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Introduction and expansion of human American visceral leishmaniasis in the state of Sao Paulo, Brazil, 1999-2011

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ABSTRACT

OBJECTIVE: To analyze the spread of human American visceral leishmaniasis and identify the key municipalities for developing surveillance and control activities.

METHODS: The area of the study was composed of the 316 municipalities in the state of Sao Paulo belonging to the five health districts in which human American visceral leishmaniasis occurs, using data on autochthonous cases and deaths according to the reporting year and municipality in which the death occurred. The incidence, mortality and case fatality rates for each municipality and for the entire area were calculated. An empirical Bayes estimator was used to calculate the local Bayesian incidence and rates of mortality per municipality, and Kriging was used to visualize the spatial distribution of temperature and rainfall.

RESULTS: A total of 73 municipalities with transmission of the disease were identified. Human American visceral leishmaniasis was first detected in areas with higher temperatures and lower rainfall, but it also spread in cooler and wetter areas. The expansion of human American visceral leishmaniasis occurred along a main axis of dissemination, from Northwest to Southeast, following the Marechal Rondon highway and the Bolivia-Brazil gas pipeline, and along a secondary axis that was derived from the main axis, which runs both North and South, following the highway network. Rates of incidence according to health district exhibit a peak, followed by a fall, except the Sao Jose do Rio Preto region. Higher concentrations of municipalities with high incidence and mortality rates were observed in the Araçatuba, Presidente Prudente and Marília health districts.

CONCLUSIONS: This study indicates possible determinants of the spread of disease, including the Marechal Rondon highway and the construction of the Bolivia-Brazil gas pipeline. Climatic factors seemed to play no role in the spread. The use of spatial analysis techniques allowed the municipalities where cases and deaths are possibly underreported to be identified, which indicated the municipalities which should be prioritized for the development of surveillance and control activities.

DESCRIPTORS: Leishmaniasis, Visceral epidemiology. Spatial Analysis. Case fatality rate. Risk Factors. Socioeconomic Factors. Abiotic Factors.

INTRODUCTION

American visceral leishmaniasis (AVL), a zoonotic infection which affects both animals and humans, is caused by the *Leishmania chagasi* parasite, transmitted by *Lutzomyia longipalpis*. Human American visceral leishmaniasis (HAVL) is characterized by causing hepatosplenomegaly, presenting fever and affecting the body's general state of health. It has a high rate of mortality if untreated and in malnourished children, affecting immune-depressed individuals, especially HIV carriers.[a]

In Brazil, HAVL was a common disease in rural areas until the 1970s; it is now found in urban areas.[a] Before 1990, 90% of cases occurred in the Northeast, the disease then expanded into all other regions of the country. The Northeast[b] is where 51.9% of cases in Brazil were recorded in 2009; 20.9% were in the North, 18.9% in the Southeast, 8.1% in the Midwest and 0.2% in the South. The number of reported cases increased by 89.9% between 1999 and 2009 (from 1,944 to 3,693) and the rate of mortality grew from 3.2% to 6.2%, almost tripling the number of deaths from the disease.[b]

The expansion of AVL is linked to the urbanization of the disease and the vector, to socio-environmental changes and to the difficulties of controlling the disease in large urban centers, where problems with malnutrition and poor housing and sanitation exist.[11] Human and canine immigration from endemic areas have contributed to this expansion, introducing the *L. chagasi* parasite into new areas.[18] Human factors, civil construction projects and highways, among others, should also appear in the AVL epidemiological picture. Antonialli et al[1] (2007) suggested that the spread of disease in Mato Grosso do Sul, MS, Midwestern Brazil, was influenced by three large scale projects: the *Novoeste* railway, the *Vitória-Corumbá* highway, and the Bolivia-Brazil gas pipeline.

Climatic factors may also be determinants in LVA epidemiology. Thus, the link between temperature, humidity, rainfall, and the presence of the sandfly have been investigated.[16,21]

Until 1998, HAVL cases recorded in the state of Sao Paulo were imported from other regions of Brazil and the first autochthonous cases appeared in Araçatuba City in 1999.[6] This occurred after the detection of *Lu. longipalpis* in urban areas in 1997,[9] followed by detection in canines in 1998.[6] Since then, the disease has expanded into municipalities in the state,[10,c] with 1,919 cases and 169 deaths recorded by 2011.

The aim of this study was to analyze the expansion of HAVL and identify the key municipalities for developing surveillance and control activities.

