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Major Article

Occurrence of *Lutzomyia longipalpis* and human and canine cases of visceral leishmaniasis and evaluation of their expansion in the Northwest region of the State of São Paulo, Brazil

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ABSTRACT

Introduction: This paper aims to describe the dispersion of *Lutzomyia longipalpis* and the autochthonous occurrence of visceral leishmaniasis (VL) in the Northwest region of the State of São Paulo between 2007 and 2013 and to analyze their expansion. **Methods**: Information about the vector and associated cases was described using maps. The incidence, mortality, and lethality of human visceral leishmaniasis (HVL) were calculated. In municipalities in which more than one HVL case occurred, incidences were calculated according to census sector, and spatial and spatiotemporal clusters were identified. **Results**: The first case of HVL was reported in the municipality of Jales in 2007. By 2013, the vector and the disease had expanded from west to east, with the vector being detected in 29 municipalities. A total of 11 municipalities had cases of canine visceral leishmaniasis (CVL), and six had cases of HVL. Vector expansion occurred by vicinity with previously infested municipalities, and the expansion of VL was related to the major highways and the capital municipalities of the micro-regions in the study area. The highest incidence of HVL occurred in children between 0-4 years old, and the highest mortality and lethality occurred among persons aged 60 and older. The occurrence of HLV was more intense in the peripheral areas of municipalities with the disease. **Conclusions**: The findings of this study may be useful for improving VL surveillance and control activities by slowing VL expansion and/or mitigating VL effects when they occur.

Keywords: *Lutzomyia longipalpis*. Visceral leishmaniasis. Spatial analysis. Brazil.

INTRODUCTION

Leishmaniasis can manifest in visceral or cutaneous form. The visceral form, if left untreated, can lead to death in most cases and is endemic in several countries, including Brazil, where it is present in all major regions[1] [2] [3].

Visceral leishmaniasis (VL) has been characterized in Brazil as a typically rural zoonosis. However, the disease vector, *Lutzomyia longipalpis*, is eclectic in its feeding habits and also anthropophilic, indicating that it has found breeding sites in the urban environment and adapted to anthropogenic areas. Since the urbanization of the vector, VL is currently most active in urban centers of the country, and it continues to expand[1] [4] [5] [6] [7].

In the State of São Paulo, *L. longipalpis* had previously been identified only in rural areas of municipalities located in the eastern part of the state[8] [9] [10]; the first detection of this vector in an urban area occurred in 1997 in Araçatuba, which is in the western region of the state[11]. This occurrence was followed by the first reports of autochthonous cases of canine visceral leishmaniasis (CVL) and human visceral leishmaniasis (HVL), also occurring in Araçatuba, with the disease expanding later to other municipalities of this region and the regions of Bauru, Marília, Presidente Prudente, and São José do Rio Preto[12].

The study of the expansion of VL in Brazil, particularly in São Paulo, makes it possible to infer its determinants and can contribute to the improvement of surveillance and control activities for this important public health problem. Geographic information systems (GIS) and spatial analysis techniques are useful tools for this purpose. Examples of these techniques are

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included in the work of Cardim et al.[12], Antonialli et al.[13], Martins-Melo et al.[14], and Guimarães et al.[15].

The present study aimed to describe the dispersion of *L. longipalpis* and the occurrence of the first autochthonous HVL and CVL cases in the municipalities of the São José do Rio Preto region, São Paulo, and to evaluate their expansion in space and space-time.

METHODS

Study type, area, and population

According to the 2010 census of the Brazilian Institute of Geography and Statistics [*Instituto Brasileiro de Geografia e Estatística* (IBGE)], the São José do Rio Preto region has a population of 1,309,239 inhabitants. It comprises 102 municipalities; is located in the Northwestern area of the State of São Paulo; and is bordered by the States of Minas Gerais, Paraná, and Mato Grosso do Sul (**Figure 1**). The region is traversed by three major radial highways (connecting the state capital): Euclides da Cunha, Feliciano Salles Cunha, and Washington Luiz. São José do Rio Preto is its capital municipality, which is located 454km from the São Paulo state capital. The region comprises the micro-regions of Catanduva, São José do Rio Preto, Votuporanga, Fernandópolis, Jales, and Santa Fé do Sul, the capitals of which are the municipalities of the same name and are characterized as poles of attraction and dispersion of the flow of people, goods, and services.

The center of the region is located at latitude 20°37'25"S and longitude 49°47'51"W, with an average altitude of 489m. The predominant climate type in the region is Aw, according to Koeppen classification[16], which is characterized as tropical rainy with a dry winter.

