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Dispersal of *Lutzomyia longipalpis* and expansion of canine and human visceral leishmaniasis in São Paulo State, Brazil

Agda Maria Oliveira[a], Carolina Portugal Vieira[b], Margareth Regina Dibo[c], Marluci Monteiro Guirado[d], Lilian Aparecida Colebrusco Rodas[e], Francisco Chiaravalloti-Neto[a,*]

[a] *Departamento de Epidemiologia, Faculdade de Saúde Pública, Universidade de São Paulo, Av. Dr. Arnaldo, 715, 01246-904 São Paulo, SP, Brazil*
[b] *Curso de Graduação em Enfermagem, Faculdade de Enfermagem da Universidade de São Paulo, Av. Dr. Enéas de Carvalho Aguiar, 419, 05403-000 São Paulo, SP, Brazil*
[c] *Laboratório de Bioquímica e Biologia Molecular, Superintendência de Controle de Endemias, Rua Cardeal Arcoverde, 2878, 05408-003 São Paulo, SP, Brazil*
[d] *Laboratório de Vetores de São José do Rio Preto, Superintendência de Controle de Endemias, Av. Brigadeiro Faria Lima, 5416, 15090-000 São José do Rio Preto, SP, Brazil*
[e] *Serviço Regional 9, Superintendência de Controle de Endemias, Rua Minas Gerais, 135, 15015-160 Araçatuba, SP, Brazil*

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ABSTRACT

Visceral leishmaniasis (VL), a neglected disease, is a serious public health problem that affects millions of people worldwide. The objectives of the study were to evaluate the sensitivity of *Lutzomyia longipalpis* and canine VL (CVL) autochthony early detection and describe the spatial and temporal dispersal of vector and expansion of VL in a Brazilian state. We obtained data on the leishmaniasis vector and VL cases in São Paulo State (SP), Brazil, from the Division of Endemic Disease Control and from the Epidemiological Surveillance Center of the São Paulo State Department of Health. Data were analyzed for 645 municipalities and 63 microregions and presented as thematic and flow maps. Following the verified presence of *L. longipalpis* in Araçatuba in 1997, the first autochthonous cases of canine VL (CVL) (1998) and of human VL (HVL) (1999) in São Paulo were reported, both in Araçatuba. From 1997 to 2014, the urban presence of the leishmaniasis vector was verified in 167 (25.9%) municipalities with cases of CVL reported in 108 (16.7%) and cases of HVL in 84 (13%). The sensitivities for vector presence early detection in relation to the identification of CVL and HVL autochthony were, respectively, equal to 76.4 and 92.5%. The sensitivity for CVL autochthony early detection in relation to the HVL autochthony identification was 75.8%. Vector dispersal and expansion of CVL and HVL were from the northwest to the southeast of the state, primarily flanking the Marechal Rondon highway at a constant rate of progression of 10, seven, and six new municipalities affected per year, respectively. We concluded that the sensitivity for vector presence and CVL autochthony presented reasonable accuracy and most of the time the vector presence and, specially, the CVL and HVL autochthony were identified in the main cities of the microregions of SP. Vector dispersal and expansion of VL started in 1997 near the state border of SP with the state of Mato Grosso do Sul. It has advanced from the northwest to the southeast flanking the Marechal Rondon highway at an arithmetic progression rate outward from the main cities of the microregions. Autochthonous cases of CVL and HVL emerged in SP, in general, after the verified presence of *L. longipalpis*.

1. Introduction

Visceral leishmaniasis (VL) is a globally transmitted parasitic disease that mainly occurs in tropical and subtropical regions (Romero and Boelaert, 2010). It is a zoonotic infection caused in the Americas by the protozoan *Leishmania (Leishmania) infantum chagasi* (Cunha & Chagas) which is transmitted by the bite of infected female sand flies of the genus *Lutzomyia.* In Brazil, *Lutzomyia longipalpis* (Lutz & Neiva) is the main vector of VL and the domestic dog is

* Corresponding author.
E-mail addresses: agdaracz@usp.br (A.M. Oliveira), carolina.portugal.vieria@usp.br (C.P. Vieira), mrdibo@yahoo.com.br (M.R. Dibo), mmguirado@gmail.com (M.M. Guirado), colerodas@gmail.com (L.A.C. Rodas), franciscochiara@usp.br (F. Chiaravalloti-Neto).

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the primary reservoir host for this protozoan (Shaw, 2006; Romero and Boelaert, 2010).

The vector was originally present in Brazil in rural areas; however, since the 1980s, it has also been present in urban environments, especially in city outskirts. This is occurring mainly determined by the introduction and adaptation of the vector to the urban environment (Arias et al., 1996; Romero and Boelaert, 2010; Harhay et al., 2011; Vilela et al., 2011; Madalosso et al., 2012; Brazil, 2013). Besides vector adaptation to urban environments, the expansion of VL has been associated with the presence of dogs in urban settings; human-mediated migration of infected domestic dogs; poverty and poor sanitation; ecosystem destruction and modification of natural environments for the construction of roads and other civil engineering projects; and difficulty controlling the sand fly (Antonialli et al., 2007; Maia-Elkhoury et al., 2008; Rangel and Vilela, 2008; Romero and Boelaert, 2010; Almeida et al., 2011; Carreira et al., 2012; Araujo et al., 2013; Cardim et al., 2013; Salomón et al., 2015).

Currently, VL is a major public health problem in Brazil. Of 45,490 cases of human visceral leishmaniasis (HVL) reported in the Americas between 2001 and 2013, Brazil accounted for 96.6% of them (PAHO, 2015). VL in humans or dogs has been reported in 26 Brazilian states with 19 reporting autochthonous HVL cases (Nascimento et al., 2013; PAHO, 2015; Madalosso et al., 2012; Karagiannis-Voules et al., 2013; Druzian et al., 2015; Salomón et al., 2015). In the São Paulo State (SP), the geographical presence of *L. longipalpis* has expanded with an increasing number of municipalities reporting canine transmission. As a result, every year new municipalities, that were previously silent for the LV occurrence, confirm autochthonous cases of HVL (CVE, 2014; Cardim et al., 2013; Casanova et al., 2015).