METHODS

Reported autochthonous cases and deaths from HAVL between 1999 and 2011 in the state of Sao Paulo were the data used in the study. The state of Sao Paulo has 645 municipalities and a population of 41,262,199. The State Health Department divides the state into 17 administrative areas. The units of study were the 316 municipalities belonging to the following areas, which had reported autochthonous cases of HAVL: Araçatuba, Bauru, Marília, Presidente Prudente and São José do Rio Preto (Figure 1A).

The data were obtained from the Sao Paulo State Health Department. Center for Epidemiological Surveillance.[c] The number of inhabitants per municipality in the years in question were used, as were the geographical coordinates of their centroids in the Lat/Long SAD-69 system.

Data on temperature and rainfall were obtained from the Center for Integrated agrometeorological information of the Agronomic Institute (CIIAGRO – *Centro Integrado de Informações Agrometeorológicas* of the *Instituto Agronômico*), Campinas.[d] Monthly values for temperature (ºC) measured in 60 meteorological posts in the municipalities in question were used.

The georeferenced map of the municipalities in the Lat/Long SAD-69 system, the route of the *Marechal Rondon* highway and the *Novoeste* railway and the populations of the municipalities were obtained from the Brazilian Institute of Geography and Statistics (IBGE).[e] The route of the Bolivia-Brazil gas pipeline was obtained from the *Transportadora Brasileira Gasoduto Bolívia-Brasil* website.[f]

A

B

Year in which first case(s) of Human American
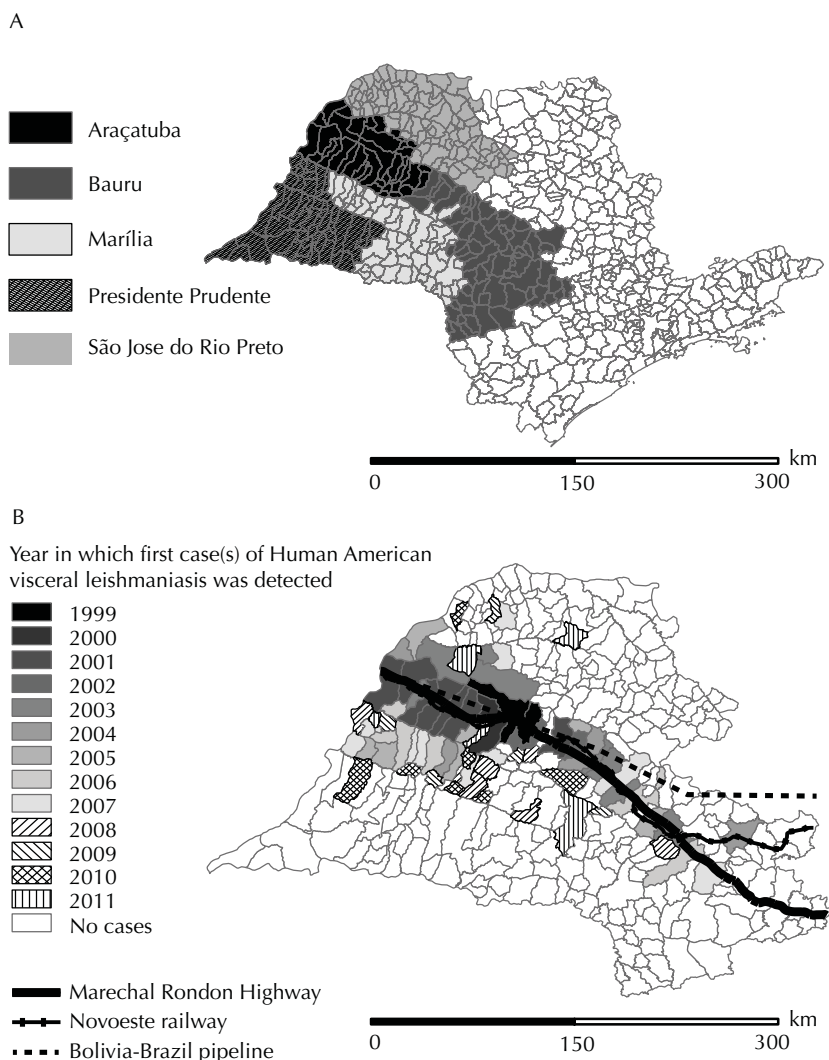visceral leishmaniasis was detected

Figure 1. Health care regions and municipalities (A) and the year in which the first case(s) of Human American visceral leish-maniasis was detected. State of Sao Paulo, 1999 to 2011 (B).

Annual rates for incidence and mortality and the case fatality rate from HAVL were calculated. Data on the year in which the first case(s) of HAVL occurred in each municipality were used to describe its expansion, evaluated together with the routes of the Bolivia-Brazil gas pipeline, the *Marechal Rondon* highway and the *Novoeste* railway.

