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Fatores de risco ambientais e socioeconômicos associados com a leishmaniose

Environmental and socioeconomic risk factors associated with leishmaniasis

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Dedicatória

To Ana María Valero

for her endless support during all my life

Epígrafe

“Cada dia que amanhece assemelha-se a uma página em branco, na qual gravamos os nossos pensamentos, ações e atitudes. Na essência, cada dia é a preparação de nosso próprio amanhã”.

Chico Xavier Indicações Do Caminho.

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Índice

Resumo

A leishmaniose é uma doença negligenciada causada por protozoários do gênero *Leishmania*. Esta doença é endêmica em regiões tropicais, áridas e Mediterrâneas afetando mais de 350 milhões de pessoas no mundo. A leishmaniose tem duas formas clínicas principais: visceral (LV) e tegumentar (LT). Sem tratamento médico LV é letal e a LT pode produzir deficiências graves devido à destruição do tecido mucoso nasal-oral. O ciclo de transmissão da *Leishmania* depende do vetor flebotomíneo (Diptera: Psychodidae); do hospedeiro, que pode ser qualquer mamífero infectado com o parasita; e do reservatório, que pode transmitir o parasita ao vetor, os três devem interagir num meio ambiente permissivo para que aconteça a transmissão da doença. A leishmaniose é uma antiga zoonose cujo ciclo de transmissão restringia-se em paisagens não modificadas, no entanto o desenvolvimento de assentamentos humanos aumentou o contato entre humanos e o ciclo de transmissão. Atualmente, a incidência da doença não só depende das condições ambientais que afetam ao vetor e o reservatório, mas também dependem das condições socioeconômicas das populações humanas. Para entender melhor como estes fatores afetam a transmissão da leishmaniose, este estudo objetiva: 1) Identificar as condições ambientais e fatores socioeconômicos que influenciam a transmissão da LV e a LT, considerando todas as regiões endêmicas tropicais, áridas e Mediterrâneas. 2) Entender como estes fatores influenciam a incidência da leishmaniose e como esta antiga zoonose tem se adaptado a novas condições de ambientes modificados pelo homem. No primeiro capítulo, realizamos uma revisão de literatura e foi proposto um modelo conceitual para LV e LT destacando as diferenças entre os fatores ambientais e socioeconômicos que influenciam o ciclo de transmissão em regiões tropicais, áridas e Mediterrâneas. A principal diferença está associada ao comportamento dos vetores de *Leishmania* e reservatórios da LV e LT e suas preferências por condições ambientais específicas de cada região; e também na possibilidade de adaptação a ambientes urbanos em países em desenvolvimento onde o baixo nível socioeconômico aumenta a vulnerabilidade ante a leishmaniose. No segundo capítulo, analisamos como os fatores ambientais afetam a transmissão da leishmaniose no estado mais rico de um país tropical, o Estado de São Paulo, no Brasil. Usamos modelos mistos generalizados para analisar as condições ambientais e socioeconômicas que influenciam a ocorrência e o número de casos de LV e LT no estado de São Paulo desde 1998 até 2015. Para LT, a ocorrência aumentou com áreas maiores de vegetação nativa, maior desigualdade econômica (Índice de Gini) e maiores precipitações média do inverno. Para LV, a ocorrência aumentou com um alto índice de desenvolvimento humano (IDH), grande numero de cabeças de gado, maiores temperaturas máximas anuais e maiores precipitações mínimas da primavera. O numero de casos tanto de LV quanto de LT aumentou com maiores temperaturas médias anuais e somente os casos de LV aumentaram com as altas precipitações médias do outono. Estes resultados podem contribuir para predizer futuros picos da doença e desenvolver politicas publicas não só no Estado de São Paulo e também em outras regiões com características similares.

Abstract

Leishmaniasis is a neglected tropical disease caused by a protozoan of *Leishmania* genus. This disease is present in tropical, arid and Mediterranean regions and affects more than 350 million people around the world. Leishmaniasis has two main clinical forms visceral (VL) and cutaneous (CL).VL is lethal without adequate treatment and CL can produce serious disability due to the destruction of naso-buccal mucosal tissue. The transmission cycle of *Leishmania* depend on the sand fly vector (Diptera: Psychodidae), the host which are any mammal infected by the parasite and the reservoir which can transmit the parasite to the vector, all three must interact in a permissive environment to occur the transmission of disease. Leishmaniasis is an ancient zoonosis which transmission cycle was present in undisturbed landscapes, but the development of human settlements increased the contact between the humans and the transmission cycle. Nowadays, the incidence of disease does not only depend on environmental conditions which affect the vector and reservoir; but also depends on socioeconomic conditions of the human population. To better understand how these factors affect the transmission of leishmaniasis this study aim: 1) Identify the environmental conditions and socioeconomic factors which influence the transmission of VL and CL, considering all the endemic regions: tropical, arid and Mediterranean regions. 2) Understanding how these factors influence the incidence of leishmaniasis and analyze how this ancient zoonosis has adapted to novel human-modified environmental conditions. In the first chapter, we conducted a literature review and propose a conceptual model for VL and CL highlighting the differences between environmental and socioeconomic factors which influence the transmission cycle in tropical, arid and Mediterranean regions. The main difference was associated with the behavior of *Leishmania* vector and reservoirs of VL and CL and their preferences in environmental conditions in each region; and also the possible adaptation to urban environments in developing countries where low socioeconomic status increases the vulnerability to leishmaniasis. In the second chapter, we analyze how environmental and socioeconomic factors influence the transmission of leishmaniasis in the wealthiest state of a tropical country, São Paulo state, Brazil. We used generalized mixed models to analyze the environmental and socioeconomic factors which affect the occurrence and the number of cases of VL and CL in the state of São Paulo from 1998 to 2015. For CL, the occurrence increased with larger vegetation cover, high economic inequality (Gini), and high mean winter precipitation For VL, the occurrence increased with high human development index (HDI), a larger number of cattle heads, high maximum annual temperatures and high minimum spring precipitation. The number of cases of both VL and CL increased with high annual mean temperature, and only VL cases increased with high mean fall precipitation. These results can inform predictions of future outbreaks and contribute to the development of public health policies not only in São Paulo state, but in other regions with similar characteristics.

General Introduction

Leishmaniasis as vector borne disease

Changes in environmental conditions and human population characteristics can prompt the emergence of infectious diseases as vector-borne diseases (Meentemeyer et al. 2012). In natural ecosystems the transmission cycle of vector-borne diseases include mostly arthropods vectors, wild hosts (e.g., infected but not necessarily with transmissibility competence) and reservoirs that maintain the cycle in the nature which interact in a permissive environment (Fig. 1) (Reisen 2010, Gubler 2009). Introduction of human settlements near areas where the cycle of vector-borne disseases is present often leads to disease emergence (Patz et al. 2004).

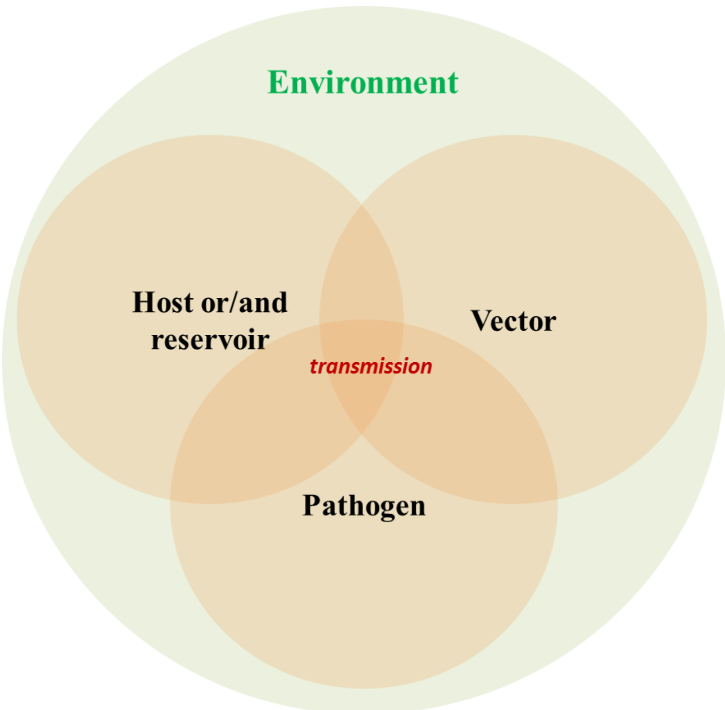

Figure 1. Transmission of vector-borne disease. Vector, host/reservoir, and pathogen populations intersect within a permissive environment to enable pathogen transmission. Adapted from (Reisen 2010).

One of the most neglected vector-borne zoonosis is leishmaniasis, a disease caused by parasites of the genus *Leishmania* (Family Trypanosomatidae, order Kinetoplastida) which includes 20 pathogenic species for human beings (World Health Organization 2010). Leishmaniasis has two main clinical forms which depend on the species of *Leishmania*: visceral leishmaniasis and cutaneous leishmaniasis (subdivided in: localized cutaneous, diffuse cutaneous and mucocutaneous) (Pace 2014). Visceral leishmaniasis (VL) affects the spleen, liver, or lymphoid tissues and is lethal without treatment. Cutaneous leishmaniasis (CL) presents ulcerative nodules, nasobronchial and buccal mucosal tissue destruction (World Health Organization 2010) (Fig. 2). In the New World the species responsible for VL is *Leishmania infantum* and for CL the responsible are several *Leishmania* spp. complex (Shaw).

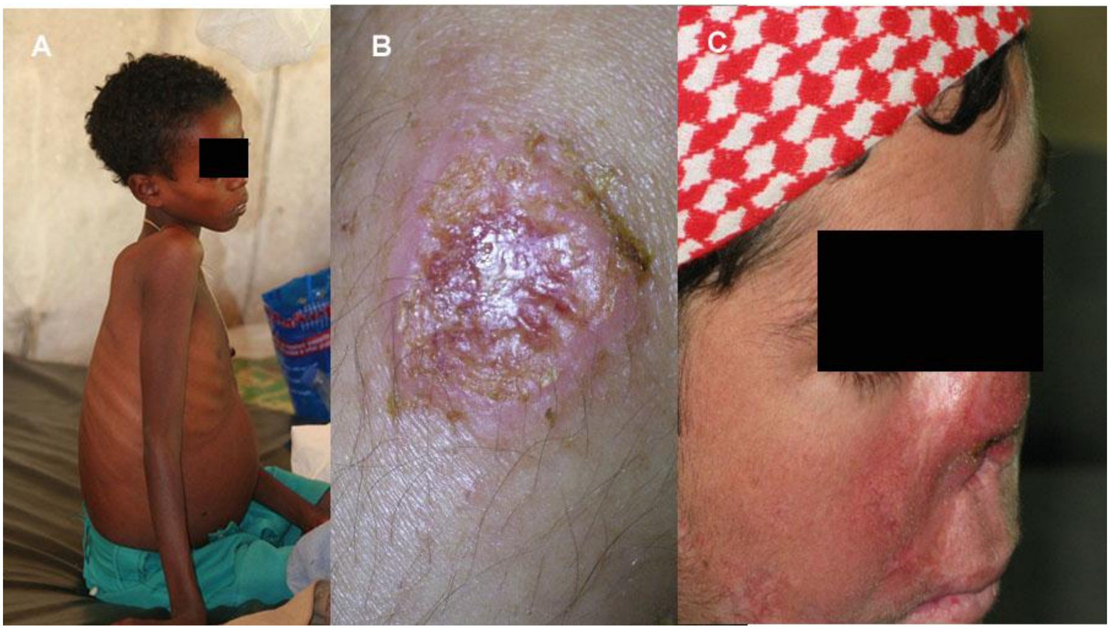

Figure 2. Clinical forms of leishmaniasis. From left to right Visceral leishmaniasis, Cutaneous leishmaniasis (localized cutaneous and muco cutaneous). Font (WHO 2017)

Parasite: *Leishmania* spp.

In the New World, the vectors of *Leishmania* spp. are sand flies of different genera, mainly *Lutzomyia* genus (Diptera: Psychodidae). Sand flies are holometabolous and have four distinct life stages: a) eggs, larvae and pupae that can live in shaded and moist terrestrial microhabitats, rich in organic nutrients, bases of trees, animal burrows, animal sheds, and rock crevices (Feliciangeli 2004); b) winged adults that as other Diptera, the female is haematophagous and feeds on blood for egg production (Rutledge and Gupta 2002). However, there are *Leishmania* spp. which are more likely to be transmitted by certain sand flies than others (Ready 2013). For instance, the main vector of *Leishmania infantum*, responsible for VL, is *Lutzomyia longipalpis* while several species of sand flies are suspected to transmit *Leishmania* spp. responsible for CL, as *Lutzomyia whitmani*, *L. migonei*, *L. intermedia* among others

(Killick-Kendrick 1990; Shimabukuro et al. 2010).

Reservoirs

Any mammal infected with *Leishmania* can act as a host but only those which maintain the parasite in the blood or the skin can act as reservoirs (Ashford 1996; Haydon et al. 2002; Roque and Jansen 2014). Among Neotropical species known to be infected with *Leishmania* spp. and probably potential reservoirs of both VL and CL are:

Wild mammals which live in native vegetation areas as (a) sloths, anteaters and armadillos (Super order Xenarthra) which live in areas close to settlements and are hunted and bred as pets in some communities of South America; (b) ocelots, tairas, coatis, wolves and foxes (Order Carnivora) which are hunted due to their potential to predate livestock; and (c) neotropical primates (Platyrrhini) which are hunted to become pets in some communities (Chaves et al. 2007; Roque and Jansen 2014).

Wild animal species which live in human modified environments (a) species of marsupials of *Didelphis* genus (Order Didelphimorphia) which usually live in peridomestic areas of rural and urban environments; (b) rodents, the most widespread mammals (Order Rodentia) that live surrounding peridomestic areas and agricultural areas, and (c) bats (Order Chiroptera) which are found in wild and urban areas (Chaves et al. 2007; Roque and Jansen 2014).

We found domestic animals which live as pets: (a) the cat (*Felis catus*) that could act as potential reservoir of *Leishmania infantum* (Savani et al. 2004; Maia and Campino 2011); and (b) the dog (*Canis familiaris*) that is the main reservoir of *L. infantum* responsible of VL (Curi et al. 2014), because its high potential to transmit this parasite in comparison with other wild or synanthropic mammals mentioned above (Richini-Pereira et al. 2014).

For CL there is not a main reservoir identified, *Leishmania* spp. responsible for CL have multiple mammal species competent for transmission for only a limited time (Chaves et al. 2007), but some species of rodents have been found as potential reservoirs of *Leishmania braziliensis*, one of the parasite species responsible for CL (Brandão-Filho et al. 2003).

The transmission cycle

The cycle of *Leishmania* spp. depend on a successful transmission between the vector and the reservoir or the host. *Leishmania* have two developmental stages: amastigotes inside the macrophages of the mammals and promastigotes in the digestive track of the sand fly (World Health Organization 2010). Sand flies females acquire macrophage infected with amastigotes of *Leishmania* when they feed on blood of a mammal infected. After, the blood meal, amastigotes transform into promastigotes and mature and divide within 3 days of ingestion in the midgut. Then, promastigotes migrate to the proboscis of the sand fly and are ready to be regurgitated into the skin of the vertebrate in the next meal blood (Fig. 3) (Dawit et al. 2013; Pace 2014; Alemayehu and Alemayehu 2017).

Figure 3. Transmission cycle of *Leishmania* spp. (A) Sand fly: After the blood meal, amastigotes inside infected macrophages transform into promastigotes and divide by simple division in the midgut of the female sand fly. Then, promastigotes migrate to the vector prosbocis to be transferred during feeding. (**B) Host/ reservoir:** During the blood meal the promastigotes are transferred and invade blood cells as macrophages. The promastigotes transform into amastigotes and divide inside the cells. Then, amastigotes leave the cells and invade new cells.

Climate

External factors influence the cycle of transmission of leishmaniasis. Climatic conditions are important environmental factors because sand flies vector species need specific temperatures and rainfall conditions for development and survival which depend on the limits of tolerance and the habitat preference of each sand fly species (Rutledge and Gupta 2002; Hlavacova et al. 2013). Warm temperatures are needed for adequate development and metabolism of the vector, and also influence the development of *Leishmania* inside the vector (Hlavacova et al. 2013). Excessive precipitation can have a negative effect on transmission because they can kill sand flies and some small mammals which are potential reservoirs while low rainfall or drought lower larval survival of the vector in the ground (Gage et al. 2008).

Climate variability as anomalous increases in temperature and changes in precipitation can affect the vector competence and *Leishmania* development, increasing the vector abundance (Chaves and Pascual 2006) and affect vegetation areas where sand flies live. Furthermore, climate extremes can exacerbate socio-economic vulnerabilities due to droughts, floods and crop losses which can increase migration from rural to peri-urban settlements, thus creating new foci of transmission (Rodríguez-Morales et al. 2009; Roy et al. 2016).

Modifications in landscape

Leishmania spp., their vectors and reservoirs were present originally in forest areas unmodified by humans (Moškovskij and Duhanina 1971). The emergence of human settlements, road constructions, and agricultural areas over forests fragmented the landscapes in regions where the cycle was present, increasing the contact of vectors and reservoirs with human populations. These changes in natural ecosystems resulted mechanisms of interaction with the environment, the vector and the reservoir, favoring the emergence of leishmaniasis in human settlements (Shaw 2007). Major infrastructure construction projects such as highways, bridges, pipelines among others contributed to increased transmission (Grimaldi and Tesh 1993).

In the last century, human modification of landscapes has been extensive in developing countries where the cycle of leishmaniasis is present, so disease incidence is increasing in these areas (Lambin et al. 2010). New risks areas of transmission have emerged in peridomestic areas where nearby vegetation can provide shelter for vectors and reservoirs (Dujardin 2006; da Silva et al. 2011). At the same time, some species of vectors have been able to adapt to urban environments and gradually cease to depend on dense vegetation environments, fostering disease transmission in urban areas (da Silva and Cunha 2007; Salomón et al. 2006)

Socioeconomic conditions

Leishmaniasis is a neglected vector-borne disease because is related with poverty. Peri-domestic areas of urban and rural environment of developing countries are usually characterized by population of low socioeconomic conditions or with lack of sanitary services. Sewage and garbage around the houses provide humid conditions to develop breeding sites of adult vectors (Boelaert et al. 2009). Low income is also associated with malnutrition depressing the immunological system of people who live in risk areas (Anstead et al. 2001). Many rural populations lack access to hospital which allows early diagnosis and treatment, so infected individuals must pay an additional travel cost to urban areas to receive healthcare and lose income as they become unable to work (Alvar et al. 2006). In addition, the treatment of leishmaniasis places a heavy economic burden for developing countries compared to malaria and pneumonia (Stolk et al. 2016).

Leishmaniasis incidence worldwide and Brazil

Leishmaniasis is a disease present in tropical, arid and Mediterranean regions (Pigott et al. 2014). In all regions, evaluation of the current risk of transmission of *Leishmania* is complex because the transmission involves various species of mammalian reservoirs and vectors, which are influenced by environmental conditions. Besides that, socioeconomic vulnerabilities of developing country population introduce further variation and may increase vulnerability to the disease (Desjeux 2001).

Worldwide approximately 350 million people are at risk of contracting leishmaniasis (Fig. 4) (World Health Organization 2010). The incidence of leishmaniasis in the world is ~0.2 to 0.4 million of cases for VL cases and ~0.7 to 1.2 million of cases for CL, with cutaneous leishmaniasis more widely distributed than visceral leishmaniasis. Global mortality was estimated to be 20,000 to 40,000 leishmaniasis deaths per year, mainly attributed to VL (World Health Organization

2010). Brazil has the largest number of leishmaniasis cases in the Americas with an estimated annual incidence of 4,200 to 6,300 cases of VL and 72,800 to 119,600 cases of CL (Alvar et al. 2012).

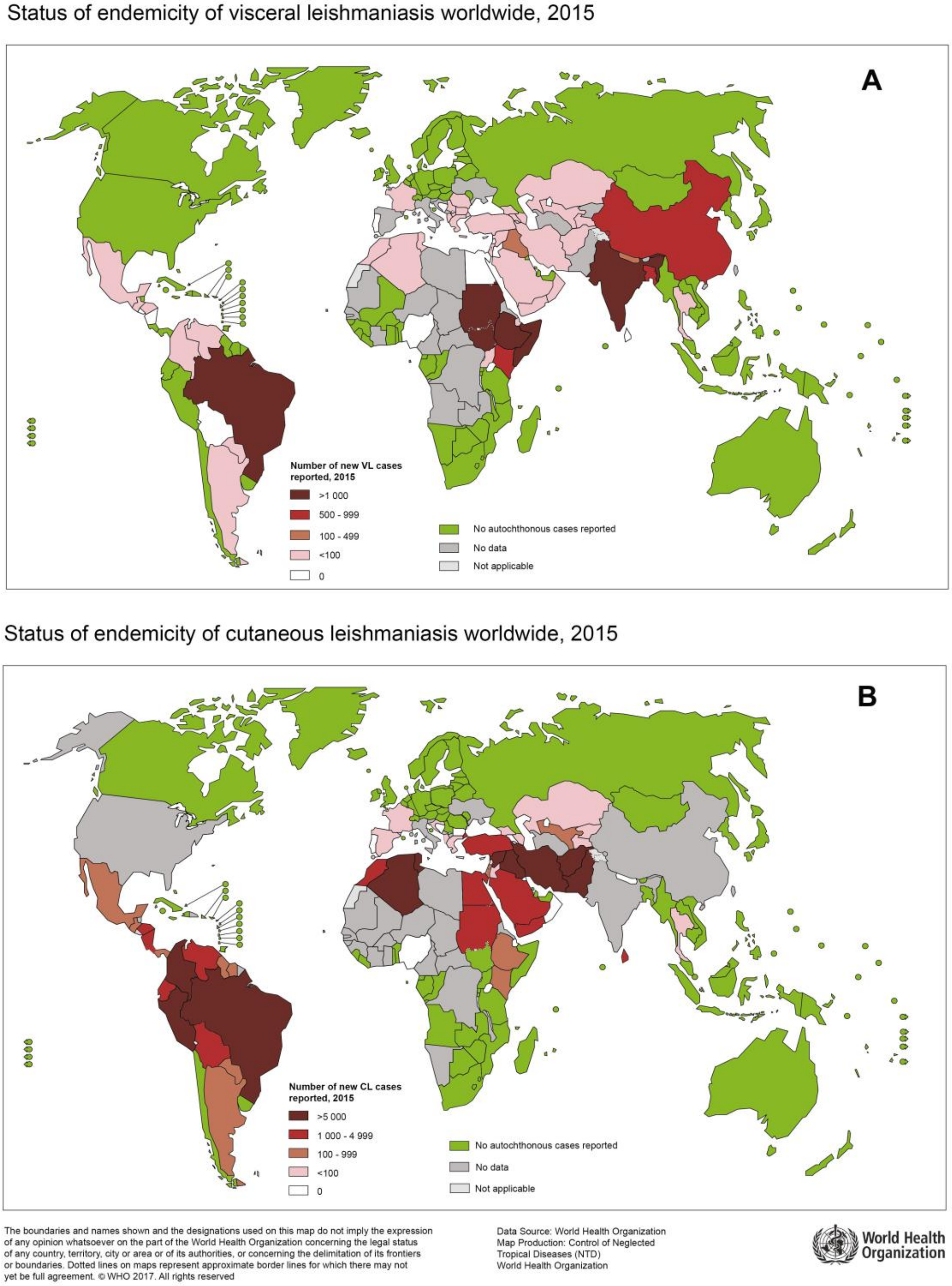

Figure 4. Number of new visceral **(A)** and cutaneous leishmaniasis **(B)** cases reported worldwide in 2015. Font: (WHO 2017)

The northern and central regions of Brazil have high incidence rates (>15 cases for CL and >0.63 cases for VL per 10,000) (Karagiannis-Voules et al. 2013). Although São Paulo state only accounts for less than 1% of leishmaniasis cases in the country (Ministério da Saúde), environmental characteristics and socioeconomic conditions of the state establish a good environment for studying the factors that influence leishmaniasis incidence. The original vegetation cover of Atlantic forest and Brazilian Cerrado (Savanna) has been reduced by more than 80% since the late 19th century and been replaced by agriculture and urban areas (Victor et al. 2005). As a result, the current landscapes contain mosaics of urban and agricultural areas interspersed with fragments of original vegetation. Although São Paulo state is the wealthiest state of Brazil, responsible for 28.70% of Brazilian GDP, it has marked socioeconomic inequalities with vulnerable populations in both rural areas and rapidly developing peri-urban areas in the São Paulo metropolitan region. Climate Köppen classification in the state also includes dry winters and marked rainy season in the summer, and average annual temperature above 18°C to 22°C (Alvares et al. 2013)., conditions favorable for the vectors (Bhunia et al. 2010; Karagiannis-Voules et al. 2013; Giannakopoulos et al. 2016; Pérez-Flórez et al. 2016) Understanding the factors that underlie leishmaniasis incidence in São Paulo state cannot only serve to contribute to develop effective control measures in the state but also to inform disease occurrence in other areas with similar environmental and socioeconomic conditions.