Further studies are thus necessary to better understand the epidemiology of VL and trace its expansion through SP in order to establish potential factors associated with disease spread and improve surveillance and control actions (Salomón et al., 2015). In this study, we, first, investigated the sensitivity of the SP entomological and epidemiological surveillance system for *L. longipalpis* early detection in relation to the identification of the CVL and HVL autochthony and for CVL autochthony early detection in relation to the identification of HVL autochthony. After that, we described space and time dispersal of *L. longipalpis* and expansion of canine and human VL in SP from 1997 to 2014.

2. Materials and methods

Descriptive studies were conducted in a region encompassing the 645 municipalities of SP with a population of 44,749,699 people (in 2016). These municipalities are divided into 63 microregions, and grouped into 15 mesoregions (Fig. 1).

From 1970 to 1995, the presence of *L. longipalpis* was verified in six municipalities (Salto de Pirapora, Pirapora do Bom Jesus, Cássia dos Coqueiros, Espírito Santo do Pinhal, Itupeva and Socorro) (Fig. 1B) in rural areas in the eastern part of SP (Forattini et al., 1970, 1976; Gomes et al., 1995). The urban presence of *L. longipalpis* was first verified in the western part of SP in the city of Araçatuba in 1997 (Fig. 1B) (Costa et al., 1997). Hence, our study covered the period between 1997 and 2014.

One of the objectives of the Brazilian LV surveillance is *L. longipalpis* early detection in the Brazilian municipalities (MS, 2014) and, the State Health Departments are responsible for this activity. In SP, it is developed by the Division of Endemic Disease Control (Superintendência de Controle de Endemias—SUCEN) of the São Paulo State Department of Health in the municipalities without confirmation of vector presence, but considered vulnerable (close to municipalities with LV occurrence or having transport or migratory flows with them). CDC light traps are installed in representative samples of properties of these municipalities in the most vector favorable period (October to May), at least once a year (SES, 2006).

Another objective of the LV surveillance is the CVL and HVL autochthony early detection (MS, 2014). In SP, the CVL autochthony early detection is carried out with the collaboration and participation of the veterinary establishment network. The technical officers of these establishments notify the LV suspected dogs for the municipal surveillance services, which provides the exams needed to confirm the disease. These results are send to SUCEN and the Epidemiological Surveillance Center (Centro de Vigilância Epidemiológica Alexandre Vranjac—CVE) of the São Paulo State Department of Health (SES, 2006). In relation to the HVL, the municipalities notify the suspected and confirmed cases and this information is referred to CVE.

We obtained information on *L. longipalpis* (confirmed presence of the vector and month and year) and status of CVL (confirmed report and month and year of first autochthonous transmission of CVL) from SUCEN. Information about the autochthonous HVL cases (symptom onset date and municipality of residence and infection) where obtained from CVE.

We also obtained information regarding geographic and road maps of the municipalities of SP from the Brazilian Institute of Geography and Statistics (IBGE). Roads in SP are categorized into radial roads (main roads connecting municipalities to the state capital) and transversal roads (minor arterial roads including local roads connecting municipalities).

We laid out a spreadsheet including information on month and year of verified vector presence, month and year of first report of autochthonous CVL and month and year of first report of autochthonous HVL by municipality. In the case of the municipalities that did not have the information about the month for one or more of these occurrences, we attributed to them the month of June (middle of the year).

We calculated two sensitivity values related to the entomological surveillance (the sensitivities for *L. longipalpis* early detection in relation to the identification of autochthony for CVL (S1) and HVL (S2)) and one value related to the epidemiological surveillance (the sensitivity for the CVL autochthony early detection in relation to the autochthony for HVL (S3)).

We considered the numbers of municipalities that early detected the vector presence before the first identification of autochthony for CVL and for HVL as true positives, respectively, for the calculation of S1 and S2. The numbers of municipalities with the vector presence and/or autochthony for CVL and with the vector presence and/or autochthony for HVL were considered, respectively, the gold standards.

We considered, for the calculation of S3, the number of municipalities with autochthony for CVL and/or HVL as the gold standard and the municipalities that early detected the autochthony for CVL before the first identification of autochthony for HVL as true positives.

We produced descriptive statistics for the time periods between the vector detection and the identification of autochthony for CVL, the vector detection and the identification of autochthony for HVL and the identification of the autochthony for CVL and HVL. For this, we only considered the situation where the early detections occurred.

Using a microregion as a unit of analysis, we laid out spreadsheets including information on the year of verified vector presence, year of first report of autochthonous HVL and CVL in the areas studied, and municipalities where these events occurred. Considering only the municipalities with urban vector presence (1997 onwards), we calculated, for each microregion, the proportion of times in which the vector presence was first verified in the main city of the microregion, regardless of whether this was with