Crude rates of incidence and mortality from HAVL were, respectively, calculated by dividing total cases and deaths by the population of each municipality in the middle of the period in question. Local Bayesian incidence and rates of mortality for HAVL were esti-mated using an empirical Bayes estimator, in which the Bayesian estimates were made locally, i.e., in relation to a local mean.[5] These rates were used to correct random fluctuation in crude rates in sparsely inhabited municipalities and to estimate possible

underreporting of HAVL cases and deaths, especially in municipalities with few or no cases.

Empirical Bayesian rates were obtained by constructing a neighbor matrix for the municipalities, neighboring municipalities being those with at least one common border. TerraView Program version 4.1.0 was used to carry out these procedures. Choropleth maps were used to represent incidence and mortality rates, obtained using the ArcGIS program version 10.

Monthly mean temperature and rainfall were calculated for each of the 60 meteorological posts for the entire period of the study. Semivariance was calculated for each variable and used to create semivariograms, adjusted to a mathematical model. These show the exis-tence of the spatial variability of the data, presenting the degree of dependence among the sample points.[2] These

analysis were carried out using the GS+ for Windows 5.0.3 Beta (GS+) Program. After detecting the spatial dependence shown in the semivariogram, values for the variables in non-sampled locations were estimated using Kriging interpolation[2] and choropleth and contour maps obtained using the Surfer 6.01 Program.

The criteria established by the Ministry of Health[a] for classifying Brazilian municipalities with HAVL transmission covers the last five years and the categories are: "no transmission" (mean number of cases = 0), "sporadic transmission" (mean number of cases > 0 and < 2.4, with values below the 80th percentile), "moderate transmission" (mean number of cases ≥ 2.4 and < 4.4, values between the 80th and 90th percentiles) and intense transmission (mean number of cases ≥ 4.4, values equal to or above the 90th percentile). These criteria were used to classify the municipalities in question with transmission between 2007 and 2011. The same percentiles as in the criteria established by the Ministry of Health were used, but rates of incidence between 2007 and 2011 were used as cutoff points, giving a different classification (low, moderate and high incidence) which was compared with that obtained from the mean number of cases.

RESULTS

Figure 1B shows how HAVL spread in the administrative area of Araçatuba, from the main town (Araçatuba) to other municipalities in the area in 1999 (Birigui); in the administrative area of Bauru, with cases recorded in Promissão in 2002; in Marília, with cases in Guarantã, in 2003; in Presidente Prudente, with cases in Dracena and Ouro Verde, in 2005; and in Sao Jose do Rio Preto, with cases detected in Jales city, in 2007. Between 1999 and 2011, there were autochthonous cases of HAVL in 73 municipalities in the state.

The spread of HAVL was along a main axis of dissemination, from Northwest to Southeast, towards the area of Bauru, following the *Marechal Rondon* highway, the *Novoeste* railway and the construction of the Bolivia-Brazil gas pipeline. There was also a secondary axis that was derived from the main axis, which runs South towards the areas of Presidente Prudente and Marília and North towards Sao Jose do Rio Preto (Figure 1B).

After the first cases were detected in 1999, there was a steady increase in rates of incidence, peaking in 2008 then falling. Case fatality rates varied greatly between 1996 and 2006, before stabilizing from 2007 onwards, when the profile of the rate of mortality started to reflect that of the rate of incidence (Figure 2A).

There was a peak in incidences in the administrative area of Araçatuba in 2003 (19.0 cases/100,000 inhabitants) and Presidente Prudente in 2007 (10.9 cases/100,000 inhabitants), followed by a decline. Incidence in Bauru and Marília peaked in 2008, then fell. The rates of incidence in the Sao Jose do Rio Preto increased, although they were lower than those in the other areas. The rates in the five regions varied between 1.3 (Sao Jose do Rio Preto) and 6.3 cases per 100,000 inhabitants (Araçatuba) in 2011 (Figure 2B).

There was a higher concentration of municipalities with high HAVL incidence and rates of mortality in the region of Araçatuba, followed by Presidente Prudente and Marília (Figures 3A and 3B). In addition to correcting random fluctuations, the Bayesian rates indicated non-zero values for HAVL incidence and mortality in municipalities with no reports of cases in humans (Figures 3C and 3D).

There were higher mean temperatures in the Western and Northern regions, (Figure 4A). Rainfall levels behaved in the opposite way to temperature, presenting lower incidence in the West and North (Figure 4B). Municipalities where HAVL occurred earlier and those with the highest rates of incidence were found in the regions with the highest mean temperatures and lowest mean rainfall (administrative area of Araçatuba) (Figures 1 and 4).