Source of data and variables

Information provided by the Superintendence of Endemic Disease Control [*Superintendência de Controle de Endemias* (SUCEN)] regarding the year of *L. longipalpis* detection and first autochthonous CVL case(s) was used. Information regarding autochthonous HVL cases was obtained from the Notifiable Diseases Information System [*Sistema de Informações de*

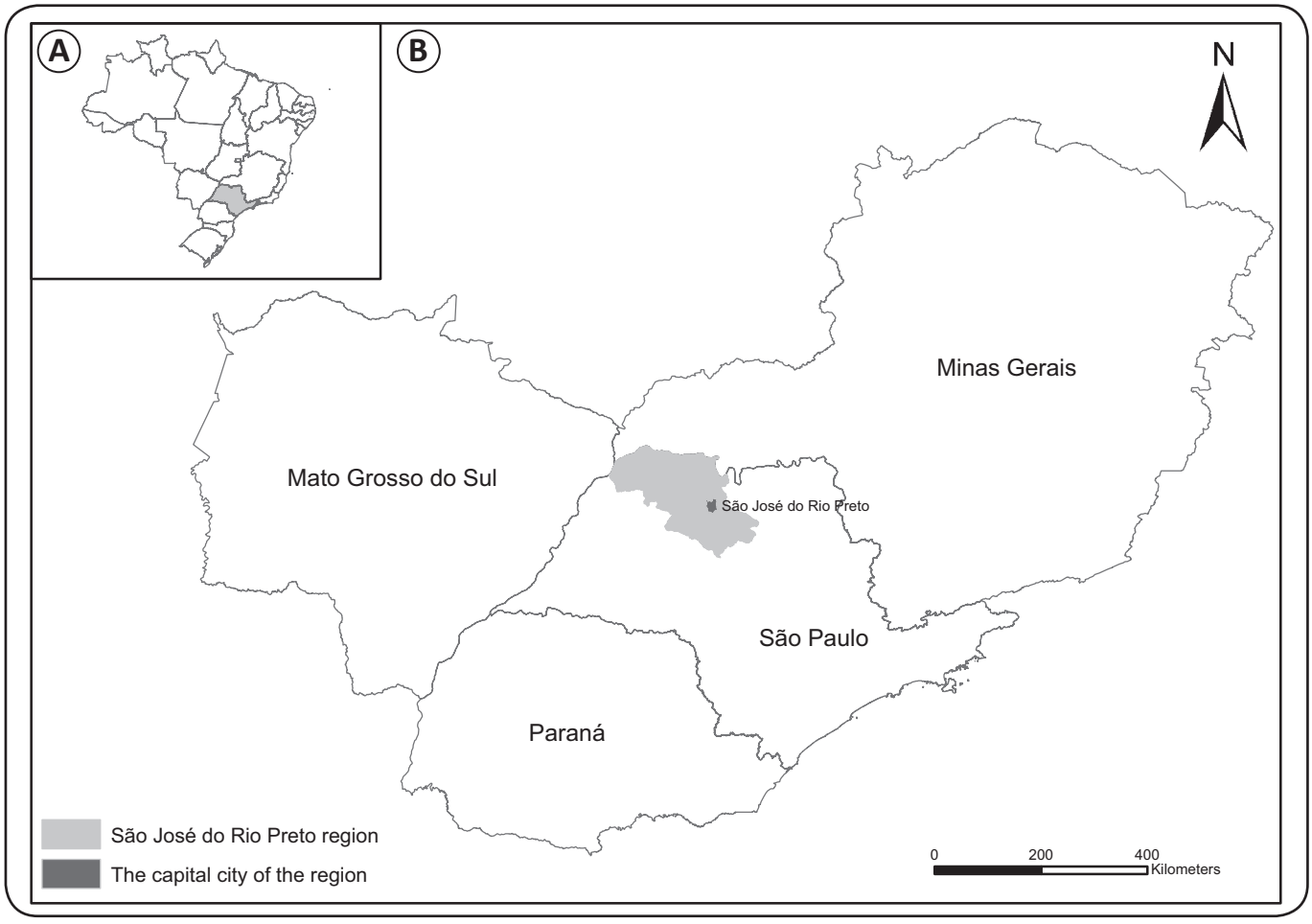

FIGURE 1 - A). Map of Brazil denoting the State of São Paulo. B). Map denoting the São José do Rio Preto region with its capital city and its location within the State of São Paulo and in relation to the States of Minas Gerais, Mato Grosso do Sul, and Paraná, Brazil.

Agravos de Notificação (SINAN)]. These data were obtained between 2007 and 2013 for each of the municipalities in the study region in which the vector's presence or the autochthonous canine and/or human case was detected.

For HVL cases, data on the first date of symptoms, age, sex, municipality and address of the probable infection site, case outcome (cure/death by VL), and year of death were collected. Information regarding the number, age, and sex of the inhabitants according to census tract and municipality was obtained from the IBGE.