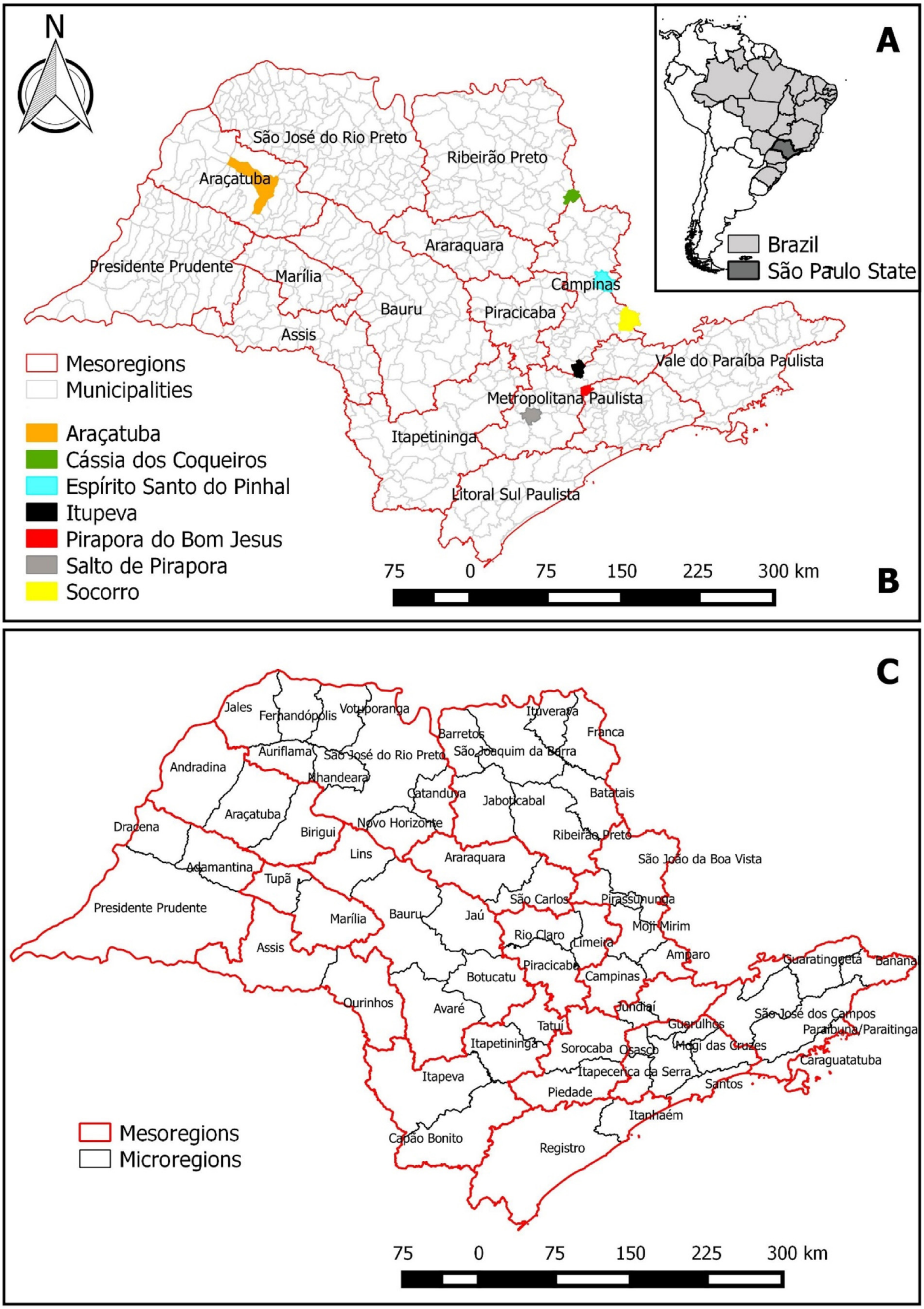

Fig. 1. Geographical location of São Paulo State, Brazil, South America (A); Mesoregions and municipalities with verified *Lutzomyia longipalpis* presence from 1970 to 1997 (B); Microregions and mesoregions of São Paulo State (C).

other concomitant municipalities of the same micoregion. Considering the municipalities with CVL and HLV and using the same calculation presented above, we obtained the proportions of times in which the identification CVL and HVL autochthony were first verified in the main cities of the macroregions.

Following this, for every microregion, we obtained the year of first verified vector presence and the year of first report of autochthonous HVL and CVL. We drew flow maps showing temporal and spatial vector dispersal and expansion of VL. To elaborate them, we made the following assumptions: the vector dispersion and CVL and HVL expansion began in the Araçatuba microregion (precisely, in its main city); the most likely place of "departure" and "arrival" for the vector, CVL and HVL would be the main cities of the microregions; the vector dispersion and the LV expansion would occur in a temporal sequence and by the shortest path between the main cities of the microregions. The flux maps allowed us to trace VL dispersal/expansion and to establish potential associated factors. We also calculated the rate of movement of the vector, HVL, and CVL (in kilometers per year).

To assess the rate at which the vector and VL have been expanding through SP, we built charts plotting the cumulative number of municipalities with verified vector presence and autochthonous CVL and HVL cases per year from 1997 to 2014. We used regression techniques to model the curves obtained.

The study was approved by the research ethics committee at Universidade de São Paulo School of Public Health and Plataforma Brasil (certificate of ethical approval: 14107313.3.3333.5421, protocol number: 257,511; date of approval: 04/26/2013).

3. Results

After the verified urban presence of *L. longipalpis* in Araçatuba—the main city of the mesoregion and microregion of Araçatuba—in 1997 (Fig. 1B), the vector has spread into other municipalities within the same area and into other parts of SP. From 1997 to 2014, the urban presence of *L. longipalpis* was verified in 167 (25.9%) of all 645 municipalities in SP. Following the verified presence of the vector in Araçatuba in 1997, the first autochthonous cases of CVL and HVL were reported in 1998 and 1999, respectively, in this city. CVL and HVL expansion occurred following vector dispersal into the municipalities. From 1998 to 2014, there were reported autochthonous CVL cases in 108 (16.7%) municipalities with no verified vector presence in seven of them.

From 1999 to 2014, there were reported autochthonous HVL cases in 84 (13.0%) municipalities. There was verified vector presence but not proven CVL cases in nine and no evidence of vector presence and autochthonous CVL in five. In this period, there were 2539 confirmed autochthonous cases of HVL in SP and 218 deaths caused by HVL.

