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# Space-time cluster analysis of American visceral leishmaniasis in Bauru, Sao Paulo State, Brazil

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# Análise de aglomerados espaço-temporais da leishmaniose visceral americana em Bauru, São Paulo, Brasil

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## Abstract

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*A space-time analysis of American visceral leishmaniasis (AVL) in humans in the city of Bauru, São Paulo State, Brazil was carried out based on 239 cases diagnosed between June 2003 and October 2008. Spatial analysis of the disease showed that cases occurred especially in the city's urban areas. AVL annual incidence rates were calculated, demonstrating that the highest rate occurred in 2006 (19.55/100,000 inhabitants). This finding was confirmed by the time series analysis, which also showed a positive tendency over the period analyzed. The present study allows us to conclude that the disease was clustered in the Southwest side of the city in 2006, suggesting that this area may require special attention with regard to control and prevention measures.*

*Visceral Leishmaniasis; Cluster Analysis; Spatial Analysis*

## Introduction

American visceral leishmaniasis (AVL) is a zoonotic disease caused by protozoan parasites of the genus *Leishmania* spp. and transmitted by phlebotomine sand flies (World Health Organization. http://www.who.int/leishmaniasis/en, accessed on 08/Aug/2011) [1]. Dogs are considered important reservoir hosts in urban areas as they carry the agent for long periods of time, favoring biologic vector-borne infections and, as a result, maintenance of protozoa [2,3]. In human begins, AVL is described as a serious disease and early diagnosis and treatment are vital to avoid fatalities [4,5].

In Brazil, AVL affects most parts of the national territory and represents an important public health issue, especially in fast-growing urban areas. Recent data shows that cases reported in this country make up 90% of all cases registered in Latin America [5]. In the State of São Paulo, canine visceral leishmaniasis occurs in 71 cities while the human form is present in 52 urban centers [6].

Despite the prevention and control measures implemented in the State of São Paulo, human and canine AVL are still spreading [6]. One of the most affected cities is Bauru, where 354 human cases were confirmed between 2003 and 2011 (data collected up to April 2011) [7]. Up to date, the space-time pattern of this disease in the City of São Paulo has not been evaluated, emphasizing the need for studies that address this question.

Epidemiologic surveys are indispensable in AVL control programs since they permit problem analysis by person, time and space, thus enabling researchers to model occurrence and determinate the extent of the disease [8].

Geographic information systems have been used in epidemiologic studies as a way to improve understanding of health patterns and complement disease prevention and control programs [9,10]. One of its applications is the identification of disease clusters, an important epidemiologic tool that determines unexpected events clustering by space and/or time [11].

The aims of the current study are to describe disease occurrence in the city of Bauru between 2003 and 2008 and identify space-time disease clusters in order to improve knowledge of this disease in the region.

## Material and methods

### Study area

The study area comprises the city of Bauru which has a total area of 673.49km² and is located in the center west of the State of São Paulo (22° 18' 53" S, 49° 03' 38" W). Bauru has a population of approximately 343,937 (Brazilian Institute of Geography and Statistics. http://www.censo2010.ibge.gov.br/sinopse/index.php?uf=35&dados=0, accessed on 08/Aug/2011) and until 2010 the rate of urbanization was 98.5% (Fundação Seade. http://www.seade.gov.br/produtos/perfil/perfil.php?loc=60, accessed on 08/Aug/2011).

### Data

Data on age, gender and place of residence of AVL patient from June 2003 to October 2008 were supplied by the Bauru City Health Department. Only one of the notified cases for the region during this period occurred in the rural zone and therefore only data for the urban area was used. Diagnostic and treatment measures were used according to the regional AVL surveillance and control program.

The present study was approved by the Ethics Committee of the Faculty of Veterinary Medicine and Zootechny of the University of São Paulo.