Data analysis

To describe the dispersion of *L. longipalpis* and the autochthonous occurrence of CVL and HVL in the municipalities, thematic maps were constructed to show the paths followed by the vector and the disease in their expansion across the study region. These maps were used to evaluate the degree of contiguity of the infestation's evolution and of the occurrence of CVL and HVL and the degree of neighborhood shown by the distributions of affected municipalities in the region.

From the perspective of the detection time of *L. longipalpis* infestation, a municipality was considered contiguous to an already infested municipality if it bordered the municipality and if infestation was detected at a later date. The infestation degree of a neighborhood was obtained by counting. For example, for each of the infested municipalities, the number of neighboring municipalities, i.e., those with common borders, also infested was counted. The degree of contiguity and neighborhood for CVL and HVL was determined by similar procedures to those used for infestation but also considered the autochthonous occurrence of these diseases. The degree of contiguity was measured as a percentage, and the degree of neighborhood was measured as the average number of neighbors.

The relationship between the region's radial highways and the presence of the vector and CVL and HVL occurrence in the municipalities was evaluated by calculating the ratio of affected municipalities traversed by highways. The proportion of micro-region capital municipalities among those infested by *L. longipalpis* and those with CVL and HVL occurrence was also calculated.

Incidence, mortality, and lethality rates, both total and by sex and age, were calculated for the entire period and study area. Incidence and mortality rates, both total and by sex, were also calculated according to the year. Total and single-sex rates were grouped by age.

For the municipalities with more than one autochthonous HVL case, the cases were geocoded based on the municipality's street layer and by probable infection site address; they were also grouped by urban census tracts. Thematic maps were constructed to represent the distribution of cases and HVL incidence rates. In these municipalities, the aim was to identify spatial and spatiotemporal clusters using scanning statistics[17] in a discrete Poisson model. The following criteria were adopted: period of time between 2007 and 2013 and maximum cluster size equal to 30% of each municipality's total population.

The thematic maps were developed using ArcGIS 10.2 software[18], and the cluster detection analysis was performed using SaTScan 9.3 software[19].

Ethical considerations

This project was approved by the Ethics Committee of the School of Public Health of the University of São Paulo (*Universidade de São Paulo*) through the Brazil Platform, CAAE: 14107313.3.3333.5421, protocol number: 257,511, on 26/4/2013.

RESULTS

Figures 2A, 2B and **2C** show the expansion of the *L. longipalpis* vector (29 municipalities) and the autochthonous occurrence of CVL (11 municipalities) and HVL (six municipalities) for the study area between 2007 and 2013 according to the detection year and municipality. A total of 50% of the municipalities with HVL are capitals of their micro-region, and among those with CVL and presence of the vector (36.4% and 13.8%, respectively), four are micro-region capitals (Fernadópolis, Jales, Santa Fé do Sul, and Votuporanga). Notably, the expansion of HVL, CVL, and vector presence occurred from west to east.

The first autochthonous case of HVL in the study area was confirmed in 2007 in the municipality of Jales, with vector presence and autochthonous CVL occurrence confirmed only in the following year. Similar situations occurred in Urânia and Santa Albertina, where presence of the vector was detected after the disease occurred in a dog. Moreover, in General Salgado, there was a confirmed case of HVL without prior detection of the vector or CVL (**Figure 2**).

The degree of contiguity in relation to the first vector detection was 86.2% (25 out of 29 municipalities), i.e., infestation occurred in a municipality neighboring a municipality already infested by the vector more than 86% of the time. In relation to CVL, the degree of contiguity was 54.5% (among the 11 affected municipalities, six neighbored municipalities with previously detected autochthonous canine cases), and in relation to HVL, the degree of contiguity was 33.3% (among the six affected municipalities, two neighbored municipalities with previously detected autochthonous human cases).

The degree of neighborhood in relation to vector presence was 3.8; i.e., each municipality with the vector had an average of four infested neighbors by 2013. With regard to the occurrence of CVL and HVL, the degrees of neighborhood were 1.5 and 0.7, respectively.

Among the 29 municipalities with the presence of *L. longipalpis*, 15 are traversed by radial highways (51.7%). Among the 11 municipalities with CVL cases and the six with HVL cases, eight (72.7%) and five (83.3%), respectively, are also traversed by this type of highway (**Figure 2**).