Figure 5A shows municipalities according to Ministry of Health classification of transmission occurring between 2007 and 2011 (mean number of cases in the last five years) and Figure 5B shows them classified according to incidence. In some situations there was no correspondence between the criteria used. Five municipalities were classed as having sporadic transmission according to the Ministry of Health criteria, but had high incidence (Irapuru, Nova Guataporanga, Pauliceia, Ouro Verde and Sao Joao do Pau D'Alho), and four municipalities with intense transmission were classified as low incidence (Araçatuba, Birigui, Lins, Bauru).

DISCUSSION

This study shows the geographical spread of HAVL in the state of Sao Paulo between 1999 and 2011, first identified in Araçatuba.[6] Many factors explain this phenomenon: movement of people and goods on the highways and railways linking different regions of the country and their urban centers, migration, urbanization and poor sanitation, movement of infected animals and adaptation of the vector, among others, as well as the need to structure health care teams.[1,3,15,18,23]

Barata[3] (2000) highlights the impact of substituting breeding livestock with sugar cane plantations in the state of Sao Paulo as having an impact on the spread of HAVL. This business involves migrant labor, often from the Northeast, where the disease is endemic. The introduction of HAVL due to migration by individuals from Minas Gerais state is also plausible. A study
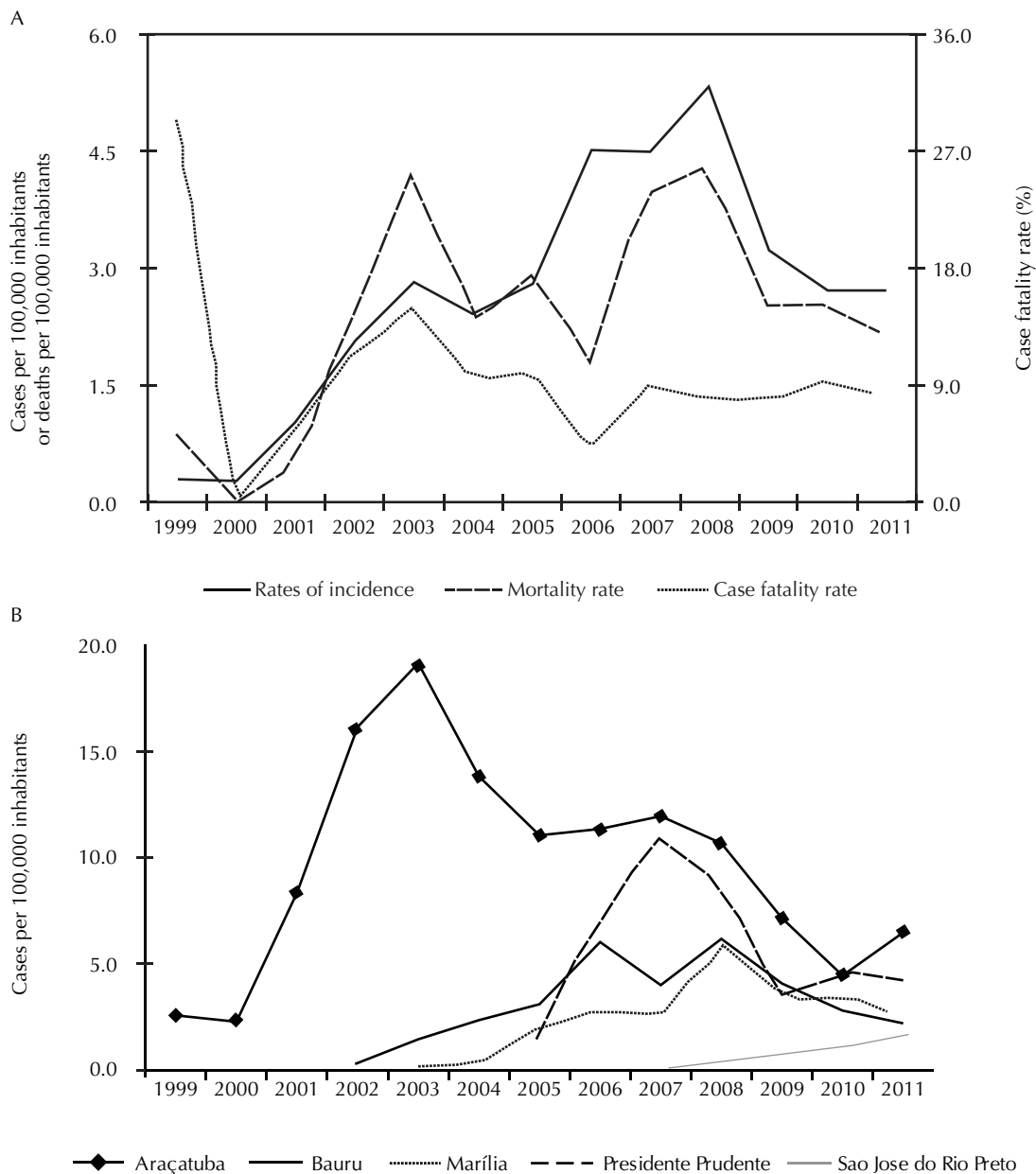
Figure 2. Incidence and mortality rates and case fatality rate for Human American visceral leishmaniasis in the whole area (A) and rates of incidence according to health care region of Araçatuba, Bauru, Marília, Presidente Prudente and Sao Jose do Rio Preto (B). State of Sao Paulo, 1999 to 2011.