Table 1 presents the results of the sensitivity analysis for *L. longipalpis* early detection in relation to the identification of autochthony for CVL and for HVL and for the CVL autochthony early detection in relation to the identification the autochthony for HVL in the municipalities of SP. These sensitivities were greater than or equal to 75.8%. Less than 4.0% of the municipalities with the vector presence or with autochthonous HVL did not have information about the month (only the year) of the vector detection or autochthony identification.

Fifty-one (47.2%) of the 108 municipalities with autochthonous CVL did not have the information about the month (only the year) of the identification of the autochthony. However, only in 15 opportunities the vector detection and the canine autochthony occurred in identical years. The same occurred for the identification of CVL and HVL autochthony in 18 opportunities.

Table 2 presents information about the time period between the vector detection and the identification of autochthony for CVL and for HVL and between the identification of autochthony for CVL and for HVL only for those situations where the early detection occurred. The average time periods between the vector early detection in relation to the identification of autochthony for CVL and HVL were, respectively, 2 years and 2 months and 3 years. The average time period between the CVL autochthony early detection in relation to HVL was 2 years.

Regarding vector dispersal, its presence was verified in 25 (39.7%) of the 63 microregions of SP (excluding those municipalities where the vector was present before 1997), totaling 29 (46.0%). When we considered only the municipalities with urban vector presence (1997 onwards), of the 25 microregions where the vector was verified, it was first verified in the main city of these microregions in 13 (52.0%) opportunities, regardless of whether this was with other concomitant municipalities.

By 2014, CVL was reported in 22 (34.9%) microregions, and the first autochthonous case was reported in the main city in 16 (72.7%) of them, whether with or without other concomitant municipalities. As for HVL, autochthonous cases were reported in 15 (23.8%) microregions, and the first case was reported in the main city in 11 (73.3%) of them, whether with or without other concomitant municipalities.

The main city of a microregion played a major role in vector dispersal and CVL and HVL expansion into urban areas of the municipalities in SP. For assessing the expansion of VL, verified vector presence and first autochthonous CVL and HVL cases were plotted for these main cities and flow maps were drawn. Figs. 2, 3A and B show vector dispersal and CVL and HVL expansion in SP. It is evident that high vector dispersal into the municipalities was followed by moderate expansion of CVL and low expansion of HCL.

Major hubs of vector progression were at the center cities of the microregions of Araçatuba, Lins and Rio Claro, with vector infestations verified in 1997, 1999, and 2005, respectively. The first hub was likely the starting point for vector dispersal into four microregions (Andradina, Auriflama, Birigui and Adamantina), the second one for three (Bauru, Novo Horizonte and Marilia) and the third one also for three (São Carlos, Piracicaba and Campinas) (Fig. 2). For both CVL and HVL, a major hub was in the microregion of Araçatuba (for three microregions for CVL and four for HVL). It should be stressed that this microregion was pivotal for both vector dispersal and expansion of VL in SP (Fig. 3A and B).

The flow maps (Fig. 3A and B) show that major radial roads are linked to CVL and HVL expansion, and the Marechal Rondon highway has been a major axis for northwest to southeast expansion of VL. However, despite a clear association between vector dispersal and this main highway and other radial roads, the entire road network of SP including both radial and transversal roads seemed determinant for vector dispersal.

The number of new municipalities affected with vector presence, CVL and HVL grew arithmetically every year (Fig. 4A), i.e., the growth rate was constant over time. As for vector dispersal, nearly 10 new municipalities were affected per year; seven were affected with CVL and six with HVL. This finding is consistent with the rates of expansion into the municipalities of SP: higher for the vector presence, intermediate for CVL and lower for HVL. Fig. 4B shows that the rate of movement in kilometers per year for vector dispersal, CVL and HVL among the microregions decreased throughout the study period with peaks in 1998–1999, 2003–2004, and 2009. The constant rate of movement of the three phenomena is consistent with a decreasing number of kilometers traveled per year. The increase in the number of municipalities affected was offset by a decrease in the rate of movement while maintaining a linear trend.

Table 1
Results of the sensitivity analysis for *L. longipalpis* early detection in relation to the identification of the autochthony for CVL and for HVL and for the CVL autochthony early detection in relation to the identification of autochthony for HVL, municipalities of São Paulo State, Brazil, 1997–2014.

Considered scenarios	Vector early detection in relation to CVL (S1)	Vector early detection in relation to HVL (S2)	CVL early detection in relation to HVL (S3)
Gold-standard	Vector and/or CLV presence	Vector and/or HVL presence	CVL and/or HVL presence
True positive values	133[a]	160[b]	91[c]
Total	174	173	120
Sensitivity (%)	76.4	92.5	75.8

[a] Municipalities, among those with the vector and/or CVL presence, where the vector early detection occurred.
[b] Municipalities, among those with the vector and/or HVL presence, where the vector early detection occurred.
[c] Municipalities, among those with CVL and/or HVL presence, where the HVL autochthony early detection occurred.

Table 2
Descriptive statistics for the time periods between the vector early detection and the CVL autochthony identification (Vector/CVL), the vector early detection and the HVL autochthony identification (Vector/HVL) and the CVL autochthony early detection and the HVL autochthony identification (CVL/HVL), municipalities of São Paulo State, Brazil, 1997–2014.

Considered scenarios	Vector/CVL	Vector/HVL	CVL/HVL
Number of considered situations	101 municipalities with vector and CVL presence	80 municipalities with vector and HVL presence	71 municipalities with CVL and HVL presence
Number of times that early detection occurred	67[a] (63.3%)	71[b] (88.8%)	54[c] (76.1%)
Descriptive statistics for the time periods where the early detection occurred			
Average	2 years and 2 months	3 years	2 years
Minimum	1 month	1 month	1 month
1° quartile	6 months	1 years and 9 months	6 months
Median	2 years and 6 months	2 years and 4 months	1 years and 5 months
3° quartile	2 years and 10 months	4 years and 4 months	2 years and 6 months
Maximum	7 years and 6 months	11 years and 4 months	12 anos

[a] Number of municipalities with vector and autochthonous CVL presence, where occurred vector early detection.
[b] Number of municipalities with vector and autochthonous HVL presence, where occurred vector early detection.
[c] Number of municipalities with autochthonous CVL and HVL presebce, where occurred CVL autochthony early detection.