### Descriptive statistics

Annual cases and frequencies of human AVL between 2003 and 2008 were calculated and plotted according to gender and age. Data from the Census 2000 was used to draw the age pyramid of Bauru inhabitants. This information was of-

ficially published by the Brazilian Institute of Geography and Statistics (IBGE. http://www.ibge.gov.br/home/estatistica/populacao/censo2010/caracteristicas_da_populacao/default_caracteristicas_da_populacao.shtm, accessed on 23/Jan/2011).

### Incidence rates and time series analysis

Annual cumulative incidence rates of visceral leishmaniasis were calculated considering the total number of notified cases and the projected population size as at July 1st of each year. The latter information was published by the State System of Data Analysis Foundation (Fundação Seade. http://www.seade.gov.br/produtos/projpop/, accessed on 17/Dec/2009).

The disease time series analysis was decomposed utilizing a multiplicative model using the statistic software Minitab v. 15 (Minitab Statistical Software, Minitab Inc., State College, USA). Confirmed case counts were arranged in monthly distributions across the five year period. The method is described as:

$Z(t) = T(t) \times S(t) \times C(t) + I(t)$

Where $Z$ is the time series variable, $T$ is time trends, $S$ is seasonal trends, $C$ is cycle trends and $I$ is irregular trends.

The seasonal indexes were plotted using rainfall data for the city of Bauru. A linear regression analysis was carried out to analyze the correlation between these variables where rainfall was considered as an explanatory variable and seasonal index as a dependent variable ($\alpha = 0.05$).

Meteorological data, consisting of monthly rainfall and temperature between 2003 and 2008, was supplied by the Institute of Meteorological Research of the State University of São Paulo (IPMet. http://web.ipmet.unesp.br/index2.php?menu_esq1=&abre=ipmet_html/estacao/historico.php, accessed on 17/Dec/2009).

### Cluster analysis

Georeferencing of AVL cases between June 2003 and October 2008 was carried out based on a cartographic street map of the city and the respective addresses of patients. Due to problems with household identification, every case was identified according to the street block centroid. Cases were then associated with their respective census tracts using a digital base containing the political boundaries in 2000. This material is available at the IBGE website (ftp://geoftp.ibge.gov.br/mapas/malhas_digitais/setor_urbano_2000/SP/3506003, accessed on 20/Oct/2009).

Space-time cluster analysis was performed using the public-domain software SaTScan v. 8.0

(http://www.satscan.org) based on space-time scan statistics. The test is carried out by gradually scanning a window across time and space, noting the number of expected and observed cases at each location. This window is defined as a cylinder in which the circular or elliptic base corresponds to space and height corresponds to time.

The window size varies between zero and a predefined maximum value related to the percentage of population. Statistics probability is chosen and calculated for each circular (or elliptic) base for each data type. The value is then computed according to observed cases inside and outside the window and compared with $L_0$ under the null hypothesis. Circles with a high proportion of cases are considered the most likely clusters and a Monte Carlo simulation is carried out to evaluate the significance level of each detected cluster [12].

In the current study, the maximum size of the circular window included 50% of the population at risk. This is the recommended value to avoid bias, since larger windows would indicate exceptionally low rates outside of the circle [12]. The Poisson distribution was calculated using annual occurrence of cases as the temporal unit and a significance level of 5%.

## Results

### Descriptive statistics

A total of 250 autochthonous cases were notified in the city of Bauru urban area between June 2003 and October 2008. Of these cases, 11 were not counted due to inadequate patient data resulting in a total of 239 studied cases, of which 37.2% (89/239) were female and 62.8% (150/239) male.

Figures 1 and 2 show the age pyramids of cases and the Bauru population (IBGE. http://www.ibge.gov.br/home/estatistica/populacao/censo2010/caracteristicas_da_populacao/default_caracteristicas_da_populacao.shtm, accessed on 23/Jan/2011).

### Incidence rates and time series analysis

Table 1 shows the number of annual cases and projected population and respective disease incidence. These results show an increase in AVL incidence during the period studied, with the greatest incidence occurring in 2006. The same trend can be observed in the time series decomposition chart shown below (Figure 3) that indicates a positive tendency over the analyzed period.