The incidence and mortality rates for human visceral leishmaniasis showed an increasing trend between the year of

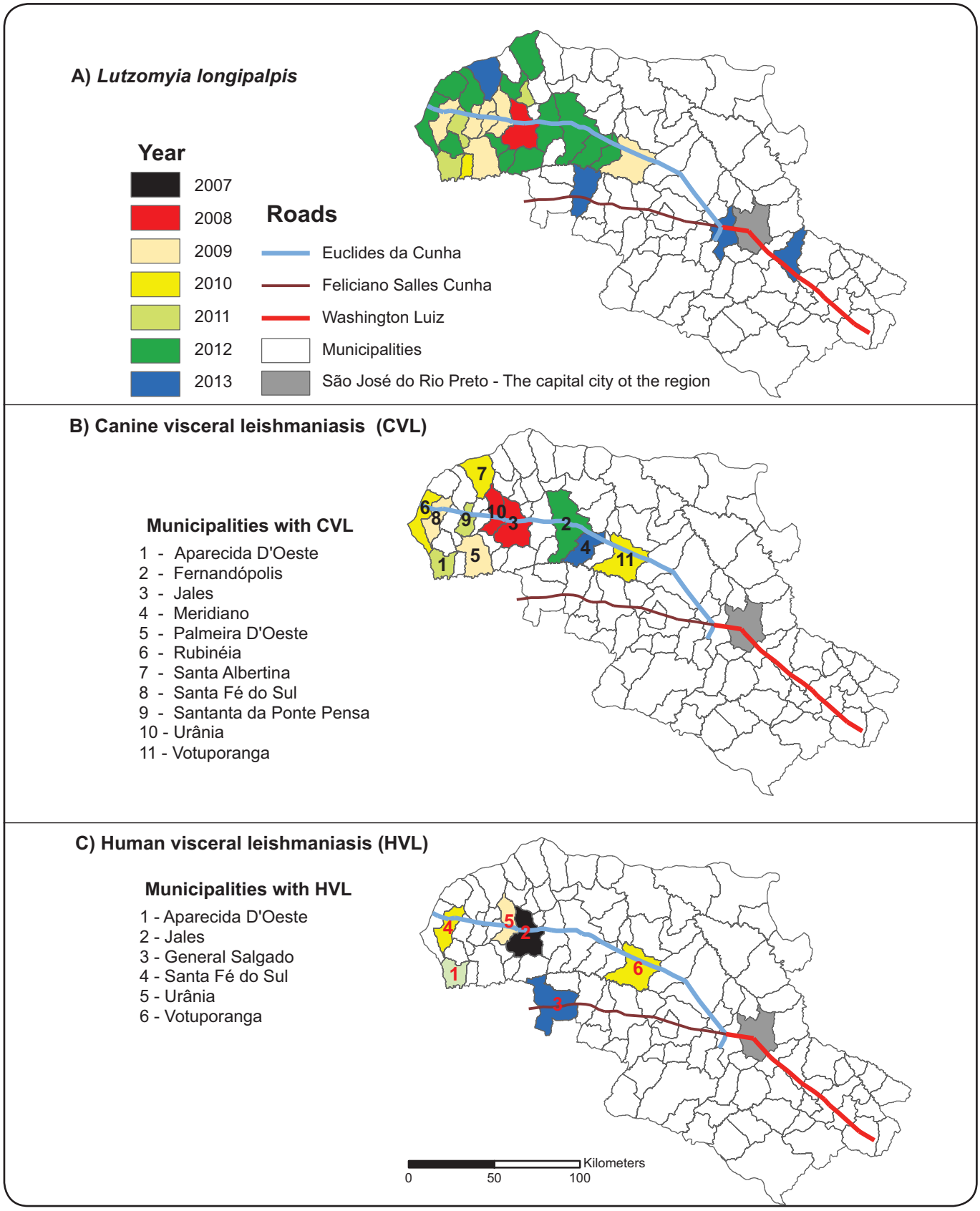

FIGURE 2 - Detection year of *Lutzomyia longipalpis* (A) and of autochthonous case(s) of canine visceral leishmaniasis (B) and human visceral leishmaniasis (C) in the municipalities of the São José do Rio Preto region and its three main highways, State of São Paulo, Brazil, 2007 to 2013.