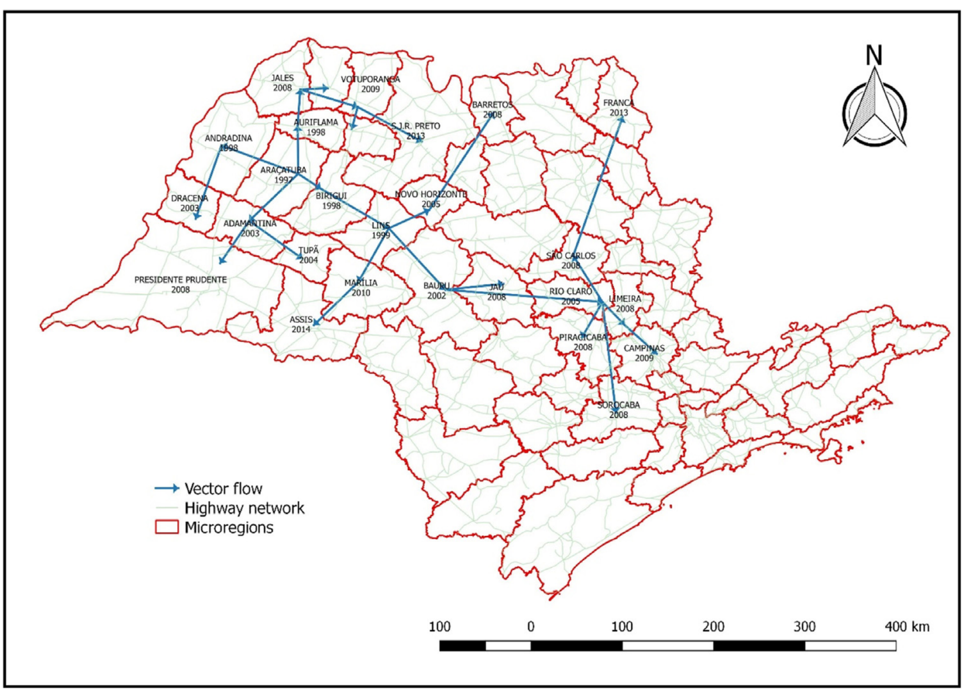

Fig. 2. Map showing *Lutzomyia longipalpis* dispersal by main cities of microregions of São Paulo State, Brazil, 1997–2014.

4. Discussion

One point that deserves a mention regarding the occurrence of autochthonous HVL cases prior to those reported in Araçatuba is that, to our knowledge, there were only two reports. In 1978, three autochthonous cases were reported in the metropolitan mesoregion of São Paulo, but the presence of *L. longipalpis* was not verified in catches of sand flies. Later, an autochthonous case was reported in a child living in the city of São Paulo but, as vector presence could not be verified, the possibility of transmission by blood transfusion was raised (Iversson et al., 1979, 1982). Therefore, it can be assumed that VL has been introduced in the state of São Paulo from the city of Araçatuba.

Among potential factors associated with VL introduction is the interstate border of SP with Mato Grosso do Sul (MS). Studies in MS from Antonialli et al. (2007) showed that, from 1913 to 1998,