Figure 4 demonstrates the seasonal indexes obtained from the time series model and the average monthly rainfall between 2003 and 2008. It shows that months with positive index values were preceded by rainy periods. From October through January there was a gradual increase of

Figure 1

Age pyramid of American visceral leishmaniasis (AVL) cases in Bauru, São Paulo State, Brazil, 2003-2008.
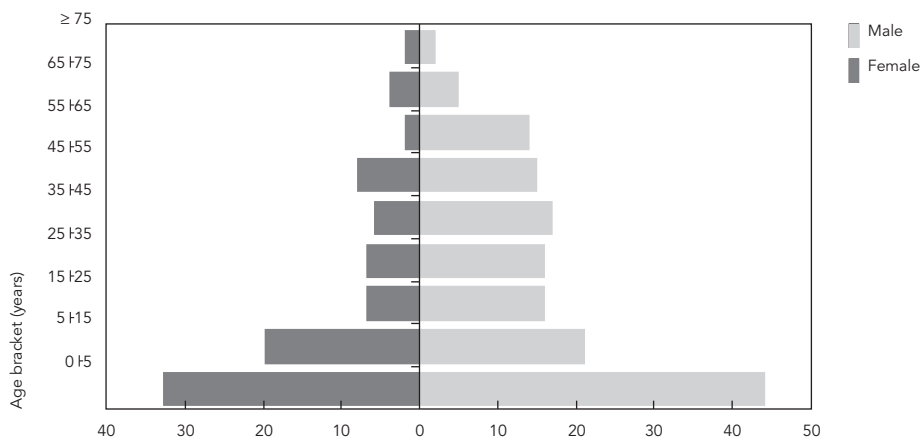
Figure 2

Age pyramid of the population of Bauru, São Paulo State, Brazil, 2003-2008.
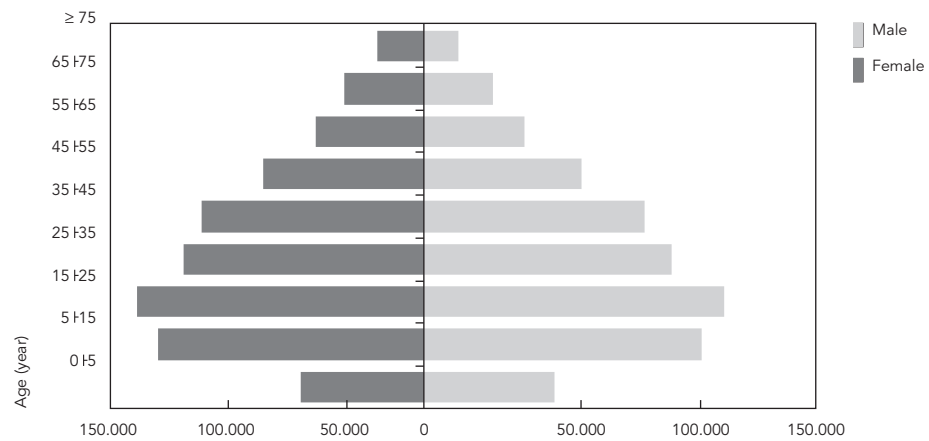


Table 1

Number of American visceral leishmaniasis (AVL) cases, projected population and AVL incidence rate in Bauru, State of São Paulo, Brazil, 2003-2008.

| Year | Cases | Projected population * | Incidence (per 100,000 inhabitants) |
|------|-------|------------------------|-------------------------------------|
| 2003 | 16 | 331,806 | 4.82 |
| 2004 | 29 | 337,492 | 8.59 |
| 2005 | 34 | 343,148 | 9.91 |
| 2006 | 68 | 347,747 | 19.55 |
| 2007 | 39 | 352,409 | 11.07 |
| 2008 | 53 | 357,132 | 14.84 |

* Fundação Seade. http://www.seade.gov.br/produtos/perfil/perfil.php?loc=60 (accessed on 08/Aug/2011).

average precipitation leading to monthly seasonal indexes greater than 1 between November and February. A linear regression analysis was carried out to test for a possible correlation between the obtained seasonal indexes and mean rainfall in the respective previous month, which showed a low, but positive, result ($R^2 = 0.35$).

