mucous membranes, and viscera. Different forms of the disease are widely distributed worldwide and is endemic in 88 countries in four continents, affecting approximately 2 million people annually[1,2]. Human clinical forms include cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL), which have a prevalence of 1 million cases and 500,000 cases per year, respectively. Cutaneous leishmaniasisis is characterized by single or multiple lesions or ulcers on the skin and mucous membranes. Mucosal lesions mainly involve the oral and nasopharyngeal regions and can be persistent, disfiguring, and difficult to cure clinically[1,3]. However, American Tegumentary Leishmaniasis (ATL) detection, the selection of therapeutic strategies, and monitoring by qualified health professionals are essential for resolving the disease[3].

Initially, ATL was considered a wild disease that affected humans accidentally. Infection was related to labor activities in the forestry, mining, and construction industries[1,4]. In *Paraná* State, vast areas with modified residual forests provide evidence for the endemicity of disease[5]. In recent years, epidemiological studies have shown that individuals can become vulnerable to infection in their peridomicile, where vectors of *Leishmania* have been captured[6,7,8,9].

In southern Brazil, 94.6% of ATL cases were reported in *Paraná* State from 1990 to 2013. Both genders are affected by CL, with a higher incidence in males, which may be associated with leisure activities that are more often practiced by men, such as fishing. The most affected age group is between 21 and 50 years old. Case detection has mainly been performed in Northern and Western *Paraná*[8,9]. *Paraná* State has a total of 399 municipalities. ATL cases were distributed among 276 cities until 2002, and since 2008, ATL has been reported in more than 300 cities[10].

Among the challenges faced by Brazil in solving health problems are its large geographical area and major socioeconomical differences. Over the years, the Ministry of Health has formulated new public health policies and developed specific strategies, such as regionalization. According to the Brazilian Federal resolution nº. 399/GM (published in February the 22nd, 2006), the National Council of Health Secretaries (*Conselho Nacional de Secretários de Saúde* - CONASS) regionalization provided a guideline for the National Health System and a structural axis for the Management Pact. The purpose of the regionalization was to guide and decentralize governmental actions and health services, aid the negotiation

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process, and foster agreements amongst regional managers. This policy also ensured the accessibility, resolution, and quality of health actions and services, which depend on the complexity and number of inhabitants, and transcends the local/municipal level[11]. The Intermunicipal Consortium of Public Health; *Paraná,* Brazil (*Consórcio Público Intermunicipal de Saúde do Setentrião Paranaense* - CISAMUSEP) is a new model of partnership between municipalities of *Paraná* State and the Federal government, where all are focused on the improvement of health care for the local population[12]. The CISAMUSEP offers consultation services which perform specialized tests and procedures in 30 cities from the 15th Regional Health of National Health System.

The *Paraná* State has a land area of 199,307.922 km^2; 10,444.526 inhabitants, and 399 municipalities[13]. In 2015, there were 22 Regional Health (RH) districts in *Paraná*. The RHs are characterized by regional and geographical clippings or limits that seek to organize the network of health activities and services to ensure compliance with the constitutional principles of universal access, equity, and comprehensive care[11].

In Brazil, the Information System for Reportable Diseases (*Sistema de Informação de Agravos de Notificação* - SINAN)[14] was developed in the 1990s to standardize the recording, consolidation, and sharing of data on reportable diseases, such as ATL. The efficient use of these data seeks to achieve dynamic diagnoses of the occurrence of an event, indicating the risk for particular populations, and determining the epidemiological reality of specific geographic areas[15,16]. In addition to collecting routine data, the interpretation of results and information is complex and requires skilled personnel. Many problems have arisen, including low coverage, over collected data, insufficient analysis, low quality, delay in analysis, and a lack of communication of the information obtained, which can all lead to the loss of appropriate intervention opportunities. Additionally, the information is often restricted to the study site, which does not allow broader interpretations[16]. Data on the evolution of reported cases of ATL in Brazil are recorded in the information area of the public health system, referred to as Health Unic System (*Sistema Único de Saúde* - SUS). Considering the high prevalence of ATL in *Paraná* State and Brazil's regionalization policy, the dearth of publications on the evolution of cases is concerning. Thus, we analyzed the evolution of reported ATL cases in *Paraná* State between 2007 and 2013 and discussed the issue considering the regional context of each RH district.