About this thesis

This thesis aims to expand our understanding of the factors that influence the transmission of visceral and cutaneous leishmaniasis in São Paulo and to highlight the socioeconomic and environmental factors that contribute to increase the transmission of the disease. To do so, the research focused on identifying the socioeconomic and environmental factors related to cases of both main clinical forms CL and VL leishmaniasis, first analyzing a global overview and then focusing on the transmission of both VL and CL in São Paulo state between 1998 and 2015 year.

Chapter 1: Environmental and social risk factors associated with leishmaniasis: A systematic review.

In this chapter we conduct a literature review on environmental and social factors involved on visceral and cutaneous leishmaniasis to propose a conceptual model which can help to better understand the interplay of the network of risk factors that influence the incidence of both clinical forms of leishmaniasis and the difference of these risk factors in the world.

Chapter 2: Environmental and social risk factors for visceral and cutaneous leishmaniasis in São Paulo, Brazil.

This chapter presents an analysis of the environmental and socioeconomic factors associated with the transmission of visceral and cutaneous leishmaniasis between 1998 and 2015 in the state of São Paulo and identifies the factors that fostered the occurrence (presence/absence) and those ones that fostered the number of cases.

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Chapter 1

Environmental and socioeconomic risk factors associated with leishmaniasis: A systematic review

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Abstract

Background: Leishmaniasis is a neglected tropical vector-borne disease that affects principally the poorest of the poor, with an estimated 350 million people at risk around the world. We performed a systematic review of the literature, focused on environmental and social risk factors for visceral (VL) and cutaneous leishmaniasis (CL) to better understand their impact on the incidence of disease.

Methods and findings: We reviewed 79 articles, 47 studies for VL, 29 for CL and 3 studies on both forms. Among these studies, 31 were conducted in Brazil, 7 in Ethiopia and 5 in India, with the remainder distributed across other countries. We identified 14 categories of risk factors which were divided into three groups: seven socioeconomic, five environmental and two climate variables.
Socioeconomic factors were considered most often (67.3% for VL and 56.2% for CL), followed by environmental (45% for VL and 53% for CL), and climate factors (16% for VL and 28% for CL). Environmental and climate factors showed significant associations wich increase the incidence of VL and CL in all the studies that considered them, because they influence the development of the vector and reservoir. Proximity to natural vegetation remnants, particularly in peri-urban environments, increases disease risk in both the New and Old World while the climate conditions favorable for disease transmission differed among regions. Socioeconomic factors were also associated with disease incidence in vulnerable human populations of arid and tropical developing regions. Despite some differences in the factors involved in the transmission cycles of VL and CL, we propose a common conceptual model for both clinical forms that highlights networks of interaction for some risk factors. In both clinical forms, the interplay of these factors played a major role in disease incidence.

Conclusions: Environmental and socioeconomic conditions mediate the incidence of leishmaniasis in tropical, arid and Mediterranean regions. Although there are similarities in the transmission cycle, the behavior of vector and reservoirs associated with the cycle in each region is different. We point out the need for more research to analyze the interactions of risk factors. Special attention should be given to the

possibility of adaptation to urban environments in endemic regions in developing countries where population with low socioeconomic status is particularly vulnerable and a better understanding of potential effects of future climates on the transmission cycle.

Keywords: Leishmaniasis, socioeconomic, environmental, risk factors, endemic regions

Introduction

Leishmaniasis is a vector-borne disease caused by a protozoan of the genus *Leishmania*, which comprises 20 species. *Leishmania* is endemic in 98 countries; more than 350 million people are at risk for the disease, and approximately 0.2 to 0.4 million cases of VL and 0.7 to 1.2 million cases of CL occur each year. A tentative estimate of mortality based on sparse data using hospital-based fatalities reported 20,000 to 40,000 deaths of leishmaniasis per year in the world (Alvar et al. 2012). Over 90% of most fatal leishmaniasis infections occur in Brazil, Ethiopia, Sudan, South Sudan, India, and Bangladesh (World Health Organization 2010; Pigott et al. 2014).

The disease has two main clinical forms in humans, visceral (VL) and cutaneous leishmaniasis (CL). In the Old World, VL is caused by parasites of the *Leishmania donovani* and *L. infantum* in the New World by *Leishmania infantum*. The cutaneous form, CL, is caused by five species of *Leishmania*: *L. major*, *L. tropica*, *L. aethiopica*, *L. donovani* and in some cases *L. infantum* in the Old World and by multiple phylogenetically distinct *Leishmania* species in the New World (World Health Organization 2010). The disease is transmitted through the bite of phlebotomine sand flies infected with *Leishmania* parasites. This parasite enters the bloodstream of the individual host and the clinical form that will develop depends of the *Leishmania* species. Visceral leishmaniasis could present splenomegaly, hepatomegaly, or affect lymphoid tissues. Depending on the form, cutaneous leishmaniasis could present cutaneous nodules, non-ulcerative nodules or naso-buccal mucosal tissue destruction (Pace 2014). The severity of the symptoms depends on the immune system of the individual. The cycle restarts when sand flies bite and ingest blood from an infected individual.

A total of 93 species of sand flies are probable vectors of *Leishmania* but information on species-specific infection rates is scarce because it is difficult to find infected sand flies in the wild (World Health Organization 2010). There are two types of *Leishmania* vectors: generalists, which support the growth of more than one species, and specialists, that support only one species of *Leishmania* (World Health Organization 2010).

In the Old World, *Phlebotomus* is the principal genus of vectors for the parasite responsible for both VL and CL forms. In the New World *Lutzomyia* *longipalpis* is the main vector of *L. infantum*, responsible for VL, while multiples sand fly vectors transmit the multiple *Leishmania* species species responsible for CL (Bates et al. 2015). In the absence of known vectors, however, many sand fly species have been considered as potential *Leishmania* vectors albeit without corroboratory evidence.

The complex transmission cycle of leishmaniasis also includes several species of mammals which can be hosts and/or reservoirs of *Leishmania* spp. (Roque and Jansen 2014). Any mammal infected with the parasite can act as a host and may or may not be important in transmission (Roque and Jansen 2014) while reservoirs are only those mammal species highly competent for *Leishmania* spp., responsible for maintaining the parasite in nature (Ashford 1996; Haydon et al. 2002; Roque and Jansen 2014). One important reservoir is the domestic dog (*Canis familiaris*), which is the principal reservoir of *L. infantum* in urban areas and is largely responsible for VL around the world and for CL in the Old World. The human is the reservoir of *Leishmania donovani* responsible for anthoponothic VL transmission in East Africa, Bangladesh, Nepal and India (World Health Organization 2010). In the New World, other specific reservoirs related to the parasite responsible for CL have not been identified (Reyes and Arrivillaga 2009), and in peri-urban areas close to the forest, other wild mammals are involved in the transmission cycle, especially small mammals such as rodents and marsupials (Roque and Jansen 2014).

The presence of vector species and potential mammalian reservoirs is favored by some environmental and climatic conditions, such as warm climates and the presence of forest (Desjeux 2001). Such favorable conditions allow sand fly development, providing shelter and protection for both the vector and the reservoir. In fact, both clinical forms of leishmaniasis were initially found only in natural, undisturbed environments (Grimaldi and Tesh 1993). Over the past few decades, however, human migration has led to the creation of settlements close to natural ecosystems, where the cycle of leishmaniasis was already present, increasing human exposure to infected sand flies (Desjeux 2001; Dujardin 2006). These developments have changed the ecology of vectors since the parasite adapted its cycle to peri-domestic sand fly species and reservoir animals (e.g., dogs).

Transmission became particularly favorable in developing countries, where rapid and extensive development of peri-urban areas close to forest or dense vegetation is often coupled with large human populations of low socioeconomic status. Peri-urban settlements in these countries are often characterized by poor housing and sanitary conditions that facilitate human contact with vectors, increasing the incidence of leishmaniasis and possibly reducing the efficiency of control programs (Dantas-Torres and Brandão-Filho 2006). Underreporting, deficiency in vector control and the lack of treatment options in these regions has turned leishmaniasis into one of the most neglected tropical diseases (Desjeux 2001).In addition, climate change in these developing regions could lead to further changes in disease incidence if shifts in temperature and precipitation conditions for the sand flies and reservoirs are altered (Moo Llanes 2016).

Previous reviews of the risk factors related to the transmission of the disease focused on visceral leishmaniasis in Asia (Bern et al. 2010) and in the Americas (Belo et al. 2013). Additionally, the last reviews describing both clinical forms and their risk factors around the world took place over 10 years ago and did not provide a description of the network of risk factors for each clinical form (Desjeux 2001; Desjeux 2004; Shaw 2007). As result, how interactions between environmental and socioeconomic factors influence leishmaniasis risk is not well understood. The aims of the present review are to (1) review literature on environmental and social factors associated with leishmaniasis in humans and (2) determine the influence of social, environment and climate factors on disease incidence with the goal of proposing a conceptual model of transmission. We hope that this approach to data synthesis will help to better understand the interplay of the network of risk factors that influence the incidence of both clinical forms and to guide control efforts.

Methods

We searched the literature for relevant publications between 1900 and December 2016 using Web of Science, Google Academic and Scielo. Search terms included “leishmaniasis” AND “risk factors”. We examined the titles and abstracts of all articles identified in the searches and the full texts if necessary in order to identify risk factors included in the studies. We excluded articles that focused on: (1) canine leishmaniasis exclusively; (2) treatment or clinical factors; (3) asymptomatic leishmaniasis; (4) genetics of the disease or its vectors; and (5) leishmaniasis associations with other disease or clinical descriptions. Additional articles were located through citations from the selected articles or from suggestions from disease experts.

All potential articles were screened for risk variables considered in this review. These variables were then split into three categories: socioeconomic and demographic factors, landscape and environment factors, and climatic factors. We identified 14 variables that were most frequently included in the studies: seven socioeconomic and demographic factors, five landscape and environmental factors, and two climatic factors (Table 1).

Table 1. List of risk factor variables for leishmaniasis.

Category	**Risk variables**	**Influence**
Social and demographic	Socioeconomic status	Influence of quality of life (type of house). Houses built with straw and mud, provide shelter to sand flies.
	Water supply /sewage system/ garbage collection	Trash, sewage water, and wells create environmental conditions suitable for sand fly breeding sites.
	Characteristics of population (age, gender, education level, migrant)	• Children and elderly people are more vulnerable. • Agricultural workers are usually males • Migration increases the number of informal settlements. • Low education level can influence the lack of adequate preventive measures
	Presence of domestic or wild animals	Potential reservoirs or blood meal source
	Behavior	Sleeping outside without protection against sand flies and working in vegetated areas increase exposure to sand flies.

	Health factors	• Immunosuppressed people with other illness or poor nutrition may be vulnerable • Contact with other leishmaniasis cases.
	Population density	Household size increase attractiveness to sand flies.
Landscape and environmental variables	Vegetation	Vegetation provides shelter to vector and reservoirs
	Presence of waterbodies	Humid conditions foster sand fly breeding
	Altitude /slope /soil type	Physical conditions favorable for breeding sites of vectors
	Urban / rural landscape	Leishmaniasis cycle presence near rural and urban areas, depending of the parasite specie increase the risk
	Construction	Anthropogenic disturbance in forested areas increase human-vector contact.
Climatic	Temperature Precipitation	Conditions may be favorable to sand fly development

Results

Selection of publications and general description

Our search resulted in 118 potentially relevant articles, of which 79 met our inclusion criteria (S1). Among these 79 articles, 29 focused on cutaneous leishmaniasis (CL), 47 on visceral leishmaniasis (VL) and 3 on both clinical forms. A total of 31 articles were studies conducted in Brazil, 7 were conducted in Ethiopia and 5 in India, with the remainder distributed across other countries (Fig. 1).

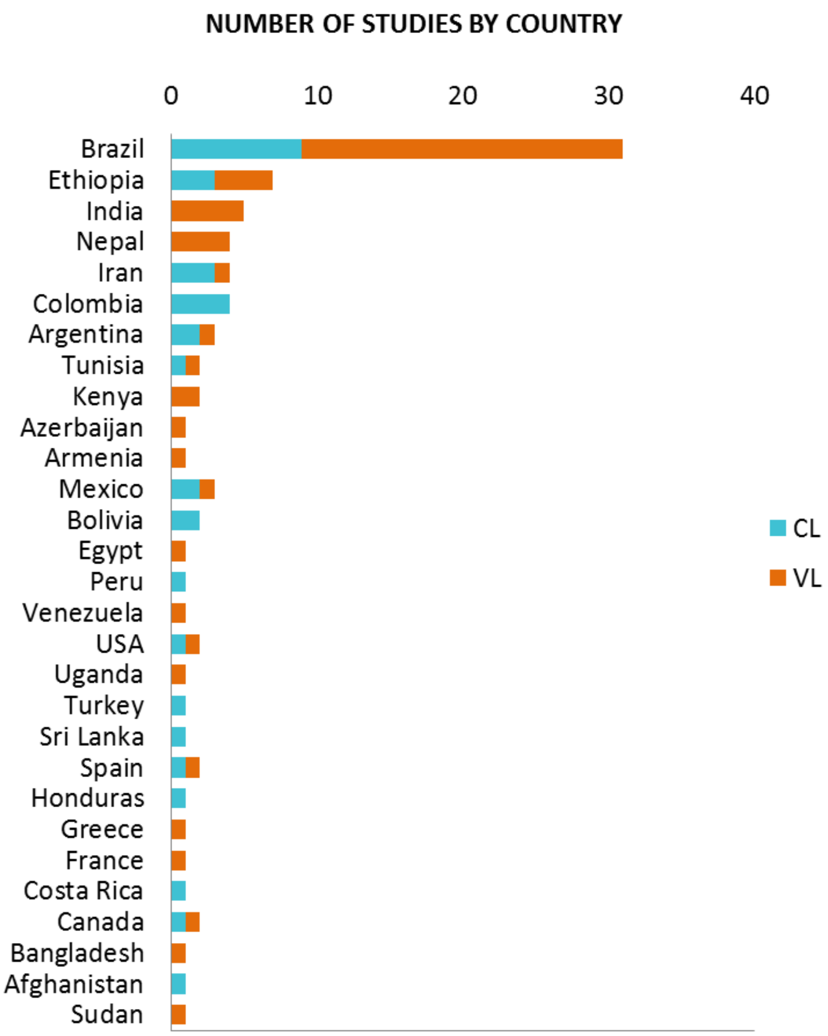

Figure 1. Geographic distribution of number of studies of leishmaniasis risk factors examined in this review (VL=visceral, CL=cutaneous).

For each clinical form, we examined the relationship between the number of times risk variables were included in studies and their significance (Fig. 2).

Landscape variables were implicated with incidence of VL in 44.8% of the studies and in 53.1% for CL. Climatic variables were associated with VL in 16.3% of the studies and in 28% for CL. Socioeconomic and demographic variables were most commonly considered for VL and CL in 67.3% and 56.2% respectively (Fig. 3).

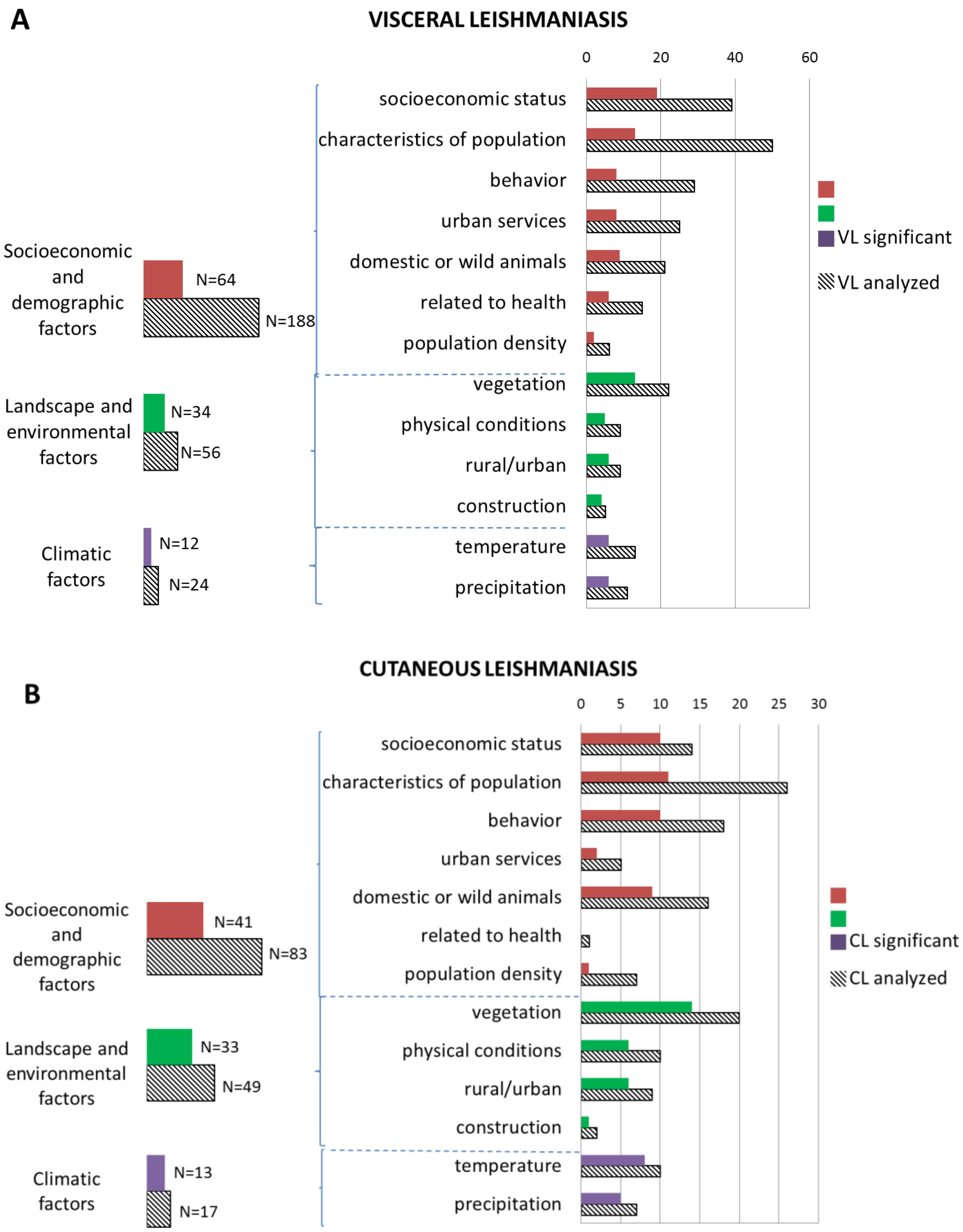

Figure 2. Number of times that each of the three category of risk variables listed in Table 1 were considered in the 79 studies and number reporting significant values for **(A)** visceral (VL) and **(B)** cutaneous (CL) leishmaniasis studies. Left panels show results aggregated for each category. Right panels show subdivisions for each category based on Table 1.