Although the relation between seasonal index and the respective previous month average temperature was also tested using linear regression analysis, no significant correlation was observed ($R^2 \approx 0.01$). This can be explained by low temperature fluctuations during this period, which varied between 18 and 25°C.

## Cluster analysis

The space-time cluster analysis detected the concentration of the disease in 70 census tracts in 2006 in the southeast side of the city ($p \leq 0.001$), of which 38 presented 52 autochthonous human AVL cases. Two secondary clusters were identified, but neither of them was statistically significant ($p \geq 0.05$). Figures 5 and 6 show the identified clusters. Annual cases of human AVL are shown in Figures 7, 8, 9, 10, 11, and 12, highlighting the spatial evolution of disease distribution. It should be noted that cases occurring at the same location (i.e., in the same block), are represented by a single point.

Figure 3

Time series decomposition of Human American visceral leishmaniasis (AVL) cases in Bauru, São Paulo State, Brazil, 2003-2008.
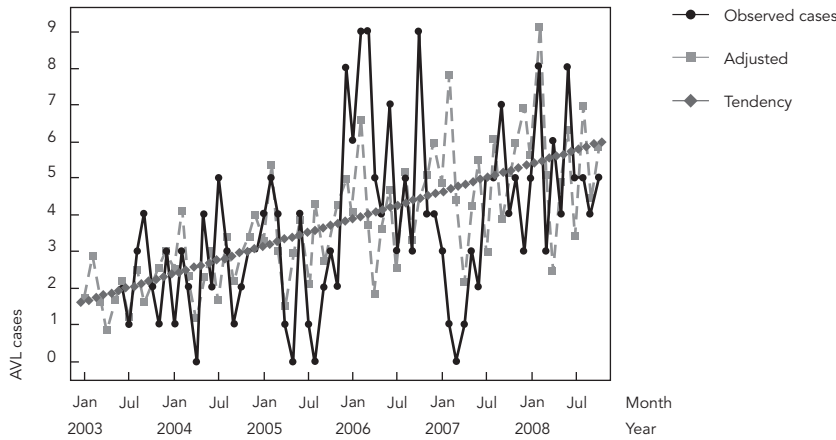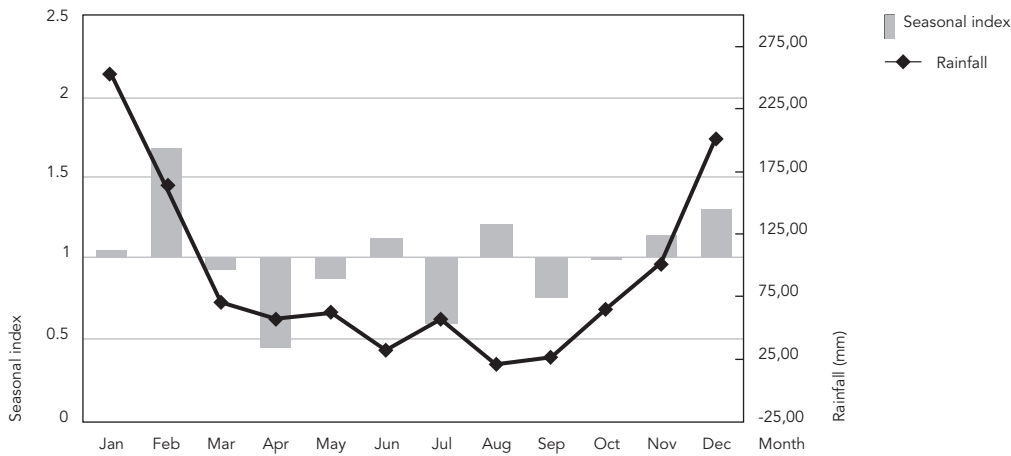


Figure 4

Seasonal indexes of Human American visceral leishmaniasis (AVL) cases. Bauru, São Paulo State, Brazil, 2003-2008.