MATERIALS AND METHODS

The present study was descriptive and cross-sectional. Data were obtained from the DATASUS database of the Department of Informatics of SUS (Brazil) from January 2007 to December 2013. This database receives information from SINAN, which records and processes data on ATL notifications and provides information as a morbidity profile analysis, thus contributing to decision-making at the municipal, state, and federal levels.

The search was performed using the following variables: RH district, municipality of residence, events taking place in the case, year of occurrence, patients who met the cure criteria, patients who abandoned treatment, patients who continued treatment in another RH district, cases in which the diagnosis of ATL changed, the occurrence of death attributable to ATL, the occurrence of death attributable to other causes (i.e., the cause of death was not related to ATL), and unknown outcomes.

The statistical analysis included all the cases of ATL in *Paraná* per year according to RH district and macroregion. The RH districts were distributed according to the regions of the state: North (RH districts: 16th, 17th, 18th, 19th, and 22nd), Northwest (RH districts: 11th, 12th, 13th, 14th, and 15th), West (RH districts: 8th, 9th, 10th, and 20th), South Central (RH districts: 5th and 7th), *Campos Gerais* (RH districts: 3rd, 4th, 6th, and 21st), and East (RH districts: 1st and 2nd)[17]. The ATL detection coefficient was calculated using the population that was estimated in 2010 by the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* - IBGE). Pearson correlations and Student's *t*-test were applied to analyze the disease progression according to time (in years). The statistical analyses were performed using the Stata 9.1 software (Stata Corp LP, Texas, USA) by considering a confidence interval of 95%.

The present study was performed according to the Helsinki Declaration of 1964, lastly revised in 2012, and also in accordance with Resolution n^o. 466/2012 of The Brazilian National Health Council (*Conselho Nacional de Saúde* - CNS) and approved by the Standing Committee on Ethics in Human Research of *Universidade Estadual de Maringá, Maringá* City*, Paraná* State, Brazil.

RESULTS

Between January 2007 and December 2013, 2,879 cases of ATL were reported in *Paraná* State, distributed among 22 RH districts. Considering that *Paraná* had a population of 10,444,526 inhabitants in 2010, the cumulative detection rate over seven years (2007-2013) was 27.6 cases per 100,000 inhabitants. In 2007, the number of reported cases was 459 (4.4 cases per 100,000 inhabitants). In 2008, a peak of the disease occurred, with 566 (21.9%) of the cases (5.4 per 100,000 inhabitants). The number of ATL cases (Fig. 1) was 461 in 2009 (4.4 per 100,000 inhabitants), 277 in 2010 (2.7 per 100,000 inhabitants), 351 in 2011 (3.4 per 100,000 inhabitants), 469 in 2012 (4.5 per 100,000 inhabitants), and 296 in 2013 (2.8 per 100,000 inhabitants). In *Paraná* State in the period of 2007 to 2013, the average ATL detection rate was 3.9 cases per 100,000 inhabitants.

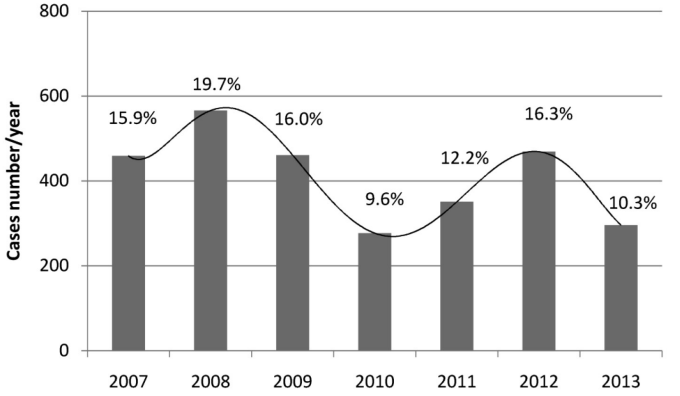

Fig. 1 - Cumulative frequency based on the number of ATL cases reported in *Paraná* State, Brazil, 2007-2013.