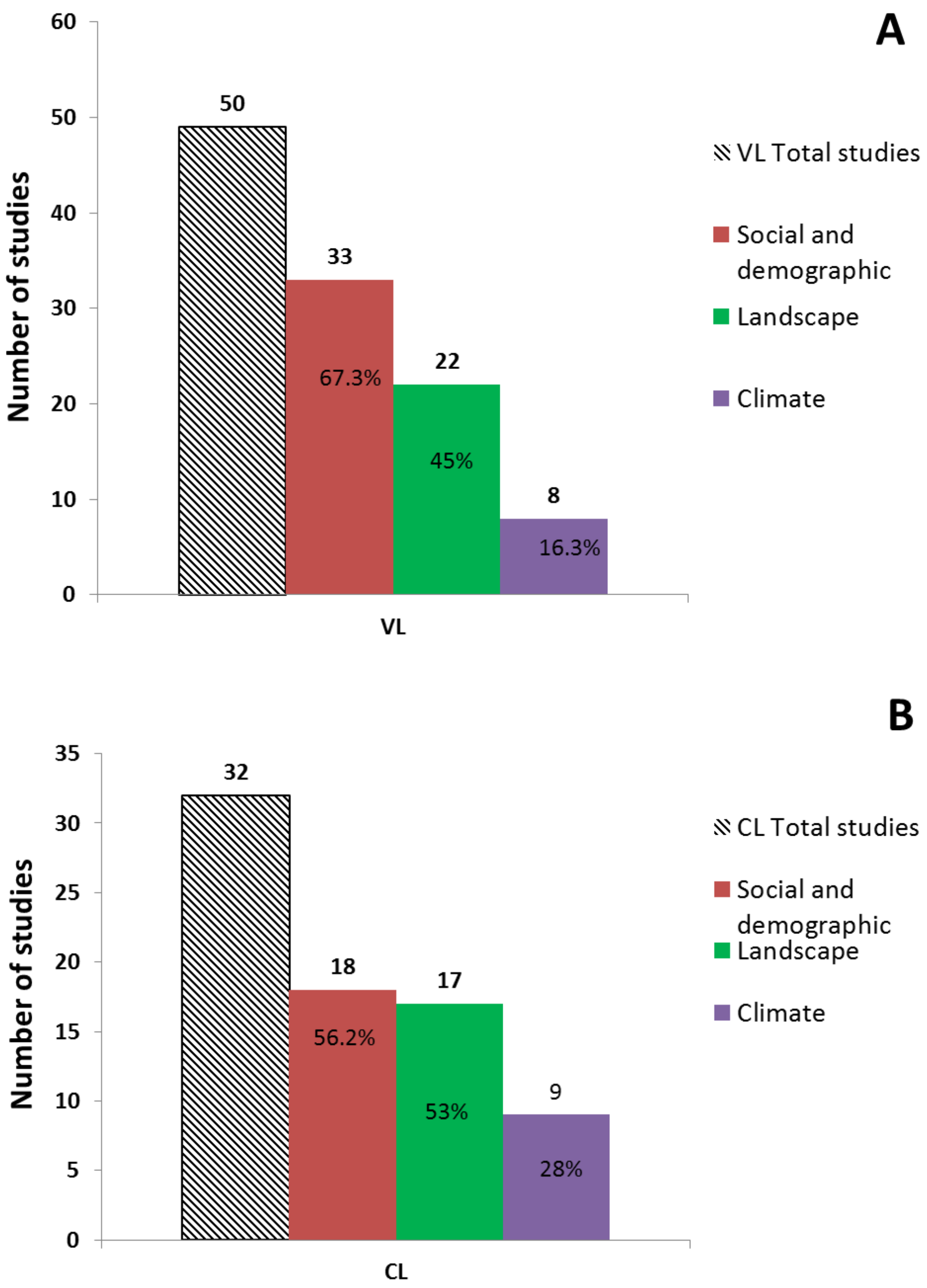

Figure 3 Number of total studies analyzed for **(A)** visceral (VL) and **(B)** cutaneous leishmaniasis (CL). Hatched bars show total number of studies. Colored bars show the number of studies that found factors in each category significant. Note that some studies examined several factors.

To summarize the information of the risk factors considered in our review, we extracted metrics of variable significance directly from the original articles. In addition, for the studies (25% of 79) that provided data for odds Ratios (OR), the ratio of disease odds given exposure status, or Relative Risk (RR), the probability of developing leishmaniasis in an exposed group compared with non-exposed group, we used average OR/RR values. Detailed information for all studies is included in Supporting Information (S1).

Socioeconomic variables

Socioeconomic and demographic factors (Table 1) were significant in 34% of VL and 49% of CL studies (Fig. 2).

(a) *Visceral leishmaniasis*. Household characteristics that reflect precarious living conditions were analyzed in 21 studies, with 62% finding significant results. For instance, in Posadas, Argentina the majority of people with VL lived in poor quality houses with sand floors, wooden walls, totally or partially open roofs, and without window screens (López et al. 2016). In Bihar, India mud-plastered walls resulted in a two-fold risk increase (OR=2.4) compared with cement-plastered ones (Ranjan et al. 2005).

Indicators of low educational status also were significant VL risk factors for 45 % of the 11 studies that considered this factor. In Belo Horizonte, Minas Gerais, Brazil, a study found a higher risk of VL for illiterate people (RR=2.9) and for households with less than 4 years of education (RR=1.8) (de Araújo et al. 2013). For the study in Bihar, India, risk for illiterate people was higher (OR=1.7) than for literate people (Ranjan et al. 2005).

Lack of access to sewage services, water supply and garbage collection also presented a significant risk for 32% of the 25 studies that included these factors. In two studies in Brazil, high incidence of VL was associated with lack of these basic sanitary services (Moreno et al. 2005; de Almeida et al. 2011). In these same localities, people with low income were also concentrated in high-risk areas in peripheral neighborhoods for VL (Werneck et al. 2007; de Araújo et al. 2013). A rapid recent increase in population density was also a characteristic of areas of high VL incidence (Cerbino Neto et al. 2009). However, low income in itself was only significant in 33% of 18 studies.

The dog as the main reservoir of *Leishmania infantum* in urban areas is associated with high risks of infection for VL in two studies in Belo Horizonte (RR=19.1, OR=2.2) (Borges et al. 2009; de Araújo et al. 2013), and in Posadas where the presence of an infected dog were associated with the risk of VL infection (OR=120.3) and reported in 100% (n=24) of VL cases analyzed (López et al. 2016).

The presence of other peri-domestic animals was a significant VL risk factor in 33% of 15 studies. In Belo Horizonte, Brazil, the presence of chickens and ducks led to a two-fold increase in risk of VL (OR=2.1) (Moreno et al. 2005) In the same city, another study found a risk increment for people who kept ducks, chickens, and other birds (OR= 4.18, 1.57, 1.47 respectively) (Borges et al. 2009). Presence of rodents (OR= 1.81) in Brazil (Borges et al. 2009) and goats (OR= 6.5) in Tigray, Ethiopia (Yared et al. 2014) also incremented the risk of VL.

Although not strictly socioeconomic conditions, certain activities such as sleeping outside the house, either on the ground (OR=4.53), under vegetation (OR= 2.77), or near dogs (OR=4.3), increased the risk ratio of VL in Tigray, Ethiopia (Argaw et al. 2013). Time spent outdoors was also a risk factor for VL in Posadas, Argentina (OR= 4.5) (López et al. 2016) and in Belo Horizonte, Brazil (OR=1.9) (Moreno et al. 2005). Finally, history of another disease in the previous year (OR=2.76) had a significant impact on the occurrence of VL in Bihar, India (Ranjan et al. 2005) and in Jacobina, Bahia, Brazil, malnutrition was associated with an increase of VL incidence (Badaró 1988).

(b) *Cutaneous leishmaniasis*. Among CL studies, household characteristics were significant for 60% of 10 studies. In Salta, Argentina, windows that cannot be locked represent a high risk for CL transmission (OR=2.93) (Sosa-Estani et al. 2001). Households built with non-durable wall material had increasing risk of acquiring CL (OR=2.36) in Alagoas State, Brazil (de Araújo Pedrosa and de Alencar Ximenes 2009; de Oliveira et al. 2012), in Matara, Sri Lanka, unplastered walls were associated with higher CL risk (Kariyawasam et al. 2015), and in Tigray Ethiopia the presence of cracks or holes in the walls led to a four-fold risk increase (OR=4.04) for VL (Bsrat et al. 2015).

Low economic level and related factors are important risk factors for CL (100% of 4). Poverty had a significant association with infection risk in Isfahan, Iran, (OR=2.034) (Nilforoushzadeh et al. 2014) and in Matara, Sri Lanka (OR= 28.66) (Kariyawasam et al. 2015). Furthermore, the absence of a gas stove in Alagoas, (OR=2.41) in houses of people with low income status in Brazil (de Araújo Pedrosa and de Alencar Ximenes 2009), were also associated with populations affected with CL.

As for VL, the presence of peri-domestic animals was important for the transmission of CL (75% of 4 studies), whether they are inside (OR=2.93) (de Araújo Pedrosa and de Alencar Ximenes 2009) or outside the house (OR= 2.38) (Sosa-Estani et al. 2001; Nilforoushzadeh et al. 2014).

Activities such as sleeping at the workplace (rural work OR =4.14) and sleeping outside the home at night (OR=6.29) were associated with higher incidence in Salta, Argentina, (Sosa-Estani et al. 2001). The absence of protection measures against sand flies bites (OR=6.13) during the time spent outdoors represented a higher risk for CL transmission in Matara, Sri Lanka (OR= 24.6) (Kariyawasam et al. 2015). Agricultural work (OR=7.75) and leisure activities inside the forest (OR=9.23) were associated with the incidence of CL in Alagoas State, Brazil (de Araújo Pedrosa and de Alencar Ximenes 2009).

Environmental and landscape factors

These factors are a range of descriptors of the area in which leishmaniasis occurred (Table 1). Land cover data were collected using *in situ* observations or satellite images coupled with Geographic Information Systems (GIS). Metrics of vegetation cover near leishmaniasis cases included the Normalized Difference Vegetation Index (NDVI), classification of the type and extent of vegetation cover within a given radius of the household, and the distance from the household to vegetation. Physical variables such as soil type and elevation were also considered in a number of studies. These environmental and landscape factors were significant in 60.7% of VL and 67.3% of CL of the cases (Fig. 2).

(a) *Visceral leishmaniasis*. For VL, distance to vegetation was a significant risk factor for 57% of the 7 studies that included this variable. In Bihar, India the presence of bamboo near the house resulted in a two-fold risk increment (OR=2.3) relative to areas with creepers, herbs, and bushes (Ranjan et al. 2005). Similarly, in Teresina, Brazil, the predominant vegetation in the city are shrubs, palm trees, and sparse mango trees. However, Teresina is surrounded by Brazilian Cerrado (Savannah) and pastureland and the high incidence rates were found in the peripheral neighborhoods close to both vegetation types (Werneck et al. 2002).

Vegetation cover type was significant in four of the five studies that considered it, particularly when vegetation was interspersed with urban development in peri-urban areas. In the Gangetic plain of NE India, the presence of woodland (< 10% tree cover) was associated with high VL risk due to the proximity to peri-urban area (Bhunia et al. 2010). On the other hand, in the Mediterranean city of Fuenlabrada, Spain, a spatial analysis located a cluster of high incidence of leishmaniasis (VL and CL) close to the forest of Bosquesur Park, an urban ecological corridor (Gomez-Barroso et al. 2015). In the Provence-Alpes-Cotes d'Azur, France a cluster of VL was located in Nice in scattered dwellings close to the Mediterranean mixed forest. These examples demonstrate that this effect is not restricted to leishmaniasis of tropical areas (Faucher et al. 2012).

Seven studies considered NDVI index as a predictor of incidence and four found significant associations (Bavia et al. 2005; Werneck et al. 2007; Cerbino Neto et al. 2009; de Oliveira et al. 2012). High NDVI values were associated with incidence of VL in Teresina and Campo Grande with vegetation typical of Brazilian Cerrado (Cerbino Neto et al. 2009; de Oliveira et al. 2012). However, incidence was higher in areas of low NDVI in Distrito Sanitário de Barra, Bahia, Brazil, where Caatinga (Brazilian Thorny scrub) seasonal loss of leaves in this habitat is associated with low NDVI (Bavia et al. 2005).

Others variables related to land use and geography include the presence of waterbodies near dwellings and the location of study sites in relation to urban or rural areas. The presence of waterbodies close to the dwellings was a risk factor for VL in 4 out of 8 studies. Increased risk of VL was greater closer to ponds in Dulari, Dharan, Nepal (OR=3.7) (Schenkel et al. 2006), rivers and waterbodies in the Gangetic plain, especially in non-perennial river banks in India (Bhunia et al. 2010; Bhunia et al. 2011), and to rivers in Kalaybar and Ahar, Iran (Rajabi et al. 2016).

The majority of studies of VL risk factors were conducted in urban areas. However, only five studies specifically consider urban cover as a risk factor with three studies finding a significant relationship between urban cover and VL risk. High incidence of VL was centered in built-up areas in northwest India (Bhunia et al. 2010), peripheral neighborhoods in Teresina, Brazil (Werneck et al. 2002), and continuous urban area in Marseille, France (Faucher et al. 2012). However, other studies found high VL risk in rural areas, for example, cultivated and irrigated land in Thessaly, Greece (Giannakopoulos et al. 2016); and in northwestern Iran (Rajabi et al. 2016). In addition, construction projects such as highways and pipelines were also associated with an increase in VL incidence in Brazil (75% of 4 studies) (Antonialli et al. 2007; Cardim et al. 2013; Cardim et al. 2016).

Three studies considered the effects of soil type on VL and two of these found significant associations. Soil characteristics are hypothesized to reflect moisture conditions suitable for breeding sites; soil types associated with high VL incidence areas include fluvisols in the Gangetic plain in India, alluvial soil characteristic of the rivers areas as the Ganges river (Bhunia et al. 2010), and vertisols (OR=24.32), lixisols, cambisols and luvisols characteristic of tropical grasslands and savannas in Ethiopia (Tsegaw et al. 2013).

Altitude of the study area has also been associated with VL incidence with three of four studies finding this variable a significant risk factor. For instance, 95% of VL cases in Ethiopia were located in areas lower than 1872 m asl out of range of 1000 -3000 m asl (Tsegaw et al. 2013). In Gedaref, Sudan, high risk areas were found in areas lower than 550 m asl (range 400-1000 m asl) (Elnaiem et al. 2003) and in Thessaly, Greece in areas lower than 200 m asl (range 27– 1083m asl) (Giannakopoulos et al. 2016).

(b) *Cutaneous leishmaniasis*. Environmental and landscape variables also are high risk factors for CL transmission. Vegetation close to the dwellings was a significant risk factor for 75% of 8 studies. Areas with a predominance of pastures and secondary vegetation close to households in Seropédica, Rio de Janeiro were favorable for CL occurrence (de Oliveira et al. 2016). In Alagoas State, Brazil, originally covered by Caatinga and Atlantic coastal forest, the presence of forest less than 200 m from households resulted in a four-fold greater risk (OR = 4.7) relative to areas farther from the forest (de Araújo Pedrosa and de Alencar Ximenes 2009). Areas characterized by residual forests and riparian forests resulting from reforestation in Campinas, São Paulo State, Brazil, accounted for 82% of the cases east of the city and 50 % of the cases in the southeast occurred in sites less than 200 m from forest (Nasser et al. 2009).

Vegetation cover was also significant risk factor for all the studies which analyzed it for CL. In the district of Matara in Southern Sri Lanka a spatial analysis found clusters of CL were more prevalent close to native xeric shrublands (Kariyawasam et al. 2015). CL transmission was also observed in the Colombian Andean region, an area characterized by a mosaic of savanna, rainforest and woodlands. Among all categories of land cover analyzed in this study, rainforest cover was positively associated with CL incidence (Pérez-Flórez et al. 2016). Other studies conducted in a department located in the same Andean region of Colombia found areas of high incidence had a 20% higher cover of wooded and shrubs relative to disease free areas (Valderrama-Ardila et al. 2010; Ocampo et al. 2012).

Other landscape characteristics, such as the extent agricultural area, were associated with CL for 71% of 7 studies. The study areas previously mentioned associated with vegetation were rural areas in the case of Seropédica (de Oliveira et al. 2016) and cultivated and livestock areas in the Colombian Andean region (Pérez-Flórez et al. 2016). Likewise, in Caratinga, Minas Gerais, Brazil ,77% of CL cases were located in rural areas (Machado-Coelho et al. 1999), and in Tsaeda-emba, Tigray, Ethiopia farm land within 300 m radius from the households (OR =1.86) increased CL risk (Bsrat et al. 2015).

Only two studies analyzed distance of households to waterbodies. Population centers affected with CL were characterized by the presence of riverbeds and embankments in Isfahan, Iran (Nilforoushzadeh et al. 2014; Rajabi et al. 2016). Altitude and elevation data (slope) were also found to be significant in two out of five CL studies. In Seropédica (range 0- 520 m asl), favorable areas of CL incidence were characterized by low altitude in areas ranging from 0-40 m asl and slope of 0 -2.5 degrees (de Oliveira et al. 2016). Human contact risk zones (between the vector and human) in Itapira, São Paulo State, Brazil (1- 1200 m asl) were at altitudes lower than 750 m asl (Aparicio and Bitencourt 2004). In contrast, altitudes between 1400 -2700 m asl (OR=2.32) and slopes higher than 4.6 degrees (OR= 4.36) were most favorable for CL incidence in Ethiopia (range 1000 -3000 m asl) (Seid et al. 2014).

Climate variables

Climate variable were analyzed in studies that considered other environmental variables (i.e. vegetation, soil type, altitude). These variables were significant in 50% of VL and 76.4% of CL of the cases in the studies (Fig. 2). The most commonly studied climate variables for both clinical forms were temperature and rainfall. The approach of most studies was to examine the range of temperatures and rainfall that were favorable to disease incidence. Other studies used Environmental Niche Models to examine the association between climate variables and disease occurrence.

(a) Visceral leishmaniasis. Temperature was significant for 4 of 10 studies and rainfall for 5 of 9 studies. Incidence areas in the Gangetic plain, India had a temperature range between 25° – 27 °C and precipitation between 100 to 160 mm with relative humidity between 66% -75% (Bhunia et al. 2010). In the Mediterranean region of Thessaly, Greece, maximum temperature (32 ±1°C) accounted for 6% of the variance in an Ecological Niche Model (ENM) for *Leishmania* infection (Giannakopoulos et al. 2016). In Africa, Ethiopia, a semiarid country, annual average temperatures between 20° and 37°C (OR=5.16) and annual rainfall below 766 mm were also predictors of VL (Tsegaw et al. 2013). In Geradaf, Sudan rainfall below 939 mm was the best predictor of VL incidence (Elnaiem et al. 2003).

(b) Cutaneous leishmaniasis. Climate variables were also significant risk factors for CL studies (71% of 7 studies). In South America, a peak of incidence of CL was found in Chaparral, Colombia with a mean temperature of 20.6 ±1.4°C (Valderrama-Ardila et al. 2010), and a ~16± 5.7°C with all areas of incidence in the Andean region of Colombia (Pérez-Flórez et al. 2016). In addition, the same study in this Andean region found CL incidence was higher in areas where annual rainfall was 1,841±660.3 mm. In a geostatistical model of leishmaniasis incidence in Brazil, a 207-530 mm range of precipitation in the warmest quarter was an important risk factor for CL (Karagiannis-Voules et al. 2013).

In North Africa, a temperature of 9.4° to 22.1° C contributed 20.7% of the variation in an Ecological Niche Model of the vector in Tunisia. Furthermore, in this country the vector occurred in the driest quarter of the year with rainfall below to 37 mm (Chalghaf et al. 2016). In addition, in Ethiopia a temperature range between 17.2° and 23.8° C was associated with CL occurrence (OR=25.70) and annual rainfall between 903.4 and 1715.8 mm increased the risk of CL (OR= 2.67) (Seid et al. 2014).

Discussion

Our analyses demonstrate that the incidence of leishmaniasis is influenced by a variety of environmental, landscape and socioeconomic factors. In the first half of the 20th century, the principal risk factors for leishmaniasis were proximity to forest areas and distance from population centers (Southgate 1964; Moškovskij and Duhanina 1971; Ashford et al. 1973; Forattini et al. 1976). In the early 1990s, studies demonstrated that deforestation and development of rural settlements near forests increased VL and CL incidence (Montoya et al. 1990; Mott et al. 1990; Grimaldi and Tesh 1993), suggesting that the parasite is able to adapt to ecological changes by adopting peri-domestic sand flies as vectors and domestic animals as reservoirs. At present, people living in urban or peri-urban areas are at the greatest risk of infection (Machado-Coelho et al. 1999; Pigott et al. 2014). These populations have a high probability of contact with sand flies coupled with socioeconomic characteristics that make them particularly vulnerable to leishmaniasis.

We found a greater number of studies of VL relative to CL, consistent with previous reviews (Perilla-González et al. 2014). VL is lethal without treatment and is more common in urban environments and as a result, has received more attention. However, CL was also present in periurban environment (Steffens 2010; Gomez-Barroso et al. 2015; de Oliveira et al. 2016) and without treatment could be associated with other health problems.

Below, we present a conceptual model to illustrate the interplay between risk factors analyzed in the studies included in this review and how such interactions can be used to understand the leishmaniasis transmission cycle (Fig. 4). The studies reviewed here not only identify several important factors related to leishmaniasis risk but also highlight how socioeconomic (Fig. 4A), landscape (Fig. 4B) and climatic factors (Fig. 4C) influence disease transmission.

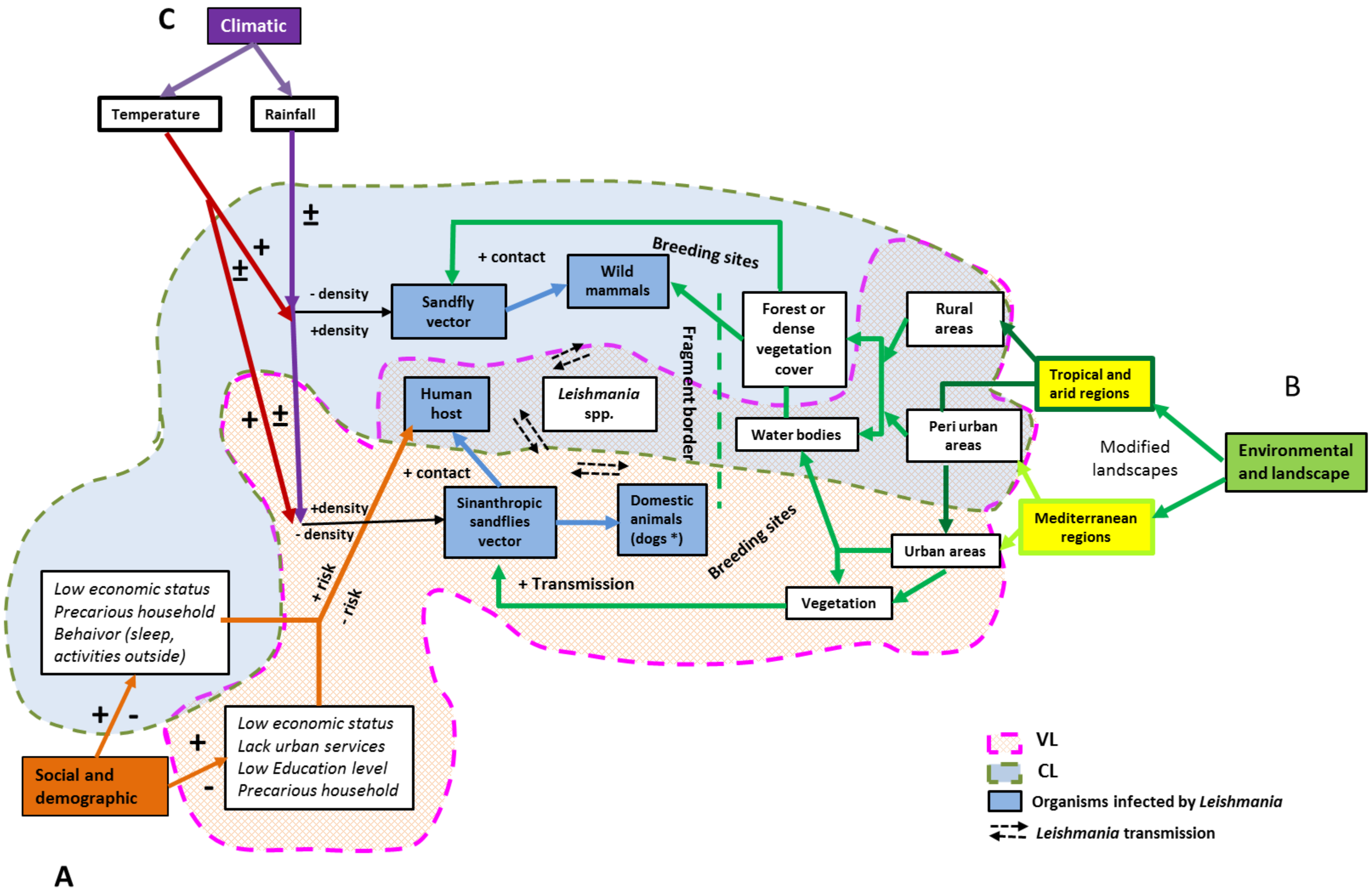

Figure 4. Interaction of risk factors which influence the incidence of visceral (VL) and cutaneous leishmaniasis (CL). Arrows show factors that influence transmission: **(A)** orange = socioeconomic factors; **(B)** green = environmental factors**; (C)** climatic factors: brown= temperature; purple = rainfall. **(±)** Represent intermediate values of temperature and rainfall **(*)** Dogs are susceptible to some species responsible of VL especially in New Word. Segmented green line represents vegetation border between landscape components.