## Discussion

Although AVL occurs worldwide, the most concentrated areas of the disease are located in developing countries (World Health Organization. http://www.who.int/leishmaniasis/en, accessed on 08/Aug/2011). In Brazil, the disease is considered endemic in several cities and diagnosed cases have been identified in the country's North, Northeast, Central West and Southeast regions.

Autochthonous AVL was first notified in Bauru in 2003 and, despite the implementation of recommended control and prevention measures, the disease continues to spread in this city.

Data on patients in Bauru showed that the disease was more common in males (62.8%) than

Figure 5

Space-time cluster of Human American visceral leishmaniasis (AVL) (2006) and distribution of cases in Bauru, São Paulo State, Brazil, 2003-2008.



● Human AVL cases

Space-time cluster (2006)

Bauru urban area

0   1,000  2.000      4,000      6,000      8,000 Meters

Figure 6

Secondary space-time clusters of Human American visceral leishmaniasis (AVL) (p = 0.936 and p = 0.214). Bauru, São Paulo State, Brazil, 2003-2008.



Space-time secondary cluster (2006)

Space-time secondary cluster (2006-2007)

Bauru urban area

0   1,350   2,700        5,400        8,100        10,800 Meters
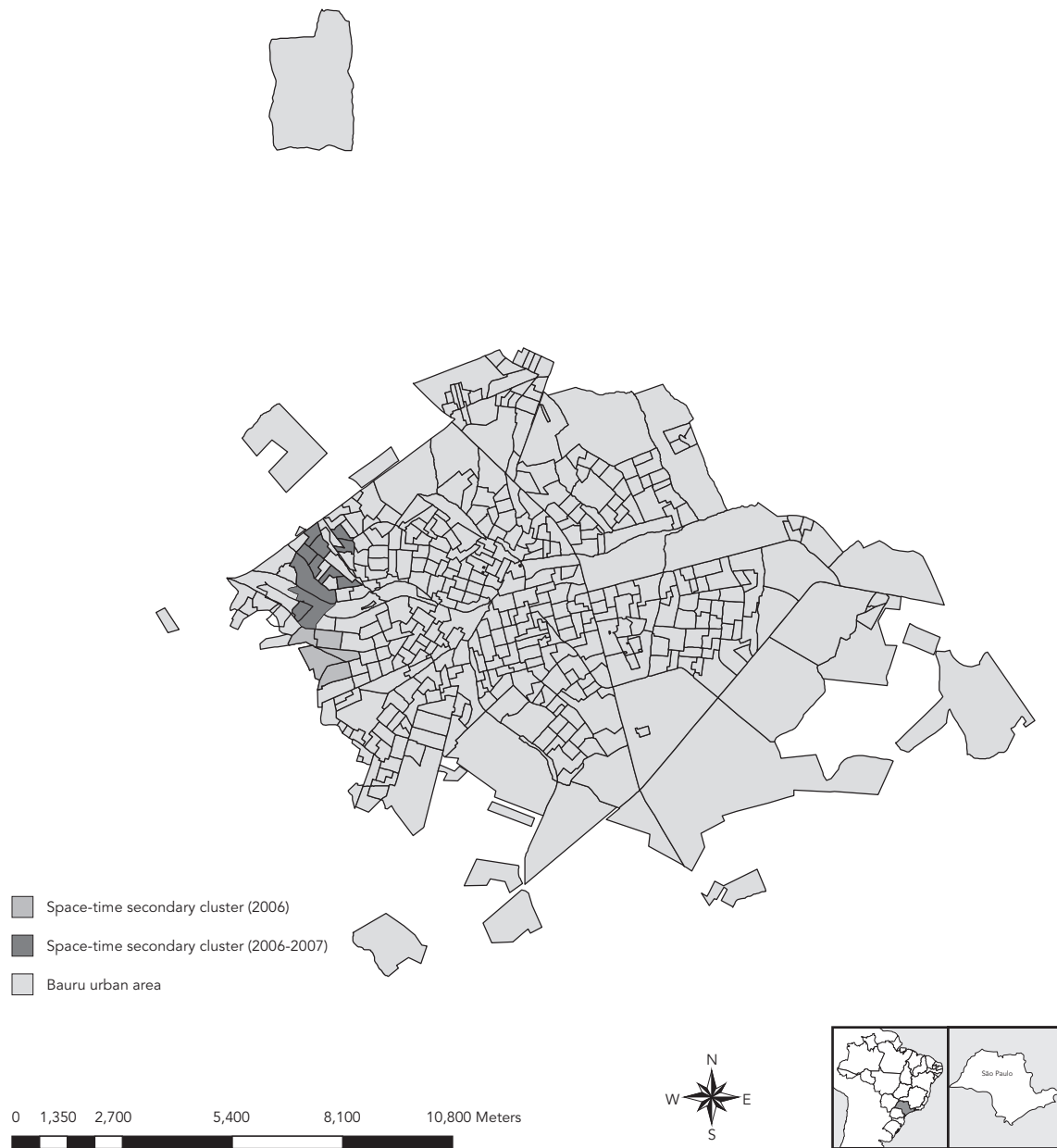
Figure 7