Of the 2,879 ATL cases, the majority (2,031 or 70.5%) were cured. A total of 643 patients (22.3%) had unknown outcomes, and the RH districts that had a high number of unknown outcomes were the 12th

district (51%), 22nd district (34.1%), 16th district (27%), and 20th district (26.7%). The other outcomes included the abandonment of treatment, continued treatment in another RH district, changes in diagnosis, and death due to ATL or other causes (Table 1).

Most of the cases were reported in the Northwestern and Northern regions (Table 2). The Northwestern region accounted for 50.1% of cases. The 13th and 15th RH districts had the highest frequency of reported leishmaniasis (18.0% and 14.5%, respectively). No notification was found in the 6th RH district during the period studied (Table 1, Fig. 2).

The highest cure rate (80%) occurred in the 7th, 9th, and 18th RH districts (Table 1). The Northern and Northwestern regions achieved 67.8% and 73.0% cure rates, respectively (Table 2, Fig. 3). The 2nd RH district had a good cure rate compared with the other districts. The lowest cure rates were found in the 1st (28.5%), 4th (33.3%), and 12th (46.3%) RH districts (Table 1).

The Northern and Northwestern regions had a higher number of reported ATL cases, and also of cases with unknown outcomes compared with the other regions ($p < 0.05$; Fig. 3). Although these regions had a significant number of cases with unknown outcomes, a higher cure rate was observed in these regions (North: 28.0%; Northwest: 48.9%), whereas *Campos Gerais* had a lower cure rate (0.5%, $p < 0.05$). The Northwest had the highest number of deaths that occurred by other causes, not specified by the SINAN database**.** The comparison between the evolution and outocome of ATL cases of Northern and Northwestern regions were not different; both played a significant role in the distribution and evolution of ATL in *Paraná* State.

DISCUSSION

The transmission standard of ATL varies according to specific regions in Brazil, with higher frequencies in the North (46.1%) and Northeast (29.4%)[1,10]. Although the Southern region in Brazil did not have the

Table 1
Evolution of reported ATL cases obtained by SINAN according to Regional Health districts in *Paraná* State, 2007-2013