Socioeconomic factors. In the Old World, Mediterranean, tropical and arid regions have a long history of human intervention that has placed human populations close to the transmission foci. In contrast, environmental modifications in tropical areas of the New World are more recent and the percentage of the landscape that remains unmodified is still considerable in proportion to the modified area.

Our analysis demonstrates that urbanization is linked with VL in the New World and with both clinical forms in the Old World. These observations are consistent with Pigott et al. who found that urban land cover is associated with an increment of VL risk worldwide and for CL in the Old World. To become urbanized, leishmaniasis depends on the main vector associated with transmission of the parasite. In the Old World where *Phlebotomus* spp. with synanthropic and anthropophilic behavior are the main vectors, the transmission of VL and CL occurs in the peri-domestic environment in tropical rural areas while in Mediterranean regions, it occurs in urban areas and other peripheral urban settlements (Ready 2013). Similarly, in the tropical New World, *Lutzomyia longipalpis* is the main vector of *Leishmania infantum* responsible of VL. This vector species can survive in urban areas, even in the absence of surrounding forests (Lainson and Rangel 2005) and *L. infantum* has the dog as main reservoir, a species that is quite susceptible to infection (Dantas-Torres 2007). However, vector species of CL in the New World tropics usually remain in peripheral areas close to forest. In fact, the reservoirs for the parasites of CL are generally wild rodents that surround peri-urban areas (da Silva and Cunha 2007).

Socioeconomic factors such as education level and poverty are frequently associated with malnutrition, poor housing, and lack of sanitary services (Navin et al. 1985; Rijal et al. 2010; Maia et al. 2013; Maia et al. 2016). These conditions can foster continued transmission of the disease (Ranjan et al. 2005; de Araújo Pedrosa and de Alencar Ximenes 2009). For example, precarious living condition increase leishmaniasis risk because some types of household construction materials offer optimal conditions for sand fly development (Reithinger et al. 2010; Singh et al. 2010; Ponte et al. 2011). Phlebotomine adults find suitable resting and breeding sites in places where cracks or holes in the walls or damp floors are available (Bern et al. 2000; Schenkel et al. 2006; Uranw et al. 2013). Lack of sanitation services can also attract wild or domestics reservoirs (Machado-Coelho et al. 1999) or be a potential breeding site for sand flies (Costa et al. 2005; Moreno et al. 2005).

All of these factors could increase the risk of leishmaniasis and also allow the development of the disease in infected individuals, especially if medical services are inadequate (Alvar et al. 2006; Perilla-González et al. 2014; Pigott et al. 2014) and households lack water supply (de Almeida et al. 2011), increasing the prevalence in areas with these characteristics (Boelaert et al. 2009). Moreover, in areas where leishmaniasis overlaps with AIDS or other diseases, the risk of leishmaniasis infection increases considerably (Desjeux 2001). Such overlap is a risk factor in urban areas of the Mediterranean region of Europe where the re-emergence of VL and CL has been caused by an increase in the number of immunosuppressed people rather than lack of sanitation and health services (Steffens 2010).

A high number of individuals per dwelling could also reflect low socioeconomic status (Alves et al. 2016). Rising population densities in peripheral neighborhoods could attract more sand flies because CO_2 attracts sand flies and larger human populations emit more CO_2 (Campbell-Lendrum et al. 1999). Migration from rural to urban areas (Alcais et al. 1997; Monteiro et al. 2009) and the exponential population growth in peri-urban areas have increased the number of dwellings lacking sanitation services (Madalosso et al. 2012).

In addition, work in agriculture, hunting or timber collection inside the forest especially at the end of the afternoon, exposes individuals to sand fly bites, increasing the incidence of the disease (Jones et al. 1987; Espejo et al. 1989; Weigle et al. 1993). Sand flies are active at twilight and night; less so at dawn when the decrease of temperature drives them to their natural hiding places (Forattini et al. 1976). Sleeping outdoors or without protection against sand flies bites, increment disease risk (Davies et al. 1997; Barnett et al. 2005; Bashaye et al. 2009). These conditions are generally more common in rural areas or areas close to forest (Almeida and Werneck 2014).

Likewise, disease risk increase with the presence of mammals that can act as potential reservoirs of the parasite. Wild, synanthropic, or domestic animals could be part of the cycle (Beier et al. 1986; Oliveira et al. 2006; Cardoso et al. 2015). The presence of dogs in households is considered a high risk factor for the incidence of VL especially in the New World (Votýpka et al. 2012). Dogs are very susceptible to infection, develop the disease, and act as a source of further infection of *Leishmania infantum* one of the principal agent responsible of VL in the New World, and both VL and CL in the Old World (Dantas-Torres et al. 2012). Although cattle can increase the risk, they may also decrease leishmaniasis (Bern et al. 2010) by serving as the principal source of sand fly blood meal and diverting bites to humans mainly in countries with anthroponotic transmission of *L. donovani* where the presence of other human VL cases in the settlements are also a high risk factor (Bern et al. 2005; Kolaczinski et al. 2008).

More research to establish control measures is needed to understand the interaction between leishmaniasis and poverty (Bern et al. 2010). In the absence of control measures, other factors such as high educational level, good nutrition, and high wealth level cannot by themselves reduce the risk of infection. Furthermore, without the presence of the vector at high densities, new settlements in periurban areas are not always at high risk for leishmaniasis (Alves et al. 2016).

Environmental and landscape factors

Conversion of natural forest to other land uses in the last decades has led to habitat fragmentation and altered landscape composition (Wade et al. 2003). The spread of the vector and disease at macro scales is associated with migration and expansion of human population into natural areas, creation of roadways, energy networks, new farm lands, and poorly planned urban development (Cardim et al. 2013). These changes in the landscape increase contact of human populations with the edges of vegetation areas which shelter sand fly vectors (Patz et al. 2004). New settlements near forests act as foci of leishmaniasis enabling the domestication of the cycle. At the same time, expansion of agricultural crops provides a new food source for natural reservoirs of leishmaniasis such as rodents (Dawit et al. 2013; de Oliveira et al. 2016).

In human modified landscapes, fragments of vegetation close to dwellings play an important role in the transmission cycle. Vegetation areas provide the environmental conditions for sand fly breeding sites and development while at the same time act as shelters of wild reservoirs (Ocampo et al. 2012; de Santana Martins 2015). Populations of many phlebotomine species increase from secondary forest to mature forests (Rutledge and Gupta 2002; Kariyawasam et al. 2015) except for the species that have adapted to urban environments and do not need dense vegetation to survive such as Lutzomyia longipalpis (Salomón et al. 2015).

High values of NDVI or vegetation near incidence areas found in several studies, suggest proximity to natural habitats connects human dwellings with the vector breeding sites (Aparicio and Bitencourt 2004; Cerbino Neto et al. 2009; Gomez-Barroso et al. 2015; Menezes et al. 2016). The presence of vegetation or forest areas near houses, increase the number of sand flies in peri-domestic areas and the probability of being infected (Miranda et al. 1998; Andrade-Narvaez et al. 2003; Dias et al. 2007). Indeed, studies that analyzed the abundance of the vector at different distances from the forest to households of infected people found the number of cases decreased with distance (Werneck et al. 2002; Feliciangeli et al. 2006). The flight range of sand flies is around 200 m, with *P. argentipes* and *P. orientalis* having flight ranges of ca. 500 m and those of *L. longipalpis* and *P. caucasicus* 1000 m or more (Rutledge and Gupta 2002). However, vegetation is a risk factor in tropical forest areas and Mediterranean forest, but not in arid areas where vegetation is not dense and the burrows of mammals and caves may serve as breeding sites of sand flies (Holakouie-Naieni et al. 2017).

The presence of waterbodies is also related to vector abundance and its distribution (Schenkel et al. 2006; Nilforoushzadeh et al. 2014; de Oliveira et al. 2016; Rajabi et al. 2016), possibly because waterbodies provide the air moisture necessary for sand fly breeding (Bhunia et al. 2011). The effects of soil type on disease incidence may also reflect moisture conditions. Studies showed that soil types characterized by water retention as fluvisols, the typical soil of river areas, and clayey soils which also retain water were associated with high disease incidence, possibly by facilitating larval development of sand flies (Sharma and Singh 2008).

Because proximity to forests and waterbodies have been associated with disease incidence, control measures in recent years have focused on forest clearing and wetland drainage near incidence areas (Wood et al. 2014). However, we do not advocate that deforestation and wetland draining is the solution for decreasing the risk of leishmaniasis. More studies are necessary to clarify how exposure to the disease agent would change the structure, composition, or function of landscape changes (Myers et al. 2013), seeking environmentally friendly alternatives of disease control.

In our review, we could not identify a range of altitudes significant for leishmaniasis incidence. Clearly, altitude is related with other environmental features that influence vector distribution (Quintana et al. 2012; Ferro et al. 2015; Prudhomme et al. 2015). Likewise, topographic characteristics such as slope show a significant impact on the presence and abundance of vectors. However, it is unclear whether these effects simply reflect the indirect effects of temperature shifts with elevation or soil moisture with topography highlighting the need for more studies that can clarify the importance of these factors in the genesis and transmission of the disease.

Climatic factors

Climatic conditions are generally important risk factors for vector-borne diseases (Cardenas et al. 2006). Their effects on leishmaniasis vary according to geographic area and depend on the clinical form and vector species. Studies in Mediterranean, tropical and arid regions suggest that sand flies thrive between 19°and 30°C (Kassem et al. 2012; de Souza et al. 2015; Giannakopoulos et al. 2016; Pérez-Flórez et al. 2016), and bite at temperatures between 20° and 30°C (Rutledge and Gupta 2002). Temperatures over 30°C negatively affect sand fly population density (Karagiannis-Voules et al. 2013; Moo Llanes 2016).

Rainfall was also associated with leishmaniasis transmission and vector abundance. High rainfall and relative humidity (Elnaiem et al. 2003; Pérez-Flórez et al. 2016) increase primary productivity (Salomón et al. 2004; Ben-Ahmed et al. 2009; de Souza et al. 2012) of forest vegetation which provides food and burrows for reservoirs (Chalghaf et al. 2016), providing an ideal environment for sand flies (Andrade-Narvaez et al. 2003; Quintana et al. 2012).

The vectors of *Leishmania* involved in each of the two clinical forms have a different rainfall range around the world. Based on the literature reviewed, we cannot specify a range of precipitation as we did with temperature. However, some modeling analysis report a high precipitation index is an important environmental factor for cutaneous leishmaniasis incidence in the tropics (Salomón et al. 2004; Chaves and Pascual 2006; Ali-Akbarpour et al. 2012) because the vectors related to this clinical form are associated with the presence of dense vegetation. However, high precipitation is not favorable for visceral leshmaniasis in the tropics (Karagiannis-Voules et al. 2013; Pigott et al. 2014). Taking into account that VL in tropical regions occurs in highly urbanized areas, we can hypothesize that moderate levels of precipitation can foster incidence areas by maintaining humidity in the environment.

Nevertheless, without the protection of vegetation, heavy precipitation could decimate sand fly populations.

Conclusion

Our review describes the complexity of transmission and incidence of a disease that presents two main clinical forms and can exist at a broad range of environmental and climatic conditions. We also highlight how complex interaction between risk factors can exacerbate or moderate the incidence of leishmaniasis.

The review highlights the main factors that influence the risk of leishmaniasis. High disease incidence is associated with several environmental, climatic, and socioeconomic conditions. Transmission patterns are similar in all regions, requiring human contact with vegetation areas that harbor reservoir vectors and mammals under warm climatic conditions. Differences among clinical forms and regions depend on the species of vectors involved in each type of leishmaniasis and if these are able to easily adapt to urban environments (e.g., VL in the tropics, arid and Mediterranean regions) or depend on less disturbed environments (e.g., CL in the Neotropics). Research is needed to analyze the interactions of risks factors and how they vary across vector, reservoir species and environmental conditions in countries where the disease is endemic. Developing effective control measures will also require a better understanding of the likely impacts of future climatic conditions on the transmission cycle.

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Supporting information

S1 Articles reviewed

Table S1. Main significant variables found in the studies reviewed

	Reference	Location	Clinical form	Desing	Statistical Analysis	Analyzed variables	Significant variables
1	Alcais et al. 1997	North La Paz and Beni, Bolivia	CL	Case study	Cox proportional hazards model to estimate Relative Risk (RR) The piecewise exponential model (PEM) to asses CL risk evolution among population	Gender Area of residence Native/migrant status Current and previous home-forest distances Current and previous activities Time of exposure: >4 hr.; 2-4 hr.; <2 hr. Age Number of initial cutaneous lesions(cl) Duration of initial cl. Localizations of initial cl Treatment	Gender Native/migrant status Activities Age: adolescence
2	Andrade-Narvaez et al. 2003	Campeche State, Mexico	CL	Case study, entomological collected and mammalian collected.	-	The place of incidence of CL in humans. The rate and time of infection in rodents and sand flies between. February 1993 and March 1995 were analyzed.	Forest Winter high humidity Low temperature
3	Aparicio and Bitencourt 2004	Itapira, São Paulo state,	CL	GIS[1]-NDVI[2]	-	Case distance to vegetation fragments Altitude	Households near vegetation fragments

		Brazil				Vegetation index (NDVI)	< 200m Altitude <750m NDVI2 0.45-1
4	Ashford et al. 1973	Ethiopia (Kutaber, Ochollo and Aleku)	CL	Entomological collected Mammalian collected for skin test and released Surveys	-	Vectors Wild animals presence	Species of vectors Presence of hyrax and other mammals infected
5	Bsrat et al. 2015	Tigray, Ethiopia	CL	Cross-sectional study	Measures of frequency in percentage Odds ratio (OR)	Cave/gorge(300 m) Hyrax near home (300m) Wall condition Animal burrow near home Animal dung near home Farm near home (300 m) Age Distribution of active lesions Number of active lesions	Presence of cave /gorge Walls with cracks /holes Animal burrow Animal dung Farmland
6	Chalghaf et al. 2016	Tunisia	CL	GIS[1], cases, entomological collected and ENM[3]	Pearson correlation tests. The Grinnellian ecological niches MaxEnt software.	Climatic data (temperature and precipitation) Elevation Slope Aspect Compound topographic index Land cover	Rainfall < 37 mm Temperature 9.4- 22.2 °C

7	Chaves and Pascual 2006	Costa Rica	CL	Non stationary time series analysis	Linear regression models and forecasts.	Climatic data (temperature and precipitation)	ENSO Temperature 23° -27°
8	Davies et al. 1997	Peru	CL	Entomological collected Epidemiological survey	Regression analysis	Spent sleeping in the fields, Number of dogs/person, Number of persons/house	Sleep in temporary shelters in crop areas.
9	De Araújo Pedrosa and Alencar Ximenes et al. 2009	Alagoas State, Brazil	CL	Case-control study	Univariate logistic regression used to estimated OR	Gas stove Forest < 200 m from home Work activity urban/rural Wall material in home Animals inside home Years of schooling Family income Forest leisure Birds inside home Dogs outside home Cats outside home	Absence gas stove Forest < 200 m away Rural activities Forest related to leisure activities Animals inside the house Non-durable wall material in the house
10	De Oliveira et al. 2016	Rio de Janeiro, Brazil	CL	GIS[1]	Geoprocessing analysis of the environment.	Altitude Slope Geomorphology categories Soil categories Soil use Plant cover categories Rural and urban cover	Low altitude 0-40 m Low slope 0-2.5 degrees Geomorphology categories: colluvial alluvial plain Soil categories:

						Distance to vegetation	Planosol Soil use and plant cover: Urban expansion: Rural areas Urban and peri-urban areas House close to vegetation Pastures Reliefs(accumulation of water)
11	Espejo et al. 1989	Yungas, Alto Beni and Pando, Bolivia	CL	Case study	Chi square test	Gender Number of lesions Professional activities	Males
12	Holakouie-Naieni et al. 2017	Iran	CL	Case study	Getis-Ord Gi statistic	Description of high/low incidence clusters	Areas dry and desert climates
13	Jones et al. 1987	Tres Braços, Salvador, Bahia State, Brazil	CL	Case study	_	Gender Position in family House characteristics location of house in relation to possible vector habitats (forest, cocoa) Water supply Toilet facilities	Males Activities
14	Kariyawasam et al. 2015	Matara, Sri Lanka	CL	Cross-sectional survey	Spatial analysis Chi square	Forest area Nature of walls	Proximity to forest areas

					Logistic regression analysis to estimated OR Kernel density.	Protective measures against insect bites Monthly income Time spent outdoors Paddy cultivation Coconut plantation Disease awareness Covering of arms and legs with clothing while outdoors Mode of water supply Presence of animal shelters Occupation	Un-plastered brick walls Absence or low usage of protective measures against insect bites Low income Excessive time spent outdoors
15	Machado-Coelho 1999	Minas Gerais, Brazil	CL	Spatial clustering	Poisson regression analysis Moran's index Empirical Bayes index Oden's index	Urbanization indicator(urban/ rural) houses without sanitary disposal houses with exposed garbage	Rural area Higher proportion of households lacking sanitary deposals High proportion of households with exposed garbage
16	Miranda et al. 1998	Vale do Paraíba and North Coast of São Paulo State, Brazil	CL	GIS[1] and cases recorded available	Satellite remote sensing	Vegetation Landscape changes Cases of leishmaniasis Precipitation data	Streams and shrub vegetation
17	Monteiro 2009	Paraná State, Brazil	CL	Cases recorded available	Chi square test	Autochthonous population Migrant population	Migrant population

18	Nasser et al. 2009	Campinas, São Paulo State, Brazil	CL	GIS[1] and cases recorded available	Chi square test Spatial analysis (kernel)	Socio-demographic (gender, age, occupation, residence time), Closeness of domicile to forest	Peri-domestic transmission. Proximity to forest.
19	Nilforoushzadeh et al. 2014	Isfahan, Iran	CL	Cross-sectional and case-control study	Chi-square test Logistic regression	Economic level low/high/medium Peri-domestic old or ruined houses Water sources distance to house Roadways distance to house Peri-domestic animal sheds or kennels House measurement Food storage Insect control Floor type Peri-domestic unutilized land Agricultural lands distance to house Job Involvement with animals Involvement with soil Bite exposure	Low economic level Old or ruined houses Distance to water source >150 m Distance to roadway > 50 m Peri-domestic animals
20	Ocampo et al. 2012	Chaparral, Colombia	CL	Entomological collected, mammals collected and surveys	Negative binomial regression	Forest coverage Altitude Gender Land use Crops House materials Use of insecticide Domestic animals	Higher coverage of forest

						Number of people per house	
21	Pérez-Flórez et al. 2016	Colombia Andean region	CL	GIS[1] and cases recorded available	Spatial analysis: Random-effects Poisson model Bayesian framework Markov Chain Monte Carlo. Bivariate and multivariate analysis	Forest and secondary vegetation Rainforests Livestock agroecosystems Temperature(annual/seasonality) Precipitation(annual/seasonality) Coffee agroecosystems in association Non-technified crop Population density	Land use Rainforest Agro-livestock Temperature (annual/seasonality) Rainfall (BIO 12)
22	Rajabi et al. 2016	Isfahan, Iran	CL	Geographic automata system and case recorded available	Agent-based model (ABM)	Land cover (desertification, farming, urban and rural areas) Accessibility(health center, roads, rivers, livestock and poultry) Population centers	Desertification areas Riverside population center
23	Reithinger et al 2010	Kabul, Afghanistan	CL	Case study	Univariate and multivariate analysis	Age Gender Household design (i.e. number of rooms, number of windows), construction materials (i.e. wall type, ceiling type) Preventive methods (i.e. number of windows screened, household bednet ownership, reported bednet use) Owner- ship of animals (i.e. household ownership of dogs, chicken, goats, sheep and cattle)	Age Brick wall type

24	Salomon et al. 2004	Argentina	CL	Entomological collected	Fisher test Chi square William's geometric means	Climatic data	Sand flies and rainfall correlated
25	Seid et al. 2014	Ethiopia	CL	GIS[1] and case study	Odds ratio (OR) of the bivariate logistic regression and OR and p-value of the multivariate analysis	Slope Altitude Rainfall Average temperature elevation Soil type	Slope > 4.6 degrees Altitude 1400 -2700m Annual rainfall 903.4-1715.8 mm Temperature 10.6-23.8°C
26	Sosa-Estani et al. 2001	Província de Salta, Argentina	CL	Cohort study	OR of multivariate model	Cattle management Outdoor activities Sleeping habits Peri-domestic animals Households characteristics Socio-demographic (age/gender) Clinical analysis	Cattle management Hunting Sleeping at the workplace Sleeping outside of the bedroom, Presence of three or more pigs in the yard Windows that cannot be locked
27	Valderrama-Ardila et al. 2010	Chaparral, Tolima, Colombia	CL	GIS[1] and cases recorded available	Conditional autoregressive Poisson model to represent spatial correlation.	Percent forest or shrub Population density Mean temperature	Higher coverage with forest or shrubs Lower population density Mean temperature

					Bayesian framework Models were fitted using Markov chain Monte Carlo		
28	Votýpka et al. 2012	South Anatolia, Turkey	CL	Case-control study	Odds ratio of multivariate model	Sleeping outdoors Presence of domestic animals and where they were kept at night Cattle House construction materials Toilet location Job travel to other areas Age Gender Occupation Education Time of living in village Family size	Sleeping without bed nets Ownership of a dog Cattle ownership
29	Weigle et al. 1993	Tumaco, Nariño, Colombia	CL	Case-control study	Maximum likelihood estimation was used to estimate OR	Age/ Gender Farming occupation Daily forest hours Entered forest Hunting and lumbering Cleaning land of trees House construction materials Fishing	Male age > 10 years Farming occupation Entering in the forest after sunset Hunting and lumbering Tall trees near the home