Human American visceral leishmaniasis (AVL) cases in Bauru, São Paulo State, Brazil, 2003.



● Human AVL cases (2003)

▢ Bauru urban area

0   1,350   2,700        5,400        8,100        10,800 Meters

Figure 8

Human American visceral leishmaniasis (AVL) cases in Bauru, São Paulo State, Brazil, 2004.



● Human AVL cases (2004)

☐ Bauru urban area

0    1,350    2,700         5,400         8,100         10,800 Meters

Figure 9

Human American visceral leishmaniasis (AVL) cases, Bauru, São Paulo State, Brazil, 2005.



Human AVL cases (2005)

Bauru urban area

0    1,350    2,700         5,400         8,100         10,800 Meters

Figure 10

Human American visceral leishmaniasis (AVL) cases in Bauru, São Paulo State, Brazil, 2006.



● Human AVL cases (2006)

Bauru urban area

0   1,350   2,700        5,400        8,100        10,800 Meters

N
W — E
S

São Paulo

Figure 11

Human American visceral leishmaniasis (AVL) cases in Bauru, São Paulo State, Brazil, 2007.

● Human AVL cases (2007)

⬜ Bauru urban area

0    1,350    2,700    5,400    8,100    10,800 Meters

Figure 12

Human American visceral leishmaniasis (AVL) cases in Bauru, São Paulo State, Brazil, 2008.



● Human AVL cases (2008)

Bauru urban area

0    1,350    2,700          5,400          8,100          10,800 Meters

in females (37.2%) and the most affected age groups were zero to four years (77/239) and five to 15 years (41/239). This kind of profile has already been reported in Brazil [16] and other countries, including Uganda [13,14], Kenya [14], Ethiopia [15], Sudan [16], Nepal [16] and India [16]. Despite being a common finding, the explanation for this trend remains uncertain. Factors that may explain this pattern include exposure, vulnerability and health-seeking behavior [16].

Considering the period June 2003 to October 2008, annual incidence rates per 100,000 inhabitants showed a clear increase in the disease, with the highest incidence occurring in 2006 (19.55).

This finding is confirmed by the time series analysis that identified a positive trend in the expansion of the disease over the study period. This analysis also determined the seasonal index that was low when compared to mean previous month rainfall.

Previous studies have shown a positive correlation between climatic variables, such as temperature, relative humidity and rainfall, and phlebotomine density [17,18,19,20]. Our findings corroborate these results, showing that vector count is related to human and canine AVL incidence [19,21].