carried out in the metropolitan area of Belo Horizonte, MG, Southeastern Brazil, showed the HAVL transmission began in 1989, increasing significantly between 1998 and 1999, when cases of HAVL were diagnosed in 15 (42%) of the 36 municipalities in the metropolitan area.[12] The period in which reporting and spread of the disease increased coincides with the period in which the first human and canine cases of the disease were detected in the region of Araçatuba.[6]

The hypothesis that the disease originated in the state of Mato Grosso do Sul should also be considered.

Cases of AVL in humans and dogs showing symptoms of the disease were observed in the municipality of Corumbá, MS, Midwestern Brazil, from 1980 onwards. HAVL spread to other municipalities from 1998. The first cases of AVL in humans in Campo Grande, MS, were diagnosed in 1999,[1] the same year in which the disease was detected in Sao Paulo State. This hypothesis is reinforced by the fact that the municipalities in Araçatuba share a border with Mato Grosso do Sul, and the link between the two regions is facilitated by the *Marechal Rondon* highway and the *Novoeste* railway.
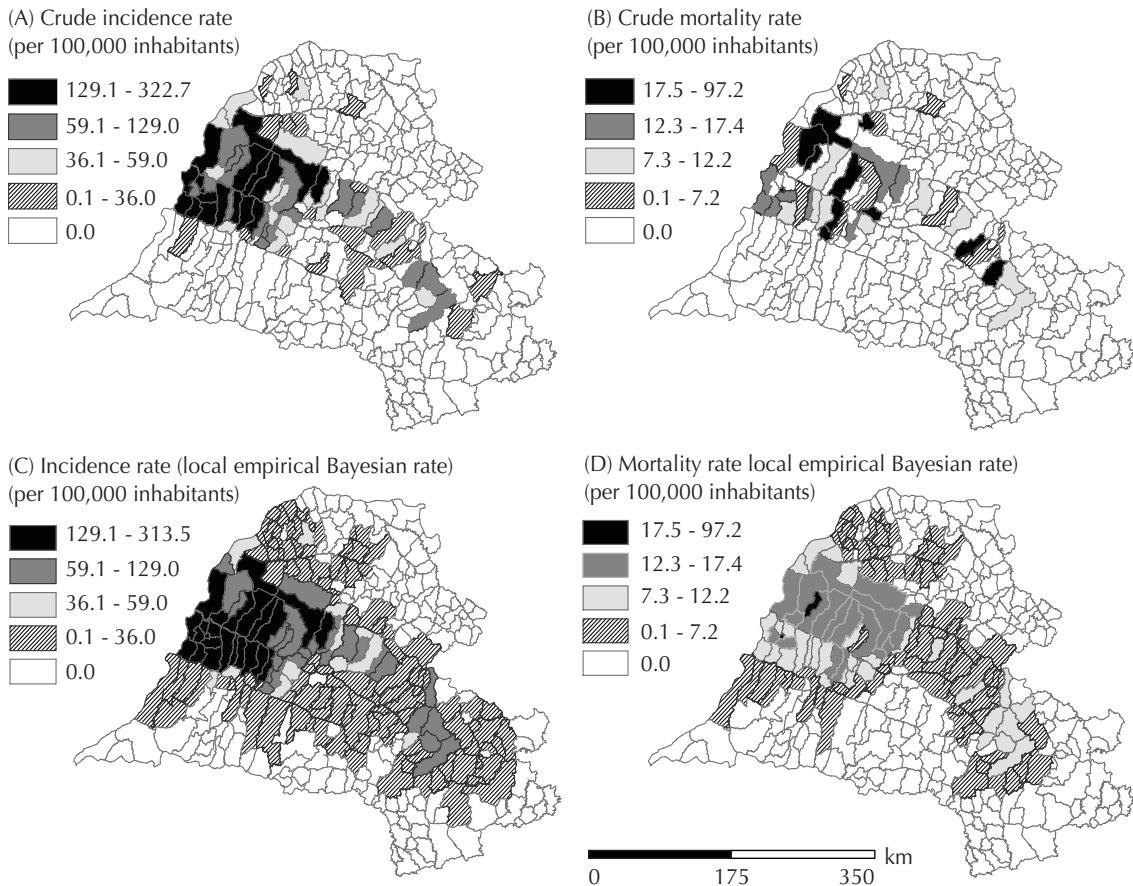
(A) Crude incidence rate
(per 100,000 inhabitants)