30	Almeida and Werneck 2014	Teresina, Piaui state, Brazil	VL	Ecologic study	CART algorithm models	Socioeconomic and demographic variables (literate, gender, age, income, residents in the house, water supply, garbage collection, years of schooling) Environmental classification(land coverage)	Larger area with covered dense vegetation Percentage of literate heads of the household Percentage of household with up to 3 residents above the third quartile
31	Antonialli et al. 2007	Mato Grosso do Sul State, Brazil	VL	Cases recorded available and spatio-temporal analysis	_	Highway Rail-road Pipeline	Pipeline
32	Argaw et al. 2013	Ethiopia and Sudan	VL	Case-control study	Univariable and backwards stepwise multivariable conditional regression	Migrants HIV infection Slept near dogs Walls of thatched grass on wood frame Slept under an acacia at night Slept on ground No formal schooling Residents Always slept under net in rainy season Slept under acacia at night Monthly expenditure ,100 birr per person Head of house left school before class 5 Ever slept under net	Migrants with HIV infection Migrants who slept near dogs Walls of thatched grass on wood frame Slept under an acacia tree at night Slept on the ground Lower education status

						Staple food is porridge	
33	Badaró et al. 1986	Jacobina, Bahia State, Brazil	VL	Case study	_	Age Nutrition Other disease House location	Young age Malnutrition Parasites
34	Barnett et al. 2005	India	VL	Case detection study	OR of multivariate models	Sleeping location and habits Number of people Electricity House construction materials Animals ownership Income Bed net ownership Case of VL present or near the house Gender Age Religion	Sleeping downstairs and outside in the summer
35	Bashaye et al. 2009	Ethiopia	VL	Case-control study	Univariate and step-wise multivariable conditional logistic regression	Sleeping location and habits. Domestic animals and where they were kept at nights. Bed net ownership and use House construction materials. Travel to the Sudan border area Socioeconomic indicators	Sleeping under an acacia tree during the day Sleeping outside at night
36	Bavia et al. 2005	Bahia, Brazil	VL	GIS[1]-NDVI[2]	Linear multiple regression	NDVI[2] image use Vegetation cover	Low NDVI[2] values Low vegetation

						Climatic data(rainfall, temperature) Demographic Sand flies presence	density
37	Beier et al. 1986	El Agamy, Alexandria Governorate, Egypt,	VL	Entomological collected	_	Rodent burrows Drainage Poultry shed Rubbish around houses Larval development sites Vector breeding sites indoors and outdoors: Fig trees Garden Rabbit/goat pen Rock piles	Rodent burrows Drainage areas Poultry sheds Rubbish
38	Bem-Ahmed et al. 2009	Tunisia	VL	GIS[1]	Poisson spatial regression	Climatic data	Mean yearly rainfall Semiarid bioclimate zone Warm winters
39	Bern et al. 2000	Nepal	VL	Case-control study	Univariate and multivariate model	Housing conditions (walls/floor). History of illness and treatment. Socioeconomic indicators Animal husbandry practices Sleeping habits.	Dampness observed in the mud floor
40	Bern et al. 2005	Bangladesh	VL	Cross-sectional study	Univariate and multivariate model	Distance of VL case Inward and outward migration	Living in the same house with a patient

						Socioeconomic factors(age, gender, occupation) Animal ownership House construction Sleeping location Bed net use Dietary practices	
41	Bhunia et al. 2010	Bihar, Gangetic plain, India	VL	GIS[1], entomological collected, and cases recorded available	Information values (Ij) as log10. Descriptive statistics, measures of kurtosis and Skewness. A linear- regression model, based on the maximum-likelihood method	Waterbody/river Woodland Urban/built-up Soil characteristics Temperature Monthly rainfall Relative humidity Evergreen forest Dense forest Grassland Closed shrubland Open shrubland Crop/ agricultural land Agro-ecological characteristics	Waterbodies Woodland Built-up areas Soil of the fluvisol type Temperature 25 - 27°C Rainfall 100 - < 160 mm Relative humidity 66% -75%
42	Bhunia et al. 2011	India	VL	GIS[1]-NDPI[4] entomological collected data clinical collected	Spatial statistical analysis. Poisson regression analysis	Associations between inland water bodies, sand fly prevalence and Leishmania infections were investigated.	non- perennial river banks

43	Borges et al. 2009	Belo Horizonte, Minas Gerais State, Brazil	VL	Case control study	_	Animals presence in the house	Ducks Rodents Birds chickens dogs
44	Brazuna et al.2012	Campo Grande, State of Mato Grosso do Sul, Brazil	VL	Case study	Chi square test	Age Gender county region of residence vector presences	>40 Male
45	Cardim et al. 2013	São Paulo state, Brazil	VL	GIS and case recorded available	Measures of frequency in percentage. Odds ratio (OR)	Climatic data (temperature and precipitation) Highway and pipeline route	Highway Pipeline
46	Cardim et al. 2016	São Paulo state, Brazil	VL	GIS and case recorded available	Bayesian incidence	Highways	Highways
47	Cerbino Neto et al. 2009	Teresina, Brazil	VL	Spatial analysis, NDVI[2]	Cook's Moran global spatial autocorrelation statistic.	Population growth NDVI Piped water Garbage collection Sewage system Schooling Income	Population growth High vegetation index

48	Costa et al. 2005	Brazil	VL	Case-control study	OR and RR	Urban services Household rubbish was regularly collected or not Socioeconomic and demographic information (age, gender, literacy, level of schooling and migration). Household structure	Inadequate sewage system no regular rubbish collection
49	de Almeida et al. 2011	Teresina, Piaui State, Brazil	VL	GIS[1]and cases recorded available	OR of logistic regression	Households connected to the water supply Households with regular garbage collection Households connected to the sewage system Mean income of heads-of- households Illiteracy rate Children less than five years of age as a Percentage of the total population	Lack in water supply Lack in regular garbage collection Few households connected to sewage system Mean income Illiteracy rate
50	de Araújo et al. 2013	Belo Horizonte, Minas Gerais State, Brazil	VL	Case study, GIS[1] and NDVI[2]	Log-relative risk of VL (log-RR). Bayesian approach and the Markov Chain Monte Carlo	Number of infected dogs per inhabitant % mean of illiterate persons % mean of householder with less than 4 years of education % mean of householder with less than 2 minimum wages. Average income (inverted) of the householder Health vulnerability index (IVS) NDVI[2] Altitude squared	Number of infected dogs per inhabitant % mean of illiterate persons % mean of householder with less than 4 years of education % mean of householder with less than 2 minimum

							wages Average income (inverted) of the householder
51	Elnaiem et al. 2004	Gedaref, Sudan	VL	Spatial analysis NDVI[2] data clinical collected	Univariate correlation analysis Multivariate analysis	Rainfall Altitude(m) Distance from rivers Direction of slope Wetness index Slope Flow accumulation NDVI[2] Soil types	Average rainfall 939 mm and Altitude 544 m
52	Faucher et al. 2012	Southeastern, France Nice and Marseille	VL	GIS[1] and case recorded available	Kulldorff's spatial scan statistic	Land cover: mixed forest, (scattered habitation, agricultural areas, foothills areas, urban areas) Wind resource Temperatures Altitude Slope	Scattered habitation Mixed forest Foothills areas Urban environment
53	Feliciangeli et al. 2006	Western Venezuela	VL	Spatial distribution analysis	Williams geometric mean Generalized lineal model	Woodland border Presence of sand flies	House in proximity to the woodland

54	Giannakopoulos et al. 2016	Thessaly, Greece	VL	GIS[1], cases recorded available, dog cases collected and ENM[3]	ENM in the Maxent modeling used the Jackknife procedure	Altitude Farms distance Max temperature of warmest month Distance from permanent water NDVI[2] Mean diurnal range Temperature annual range Population density Temperature seasonality	Low altitude < 200m Irrigated and cultivated areas Max temperature of warmest month (BIO 5)
55	Kolaczinski et al. 2008	Kenya and Uganda	VL	Case-control study	Univariate and multivariate analysis using conditional logistic regression to estimated OR.	Socioeconomic status Treating livestock with insecticides Termite hill near house Acacia trees near house Number of rooms Sleeping area (above ground vs. on ground) Occupation Daily activity /sleeping habit Use of a mosquito net and duration of use Knows about VL symptoms Knows about VL transmission Stunted Underweight Wasted Current malaria infection	Low socioeconomic status Treating livestock with insecticides
56	López et al. 2016	Posadas, Argentina	VL	Control-case study	Odds ratio (OR)	Socioeconomic profile and quality of housing(income, level of education,	Precarious house conditions

						household materials, number of residents) Stay outside home after 18h Dogs ownership Population and sociodemographic characteristics of the household group (sex, age, educational level, occupational situation of its members) Use of insect repellents Knowledge about VL Urban service Garbage collected	Stay outside home after 18h Dogs ownership
57	Maia et al 2013	Pernanbuco , Brazil	VL	Cross-sectional study	Frequency and percentages	Garbage collection Sewage system Age and Gender Symptoms appeared Treatment was done Family members affected, Dog with VL euthanized Presence of sand flies Protection against mosquitoes use Chicken in the house Had some knowledge of the relationship of the disease with dogs and organic matter	Deficiency of garbage collection Lack of sewage system
58	Maia et al. 2016	Bahia, Brazil	VL	Cross-sectional study	Chi square test, McNemar test, Fisher's exact test,	Presence of backyard Type of the yard Presence of animal pets	Household without a sand backyard

					Kruskal–Wallis test, and Mann– Whitney test.	Specific type of pet Use of repellents Presence of cohabiting resident with *Leishmania* infection	
59	Menezes et al. 2016	Formiga, Minas Gerais, Brazil	VL	Case study	Frequency, percentages and OR.	Characteristics of population: Age and gender Education level Family income Number of residents per household Risk factors: Having a pet Hematophagous insects Rodents Presence of an vacant lot watercourses and green areas near the residence regular waste collection presence of a yard with a plantation regular cleaning of the house area place of residence	Place of residence and a higher number of risk factors
60	Moreno et al. 2005	Belo Horizonte, Minas Gerais State, Brazil	VL	Cross –sectional study	Univariate analysis to estimate OR	Domestic refuse storage and disposal Time spent outdoors Presence of domestic animals Demographic variables(age, gender, birthplace) Socioeconomic status Household characteristics including all annexes, buildings and waste in the back	Garbage not collected by the public system and not buried Vector Time spent outside the house between 6-10pm Ownership of birds

						yard Wastewater disposal Existence of eroded areas near the house Dogs Knowledge of human and canine leishmaniasis and vectors Factors related to control measures	
61	Navin et al. 1985	Honduras	VL	Case-control study	_	Type of house Domestic animals Family lived in when the patient became ill.	Type of house poorly constructed.
62	Oliveira et al 2006	Belo Horizonte, Brazil	VL	Case-control study	Univariate analysis Conditional logistic regression to estimated OR Chi-square tests	Microenvironment (indoor, outdoor, animal indoor, and animal outdoor), and also considered the level of urbanization of the area	Animals in the neighborhood
63	de Oliveira et al. 2012	Mato Grosso do Sul, Brazil	VL	GIS[1], NDVI[2] and entomological collected	Simple linear correlation analysis (Spearman correlation coefficient)	NDVI[2] Percentage of vegetation cover	Positive correlation between abundance of sand flies and the percentage of vegetation cover and NDVI[2]
64	Ponte et al. 2011	Maranhão , Brazil	VL	Cross-sectional study	Univariate and multivariate logistic regression models	Households materials Place of bathing Presence of vector Age/Gender	Straw roof and mud walls Bathing outdoors Sand flies inside or

						Income Garbage destination Insecticide spraying Animals domestic/Peri-domestic Use of mosquito net Use of repellents	outside dwelling
65	Rajabi et al. 2016	Southern Caucasus	VL	GIS and cases recorded available	Weights of evidence (WofE) Logistic regression Fuzzy logic	Proximity to nomadic villages Proximity to rivers Climate data Distance to health centers Land cover Altitude Population density	Environmental factors, such as proximity to rivers and rural lifestyle
66	Ranjan et al. 2005	Bihar, India	VL	Case-control	Mantel-Haenszel chi- square test On the basis of the OR in univariate analysis. Multiple logistic regression models	History of other diseases in last year Education level Presence of vegetation Structure of the house (wall, roof, surface, and mosquito proofing in doors/windows, granary) Family history of Kala-azar Age and gender Family members Persons sleeping with index case Ownership of selected consumer items such as TV, radio, liquid petroleum gas for cooking Nutritional factors (types of foods consumed)	History of another disease in the last year Low education level Granary inside de house Bamboo trees near the house Type of wall in the house

						Congenital deformities Household Information General condition of the house Lavatory facility in the house	
67	Rijal et al. 2010	Terai, Nepal	VL	Cross-sectional survey	Spatial analysis cluster generalized estimating equation model	Age, gender, family size, occupation, household characteristics, livestock and past history of VL. Socioeconomic status (ownership of consumer durables, dwelling characteristics)	Male-gender Poverty
68	Schenkel et al. 2006	Nepal	VL	Cross-sectional study	Bivariate and multivariate analysis	Proximity of the household to stagnant water (within a radius of 50 m) House type (mud, brick, wood, cement) Age and Gender Family size Ownership of cows/ buffaloes or small animals such as fowl Number of rooms per house electricity Yearly family Income Sleeping site Use of bednets	Proximity the house of ponds House contributed in mud poor condition
69	Singh et al. 2010	India	VL	Case-control study	Univariate analysis Multivariate logistic regression model	Ownership of animals, keeping animals inside the house and sleeping outside in the vicinity of animals Socioeconomic status	Living in a thatched house Damp floors

						Housing conditions Bednet use and presence of (other) cases of VL Dampness of floor	
70	Southgate 1964	Nairobi, Kenya	VL	Case-study	Proportional risk ratio (RR)	Age and Gender Number of individual huts Details of construction Distance of huts from the nearest termite hill Presence of domestic animals Staple diet Source of water Family history of kala-azar.	Age and Gender (men between 20 and 60 years) Proximity to termite hills
71	de Souza et al. 2012	Bauru, São Paulo State, Brazil	VL	Space-time-analysis	Incidence rates and time series analysis. Linear regression analysis.	Meteorological data (temperature and precipitation) Data on age, gender and place of residence	Temperature was positively correlated
72	Tsegaw et al. 2013	Ethiopia	VL	GIS[1] and case study	Binary and multivariate logistic regression to estimate Odds ratio (OR)	Average temperature Soil type Altitude Rainfall Slope	Temperature 20-37°C Soil type: vertisols, lixisols, cambisols and luvisols Low altitude <1872 m Rainfall < 766 mm
73	Uranw et al. 2013	Dharan, Nepal	VL	Case-control study	Binominal multilevel model	Socioeconomic status Housing characteristic subdivided into	Poorest Thatched house

						'thatched houses without windows' 'thatched houses with windows' and 'brick houses' Gender Literacy Intravenous drug use Migration status and regular forest visit Proximity to previous VL cases	without windows
74	Werneck et al. 2007	Brazil, Teresina	VL	Spatial analysis, NDVI[2]	Multilevel and general model	Family income NDVI Running water Indoor sanitation Garbage collection Level of education Adequacy of housing Urbanization index	Poor socioeconomic conditions Increased vegetation NDVI
75	Werneck et al. 2002	Teresina, Piauí State Brazil	VL	GIS[1], cases recorded available and spatial analytical techniques	Locally weighted regression model	Peripheral neighborhoods Bordered forestland and pastures	Peripheral neighborhoods Bordered forestland and pastures

76	Yared et al. 2014	Ethiopia	VL	Case-control study	Chi square Univariate and backward multivariate conditional logistic regression Odd ratio	House construction material and its condition Domestic animal ownership Demographic and socioeconomic characteristics (age, gender, occupation, education, time of living in village and family size) Individual activity in the agricultural fields Sleeping habits Use of bed net	Houses with cracked wall Goat ownership Increased family size The number of days spent in the farm field
77	Gomez- Barroso et al. 2016	Madrid, Spain	VL/CL	GIS[1] and spatial analysis	SaTScan spatial statistic estimator developed by Kulldorf. Moran's index.	Population data (sex, age, migration) Vegetation	Migration Urbanization close to vegetation areas
78	Gonzáles et al. 2010	North America USA and Canada	VL/CL	ENM[3] and GIS[1]	Maxent software package	19 bioclimatic data layers Vector occurrences data base	Climate changes Scenario AR
79	Karagiannis-Voules et al. 2013	Brazil	VL/CL	GIS[1], NDVI[2], and cases recorded available	Bayesian geostatistical negative binomial model	Precipitation Rural population and human development index Unsatisfied basic needs Infant mortality rate	Precipitation Socioeconomic level

			Human influence index Land surface temperature (LST) for day and night Normalized difference vegetation index (NDVI) Enhanced vegetation index (EVI) Temperature

[1]GIS Geographic information system. [2]NDVI normalized difference vegetation index. [3] ENM Ecological niche modeling. [4]NDPI Normalized Difference Pond Index. *The model was based in literature analysis about *Leishmania* and its vectors. (-)Not statistical analysis specified.

Chapter 2

Environmental and socioeconomic risk factors for visceral and cutaneous leishmaniasis in São Paulo, Brazil

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Abstract

Leishmaniasis is a vector-borne disease mainly affecting individuals of low socioeconomic status in tropical regions. The disease is caused by the protozoan parasite *Leishmania* spp. The transmission cycle involves phlebotomine sand flies (Diptera: Psychodidae) as vectors and any susceptible mammals as reservoirs. The intensity of transmission to humans in tropical regions depends not only on environmental factors but also on the socioeconomic characteristics of human populations. Understanding how these factors influence the incidence of leishmaniasis is necessary to understand how this ancient zoonosis has adapted to novel human-modified environmental conditions and to predict future outbreaks. This study examines the associations between leishmaniasis incidence between 1998 and 2015 in the state of São Paulo, Brazil and socioeconomic and environmental predictors. We consider the two main clinical forms of leishmaniasis, cutaneous (CL) and visceral (VL). Specifically, we use generalized linear mixed models to quantify the association between landscape (native vegetation cover), climate (precipitation and temperature) and social factors (population characteristics, number of cattle heads, Human Development Index, Gini income inequality index and income per capita) and the incidence of CL and VL cases across the 645 municipalities in the state. Because the predictors of municipal-level occurrence (presence or absence of the disease) are likely to differ from those of the number of cases, we fitted mixed models of occurrence using logistic regression and used a negative binomial model for the number of cases. For CL, probability of occurrence increased with higher vegetation cover, greater economic inequality (Gini index), and high mean winter precipitation. For VL, probability of occurrence increased with high human development index (HDI), a larger number of cattle heads, and high values for maximum annual temperatures and minimum spring precipitation. The number of VL cases increased with high mean fall precipitation and the number of cases for both CL and VL was greater in years of high annual mean temperature. Understanding how these risk factors influence leishmaniasis transmission can inform predictions of future outbreaks and contribute to the development of public health policies.

Keywords: Leishmaniasis, São Paulo state, climate, municipalities, socioeconomic factors, vegetation cover

Introduction

In the last century tropical landscapes have been drastically transformed, with half of the potential forest areas converted to agricultural uses, cattle pastures, and urban areas (Laurance 2004; Wright 2005). Since landscape characteristics influence the biology of disease vectors and their reservoirs (Rodríguez-Morales 2013), these transformations can alter the distribution and incidence of vector-borne diseases (Reisen 2010). Loss and fragmentation of natural habitats may concentrate animal populations in small areas, leading to disease outbreaks or spillovers to adjacent habitats (Brearley et al. 2012). At the same time, expansion of human settlements near natural habitats for disease reservoirs (e.g., forests) can increase contact between humans and reservoirs and disease incidence (de Coster et al. 2014). Since the effects of landscape modification, are likely to depend on the ecology of the disease, predicting and managing disease risk for human populations will require a clearer understanding of the relationship between environmental conditions and disease risk (Myers et al. 2014).

One neglected tropical disease affected by environmental characteristics is Leishmaniasis. The disease is caused by protozoans of the *Leishmania* genus. In the Americas, female phlebotomine sand flies mainly of the *Lutzomyia* genus transmit the parasites to mammalian reservoirs (World Health Organization 2010). There are two main clinical forms: visceral Leishmaniasis (VL) is lethal without treatment, while cutaneous Leishmaniasis (CL) causes skin and mucosal ulcerative lesions but does not cause mortality (Dantas-Torres et al. 2012). In the world, the estimated annual number of cases ranges from 0.2 to 0.4 million cases of VL and 0.7 to 1.2 million cases of CL, and is responsible for more than 30,000 deaths each year (Alvar et al. 2012).

Human landscape modifications in tropical regions have resulted in increased contact between humans and *Leishmania* vectors (de Santana Martins 2015). Initially, the leishmaniasis transmission cycle was largely restricted to wild areas with dense vegetation (Grimaldi and Tesh 1993). In the past three decades, however, fragmentation and loss of natural vegetation driven by agricultural development and expansion of human populations have led to the proliferation of the disease in settlements close to forests (Shaw 2007), where conditions are suitable for development of phlebotomine sand flies (Dujardin 2006; Casanova et al. 2013). Rural-urban migration and expansion of human settlements in peri-urban areas have also increased contact between vectors and both humans and domestic animals. As a result, sand flies have adapted the transmission cycle to urban environments where rather than depend on reservoirs restricted to areas with dense vegetation, they rely on domestic animals (Lainson and Rangel 2005; da Silva and Cunha 2007; Vianna et al. 2016).

The transmission cycle of CL leishmaniasis is still maintained in Neotropical regions in areas with dense vegetation (i.e, forest or vegetation surrounding rural and peri-uban areas) because the vector species of *Leishmania* responsible for the cutaneous form and the reservoirs are more restricted to natural environments and depend on vegetation (Alcais et al. 1997; de Araújo Pedrosa and de Alencar Ximenes 2009; Kariyawasam et al. 2015). For VL, *Leishmania infantum*, the main parasite of this form, is transmitted by a synanthropic vector, *Lutzomyia longipalpis* and has the domestic dog (*Canis familiaris*) as the main reservoir, consequently affecting urban and peri-urban populations (Moškovskij and Duhanina 1971; Pace 2014).

Climate is also an important determinant of the distribution of vectors and pathogens. Temperature, precipitation and humidity affect the reproduction, development, behavior and population dynamics of vector-borne diseases such as leishmaniasis (Gage et al. 2008; González et al. 2010; Casaril et al. 2014; Carvalho et al. 2016) but it is unclear what climate variables influence disease occurrence because each vector responds to different climate variables. In general, sand flies need warm temperatures and sustained precipitation to maintain favorable humid conditions (Desjeux 2001). Too much precipitation can kill them while drought prevents larval development (Ready 2013). Neotropical sand flies are generally present year around. Their abundance, however, depend on climate seasonality especially in regions with defined wet-dry and hot-cold seasons because sand flies exhibit diapause in the first instars (i.e., larvae and pupae) to survive until climate conditions for emergence are favorable (Rutledge and Gupta 2002; Ready 2013; Pinheiro et al. 2016). However, suitable temperature and precipitation conditions vary for each sand fly species and also according to its geographical distribution. Understanding the effects of climate factors on the epidemiology of leishmaniasis is needed to predict disease risk under a changing climate (World Health Organization 2010).