Bauru is characterized by a constantly warm climate, with average temperatures over the analyzed period between 18° and 25°C, which may suggest why this variable did not influence the obtained seasonal index.

A similar result was noticed in a study realized in Porteirinha in the State of Minas Gerais, Brazil where no correlation between temperature and increases in density of sand flies was found, probably due to a lack of significant temperature fluctuations over the study period. According to the authors, rainfall index and relative humidity were decisive factors for the population dynamics of the phlebotomine sandfly in the region [22].

The use of geographic information system (GIS) tools in epidemiologic studies has increased and improved over recent years, allowing a better understanding of disease distribution in both space and time.

Although spatial and space-time analysis using GIS and remote sensing have been the focus of several studies concerning leishmaniasis [23,24,25,26,27,28,29], few studies in Brazil have addressed AVL cluster analysis.

It was possible to detect whether the disease was homogeneously distributed throughout the city of Bauru between 2003 and 2008. In 2006, a cluster was localized in the Southeast and Central regions of the city. Despite high incidence in 2007 and 2008, AVL cases were spread throughout the city, explaining the absence of space-time cluster identification during these periods.

Unfortunately, data on the density of *Lutzomyia longipalpis* and the distribution of canine AVL cases, an important input for explaining the results obtained by this study, was unavailable.

The current study allowed us to verify that AVL is restricted almost exclusively to the Bauru urban area and disseminated throughout virtually the whole of this area, confirming previous research that emphasizes that this disease is associated with urbanization [30,31,32]. It was not possible to carry out a socioeconomic analysis due to lack of case information. Several studies in other areas have reported that socioeconomic variables, such as household structure, malnutrition and poverty are important risk factors for visceral leishmaniasis [33,34,35] and we therefore suggest that further research should be carried in this field.

The possible participation of wild and synanthropic animals in the *Leishmania* spp. cycle should also be noted. Santiago et al. [36] tested samples of sera collected from opossums captured in urban and periurban areas in the city of Bauru for cutaneous and visceral leishmaniasis to test the hypothesis that this species could have influenced the occurrence of AVL in the region. The authors reported that the migration of opossums to urban areas has been happening since 1999, before the detection of canine AVL at the city [36].

Our study allows us to conclude that, up until now, human AVL has been clustered in Bauru, and that the Southeast area of the city may require special attention regarding the implementation of control and prevention measures. These findings are a first approach and complementary research is necessary to confirm and obtain a better understanding of our results.

## Resumo

*Uma análise espaço-temporal da leishmaniose visceral americana (LVA) em Bauru, São Paulo, Brasil, foi realizada com base em 239 casos diagnosticados entre junho de 2003 e outubro de 2008. A análise espacial da doença demonstrou que os casos ocorreram especialmente na área urbana da cidade. A incidência anual de LVA foi calculada, demonstrando que a taxa mais elevada foi verificada em 2006 (19,55/100 mil habitantes). O fato foi confirmado pela análise da série histórica, que também apresentou uma tendência positiva durante o período analisado. O presente estudo permitiu concluir que a doença esteve aglomerada na região sudoeste de Bauru no ano de 2006, e que tal área pode exigir atenção especial com relação às medidas de controle e prevenção.*

*Leishmaniose Visceral; Análise por Conglomerados; Análise Espacial*

## Contributors

V. A. F. Souza contributed to study design, data analysis and interpretation, writing of this manuscript, and approved the final version of this article. L. R. P. B. Cortez contributed to study design, data acquisition, critical review of the intellectual content, and approved the final version of this article. R. A. Dias, M. Amaku, J. S. Ferreira Neto and R. B. S. Kuroda contributed to data analysis and interpretation and the critical review of the intellectual content, and approved the final version of this article. F. Ferreira contributed to study design, data analysis and interpretation and critical review of the intellectual content, and approved the final version of this article.

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