129.1 – 322.7
59.1 – 129.0
36.1 – 59.0
0.1 – 36.0
0.0

(B) Crude mortality rate
(per 100,000 inhabitants)

17.5 – 97.2
12.3 – 17.4
7.3 – 12.2
0.1 – 7.2
0.0

(C) Incidence rate (local empirical Bayesian rate)
(per 100,000 inhabitants)

129.1 – 313.5
59.1 – 129.0
36.1 – 59.0
0.1 – 36.0
0.0

(D) Mortality rate local empirical Bayesian rate)
(per 100,000 inhabitants)

17.5 – 97.2
12.3 – 17.4
7.3 – 12.2
0.1 – 7.2
0.0

km
0   175   350

Figure 3. Crude incidence (A) and mortality rates (B) and local empirical Bayesian rates of incidence (C) and mortality (D) from Human American visceral leishmaniasis. State of Sao Paulo, 1999 to 2011.

Antonialli et al[1] (2007) noted that the spread of AVL in Mato Grosso do Sul followed the construction of the Bolivia-Brazil gas pipeline, both in space and time, and raised the hypothesis that this may have been a factor in the spread of the disease in this state. The same hypothesis can be considered as partially explaining the spread of the disease in Sao Paulo, where the pipeline was constructed between 1997 and 1999, linking the cities of Castilho – in the area of Araçatuba, bordering Mato Grosso do Sul – with Campinas. Construction of the pipeline involved recruiting large numbers of workers from different regions of Brazil, among them Mato Grosso do Sul, Minas Gerais and the Northeast, who were constantly moving as the gas pipeline construction advanced.[f]

Transporting infected and/or ill dogs, from various regions of Brazil with AVL transmission may have contributed to the introduction and spread of the disease in other areas.[15] Scandar et al[18] (2011) indicate that the introduction of the parasite in regions with no transmission may have occurred by asymptomatic dogs, which were thus not put down, arriving from other areas. Circulation of people, animals and goods between municipalities in the same endemic area may

have influenced the spread of the disease, as observed by Mestre & Fontes[15] (2007).

Rates of incidence peaked then fell, which may be linked to the surveillance and control activities developed and/or to the cyclical behavior of the disease, except in Sao Jose do Rio Preto, where HAVL was most recently introduced. Ximenes et al[23] (2007) showed the cyclical pattern of the disease in the state of Rio Grande do Norte, Northeastern Brazil, and suggested a period of ten years per cycle. Werneck et al[22] (2008) identifies a similar pattern in Teresina, PI, Northeastern Brazil. Although the foundations of the control measures are backed up by theory, there is no evidence of their effectiveness.[22] These measures have not been effective in controlling the spread of the disease, which is spreading throughout the state of Sao Paulo, an example of what is occurring in the country as a whole.[a]

Using local empirical Bayesian rates meant that random fluctuations in incidence and rates of mortality were reduced.[20] By indicating locations with no reports of HAVL, but with estimated incidence > 0, these rates allowed to identified the key municipalities for the development of surveillance and control activities,
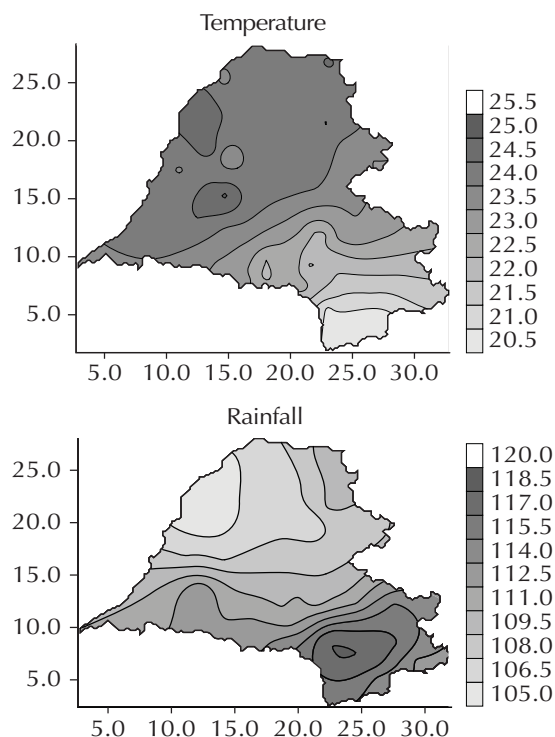
Figure 4. Mean annual temperature in ºC (A) and mean annual rainfall (B). State of Sao Paulo, 1999 to 2011.