RH/PR	Cure		Abandonment		Transfer		Diagnostic Change		Death / ATL		Death / other causes		Ignored / blank		Total notif./RH	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1st	2	28.57	0	0	2	28.57	2	28.57	0	0	0	0	1	14.29	7	0.24
2nd	200	67.11	3	1.01	14	4.70	8	2.68	0	0	2	0.67	71	23.83	298	10.35
3rd	3	42.86	0	0	0	0	2	28.57	0	0	1	14.29	1	14.29	7	0.24
4th	2	33.33	0	0	0	0	1	16.67	2	33.33	0	0	1	16.67	6	0.21
5th	22	61.11	0	0	1	2.78	7	19.44	0	0	1	2.78	5	13.89	36	1.25
6th	0	0.00	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7th	10	90.91	1	9.09	0	0	0	0	0	0	0	0	0	0	11	0.38
8th	20	57.14	0	0	1	2.86	7	20.00	1	2.86	1	2.86	5	14.29	35	1.22
9th	67	83.75	1	1.25	2	2.50	2	2.50	0	0	0	0	8	10.00	80	2.78
10th	73	73.00	1	1.00	1	1.00	2	2.00	3	3.00	1	1.00	19	19.00	100	3.47
11th	187	73.62	1	0.39	2	0.79	4	1.57	1	0.39	4	1.57	55	21.65	254	8.82
12th	90	46.39	2	1.03	0	0	0	0	0	0.00	3	1.55	99	51.03	194	6.74
13th	373	72.01	8	1.54	3	0.58	1	0.19	1	0.19	4	0.77	128	24.71	518*	17.99
14th	46	75.41	2	3.28	0	0	3	4.92	0	0	2	3.28	8	13.11	61	2.12
15th	297	71.39	17	4.09	2	0.48	1	0.24	3	0.72	9	2.16	87	20.91	416*	14.45
16th	93	64.58	4	2.78	4	2.78	2	1.39	0	0	2	1.39	39	27.08	144	5.00
17th	189	78.42	12	4.98	3	1.24	2	0.83	0	0	5	2.07	30	12.45	241	8.37
18th	181	83.80	0	0	1	0.46	5	2.31	1	0.46	5	2.31	23	10.65	216	7.50
19th	81	77.14	0	0	1	0.95	0	0	0	0	2	1.90	21	20.00	105	3.65
20th	65	64.36	5	4.95	0	0	2	1.98	0	0	2	1.98	27	26.73	101	3.51
21st	5	62.50	0	0	1	12.50	0	0	0	0	1	12.50	1	12.50	8	0.28
22nd	25	60.98	0	0	0	0	2	4.88	0	0	0	0	14	34.15	41	1.42
Total	2,031	70.5	57	2.0	38	1.3	53	1.8	12	0.4	45	1.6	643	22.3	2,879	100.0

Table 2
Evolution of reported ATL cases obtained by SINAN according to the region in *Paraná* State, 2007-2013

Region	Cure		Abandonment		Transference		Diagnostic Change		Death / ATL		Death / other causes		Ignored / blank		Total notif.	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
North	569	28.0*	16	28.1	9	23.7	11	20.7	1	8.3	14	31.1	127	19.8*	747*	26.0
Northwest	993	48.9*	30	52.6	7	18.5	9	17.0	5	41.7	22	49.0*	377	58.6*	1,443*	50.1
West	225	11.1	7	12.3	4	10.5	13	24.5	4	33.3	4	8.9	59	9.2	316	11.0
South Centre	32	1.6	1	1.7	1	2.6	7	13.2	0	0	1	2.2	5	0.8	47	1.6
Campos Gerais	10	0.5*	0	0	1	2.6	3	5.7	2	16.7	2	4.4	3	0.5	21	0.7
East	202	9.9	3	5.3	16	42.1	10	18.9	0	0	2	4.4	72	11.1	305	10.6
Total	2,031	70.5	57	2.0	38	1.3	53	1.8	12	0.4	45	1.6	643	22.3	2,879	100.0

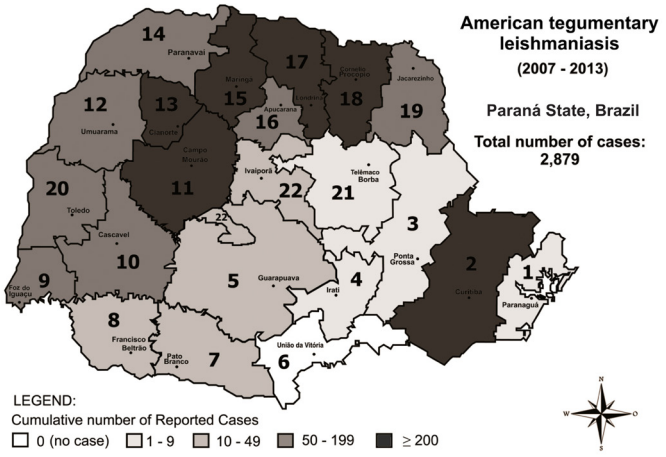

Fig. 2 - Distribution of ATL cases according to Regional Health districts in *Paraná* State, 2007-2013. Bold numbers in the map indicate the Regional Health geographical reference according to[10].