Socioeconomic conditions also influence leishmaniasis risk (Alvar et al. 2006). Poverty is usually associated not only with decreased access to health services but also with housing and working conditions that facilitate transmission (Houweling et al. 2016). Populations located in rural and peri-urban areas in tropical regions often settle near vegetation areas where the transmission cycle of leishmaniasis is present. In these areas, housing is constructed of low-quality materials, like straw, mud, or bamboo, which can shelter sandflies and favor leishmaniasis transmission (de Araújo Pedrosa and de Alencar Ximenes 2009; Argaw et al. 2013). Lack of sewage and garbage collection services, leading to accumulation of waste can also attract potential reservoirs (e.g., domestic mammals) and provide humidity necessary for vector breeding sites (Machado-Coelho et al. 1999; Costa et al. 2005). Agriculture and livestock husbandry can increase risk in rural regions because, these activities expose human to sand flies bites and the presence of cattle attract sand flies looking for blood meal (Bern et al. 2010; Chaves 2011).

Interactions between the environmental characteristics of a region and socioeconomic characteristics of the population are likely to contribute to the incidence of leishmaniasis (Desjeux 2001). Nevertheless, the magnitude of the impact on human populations depends on the species of parasite, vectors, and reservoirs involved in the transmission cycle (Sharma and Singh 2008; Reisen 2010). For instance, in tropical regions *Leishmania infantum*, the main parasite of VL, is transmitted by a synanthropic vector, *Lutzomyia longipalpis* and has the domestic dog (*Canis familiaris*) as its main reservoir, affecting mainly urban and peri-urban populations (Moškovskij and Duhanina 1971; Pace 2014). In contrast, the phylogenetically distinct species of *Leishmania* responsible for the cutaneous form uses reservoirs that are more restricted to natural environments with dense vegetation (Lainson and Rangel 2005).

The goal of this study is to analyze the environmental and socioeconomic factors associated with incidence of leishmaniasis between 1998 and 2015 in the state of São Paulo, Brazil. Brazil has the largest number of leishmaniasis cases in the Americas with an estimated annual incidence of 4,200 to 6,300 cases of visceral and 72,800 to 119,600 cases of cutaneous leishmaniasis (Alvar et al. 2012). Although São Paulo accounts for less than 1% of cases (Ministério da Saúde), understanding the dynamics of leishmaniasis in the state is important because marked climate seasonality coupled with the loss of natural vegetation, agricultural expansion, and urbanization portend changes that are likely to occur in other developing tropical regions within and outside Brazil (Klink and Machado 2005; Alvares et al. 2013). In this study we ask:

(1) How does incidence of visceral and cutaneous leishmaniasis cases vary across municipalities and years? We hypothesize that the spatial distribution of leshmaniasis reflects the environmental and socioeconomic characteristics of municipalities across the study period. We also expect that the occurrence and number of cases of both VL and CL will be higher in years and seasons with warm temperatures and sustained precipitation.

(2) What socioeconomic, climate, and landscape factors influence the occurrence and number of leishmaniasis cases? We hypothesize that:

2a. The occurrence and number of cases of CL, but not of VL, will be higher in municipalities with high vegetation cover.

2b. The occurrence and number of cases of both clinical forms will increase in municipalities with low socioeconomic conditions and with large at-risk populations.

2c. The occurrence and number of cases of both VL and CL will increase in years and seasons with warm temperatures and sustained precipitation.

Material and methods

Study Area

São Paulo state is located in the southeast region of Brazil and is divided into 645 municipalities. The state accounts for 33.5% of national GDP and 22 % of the country's population (http://www.imp.seade.gov.br). Urban and agricultural areas surround remnants of original native vegetation of the Atlantic Forest and Brazilian Cerrado (savanna), which have been reduced from more than 80% to 12% of the state land cover (Victor et al. 2005). The principal agricultural crops are sugar cane, cattle pastures, and eucalyptus plantations (Durigan et al. 2007; Farinaci and Batistella 2012).

Data

Disease incidence. We obtained the number of CL and VL cases available reported until 2015 for the 645 municipalities from the Center for Epidemiological

Surveillance of the State of São Paulo (http://www.saude.sp.gov.br). Leishmaniasis is a disease that requires mandatory notification in Brazil and is reported and confirmed by laboratory analysis in each hospital.

Landscape data. Total native vegetation cover was derived from the forest inventory maps of 2000 and 2010 obtained from the Forest Institute of the State of São Paulo (http://www.iflorestal.sp.gov.br). These maps are generated at a 1:50.000 scale, with a minimum mapped area of 2.5 ha, a resolution that allows identification of small vegetation areas. We used the 2000 map to analyze data cases from 1998 to 2006 and the 2010 map for cases between 2007 and 2015 (Fig.1).

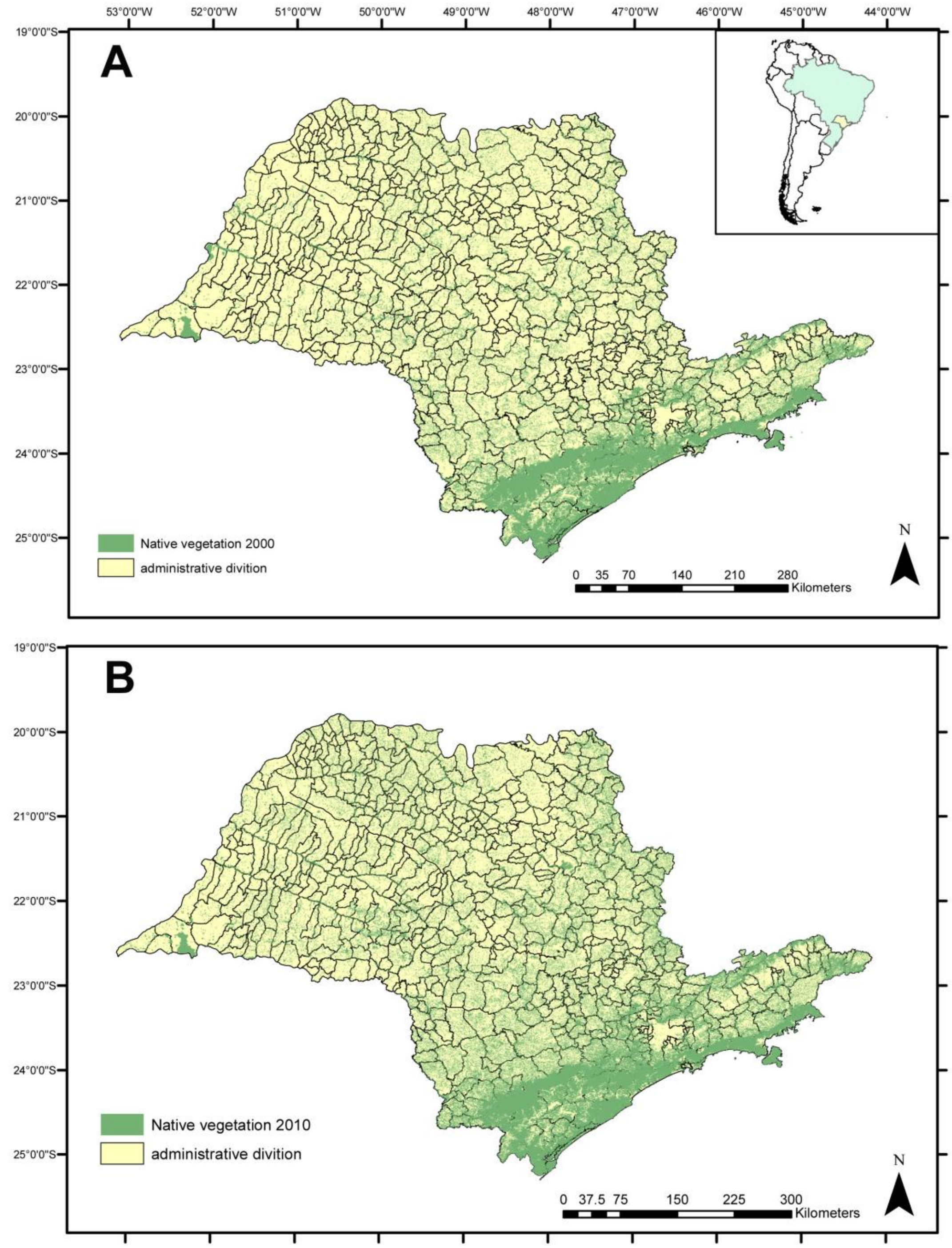

Fig. 1. Amount of native vegetation cover**.** Map of 2000 (A) and 2010 (B) (data: Forestry Institute).

***Socioeconomic*.** Municipality-level data for rural and urban population sizes were obtained from the State System of Data Analysis (SEADE http://www.imp.seade.gov.br). The number of agricultural workers was available for 1996 and 2006 and was obtained from Brazilian Institute of Geography and Statistics (IBGE http://www.ibge.gov.br). We used a numbers of agricultural workers from 1996 to analyze disease data from 1998 to 2001 and data from 2006 for disease data from 2002 until 2015. Number of cattle head per year in each municipality was obtained from the Institute of Agricultural Economics (http://www.iea.agricultura.sp.gov.br).

We included three socioeconomic indicators of human wellbeing. Income per capita is a metric of economic wellbeing. The Gini coefficient captures income inequality. The Human Development Index (HDI) is a composite of three elements: standard of living, life expectancy, and literacy level. Municipality scale average income per capita data were obtained from SEADE, inequality index (Gini) and the human development index (HDI) were obtained from IBGE. We used HDI information available for 2000 to analyze disease data from 1998 to 2006, and data from 2010 for disease data from 2007 to 2015. We used Gini information available for 2003 and average income per capita data for 2010 to analyze the entire period. To identify the strongest socioeconomic predictors of each form of leshmaniasis, each socioeconomic index was considered separately in models.

Climate. The central and eastern regions of the state are characterized by dry winters (Jun-August), with subtropical climates and a marked rainy season in the summer (December–February) with an average temperature above 22°C. In the northwest region, temperatures are warmer and the coldest months are typically above 18 °C. The coastal strip lacks a dry season with an average precipitation over 60 mm in the driest month (http://www.cpa.unicamp.br).

To obtain climate data for each municipality, monthly temperature and precipitation data were obtained from the International Research Institute for Climate and Society of Columbia University (http://iridl.ldeo.columbia.edu).

Temperature data were derived from the global monthly land surface air temperature data set (ts) at 0.5°C of National Centers for Environmental Prediction

(NOAA NCEP) (Fan and van den Dool 2008) and for precipitation from Climate Hazards Group Infrared Precipitation with Stations (CHIRPS) with a spatial resolution of 0.05°(Funk et al. 2014). These data were extracted for each month of each year analyzed (1998 to 2015) for each municipality. Because the state presents marked rainfall and temperature seasonality that can influence the abundance of vector and therefore the disease incidence, we calculated the mean, minimum and maximum temperature and precipitation for each year and each season (Spring, Summer, Fall and Winter). Because each vector responds to different climate variables, we evaluated the predictive values of several annual or seasonal precipitation and temperature conditions on disease incidence. Details of range of annual and seasonal climate values and maps are in S1.

Statistical analysis

Leishmaniasis cases vary across years in our study period (1998-2015) and across municipality (Table 1). We fitted generalized linear mixed models to identify significant predictors for leishmaniasis. We first fitted a model of occurrence using logistic regression. We also fitted data for the number of cases per municipality using a negative binomial mixed model. This two-part approach allowed us to separately examine the factors influencing the presence of leishmaniasis from those related to the number of cases. All the models included socio-economic, landscape and climate factors as covariates and random effects for year and municipality considering the variability and among municipalities and years not account in the fixed covariates. All continuous predictor variables were centered and standardized to facilitate model convergence (Gelman and Hill 2007). To avoid collinearity, we verified that the Pearson's correlation coefficient among all the variables in the models was $r < 0.4$ and the VIF (variance inflation factor) of the model was < 5. Since temperature and rainfall variables are highly correlated, we used model selection to identify the best climate predictors. All the logistic regression models included the size of the population as covariate and as an offset in negative binomial models, considering the whole population exposed to leishmaniasis. We also used model selection to identify the presence of at risk population group in the analyses between rural population (considering men, women and children in rural areas) or the number of agricultural workers (only men and women workers in rural areas >14 years old), because this population is exposed to vegetated areas and have also low socioeconomic status. In case there is no risk population group significant to include as covariate together with population size in the model, we only remain with the size of the total population. We used marginal likelihood ratio tests for variable selection to compare reduced models lacking each predictor variable with full models containing them. All analyses were conducted in R statistical software packages ‘lme4’ for logistic regression (Bates et al. 2014 Jun 23) and ‘glmmADMB’ for negative binomial model (Skaug et al. 2013). All the maps was constructed using Arc Gis Software 10.2.

Table 1. Predictor variables. Variables considered in the mix models and their influence on the disease.

Type	**Predictor variable**	**Influence on the disease**
Landscape	Total area of native vegetation	Vegetation surrounding an area increases the incidence of leishmaniasis.
Socioeconomic	Total population	Population at risk
	Agricultural workers/ rural population/urban	at risk population group exposed to disease
	Human Development Index (HDI)	Low HDI, high GINI, low income are predictors of poverty that are associated with disease vulnerability
	Index to measure inequality (GINI)	
	Income per capita	
	Heads of cattle	Cattle could serve as blood-meal source for sand flies
Climate	Mean, maximum and minimum temperature and precipitation by year and season at municipality scale	Seasonality of precipitation and temperature influence larval development of sand fly vectors

Results

Spatiotemporal distribution of visceral and cutaneous leishmaniasis

Between 1998 and 2015, São Paulo had a total of 5,583 cases (cumulative incidence of 15.54 per 100,000 inhab.) of cutaneous leishmaniasis and 2,574 cases (cumulative incidence 7.081 per 100,000 inhab.) of visceral leishmaniasis. The municipalities of Itariri, Iporanga, Pedro de Toledo, Eldorado, Ribeira and Ubatuba had the greatest cumulative incidence of CL (range from 16.93 to 31.02 cases per 1,000 inhab.) and the municipalities of Ouro Verde, Dracena, Flórida Paulista, Panorama and Nova Guataporanga for VL (range from 3.34 to 4.05 cases per 1,000 inhab). Cutaneous leishmaniasis cases were distributed throughout the state, but were more common in the southeast (Fig. 2A) while cases of visceral leishmaniasis were aggregated in the northwest region of the state (Fig. 3A).

Temporal variation in the number of cases was greater for CL than for VL. The total annual number of CL cases over the study period had a low of 66 cases in 1998, peaking between 2002 and 2004, with a maximum of 925 in 2003 and leveling off to an average number of 260 cases between 2005 and 2015 (Fig. 2B). For VL, the minimum number of cases occurred in 2000 with only 16 cases recorded and then increased steadily starting in 2001 until peaking between 2006 with 250 cases and with maximum of 294 cases in 2008 and then leveling off to an average number of 169 cases per year and increasing again in 2012 with 206 cases (Fig 3B).

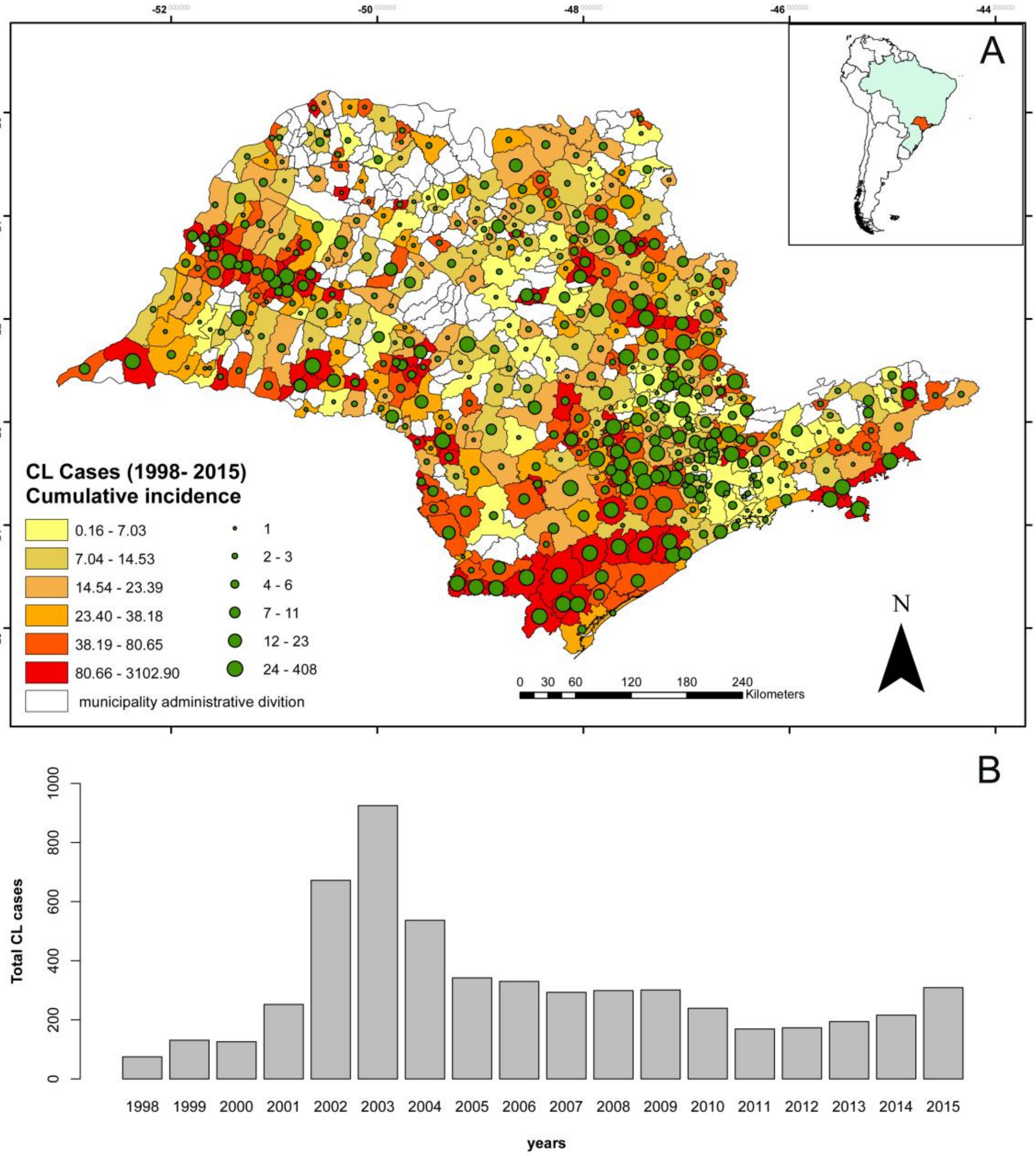

Fig. 2. (A) Number of cases and cumulative incidence (rate per 100000 inhab.) in quantiles across 645 municipalities from 1998 to 2015 for cutaneous leishmaniasis. **(B)** Total number of leishmaniasis cases per year (1998-2015).

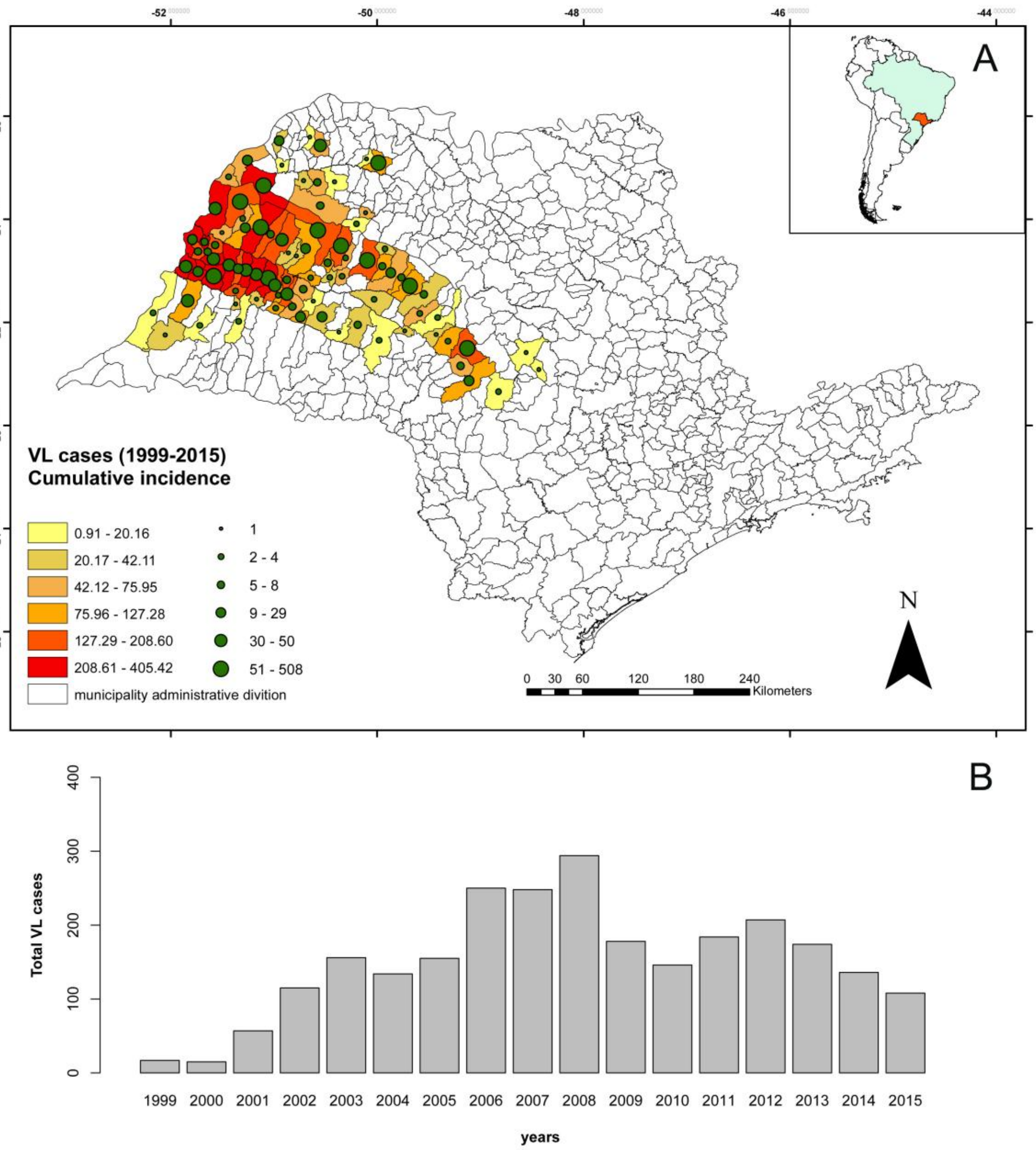

Fig. 3. (A) Number of cases and cumulative incidence (rate per 100000 inhab.) in quantiles across 645 municipalities from 1999 to 2015 for visceral leishmaniasis. **(B)** Total number of cases per year of visceral leishmaniasis (1999-2015).