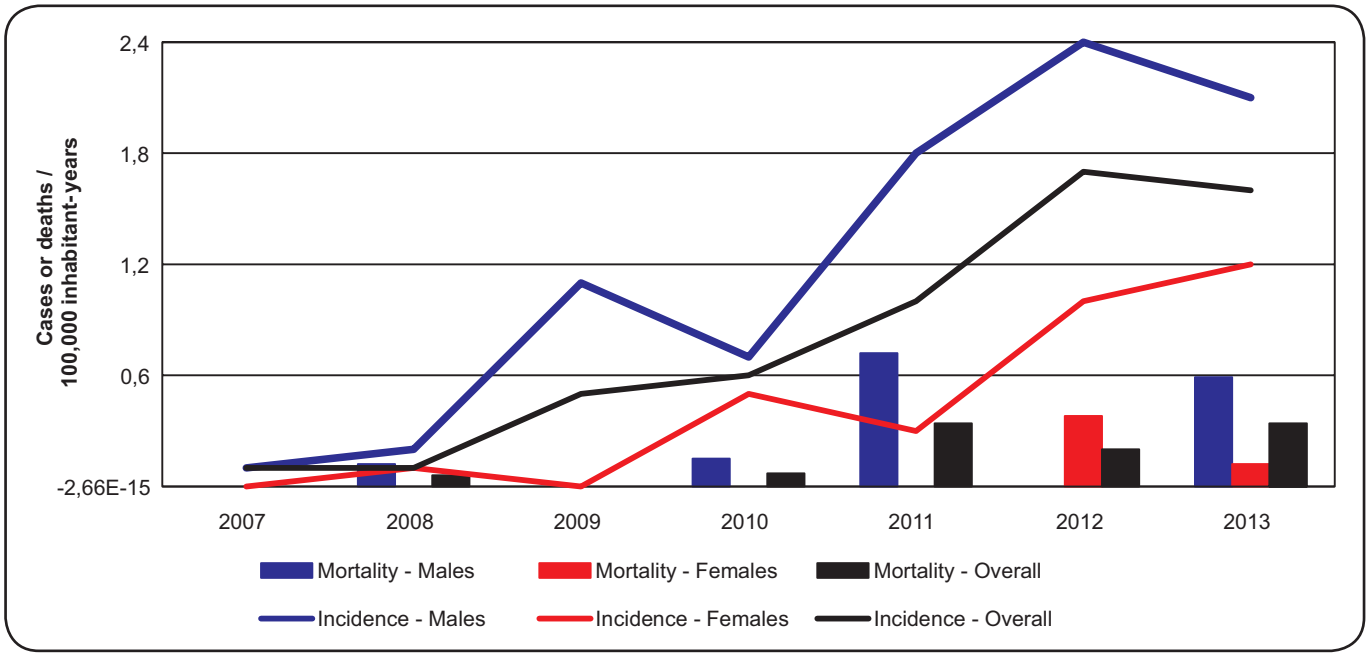

FIGURE 3 - Human visceral leishmaniasis incidence and mortality rates by year and sex, São José do Rio Preto region, State of São Paulo, Brazil, 2007 to 2013.

detection of the first case and 2013. These rates were higher for men (**Figure 3, Figures 4A** and **4B**). The highest incidence rates were in the 0-4-year age group, followed by the 60 and older group, which also had the highest mortality rate (**Figures 4A** and **4B**). Between 2007 and 2013, the highest lethality occurred among those aged 60 and older, reaching 34.5% in this age group and 17.9% overall (**Figure 4C**).

In terms of incidence and mortality, the municipality of Votuporanga is noteworthy because it had the highest number of cases and deaths of all of the municipalities in the São José do Rio Preto region. Between 2010 (the year the first autochthonous HVL case was detected) and 2013, 46 cases and eight deaths were reported.

Figures 5A, 5B and **5C** show HVL incidence rates for the municipalities of Jales, Santa Fé do Sul, and Votuporanga, according to census tracts, for the entire study period. In general, the tracts with the highest rates were located in the more peripheral areas of the cities. A spatial cluster of HVL cases in Jales and a spatio-temporal cluster in Votuporanga could be identified; these clusters were also located on the outskirts of these cities. No clusters were detected in Santa Fé do Sul (**Figures 5D, 5E** and **5F**).

DISCUSSION

The expansion of the disease and vector presence in the São José do Rio Preto region followed the same pattern that was detected in the State of São Paulo by Cardim et al.[12], i.e., an expansion from west to east. The spatial pattern of vector infestation in the municipalities was more aggregated (with higher degrees of contiguity in infestation occurrence in municipalities not previously infested by *L. longipalpis* and higher degrees of neighborhood between infested municipalities) than that of CVL and HVL occurrence. The latter two, by contrast, showed a stronger relationship with the radial highway routes and micro-region capitals than with vector presence in the municipalities.

Virtually all types of transport between the region's municipalities and between neighboring regions travel along radial and transverse highways (the links between the municipalities that do not lead to the state capital, which are generally vicinal highways in the study area); thus, both passive vector dispersion and the expansion of CVL and HVL occurrence must be related to these highways, making it important to discuss the role they play in such processes.

The relationship between major highways and HVL expansion has been discussed by Antonialli et al.[13] and Cardim et al.[12]. The former showed the role of the BR-262 (the highway linking Corumbá to the state capital of Mato Grosso do Sul and the state capital to Três Lagoas, on the State of São Paulo border) in HVL expansion in the State of Mato Grosso do Sul (MS)[13]. The latter group of authors showed the role of the Marechal Rondon Highway (a radial highway that crosses the regions of Araçatuba, Marília, and Bauru, connecting MS and the State of São Paulo capital) in HVL expansion in the State of São Paulo[12].