highest prevalence of ATL, 13,893 cases were reported between 1990 and 2013, 94.6% of which occurred in *Paraná* State. The Southern region consists of only three states, and *Paraná* had the highest number of ATL cases. The transmission pattern also revealed an increase in the incidence of ATL every five years[1]. In *Paraná* State, the cyclical tendency of ATL appears to occur every three years, which was observed in the present study (Fig. 1). This fact may be related to extrinsic factors and macro environmental ones[18,19]. The "El Niño" climate phenomenon may have influenced the transmission of ATL. The same phenomenon has also been observed in Colombia, which borders Brazil. "El Niño"occurs at intervals of 2-7 years, with an average of every three years. This climate change favors the spread of vectors that aid ATL transmission[1,19,20]. Furthermore, variability in the prevalence of the spread of diseases by vectors should be considered in social and political contexts, which has been discussed in other studies[18, 19].

Brazil had an average of 18.5 reported cases of ATL per 100,000 inhabitants between 1985 and 2005[1,10]. In *Paraná* State between 1993 and 1998, the average detection rate was 4.81 cases per 100,000 inhabitants, based on notifications from 35 of the 399 municipalities in the state[5]. The findings of the present study revealed an average rate of 3.9 cases per 100,000 inhabitants, with data obtained from 276 municipalities. This result demonstrates the geographic expansion of ATL in this state and highlights the importance of regional studies that support the proper allocation of resources, and development of appropriate strategies that are geared toward local realities.

We observed a heterogeneous distribution among RH districts. The number of reported cases was greater in the Northern and Northwestern regions, but both of these regions also presented the highest cure rates and the greatest number of cases with unknown outcomes. *Campos Gerais* had the lowest cure rate. The Northwestern region had the highest death rate of causes that were unrelated to ATL. These different outcomes reveal that the profile of this endemic disease does not have a definitive and homogeneous distribution pattern, which complicates the adoption of measures by the Brazilian Ministry of Health.

The literature reports that the mentioned regions are the most important areas for the progression and maintenance of ATL. Several studies have discussed many variables that are involved in this process, such as the increasing number of infections in women and children, vector adaptation in domestic environments, the proven presence of *L. (V.) braziliensis* strains in *Paraná* State, and the maintenance of ATL focus sites[3,5,7,8, 9,18,21,22].

Identification of sand flies is one of the determining factors for the occurrence of ACL, and in this sense, entomological studies in *Paraná* State have shown the presence of the following species: *Nyssomyia whitmani, Nyssomyia neivai, Pintomyia pessoai, Migonemyia migonei and Pintomyia fischeri*. The most prevalent is *Nyssomyia whitmani*, but all of them have the capacity to transmit *Leishmania*[8,22,23,24,25,26,27,28].

The complexity that characterizes prevention and control measures requires more effort and joint efforts among district/municipal managers, health professionals, and research institutions to optimize resources, which may prevent the advance of leishmaniasis in all regions of *Paraná* State.

Regarding the evolution of reported cases by RH districts, the majority of cases had achieved a cure, especially in the 7th, 9th, and