Predictors of cutaneous leishmaniasis

Occurrence model. Landscape, climate, and socioeconomic factors influenced the probability of CL occurrence in the state. CL probability of occurrence increased in municipalities with high vegetation cover and greater economic inequality (Gini). Probability of occurrence also increased in municipalities with high mean winter precipitation and with low maximum spring temperatures during the study period (Fig. 4A & S2.1).

Number of cases. Number of CL cases was greater in municipalities with high annual mean temperatures and low mean fall precipitation during the study period (Fig. 4B & S2.1). Municipalities with high per capita income and a larger number of agricultural workers had significantly lower numbers of CL cases.

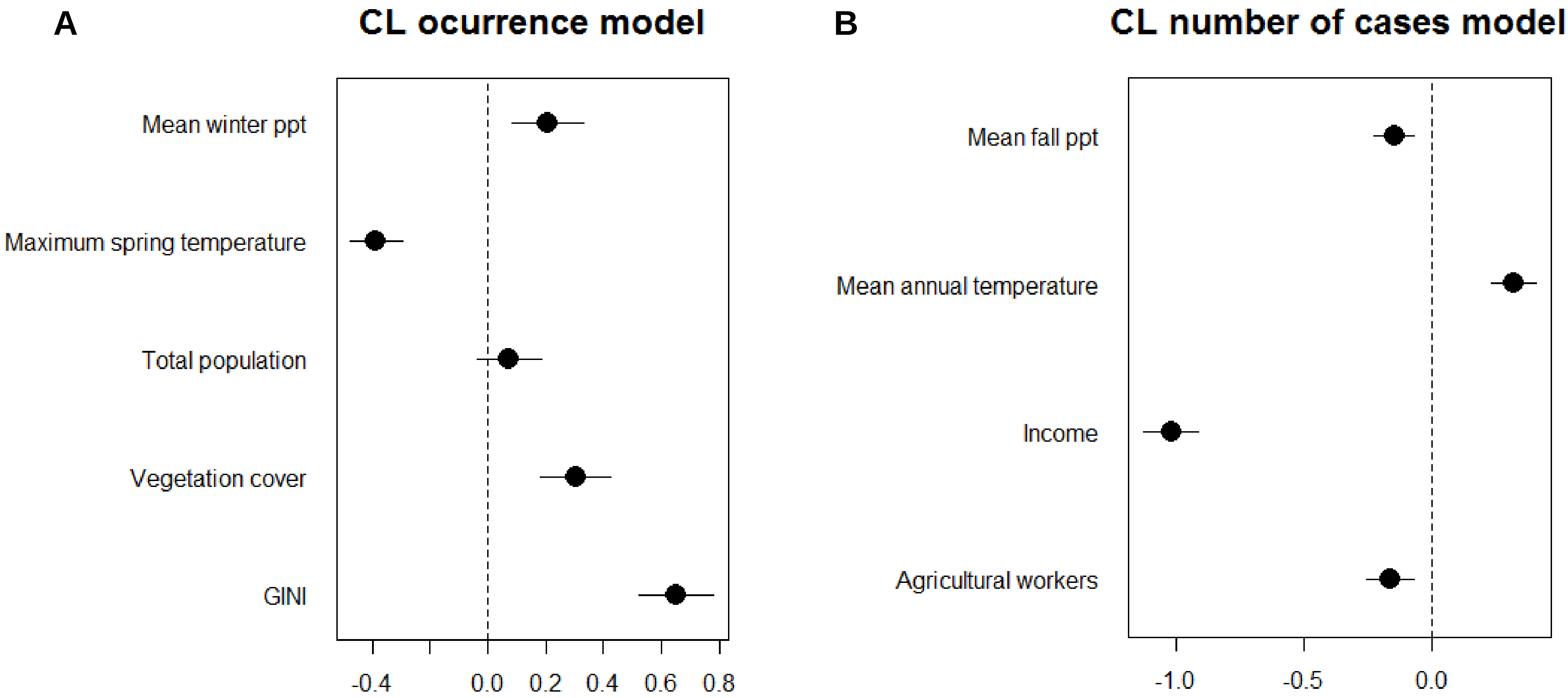

Fig. 4. Standardized coefficients of binomial and negative binomial model of cutaneous leishmaniasis. Black dots show mean parameter estimates, lines show confidence intervals (2.5 - 97.5%) for predictors of CL. ppt=precipitation.

Predictor of visceral leishmaniasis

Occurrence model. The probability of VL cases increased in municipalities with high human development index (HDI) and with large numbers of cattle. VL occurrence was higher in municipalities with high maximum annual temperatures, high minimum spring precipitation and low minimum winter precipitation during the study period (Fig. 5A and S2.2).

Number of cases. High mean fall precipitation and high annual mean temperatures increased the number of VL cases in municipalities affected. Municipalities with high vegetation cover, greater social inequality index (Gini) were associated with a lower number of VL cases (Fig. 5B & S2.2).

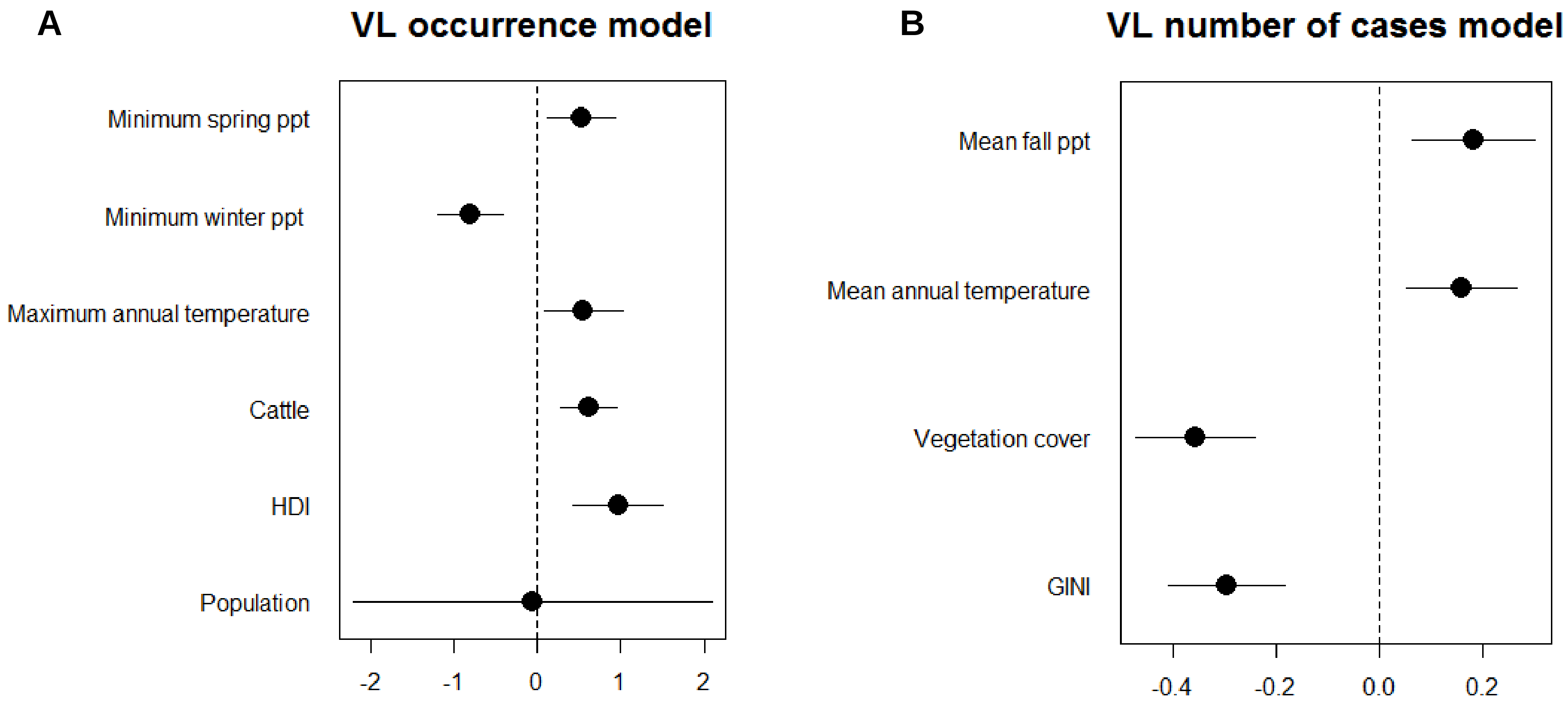

Fig. 5. Standardized coefficients of occurrence and number of cases model of visceral leshmaniasis. Black dots show mean parameter estimates, lines show confidence intervals (2.5 - 97.5%) for predictors of VL, ppt=precipitation.

Discussion

Leishmaniasis is one of the most neglected diseases in Brazil and is distributed through the country (Marzochi and Marzochi 1994; Alvar et al. 2012). Both clinical forms, cutaneous and visceral leishmaniasis have similar transmission cycles, but differ in their eco-epidemiology (Karagiannis-Voules et al. 2013). In São Paulo spatio-temporal patterns in disease incidence reflect landscape, socioeconomic and climatic characteristics.

Spatio-temporal variation in incidence of visceral and cutaneous leishmaniasis across the state of São Paulo

Urban development and landscape modification increased the incidence of CL and VL in São Paulo state in the last decades (Tolezano 1994). However, differences in the drivers of interannual variability in the number of cases reflect variation in the spatial distribution of the disease and in the transmission cycles of the two forms. Cutaneous leishmaniasis has been historically present in native forest areas of the state; however activities have altered its epidemiology. CL incidence first increased in the 1920 with the construction of the railroad system and was later associated with forest clearing for highway construction. Over the study period, CL incidence reflects patterns of human development in rural and peri-urban environments close to CL cases are reported in 70 % of the municipalities of the state of São Paulo and the greatest numbers of cases were observed in areas with high vegetation cover in the SE part of the state. The municipality of Itariri has the highest cumulative incidence of CL followed by Iporanga, Pedro de Toledo, Eldorado, Ribeira and Ubatuba (Forattini et al. 1976; Lopes et al. 2009). Forest cover in these municipalities ranges between 90 and 45% and CL incidence in recent years has been high in densely populated peri-urban areas with surrounding vegetation (Secretaria de Estado da Saúde de São Paulo and Superintendência de Controle de Endemias 2004; Lopes et al. 2009; Silva and Gurgel 2011).

On the other hand, VL incidence is highly aggregated in the NW part of the state. The disease in this region is associated with the recent introduction of the vector *Lutzomyia longipalpis* to urban areas. The sand fly was first recorded in Araçatuba and Birigui in 1997, and was followed by an increase in reported cases of canine and human cases of VL. Vegetation cover in the five municipality highest cumulative incidence of VL ranged between 1.4 and 3.8%. These municipalities were classified by other studies as intense to moderate transmission areas (Cardim et al. 2016; de Paula 2016). and are located in the west of the state, close to Mato Grosso do Sul state, where studies suggest the expansion of the disease started after the Bolivia – Brazil pipeline (Gasbol) construction (Antonialli et al. 2007; Oliveira 2016).

The incidence of leishmaniasis can also be affected by climate conditions. The survival of sand flies involved in leishmaniasis cycle depends on climate factors (Cardenas et al. 2006; Dias et al. 2007). We observed that the number of CL cases peaked between 2002 and 2004, and for VL, between 2008 and 2012. Mean annual temperature increased during 2002, 2006, 2007 and 2012, and total annual precipitation peaked in 2009 and 2011-2013 (Fig.6A 1 Fig. 6B). These anomalous climate conditions are probably related to episodes of El Niño and La Niña Southern Oscillation. El Niño is a warmer condition which decreases the amount of rainfall and moisture supply and the opposite conditions are present during La Niña (Miralles et al. 2013).

The state also presented climate differences among municipalities (S1). Municipalities with high CL incidence in the SE of the state have high total annual precipitation (range from 1264 to 2671 mm/month) relative to the rest of the state but areas in the NW with high VL incidence have warmer temperatures range from 22 to 25°C. This variability among municipalities together with vegetation cover and socioeconomic conditions could also contribute to variability in the incidence across the years.

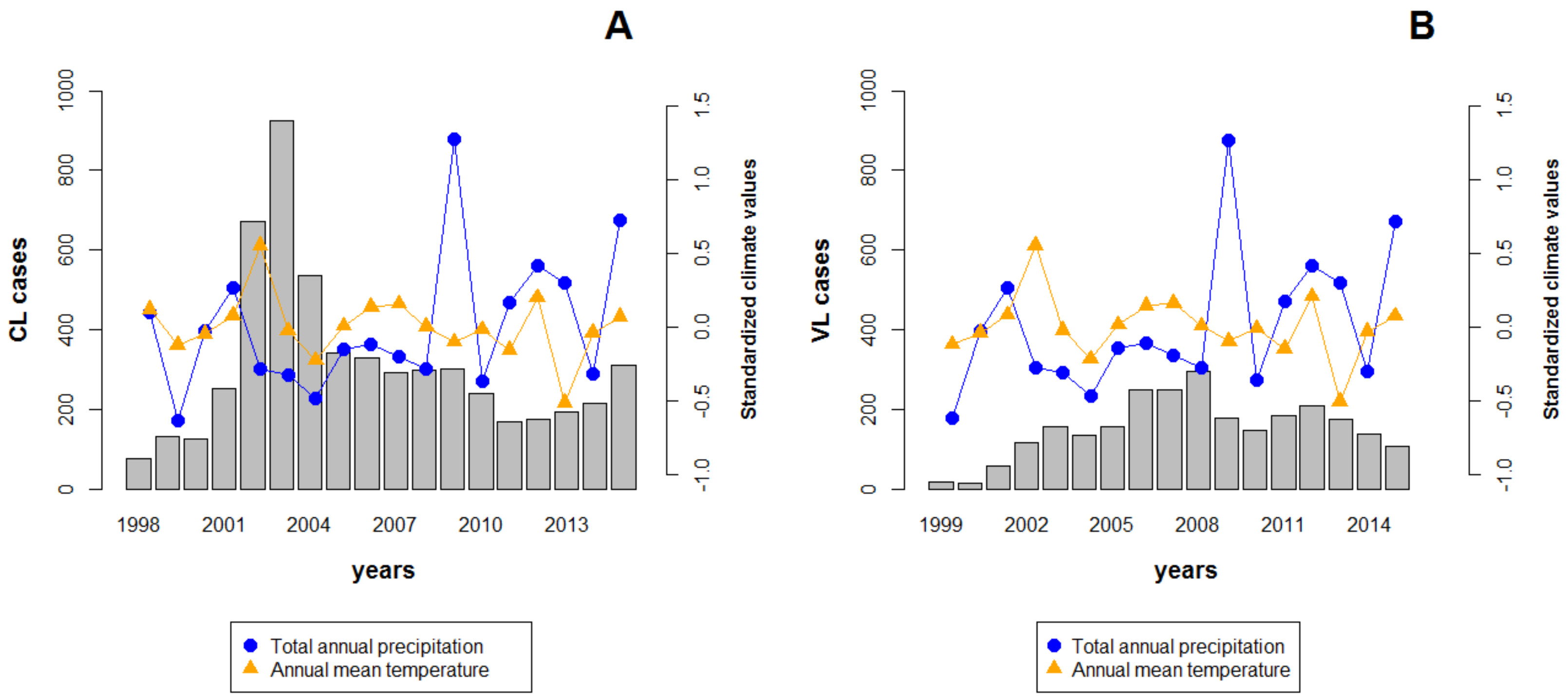

Fig. 6. Inter-annual mean temperature and total precipitation variability in the state of São Paulo (1998 -2015). Grey bars show number of cases of CL (A) and VL (B). Precipitation and temperature were standardized by centering each variable on its mean and divided by its standard deviation.

Effects of socioeconomic and environmental factors on disease incidence

(a) Influence of vegetation cover

Our results show that the presence of large natural vegetation areas contributed to the occurrence of CL. The majority of vectors and potential mammal reservoirs involved in the CL cycle depend on remnant vegetation patches (Valderrama-Ardila et al. 2010; Fernández 2012; Ocampo et al. 2012). The abundance of sand fly species involved in CL transmission(e.g., *Lutzomyia intermedia, L. neivai*) is positively associated with denser vegetation (e.i. *Lutzomyia whitmani*) (Nasser et al. 2009; Quintana et al. 2012), likely because immature sand fly instars are dependent on the presence of leaf litter and trees (Carvalho et al. 2010; Souza et al. 2014). The number of cases of CL, however, was not influenced by vegetation cover, probably because an adaptation of suspected vectors to urban environments as *Lutzomyia whitmani* formerly related to forest environments and now associated with peri-urban transmission of CL. This vector can survive in low amount of vegetation areas (Zeilhofer et al. 2008; Santos et al. 2009).

Native vegetation cover was not a significant predictor of VL occurrence in our analyses. VL incidence was also not associated with vegetation areas in a model simulation in Brazil (Karagiannis-Voules et al. 2013), but other regional studies have found significant positive associations between VL and native vegetation cover (de Oliveira et al. 2012; Belo et al. 2013; Almeida and Werneck 2014). Although vegetation did not influence the probability of occurrence, a lower number of cases were observed in areas with high native vegetation cover. This may reflect the fact some synanthropic vectors such as *L. longipalpis* prefer areas with low vegetation cover (e.g., urban areas) (Carneiro et al. 2004; Lainson and Rangel 2005; Rangel and Vilela 2008; Casaril et al. 2014). Vegetation areas also decreased the incidence of visceral form in Belo Horizonte, Minas Gerais while high urbanization was found to be directly related to the incidence of VL (de Araújo et al. 2013).

(b) Influence of socioeconomic conditions

Our results show that the probability of CL occurrence increased in municipalities with high economic inequality. In addition, the number of cases decreased in municipalities with higher per capita income. This finding is consistent with the observation that low socioeconomic status in peri-urban settlement lead to higher exposure to CL vectors (de Araújo Pedrosa and de Alencar Ximenes 2009; Rodríguez-Morales et al. 2010).

Although no risk population group influenced the probability of occurrence for CL, the number of CL cases was lower in municipalities with a low number of agricultural workers. This finding suggests CL risk of transmission is mainly affecting areas distant from agricultural activities (Filho 1981; Tolezano 1994). The census of 2000 confirmed extensive migration of agricultural workers to urban areas with more than 50% of population living in rural areas holding nonagricultural jobs (Caiado and Santos 2003; Kageyama 2003), as a result the rural areas of the state are becoming urban environments.

For VL, the probability of occurrence cases was greater in municipalities with a high human development index (HDI) and large numbers of cattle. Higher HDI could characterize municipalities with extensive urban areas where the transmission cycle of VL is present (Salomón et al. 2015). Studies suggest that the presence of cattle close to human settlements increases the risk of transmission because sand flies feed on cattle and construct their breeding sites in cattle sheds (Barnett et al. 2005; Bern et al. 2010). The number of cases of VL decreased with high inequality index values (Gini). High Gini values are common in urban municipalities with high economic development and low native vegetation cover. The majority of VL cases in São Paulo state occur in urban areas (Madalosso et al. 2012). Although other studies relate VL cases with low income in urban environments (de Almeida et al. 2011; de Araújo et al. 2013; Almeida and Werneck 2014), municipalities of the NW of the state have high agro-livestock industrial development and high HDI values. HDI values in these municipalities (S3), however, could mask the presence of populations with low socioeconomic conditions (Bern et al. 2000).

(c) Influence of climate

Temperature and precipitation ranges favorable to the abundance of sand flies vary for each species so vector proliferation may increase disease incidence (Ebi and Hess 2017). Adverse climate conditions delay the emergence of new adults and foster larval diapause, extending average developmental times from eggs to adults from 40 days to 3-9 months (Ward 1977; Nieto et al. 2006). São Paulo exhibits marked climate seasonality in most of the state with a hot rainy season and a dry season where both precipitation and temperature decrease. This climate variability across the state and during years affects the occurrence of both clinical forms (Fig. 7).

High mean winter precipitation increased the probability of CL occurrence. The winter months (June, July and August) are the dry season in most of the state. In other Brazilian states, an increase in the abundance of *Leishmania* vectors of CL as *Lutzomyia whitmani* was also observed during the dry season (de Souza et al. 2004; Nascimento et al. 2013) and periods of moderate precipitation (Colla-Jacques et al. 2010; Barata et al. 2011). High maximum spring temperatures (September, October and November) were not favorable for CL occurrence in the state probably because high temperatures affect Neotropical sand flies species involved in CL transmission, which do not tolerate temperatures over 25°C (Valderrama-Ardila et al. 2010; Barata et al. 2011).

We observed that warmer annual temperatures (annual mean temperature) were associated with a greater number of CL cases, while high mean fall precipitation was associated with a decrease in this number. Warmer temperatures are favorable for the development of both sand flies and parasites within the vector (Sharma and Singh 2008; Hlavacova et al. 2013). An increase in the abundance of vector involved in CL transmission was also observed during the dry season (winter) in the neighboring state of Minas Gerais (de Souza et al. 2004; Nascimento et al. 2013). In years of high mean fall precipitation may reduce the survival of first instars which seek shelter in the soil and in turn, reduce the abundance of sand flies during the dry season (winter), contributing to the decrease of CL (Karagiannis-Voules et al. 2013)

Our results show that high mean annual temperature lead to an increase in the number of CL cases (Fig. 7A). This is probably because during 2002 and 2004 the greatest peak of CL in São Paulo state, total precipitation decreased due to climatic anomalously related to a not strong El Niño Southern Oscillation (warm ENSO conditions) (Kayano and Andreoli 2006). Other study also suggests of CL in Colombia also found a greater number of cases during a warm ENSO year (Acosta Cardona 2015), but others related precipitation to the incidence of CL in Sucre, Venezuela during La Niña (cold rainy ENSO conditions), and also in Brazil (Karagiannis-Voules et al. 2013). Although high rainfall areas predicted maximum CL occurrence rates in a simulation study of the Amazonian region and low in the SE of Brazil (Karagiannis-Voules et al. 2013). The environmental conditions of the Amazonian region strongly differ from São Paulo state in the SE where the suspected vector as *L. whitmani* and *L. intermedia* prefer warm conditions with moderate precipitation as the dry season of São Paulo (Peterson and Shaw 2003).