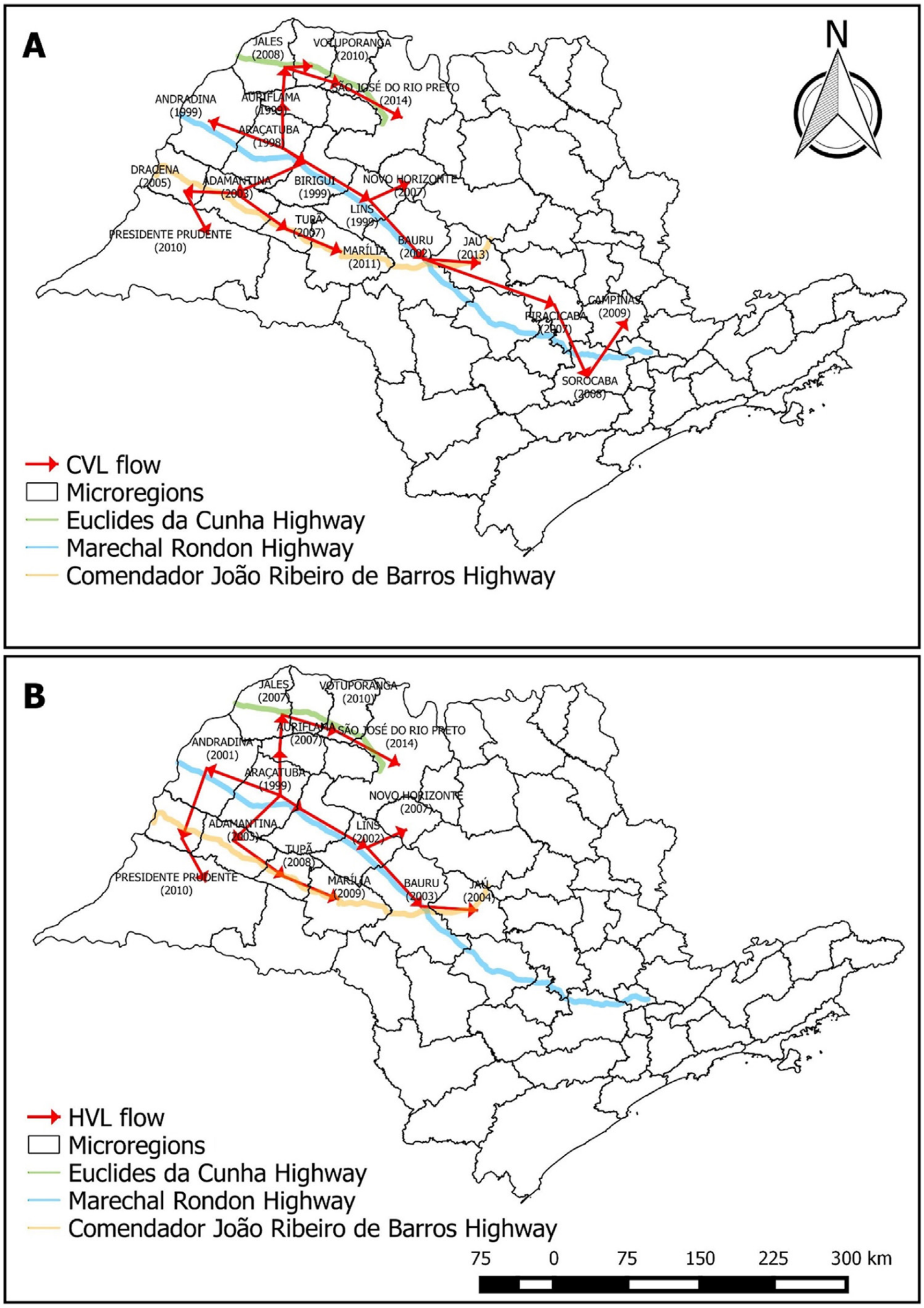

Fig. 3. Maps showing the expansion of canine (A) and human visceral leishmaniasis (B) by main cities of microregions of São Paulo State, Brazil, 1998–2014.

VL solely occurred within the cities of Corumbá and Ladário, at the border with Bolivia. The geographic expansion of VL began in 1998 reaching the state capital Campo Grande in the same year and Três Lagoas at the border of the Araçatuba mesoregion in the next year. Araçatuba is a bordering mesoregion, and the federal highway BR 262 connecting Três Lagoas to Corumbá in MS is an extension of the Marechal Rondon highway in SP, where BR 262 connects Andradina to Castilho, a neighboring municipality to Três Lagoas.

According to Antonialli et al. (2007), potential factors for the expansion of VL in MS mentioned include the construction of BR 262 and, most importantly, the construction of the Bolivia–Brazil natural gas pipeline that runs parallel to this federal highway. Expansion of VL in MS coincided with the gas pipeline construction from 1997 to 1999 and is considered a contributing factor for VL spread in SP because vector presence and autochthonous HVL and CVL were verified in Araçatuba during this same period (Cardim et al., 2013; Motoie et al., 2013).

Several authors have been discussed the issue about the VL arrival in SP. They have, in general, supported the hypothesis that this introduction occurred from MS (Galimberti et al., 1999; Cardim et al., 2013, 2016; Casanova et al., 2006, 2015; Oliveira et al., 2016). This hypothesis is reinforced by the results achieved by Casanova et al. (2006) and Bray et al. (2009). They showed that vector population in Araçatuba and MS share the (*S*)-9-methylgermacrene-B sex pheromone.

Another contributing factor for VL introduction in SP is human migration and human-mediated migration of animals. Barata (2000) stressed the impact of replacing cattle rearing with sugar

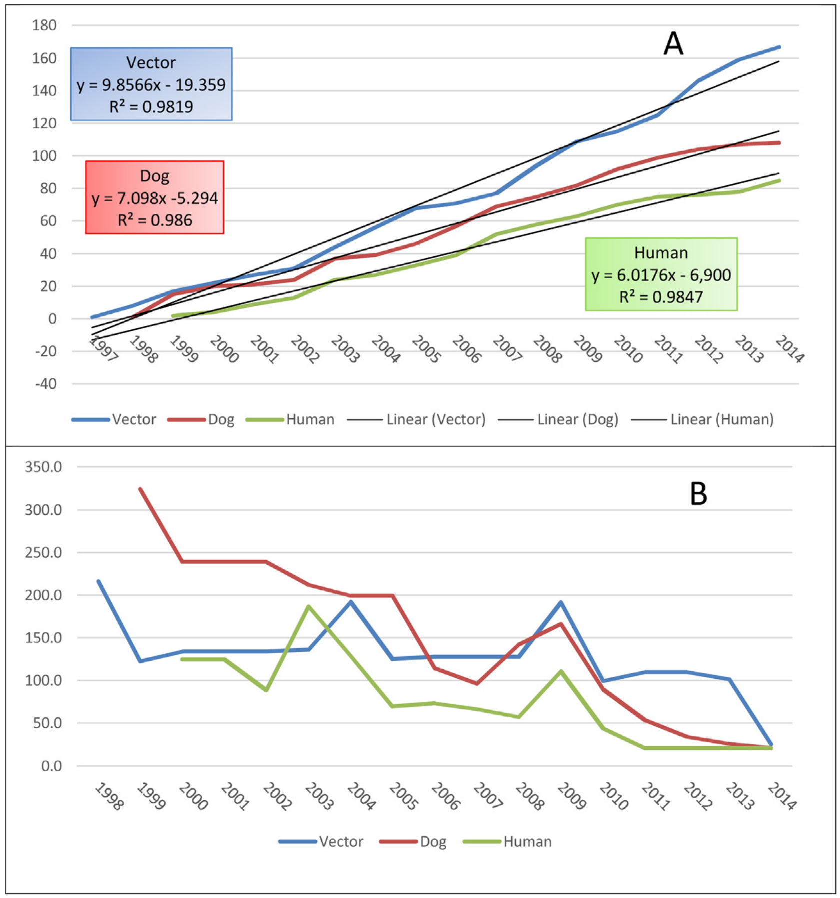

Fig. 4. Number of municipalities affected yearly by VL vector, CVL and HVL and related trend lines and regression equations (A); distances (km/year) traveled by VL vector, CVL and HVL by main cities of microregions (B), São Paulo State, Brazil, 1997–2014.

cane plantations (during the 1990s and 2010s in the western areas of SP) on the expansion of VL due to extensive use of migrant labor. The construction of the natural gas pipeline that crosses 135 municipalities in the Brazilian territory also saw a huge inflow of over 10,000 migrant workers coming from several different states in Brazil and neighboring countries such as Bolivia, a country where VL is endemic (Antonialli et al., 2007).