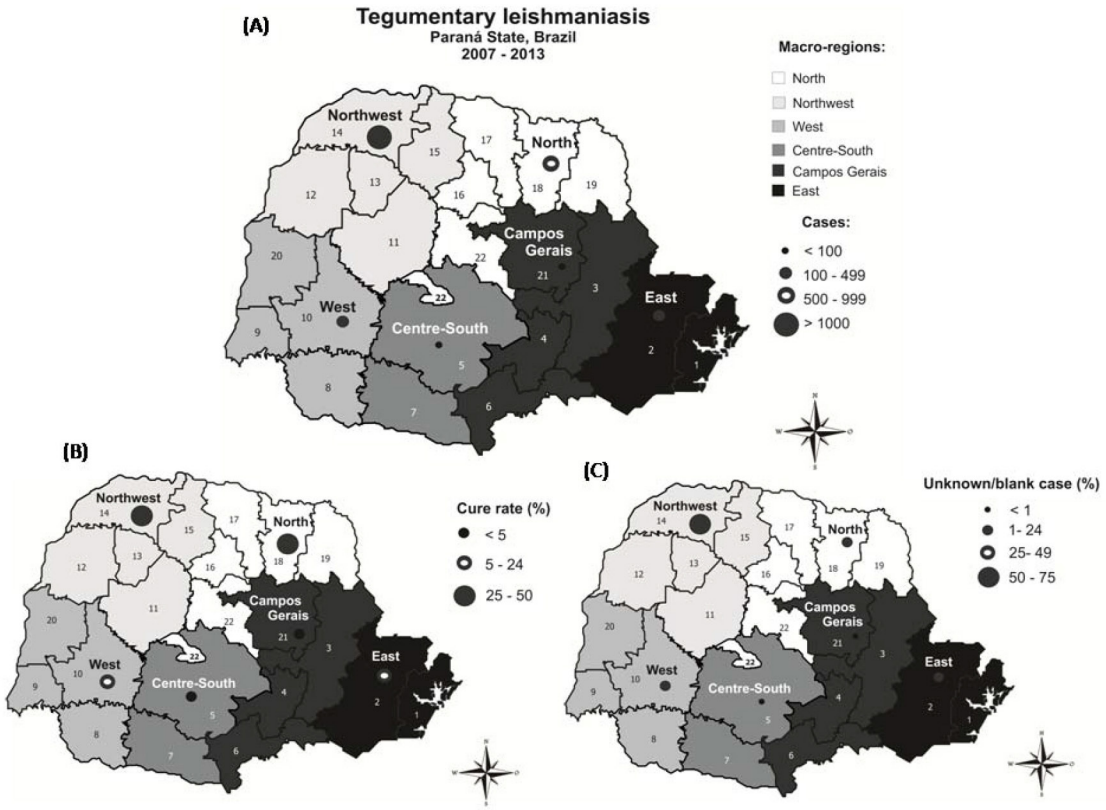

Fig. 3 - (A) Reported cases of American Tegumentary Leishmaniasis (ATL) according to the macroregions of *Paraná* State, 2007-2013. (B) Cure rate. (C) Unknown outcomes.

18th RH districts. The healing of ulcerative lesions and total regression of infiltrators and erythema up to three months after completing the therapy are considered as the criteria for ATL cure[1,2]. The Northern and Northwestern regions had a cure rate of 69.6%, which is consistent with the cure rate that is observed nationwide[1,10]. In Brazil, in 2009, 90.9% of 23,399 confirmed ATL cases received first-line treatment with meglumine antimoniate, 73.5% of which were cured. However, 16 patients died because of ATL, 122 died because of other causes, and 4,961 cases (21.2%) had no information on the progression of the disease[16]. The criteria for the choice of treatment should consider the current state of the patient's health, lesion characteristics, if the patient is pregnant and comply with the standardization that has been recommended by the World Health Organization[1,2]. Although the number of cases that were cured after ATL treatment is recorded in the SINAN information system, the total number of patients who received treatment for ATL was not recorded. These results may be explained by a failure of data collection or the non-inclusion of these data in the information system. It is important to know the number of patients who have access to recommended ATL treatment.

The 2nd RH district is located in southern *Paraná* State and corresponds to the metropolitan region of *Curitiba* (the state capital). The 2nd RH district comprises 29 municipalities and is one of the ATL focus sites, such as the area of *Alto Ribeira*[29]. The ATL cure rate in the 2nd RH district stoodout compared with the other RH districts. The State of *Paraná* Central Laboratory (*Laboratório Central do Paraná* - LACEN) located in the 2nd RH district has the infrastructure to provide early diagnosis and a better prognosis and also does have technologies that, combined with health services, have high quality standards[30].