The radial highways of the São José do Rio Preto region represent important links between this region and the state capital; between its micro-regions, particularly its capital municipalities; and with disease-endemic areas, such as MS (via the Euclides da Cunha highway) and the Araçatuba region, SP (via the

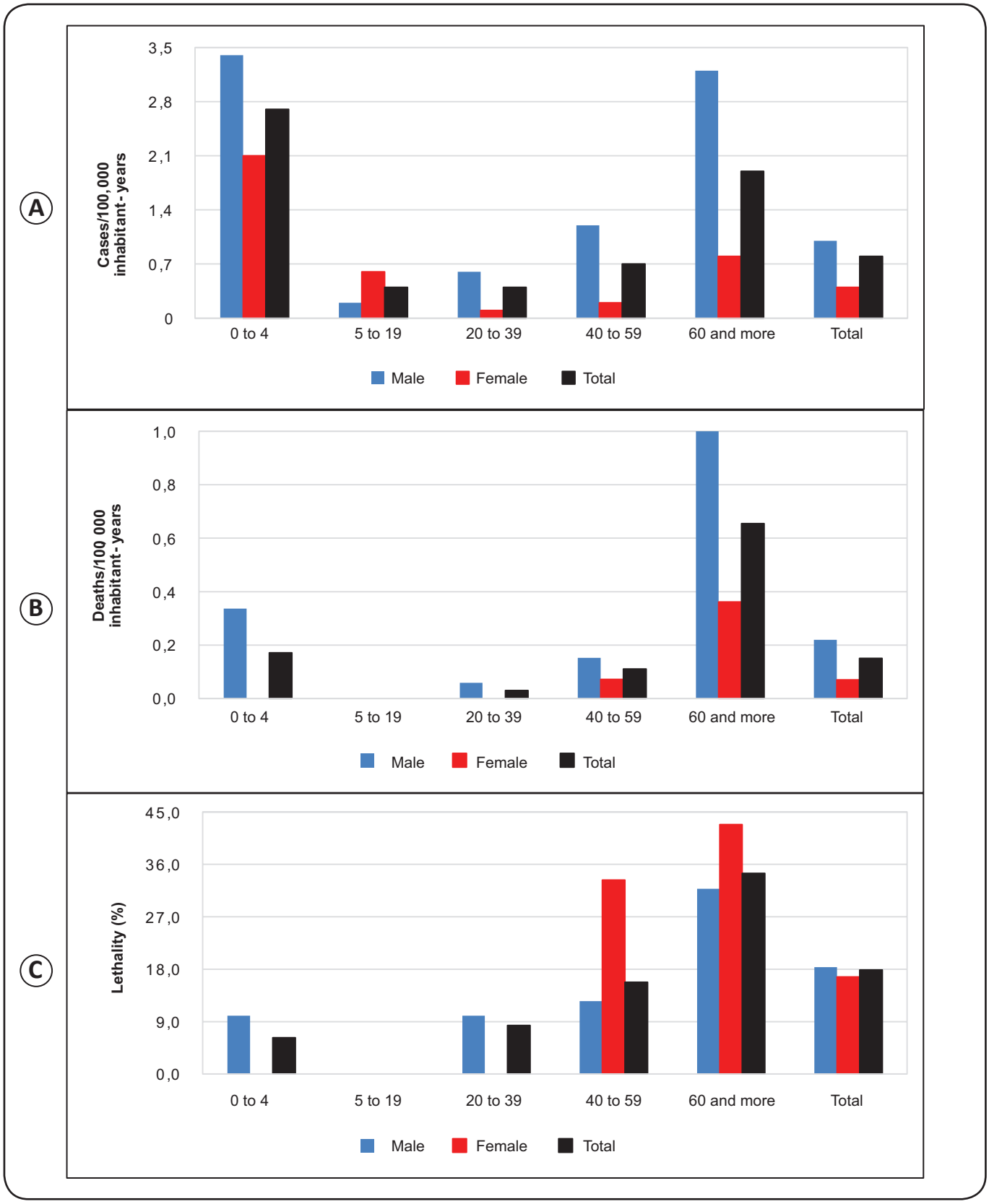

FIGURE 4 - Incidence (A) and mortality rates (B) and lethality (C) according to gender and age, São José do Rio Preto region, State of São Paulo, Brazil, 2007 to 2013.