Following VL introduction into SP, both human migration and the construction of the natural gas pipeline—that runs parallel to the Marechal Rondon highway in the mesoregions Araçatuba and Bauru—can also explain the expansion of VL from Araçatuba to neighboring municipalities and areas. The gas pipeline construction in SP was from 1997 to 1999, when several municipalities of Araçatuba and Bauru mesoregions reported vector presence and autochthonous CVL and HVL (Cardim et al., 2013).

Other contributing factors include movement of people and goods on roadways; displacement of animals infected with VL to prevent them from being euthanized; poor sanitation, especially in the outskirts of cities; and ineffective or partially effective vector and disease control measures (Thomaz-Soccol et al., 2009; Barreto et al., 2011; Scandar et al., 2011; Cardim et al., 2013; Salomón et al., 2015). Hence, favorable conditions remain for expansion of VL in SP.

Although there were earlier reports of *L. longipalpis* presence in the eastern part of SP before the vector detection in Araçatuba, the VL began to occur in this city. Furthermore, the LV spread followed the vector dispersion in the western part of the state.

For Casanova et al. (2015), the association of early *L. longipalpis* presence in western SP with the expansion of VL pointed to the existence of two different vector populations in SP: the vector population found in eastern SP with the isolation of *L. longipalpis* sex pheromone cembrene-1; and the population found in western SP with the isolation of sex pheromone (*S*)-9-methylgermacrene-B. These authors also described pheromone-specific sexual behaviors with different epidemiological patterns of VL in SP municipalities.

Casanova et al. (2015) also proposed that the (*S*)-9-methylgermacrene-B population of *L. longipalpis* has a greater vectorial capacity than the cembrene-1 population and thus can be linked to the expansion of VL in SP. This finding is corroborated by that of earlier studies by Casanova et al. (2006) and Bray et al. (2009) that isolated (*S*)-9-methylgermacrene-B sex pheromone from vector populations in both Araçatuba and MS.

The sensitivity of the early detections of the vector presence and of the identification of the CVL autochthony presented a reasonable accuracy. These results together with the fact that HVL being a compulsory reporting disease, also with a reasonable accuracy, show that the information about the vector presence and CVL and HVL autochthony identification could be used to track the VL spread in SP. Furthermore, the fact that most of the times the vector presence and, specially, the CVL and HVL autochthony were identified in the main cities of the microregions allowed us to simplify the use of the flow map technique, clarifying the spread of VL in SP.

Casanova et al. (2015), using the same data used in the present study, presented three maps with the spread of the vector, CVL and HVL were is also possible to see that, in a great amount of the situations, there was the vector early detection in relation to the identification of the CVL and HVL autochthony and there was CVL autochthony early detection in relation to the identification of HVL autochthony.

This study found vector dispersal and expansion of VL to be associated with the SP road network. Movements of people, animals, goods, and even vectors in Brazil are largely via roads, which may explain the emergence of human and canine leishmaniasis cases and vector presence in settings with no prior VL records (Mestre and Fontes, 2007; Ximenes et al., 2007). However, the state road network played a key role for vector dispersal in SP. A study on VL spread in the region of São José do Rio Preto (SP) have showed that vector spread between neighboring municipalities via both radial and transversal roads (Oliveira et al., 2016). This pattern may be due to passive vector dispersal, i.e., short- and medium-distance transport of goods infested by immature forms of the vector (Brazil, 2013) or adult vectors in vehicles (Marzochi and Marchozi, 1997). This form of dispersal takes place via both radial and transversal roads, in particular local roads connecting SP municipalities.

CVL and HVL expansion coincided with the route of three radial roads: Marechal Rondon, Euclides da Cunha and Commander João Ribeiro de Barros. The first one is the main route for expansion of VL as it runs parallel to the Bolivia–Brazil natural gas pipeline connecting to the BR 262 highway in MS. These roads are associated with expansion of VL in SP because they are the main routes for transporting people and goods from inner state areas and across the country.

The Marechal Rondon highway was duplicated between Araçatuba and Bauru from 1990 to 1999. Euclides da Cunha was also duplicated from the border of the mesoregion of São José do Rio Preto with MS to its main city (São José do Rio Preto) from 2010 to 2014. These two periods coincide with verified vector presence and VL cases in several municipalities in these mesoregions. Similar to the impact described by Antonialli et al. (2007) of the construction of the natural gas pipeline and BR 262 in MS, these works of construction may have contributed to vector dispersal and expansion of VL in SP due to an inflow of migrant workers from SP and neighboring states and their environmental impact (Salomón et al., 2015).

The role played by the main cities of microregions in SP is certainly noteworthy. The main city was the first area of vector colonization in over half of the time and the first area of autochthonous HVL and CVL cases in nearly three quarters of the time. Microregions are territorial divisions with a small number of municipalities with specific spatial characteristics such as structure of agricultural production, iron ore production, industry, and services (IBGE, 1990). These, in turn, are grouped into larger regions called mesoregions. The geographic space of a mesoregion is structured into three dimensions: the social process, the natural environment, and the communication network between settlements (IBGE, 1990).

This same pattern was described in a study by Cardim et al. (2015) in the microregion of Adamantina, SP. The main city has a large concentration of higher education institutions attracting people from neighboring mesoregions—which might explain the first autochthonous VL case from this microregion—potentially explaining the subsequent expansion of VL to other municipalities in this region.