In the present study, evolution with an unknown outcome was observed in 23.6% of ATL cases. Other studies also found a high incidence of unknown outcomes regarding the evolution of leishmaniasis[15,22]. In 1991, the index of unknown outcomes was 49.3%. After two decades, the optimization of actions, and the population attending health services[22], it is clear that these actions are still far from those required by the Brazilian Ministry of Health, which recommends the patient follow-up after medical discharge[1].

The reporting of ATL follows the standards of SINAN, requiring confirmation based on laboratory diagnosis, and clinical/epidemiological criteria that may also be adopted mainly in endemic areas where people are persistently positive for ATL based on laboratory diagnosis[1]. Some cases could not be confirmed during the evolution of ATL because of changes in the first diagnosis (1.6% of cases), and the subsequent diagnosis was not documented in SINAN. We believe that these subsequent diagnoses should be identified to clarify this point.

The unfavorable outcomes that were found in the present study included abandonment (2.1%) and death from ATL (0.4%). The Brazilian Ministry of Health considers treatment abandonment as ATL patients who have not been discharged or patients who do not attend the medical consultation within 30 days after the third scheduled visit to evaluate clinical cure, according to the recommended regimen. In the

present study, ATL was not the main cause of death, but the side effects of leishmaniasis therapy and other diseases may be associated with death. Therefore, the cause of death in most cases could be iatrogenic and related to other morbidities[31,32].

The other outcomes of the notifications were death from other causes (1.4%) and the patient's transfer (1.3%), and referral to other units for treatment and monitoring. For patients who died during treatment, reasons that are not associated with ATL or not associated with the side effects of the drugs that are used for ATL treatment must be declared and certified that they were not associated with ATL[31,32].

The evolution of ATL of the reported cases in *Paraná* revealed a cyclical tendency for its occurrence. The cure rate achieved by patients after the ATL treatment followed the same tendency as the cure rate that is observed in other regions of Brazil. Still worrisome is the percentage of unknown outcomes and consequently the actual health conditions of patients who received the diagnosis of ATL.

The literature databases have a dearth of studies that explain the causes of ATL treatment abandonment. Studies on treatment abandonment are required, especially because ATL treatment is freely offered by the public health system (SUS) in Brazil, and leishmaniasis is a disease with a good prognosis when treated properly[15]. The high rate of abandonment of the leishmaniasis therapy encourages the search for alternative therapies for leishmaniasis because of drug toxicity and deaths that are caused by the current treatments. The treatment of ATL needs to be improved. Some studies have been conducted to discover new candidates for leishmaniasis treatment, but few of these products have reached patients, and most initiatives remain in the experimental phase[32,33,34,35]. Additionally, the pharmaceutical industry has been unenthusiastical regarding leishmaniasis, and the therapeutical arsenal is still limited, so that people who live in endemic areas become dependent on traditional medicine to relieve their symptoms[35,36,37].

Social and environmental factors still need to be investigated to elucidate the pattern of transmission of leishmaniasis from the perspective of all health care spheres (national, state, and municipal). If the transmissibility profile can be defined, then measures can be adopted to control and cure ATL according to specific localities, and these results may be gradually optimized to further improve healthcare.

The present study explored secondary research data. Considering the heterogeneity of the number of notifications in each RH district, the possibility of underreporting ATL should not be forgotten, and the actual health conditions of local populations should be ascertained. The heterogeneity of the prevalence of ATL among regions, underreporting, and the high number of patients with unknown ATL outcomes make it difficult to plan, execute, and refine public health measures and policies. The collection and interpretation of health data should be routinely performed by qualified health professionals, specialized in information systems. Moreover, information should be disclosed to provide a better understanding of health problems, the results of public health programs, and also the health service coverage. Health professionals should also be trained on the collection, use, and interpretation of data that are obtained by health services and other institutions to identify actual health problems associated with particular local populations. Thus, health organizations should implement specific measures to control and treat ATL more effectively.

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