either for being in the neighborhood of municipalities with confirmed transmission or due a possible under-reporting of HAVL cases, estimated at between 42% and 45% by Maia-Elkhoury et al[13] (2007).

The vector was present in some municipalities with empirical Bayesian rates of incidence > 0 and with no reports of HAVL cases. The others are included in the list of the 363 municipalities in the state of Sao Paulo which are classified as vulnerable, due to proximity and/or movement of people and goods from areas with transmission.[8] Municipalities in this situation could be viewed as key for surveillance and control activities.

Municipalities with identified incidence of HAVL, with no mortality and empirical Bayesian rates > 0, need to be investigated to verify the occurrence of underreporting of deaths, estimated at between 46% and 53%.[13] This should take place mainly in those with recent transmission, where neither the population nor the health care professionals are alert to the problem of the disease.

The stratification proposed by the Ministry of Health[a] enabled those municipalities with cases reported in the last five years to be assessed and prioritized. Of the 64 municipalities with autochthonous cases between 2007 and 2011, 12 had intense transmission, seven with high rates of incidence (Dracena, Panorama, Junqueirópolis, Tupi Paulista, Pacaembu, Flórida Paulista and Adamantina). Five municipalities with high rates of
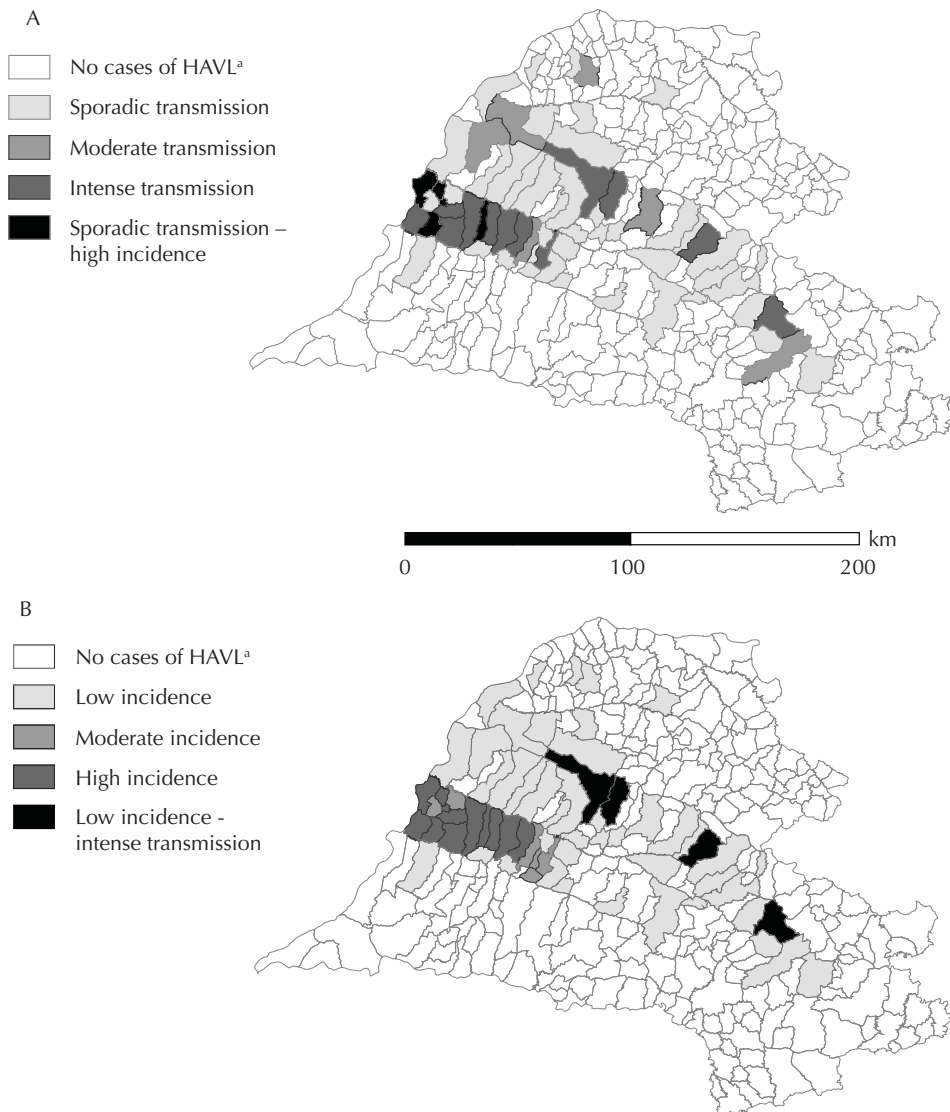
incidence were classified as having sporadic transmission due to their small populations. Regional centers playing a significant part in the spread of AVL, such as Araçatuba, Birigui, Bauru and Lins, considered as having intense transmission by the Ministry of Health, were classes as having the lowest level of incidence.