Despite the predominance of vector distribution over CVL occurrence and the predominance of vector distribution and CVL over HVL occurrence found in this study as well as other studies (Costa et al., 2013; Casanova et al., 2015; Oliveira et al., 2016), there is a need to discuss why some municipalities showed autochthonous transmission of HVL but no CVL or HVL and CVL with no verified vector presence. It has been postulated that other animals such as fleas and ticks may act as vectors of *Leishmania* (Dantas-Torres, 2011; Paz et al., 2013) or even other phlebotomine species of flies may also be involved in the transmission of VL (Pita-Pereira et al., 2008; Carvalho et al., 2010; Guimarães et al., 2016).

Canine infection has been reported by vectorless sexual or vertical transmission (Silva et al., 2009; Naucke and Lorentz, 2012; Turchetti et al., 2014). Recent research in endemic areas have shown that feline species can be infected and develop symptoms of VL. It is suggested that this animal species can act as a secondary reservoir of *Leishmania*, but its role in the disease epidemiology is still uncertain (Coelho et al., 2010; Vides et al., 2011; Sobrinho et al., 2012).

One should bear in mind that, for operational reasons, vector surveillance is not carried out year round, which may likely explain canine and/or human cases before vector presence is verified (Costa, 2005; Silva et al., 2011). This finding may also be related to the type of vector capture trap used (e.g., CDC light trap). Some authors have questioned the use of light traps in well-lit urban settings because of competing light sources and incorrect trap installation by people without proper training (Pugedo et al., 2005; Hoel et al., 2010; Junnila et al., 2011; Salomón et al., 2015).

Let us discuss another questions related to the accuracy of the vector flow map. It took a long time to *L. longipalpis*, CVL and HVL to arrive in the microregion of Jales and one should ask if the spread of VL to this area occurred from the Minas Gerais State (MG) or from MS (Jales has borders both with MS and MG). By 2008, the closer MG and MS municipalities with HVL autochthony were more than 130 km from the Jales microregion and it is most likely that this spread occurred from the Auriflama microregions (distancing each other 40 km) (DATASUS, 2016).

By the hand we may suppose that it is most likely that the spread of VL to Barretos and Franca microregions (boths in the border with MG) came from MG than from Novo Horizonte and São Carlos microrregions. Out of these two situations, it is most likely that the spread of VL occurred in SP from the microregion of Araçatuba through other microrigions also SP (DATASUS, 2016).

Given the difficult control of VL, questionable effectiveness of current control measures (Romero and Boelaert, 2010; Barreto et al., 2011; Salomón et al., 2015), predominance of vector distribution over HVL (Costa et al., 2013; Casanova et al., 2015; Oliveira et al., 2016), and vector dispersal of greater magnitude than expansion of VL, it is hypothesized that new regions of SP will have autochthonous CVL and HVL cases. If vector dispersal continues, *L. longipalpis* populations producing two different terpenes (the one originally found in eastern parts and the one found in western parts) will overlap and VL will emerge in eastern SP.

The analyses of this study, particularly flow analysis, allowed for identifying factors associated with vector dispersal and expansion of VL in SP. The study results can help improve vector and disease surveillance activities. Because expansion of VL has followed vector dispersal first affecting the main cities of microregions, they are considered high-risk areas for VL. As for the vector, flow maps have provided input on *L. longipalpis* dispersal trends, which may be valuable in devising more effective and efficient strategies to verify the presence of vectors as early as possible (Fisher et al., 2011).

The main limitation of this study lies on the use of secondary data of verified vector presence and autochthonous CVL and HVL cases reported in SP municipalities. This limitation was in part overcome with the use of a spatial analysis tool for the representation of the phenomena studied here – flow analysis – though not yet widely used in public health (Oliveira et al., 2011; Grabois et al., 2013). The main cities of microregions were found to be key for vector dispersal and expansion of VL, and flow analysis allowed for accurately tracing the routes of vector dispersal and expansion and understanding the role of main radial roads.

The use of geographic information systems (GIS) and other spatial analysis tools also helped to overcome this limitation. They allowed for geocoding vector and VL information from SP municipalities and for examination by micro- and mesoregion. In agreement with this, several authors have supported the use of GIS and spatial analysis as valuable tools for the study of VL and associated factors (Araujo et al., 2013; Barbosa et al., 2014; Silva et al., 2011; Menezes et al., 2015).

5. Conclusions

The sensitivity analyses presented reasonable accuracy and showed that the information about the vector presence and the CVL and HVL autochthony identification could be used to track the VL spread in SP. The average time periods between the identification of these situations (vector presence/CVL autochtony, vector presence/HVL autochthony and CVL/HVL autochthony) were around two and three years. Most of the times the vector presence and, specially, the CVL and HVL autochthony were identified in the main cities of the microregions of SP.

L. longipalpis dispersal in SP began in 1997 near the inter-state border with MS, and then the vector dispersed from West to East into urban parts of municipalities. From 1997 to 2002, vector dispersal followed the route of a major radial road of SP – Marechal Rondon highway – and then spread across the state road network. *L. longipalpis* found in the eastern part of SP form 1970 to 1995 were different from those found in the western part of SP from 1997 because they were verified in rural and urban areas, respectively. Moreover, the latter have also been associated with autochthonous CVL and HVL and expansion of VL statewide.

CVL and HVL expansion in SP started in 1998 and 1999, respectively (Galimberti et al., 1999), near bordering areas with MS and then spread from west to east along the vector dispersal route. Unlike vector dispersal, VL spread throughout the flanking areas' major radial roads, especially the Marechal Rondon highway. Vector dispersal and expansion of VL in SP have progressed arithmetically, moving forward at a constant rate from the main cities of microregions.

Finally, we consider our presented conclusions as findings that be used by the responsible services for the surveillance and control of VL to improve the surveillance and control actions related to this Brazilian important public health problem.

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