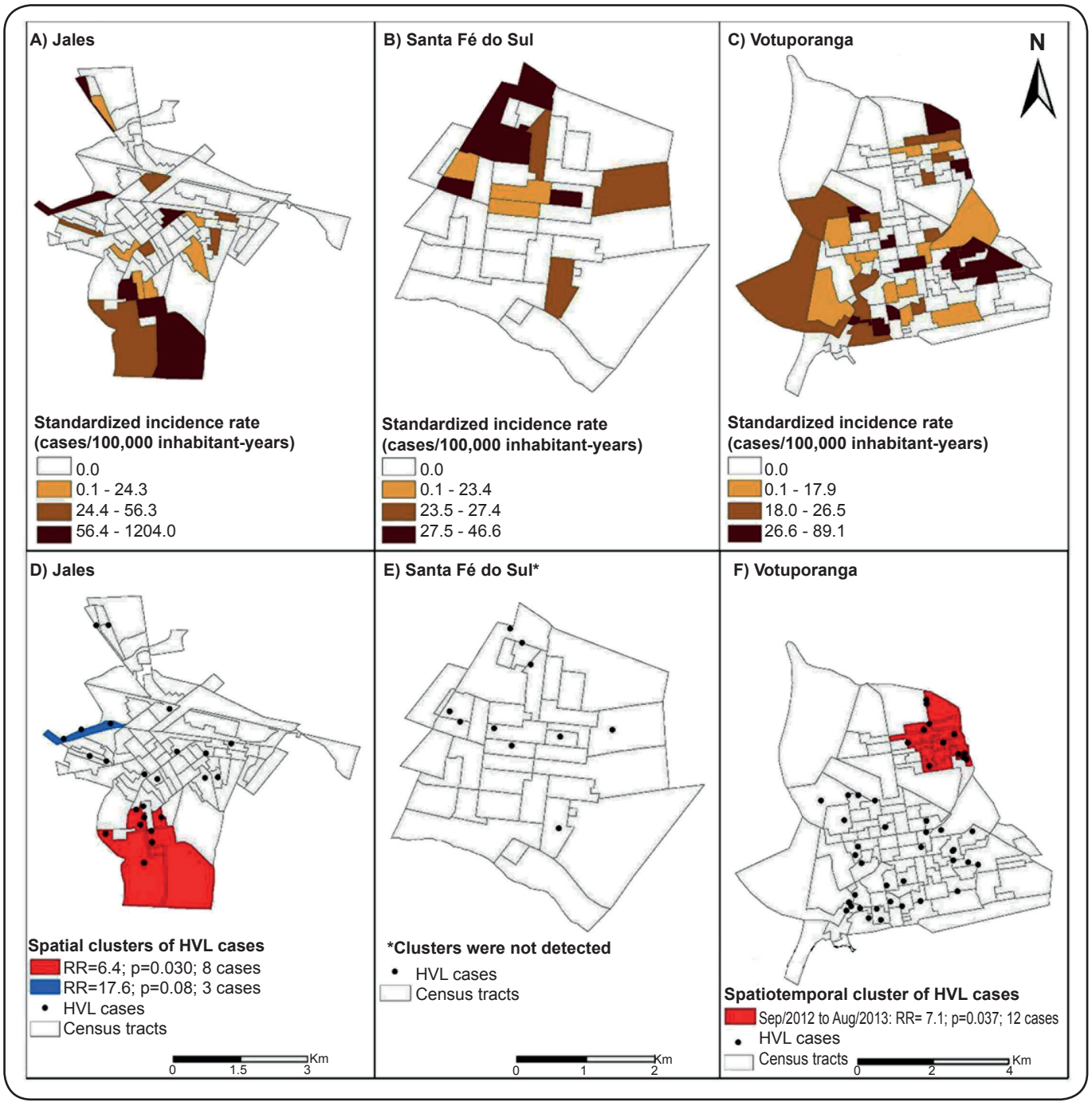

FIGURE 5 - Human visceral leishmaniasis incidence rates according to census tracts for Jales (A), Santa Fé do Sul (B), and Votuporanga (C); HVL cases in Jales and spatial clusters (D); HVL cases in Santa Fé do Sul (E); HVL cases in Votuporanga and spatiotemporal clusters, São José do Rio Preto region, State of São Paulo, Brazil, 2007 to 2013 (F). HVL: human visceral leishmaniasis; **RR:** relative risk**.**

Feliciano Salles Cunha highway). Among the roles played by these highways in the expansion of the disease is the channeling of migratory flows from other states for the sugarcane harvest. At the beginning of the new millennium, Barata[20] noted that the increase in sugarcane cultivation areas in the state's western region could be a risk factor for the increased incidence of infectious diseases including leishmaniasis.

Moreover, these highways are also responsible for the large movement of people in the region and between its neighboring regions[12] [21] [22]. The fact that half of the municipalities with HVL are micro-region capitals relates to the role that these capitals play as poles of attraction and dispersion for the flow of people. This movement mainly occurs via the radial highways because they connect all micro-region capital municipalities.

Furthermore, the movement of people via these highways is also associated with the movement of their animals, resulting in the migration of dogs with CVL or those infected by the parasite. Again, this phenomenon highlights the role of the micro-region capitals, because more than one-third of municipalities with CVL are such capitals[21] [23] [24].