Both sets of criteria have some faults. That of the Ministry of Health, as it only considers the mean number of cases and so is not sensitive in identifying municipalities with high rates of incidence, and the classification according to the incidence fails to identify epidemiologically important municipalities. Using the mean number of cases together with incidence would produce classification criteria better able to identify key municipalities for developing surveillance and control actions, especially those municipalities with a high rate of incidence and a small number of cases.[a] These are those on the secondary axis of AVL spread, south towards the regions of Presidente Prudente and Marília (SP). Surveillance and control measures such as educational activities aimed at reporting cases, censuses of canines and environmental management need to be intensified.

The large variation in case fatality rate from HAVL between 1999 and 2006, before the figures stabilized in 2007, may be related to the learning curve of the health care professionals providing care. Oliveira et al[17] (2010) reported that early identification of certain clinical and laboratorial characteristics of HAVL is extremely important in reducing mortality, as the appropriate treatment and preventative measures are taken. These procedures are more necessary in municipalities where transmission has most recently been identified.

The occurrence of the first cases of HAVL in the region with higher mean temperatures and lower mean rainfall may reflect the preference of *Lu longipalpis* for the drier, hotter areas of the state. Therefore, the spread into cooler more humid regions, such as municipalities in the areas of Bauru and Marília, show how the vector has adapted to other climates. Microclimate may be more significant to the vectors survival than macroclimate, as the adults prefer to live in humid locations.[4] Silva et al[19] (2007), in a yearlong study, stated that the most humid months coincide with higher frequency of the vector and with a greater number of vectors infected with *Leishmania* sp.

If the macroclimate in the state of Sao Paulo did not play an essential role in the spread of AVL, the factors which would determine the spread of the disease to parts previously untouched may be deemed to be the same as those which affect or affected the spread to the regions studied. This conclusion, to be verified in future studies, together with accumulated experiences of surveillance and control, may serve as the basis for structuring activities aiming to at least delay the spread of AVL in the state of Sao Paulo.

A

☐ No cases of HAVL[a]

▨ Sporadic transmission

▨ Moderate transmission

▨ Intense transmission

■ Sporadic transmission –
   high incidence

km

0   100   200

B

☐ No cases of HAVL[a]

▨ Low incidence

▨ Moderate incidence

▨ High incidence

■ Low incidence -
   intense transmission

[a] HAVL: Human American visceral leishmaniasis

Figure 5. Municipalities with sporadic, moderate and intense transmission (according to mean number of cases of Human American visceral leishmaniasis in five years) (A) and with low, moderate and high incidence rates of Human American visceral leishmaniasis (B). State of Sao Paulo, 2007 to 2011.

Using Geographic Information Systems (GIS) and spatial analysis aids in describing the spread of disease, enabling patterns of occurrence and probable risk factors to be identified.[7,14] Using empirical Bayesian estimator in this study meant that random variations in incidence and mortality rates were reduced and highlighted key municipalities for developing surveillance and control activities. Using geostatistics, another technique of spatial analysis, it was possible to visualize climatic variables and compare them with the behavior of HAVL.

Using secondary data and passive notification, with the likelihood of underreporting of cases, and the use of an ecological design, are some of the limitations of this study. In spite of this, the study enabled the spread of HAVL in the state of Sao Paulo to be described and indicated possible determinants. Among these, the *Marechal Rondon* highway, the *Novoeste* railway and the construction of the Bolivia-Brazil gas pipeline and the role of climatic, environmental and socio-economic variables in spreading AVL will be the target of more in-depth studies.

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