The aggregate spatial pattern of vector presence in the region may be related to the ways in which the vector can be passively dispersed, such as via transport over short and medium distances; through materials and products that can be infested with its eggs, larvae, and pupae (such as soil, grasses, organic fertilizers, and other gardening products, or in animal feces, particularly that of chickens, by their transportation, among other possibilities)[7]; or by adults, which can be transported in cars or trucks (during the movement of household items, for example)[25]. This transportation, given the degree of contiguity and neighborhood found, could occur via both radial and transverse highways.

The strong relationship between vector occurrence and presence within the municipalities' local neighborhood and the association of CVL and HVL expansion with major highways and micro-region capitals could be used to identify priority municipalities for the early adoption of surveillance and control measures, with the aim of mitigating or delaying the occurrence of the problem. Marzochi & Marzochi[25] noted that municipalities close to major highways deserve more attention from health authorities.

In the cities considered most at risk, education and environmental management activities should be developed; professionals in veterinary clinics should be prepared to deal properly with CVL; and there should be investments in the care, diagnosis, and treatment infrastructure so that HVL can be diagnosed early and appropriate treatment can be given to prevent deaths[26] [27].

Votuporanga, which is the capital of the micro-region of the same name and is traversed by the Euclides da Cunha highway, is an example of a priority municipality where the development of surveillance and control actions could have minimized the occurrence of cases and, more importantly, deaths. Examples of municipalities in a similar situation to Votuporanga, but still without autochthonous HVL occurrence, include Fernandópolis, São José do Rio Preto, and Catanduva, which are also micro-region capitals traversed by one of the region's radial highways. These municipalities should be prioritized to avoid the fatalities that occurred in Votuporanga.

Contrary to what occurred in other State of São Paulo regions[11] [12] [28], in the Jales region, HVL was detected before vector presence or CVL occurrence. Similar situations occurred in General Salgado, Urânia, and Santa Albertina. For operational reasons, vector surveillance activity may not always occur throughout the year, which is a possible explanation for canine and/or human cases being detected prior to the confirmation of vector presence[29].

Moreover, vector detection after the detection of human and/or canine cases can also be related to the type of trap used to catch sandflies (luminous CDC), which may have reduced capturing efficiency in urban areas that are generally very bright (due to the competition with artificial lighting), particularly in low-vector-density situations. In addition, other possibilities can be considered, such as the involvement of other sandfly species in the VL transmission cycle such as *Nyssomyia whitmani* and *Migonemyia migonei* (EAB Galati: personal communication), which are present in the study area[30] [31].

Luz et al.[26] and Barbosa et al.[27] identified difficulties faced by health professionals in detecting and treating people with HVL, particularly when there are no confirmed cases and in locations where the vector's presence and/or canine cases have not been confirmed, which may have an effect on the disease's expansion speed and interfere with incidence, mortality, and lethality. The high lethality rates among HVL cases in the region, particularly among the elderly, may be explained by this scenario, because the observed values for this group were much higher than the national average (approximately 7%)[32].

The finding of the present study that there was a higher incidence in males, children under five years of age, and adults aged 60 or older corroborated those performed in other regions of the state and country. This result may be related to the incomplete development of the immune system in the children the comorbidity of HVL with chronic diseases, and the decline of the immune system in the elderly[33] [34] [35] [36]. The higher incidence in males is consistent with the literature[33] [34] [36] [37]. The mortality rate was also higher in males and those aged 60 and older, which may also be related to immune factors and complications from pre-existing conditions.

Along with their critical role in the characterization of the expansion process and disease dissemination across the region, the use of GIS and spatial analysis enabled the identification of spatial clusters on the outskirts of the Cities of Jales and Votuporanga and the identification of major incidents on the outskirts of Santa Fé do Sul. The peripheral areas of cities lack adequate infrastructure (absent or inadequate basic sanitation, unpaved streets, etc.). These areas are also typified by the presence of chicken coops next to homes, abundant trees, concentrations of animals in and around the home and overcrowding under conditions of inequality, all of which favor the expansion of the vector and the disease[13] [22] [34] [38] [39] [40] [41] [42]. This finding may prove useful in improving control and surveillance measures, because the prioritized development of these activities in the city's periphery could render VL control programs more effective.

The main limitation of the present study is the use of information from epidemiological surveillance to characterize the occurrence of HVL, CVL, and vector presence due to possible underreporting of canine and human cases and a delay in vector detection.

Despite this limitation, it was possible to draw the following conclusions: the expansion of the disease occurred westward to eastward; *L. longipalpis* dispersion in the municipalities of the region most frequently occurred by contiguity and was more aggregated than the occurrence of CVL and HVL; these disease in turn, were more related to radial highways and the micro-region capital municipalities; the incidence rates showed an

upward trend and were higher for men and for the 0- to 4-year-old age group; mortality and lethality were higher for people aged 60 and older; and among the municipalities, HVL had a higher incidence and case clustering in peripheral urban areas. These findings may be useful for improving the surveillance and control of VL in the study area as well as in similar regions of the State of São Paulo and Brazil.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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