For VL, the probability of occurrence increased in years with high maximum temperatures values. The main vector of VL, *Lutzomyia longipalpis,* requires temperatures around 25°C for development and reproduction (Nieto et al. 2006). High temperatures also seem to influence vector dispersal (França-Silva et al. 2005; Oliveira et al. 2008; Sevá et al. 2017). We also found that high minimum spring precipitation (September, October and November) increases the number of VL cases. *Lutzomyia longipalpis* is generally abundant during the rainy season (December, January and February) (de Souza et al. 2004; Machado et al. 2012; Belo et al. 2014). Spring humidity directly affects the survival and development of eggs and later sand fly instars in diapause (Carvalho et al. 2011; Pérez-Cutillas et al. 2015).

Our results suggest that years with more humid springs could favor both an increase in the abundance of sand flies, and a subsequent rise in VL incidence, as we observed in 2004 -2008 and 2011-2013 (Fig. 7B). VL is a disease that can be delayed in its diagnosis, so the effects of climate conditions on the incidence of cases can be observed also in the following years. High minimum winter precipitation seems to negatively influence the occurrence of VL cases. Although an increase in precipitation generally favors *Lutzomyia longipalpis,* years with more humid winters than normal can exceed the precipitation tolerance limits of the vector and have negative repercussions for the survival of larvae and pupae by flooding the ground and destroying sand fly breeding sites in the soil (Rutledge and Ellenwood 1971; Casanova et al. 2013).

Warmer mean annual temperatures lead to a greater number of VL cases. These results suggest that the state has an annual range of temperature favorable for the development of vector and parasite (Sharma and Singh 2008; Hlavacova et al. 2013). An increase in mean fall precipitation leads to a corresponding increase in VL cases, as was found by other studies where an increment of cases of VL was reported during the fall months after a peak in the abundance of vector during the summer and early fall (Sherlock 1996; de Souza et al. 2004; Machado et al. 2012). The increment of mean fall and mean winter precipitation together by an increment in temperature conditions seems to contribute to the increase of VL cases (2006-2008 and 2011-2013) across our study period (Fig. 7B).

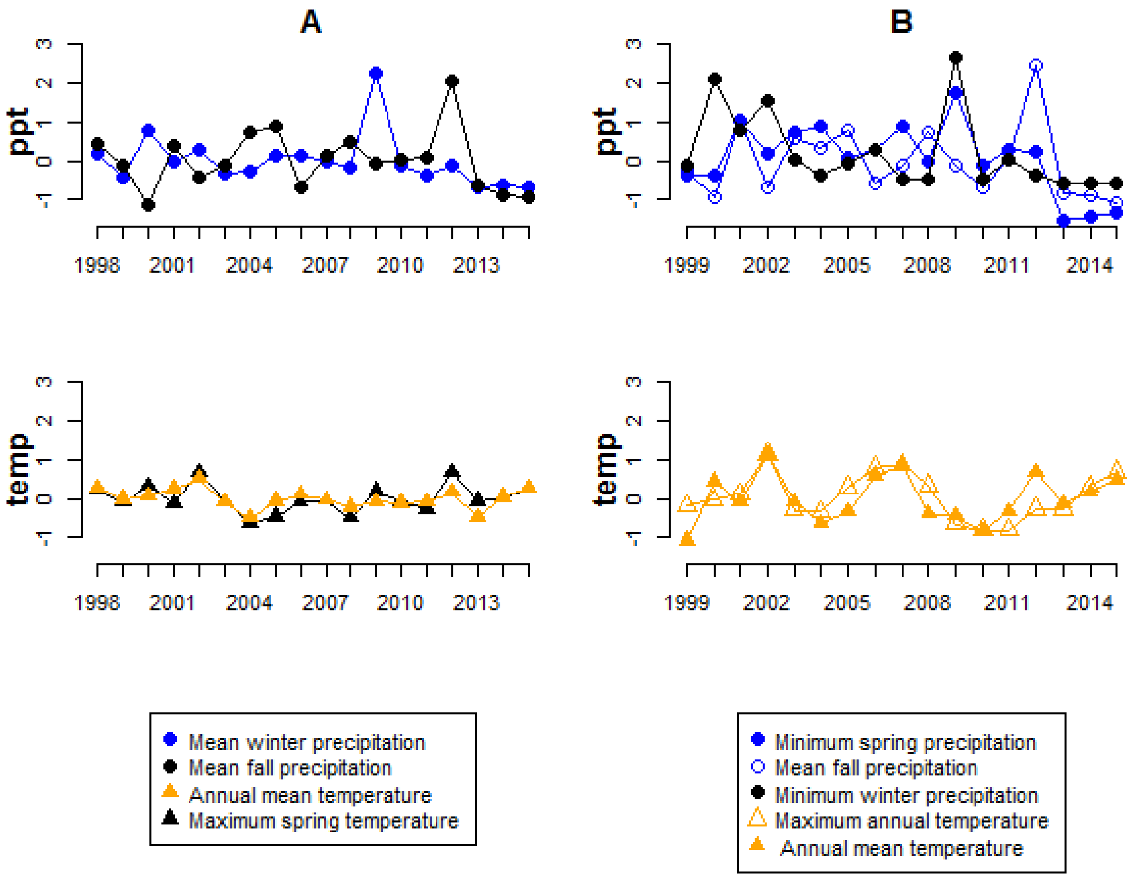

Fig. 7. Climate predictor variables for cutaneous (A) and visceral (B) leishmaniasis for 1998-2015. Climate data were standardized by centering each variable on its mean and divided by its standard deviation. Among variables with positive effect on disease risk, precipitation variables are in blue and temperature variables are in orange. Climate variables with negative influence are in black.

Final remarks

São Paulo is the most urbanized state in Brazil with many formerly rural areas becoming highly urbanized in recent decades (Caiado and Santos 2003). Our results show high leshmaniasis incidence in peri-urban areas: VL is present in urban areas of the NW and CL is no longer restricted to remote rural environments but has expanded to urban areas (Condino et al. 1998; Condino et al. 2008). Although CL transmission still depends to some degree on a certain amount of vegetation over, it is most strongly linked to peri-urban areas in the metropolitan region of the state. The socioeconomic conditions of populations living in these areas exacerbate disease occurrence. These results highlight some of the health risks associated with rapid, unplanned urban development. In addition, climate factors increased the number of VL and CL cases in our analyses. These findings corroborate results from studies in developed regions, where changes in disease incidence are mainly related to climatic conditions (Ready 2008). Although global climate models do not predict significant changes in precipitation in the state, expected increases in temperature under a changing climate are likely to elevate leshmaniasis risk in the state.

Public policy regarding the control of both clinical forms of leishmaniasis continues to focus on reducing contact between human, domestic animals and vectors. In the case of CL, control measures for those who live in areas near dense vegetation should include adequate protection against sand flies bites measures (e.g., insect repellent, indoors mosquito nets). For VL, the elimination of sources of moisture around houses, and proper waste disposal can reduce vector proliferation. Therefore, measures of entomological surveillance of sand flies fumigation must continue after the rainy season for CL (Departamento de Vigilância Epidemiológica 2010) and during and after the rainy season for VL (Departamento de Vigilância Epidemiológica 2014), as well as during years in which an increase in average vector density is observed. Further entomological research is required in the large number of municipalities where leishmaniasis is present but potential sand fly vectors have not yet been identified. In addition, is also necessary combined the entomology surveillance with education about leishmaniasis to limit activities that increase human-vector contact especially during the seasons when vector densities are high.

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Support Information

S1 Climate maps and values

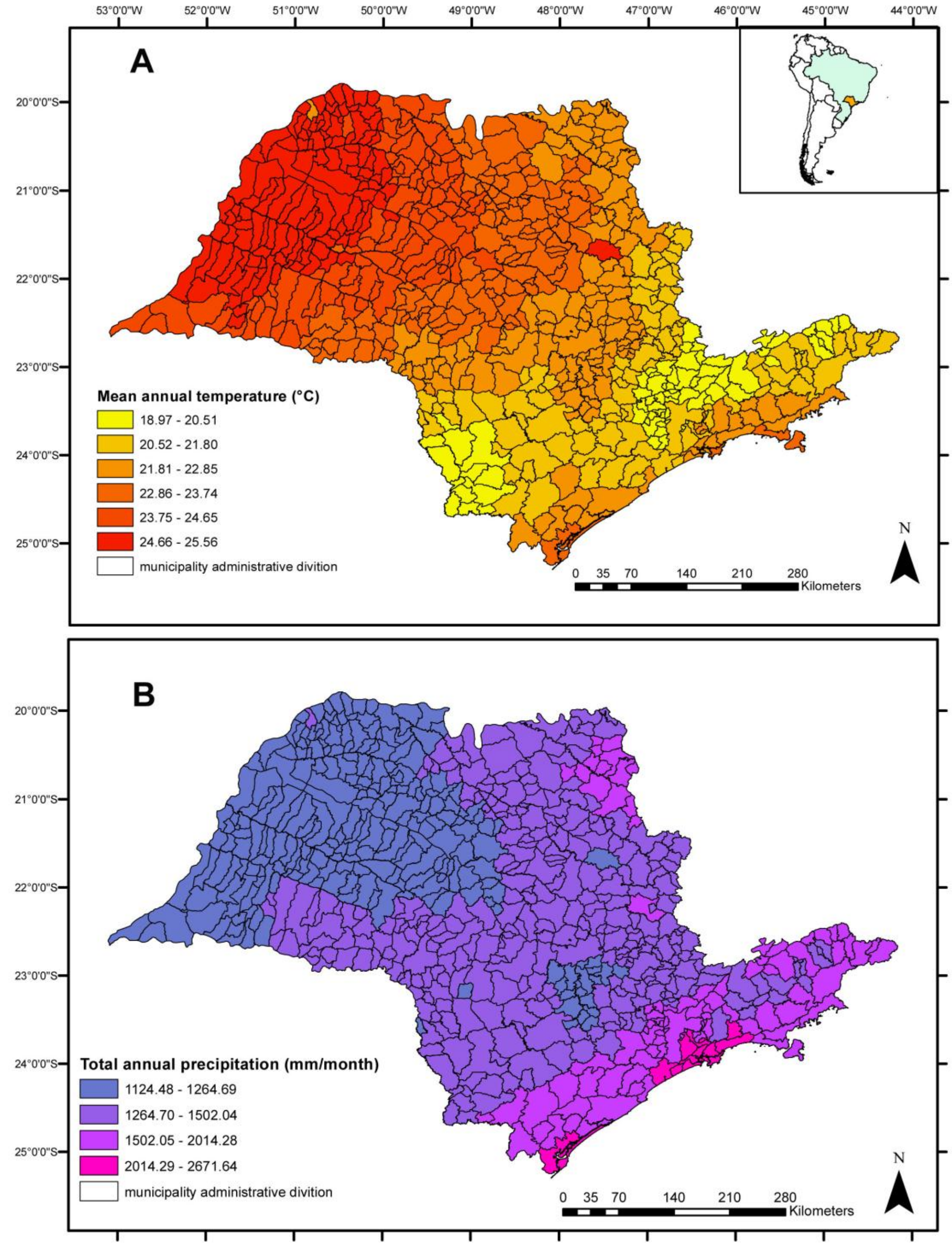

Fig. S1 Mean annual temperature and total annual precipitation for 1998-2015. Mean annual temperature °C **(A)** obtained from National Centers for Environmental Prediction and total annual precipitation mm/month **(B)** obtained from Climate Hazards Group Infrared Precipitation with Stations.

Table S1.1 Average and range from 1998-2015 values of temperature and precipitation for São Paulo state.

Season	Variable	Mean and range	Variable	Mean and range
ANNUAL	Annual mean temperature	22.36 (18.07-27.28)	Annual mean precipitation	100.25 (27.37-328.00)
	Maximum annual temperature	26.14 (20.42-30.88)	Maximum annual precipitation	271.58 (71.19-842.38)
	Minimum annual temperature	18.61 (13-23.26)	Minimum annual precipitation	8.61 (0.53- 95.81)
SUMMER[1]	Mean summer temperature (D-J-F)	25.16 (19.47- 29.82)	Mean summer precipitation (D-J-F)	185.35 (34.74-547.28)
	Maximum summer temperature	25.87 (19.72- 30.88)	Maximum summer precipitation	263.20 (52.76-842.38)
	Minimum summer temperature	24.45 (19.32- 29.23)	Minimum summer precipitation	120.24 (3.14 -368.40)
FALL[2]	Mean fall temperature (M-A M)	21.02 (16.02 - 26.06)	Mean fall precipitation (M-A M)	45.16 (2.19-287.46)
	Maximum fall temperature	23.43 (17.19 - 29.30)	Maximum fall precipitation	73.77 (3.05 -358.84)
	Minimum fall temperature	19.30 (13.49 - 25.12)	Minimum fall precipitation	21.28 (0.94 -179.42)
WINTER[3]	Mean winter temperature (J -J -A)	21 (14.73 - 25.74)	Mean winter precipitation (J -J -A)	32.8 (3.23-369.84)
	Maximum winter temperature	22.66 (16.17 - 27.96)	Maximum winter precipitation	61.07 (4.72-489.75)

	Minimum winter temperature	19.38 (13 - 24.14)	Minimum winter precipitation	13.05 (0.53-308.05)
S[4] P R I N G	Mean spring temperature (S - O -N)	24.37 (18.15 - 29.64)	Mean spring precipitation (S -O -N)	137.70 (31.18-397.81)
	Maximum spring temperature	25.39 (19.78 - 30.41)	Maximum spring precipitation	196.7 (53.20-553.40)
	Minimum spring temperature	23.39 (16.06 - 29.40)	Minimum spring precipitation	116.02 (2.29-283.41)
			Total annual precipitation	1361.40 (804.60-3936)

[1]Summer: December, January and February. [2] Fall: March, April and May. [3] Winter: Jun, July and August. [4] Spring: September, October and November. Temperature values in °C and precipitation values in mm/month.

Table S1.2 Average values per year of temperature and precipitation for São Paulo state.

Season	year	Temperature °C			Precipitation mm/month		
	year	Mean	Minimum	Maximum	Mean	Minimum	Maximum
ANNUAL	1998	23.10	18.57	26.77	115.70	9.79	269.04
	1999	22.66	18.68	25.80	98.88	8.15	318.34
	2000	22.80	17.64	26.14	112.72	9.63	299.96
	2001	23.02	19.08	25.98	119.39	20.17	277.42
	2002	23.87	18.98	27.36	106.88	8.76	277.51
	2003	22.83	18.70	26.62	106.00	12.50	332.71
	2004	22.48	18.44	25.47	102.35	5.48	243.31
	2005	22.89	19.02	25.43	109.99	8.25	327.06
	2006	23.13	19.45	26.21	110.66	11.30	289.00
	2007	23.16	18.64	26.21	108.76	6.40	323.50
	2008	22.88	19.26	25.45	106.83	5.27	289.21
	2009	22.70	17.30	25.97	142.55	25.47	325.54
	2010	22.85	18.89	26.18	104.94	4.43	349.53
	2011	22.60	17.54	26.24	117.25	8.34	327.67
	2012	23.24	19.02	26.95	122.96	4.28	284.66
	2013	21.96	18.00	25.14	40.04	2.37	124.81
	2014	22.81	18.48	26.15	35.39	2.26	108.20
	2015	23.00	19.36	26.38	43.30	2.19	121.06
SUMMER	year	Mean	Minimum	Maximum	Mean	Minimum	Maximum
	1998	26.00	25.55	26.44	207.46	157.90	260.09
	1999	25.37	24.95	25.68	224.28	131.46	318.34
	2000	24.57	24.02	25.20	227.60	171.71	294.57
	2001	25.67	25.33	25.98	213.64	158.25	272.19
	2002	25.32	23.96	26.80	197.39	104.80	274.95
	2003	25.56	24.63	26.62	213.69	137.58	332.35
	2004	24.31	23.90	24.84	169.33	101.88	219.49
	2005	24.60	24.13	25.11	191.54	92.60	326.93
	2006	25.72	25.30	26.21	217.62	160.30	281.80
	2007	25.26	24.55	25.95	209.02	129.76	322.31
	2008	24.88	24.46	25.28	211.97	142.53	285.83
	2009	25.25	24.67	25.70	230.59	171.07	305.25
	2010	25.58	25.04	26.15	211.10	125.54	347.75
	2011	25.30	23.94	26.24	243.76	169.98	327.07
	2012	24.90	23.83	26.15	177.51	124.26	237.13
	2013	24.17	23.72	24.74	71.88	30.51	123.29
	2014	25.51	24.32	26.15	52.41	21.20	97.40
	2015	24.94	23.82	26.35	65.57	32.99	110.86

	year	Mean	Minimum	Maximum	Mean	Minimum	Maximum
FALL	1998	20.66	18.58	23.48	60.79	16.27	102.40
	1999	20.26	18.72	22.50	46.10	31.64	62.40
	2000	21.57	20.30	23.24	16.32	9.63	23.63
	2001	21.25	19.15	24.51	58.68	27.67	89.56
	2002	23.07	21.50	25.85	30.79	9.21	65.43
	2003	21.37	19.86	23.34	48.07	19.55	78.79
	2004	20.56	18.53	23.76	63.18	38.66	91.11
	2005	22.14	20.73	24.00	63.71	41.45	87.20
	2006	20.99	19.48	23.40	27.53	17.14	38.68
	2007	21.52	19.71	24.25	45.15	17.47	73.35
	2008	20.94	19.27	23.48	55.19	20.01	109.13
	2009	20.42	17.30	22.83	42.05	27.80	54.78
	2010	20.50	18.95	22.53	41.55	15.41	72.37
	2011	20.08	17.54	23.07	46.28	14.79	85.21
	2012	20.86	19.18	23.64	99.10	62.91	134.10
	2013	20.51	19.43	22.03	27.79	4.77	65.13
	2014	20.83	19.65	22.86	20.91	4.09	50.17
	2015	20.79	19.45	22.91	19.74	4.72	44.45
WINTER	**year**	**Mean**	**Minimum**	**Maximum**	**Mean**	**Minimum**	**Maximum**
	1998	21.45	20.06	22.53	45.18	11.20	82.47
	1999	21.45	20.64	22.56	24.91	8.15	48.41
	2000	19.97	17.64	21.65	58.22	34.81	89.37
	2001	21.16	20.16	22.19	35.89	24.40	51.38
	2002	21.13	18.98	22.79	42.69	26.39	61.99
	2003	20.01	18.70	21.80	25.55	16.10	36.62
	2004	21.66	18.92	24.89	20.18	5.48	40.44
	2005	20.69	19.02	22.04	32.36	8.27	69.70
	2006	21.57	20.89	22.25	33.57	11.95	65.16
	2007	21.21	18.70	23.76	27.93	6.62	64.44
	2008	21.37	20.42	22.10	24.43	5.39	40.71
	2009	20.67	19.35	22.58	87.68	50.55	129.05
	2010	21.44	20.05	23.48	29.62	4.44	65.51
	2011	21.33	19.98	22.67	21.05	10.08	31.96
	2012	21.46	19.43	23.64	30.87	4.28	62.89
	2013	19.48	18.00	21.22	15.09	2.43	55.17
	2014	20.60	18.48	22.67	17.85	2.33	56.09
	2015	21.43	19.48	23.03	17.34	2.19	47.98
SPRING	**year**	**Mean**	**Minimum**	**Maximum**	**Mean**	**Minimum**	**Maximum**
	1998	24.29	22.74	25.84	149.35	59.04	229.43
	1999	23.55	22.42	25.00	100.22	56.66	160.73
	2000	25.09	24.41	25.98	148.72	77.32	216.15

	2001	24.00	23.10	24.81	169.34	131.88	220.07
	2002	25.95	25.09	26.89	156.64	77.09	216.09
	2003	24.40	23.48	25.45	136.71	93.83	180.06
	2004	23.38	22.05	24.57	156.70	117.80	208.76
	2005	24.14	23.55	24.79	152.35	94.78	203.77
	2006	24.22	23.47	24.97	163.91	108.13	235.99
	2007	24.65	23.77	25.72	152.92	118.65	186.22
	2008	24.34	23.87	24.81	135.72	87.29	196.34
	2009	24.44	22.82	25.66	209.87	153.07	288.34
	2010	23.88	22.47	25.41	137.47	85.29	214.02
	2011	23.70	22.99	24.66	157.93	118.03	202.25
	2012	25.73	24.57	26.86	184.35	108.84	277.30
	2013	23.67	22.31	24.99	45.43	15.35	89.46
	2014	24.31	23.84	24.99	50.39	12.58	99.16
	2015	24.86	24.16	25.67	70.56	14.03	115.83

S2 Mean and SE of mixed models

Table S2.1. Mean and SE for parameters of the best model for cutaneous leishmaniasis. P-values and degrees of freedom refer to the marginal LRT, in which the full model was compared with a reduced model without each of the predictor variables.

Model	Predictor	Estimate	SE	X^2	DF	P-value
Binomial	GINI	0.65079	0.06720	89.73	1	<0.0001
	Vegetation area	0.30205	0.06083	23.88	1	<0.0001
	[1,2]Total population	0.07395	0.05708	1.66	1	0.197373
	Maximum spring temperature	-0.38600	0.04555	68.40	1	<0.0001
	Mean winter precipitation	0.20789	0.06296	10.33	1	<0.0001
[1,4] Negative binomial	[3]Agricultural workers	-0.1649	0.0476	11.90	1	<0.0001
	Income per capita	-1.0214	0.0553	247.42	1	<0.0001
	Mean annual temperature	0.3181	0.0435	51.34	1	<0.0001
	Mean fall precipitation	-0.1491	0.0405	13.72	1	<0.0001

Table S2.2. Mean and SE for parameters of the best model for visceral leishmaniasis. P-values and degrees of freedom refer to the marginal LRT, in which the full model was compared with a reduced model without each of the predictor variables.

Model	**Predictor**	**Estimate**	**SE**	**X^2**	**DF**	**P-value**
[4]**Binomial**	[1,2]Total population	-0.1514	0.5982	0.0162	1	0.8987408
	HDI	0.9575	0.2654	10.2685	1	<0.0001
	Cattle	0.6156	0.1718	12.5002	1	<0.0001
	Highest annual temperature	0.5442	0.2405	6.9102	1	0.0085704
	Lowest winter precipitation	-0.7742	0.1894	17.2933	1	<0.0001
	Lowest spring precipitation	0.5188	0.1991	6.6424	1	0.0099582
[1]**Negative binomial**	GINI	-0.2954	0.0576	21.78	1	<0.0001
	Forest area	-0.3549	0.0593	31.08	1	<0.0001
	Annual mean temperature	0.1609	0.0543	10.36	1	0.004189
	Mean fall precipitation	0.1848	0.0610	8.06	1	0.004943

- [1]Size of population was included in negative binomial model as an offset. [2] No at risk population group significant, we remained with the size of the population although it was not significant because they are the population exposed to leishmaniasis. [3]The number of agricultural workers per municipality was at risk population group significant in this model. [4]Landscape variables were not significant in CL Negative Binomial model and VL Binomial model.
- SE= Standard deviation, LRT= Likelihood RatioTest, DF= Degree Freedom

S3 Human Development Index maps and values of 2000 and 2010

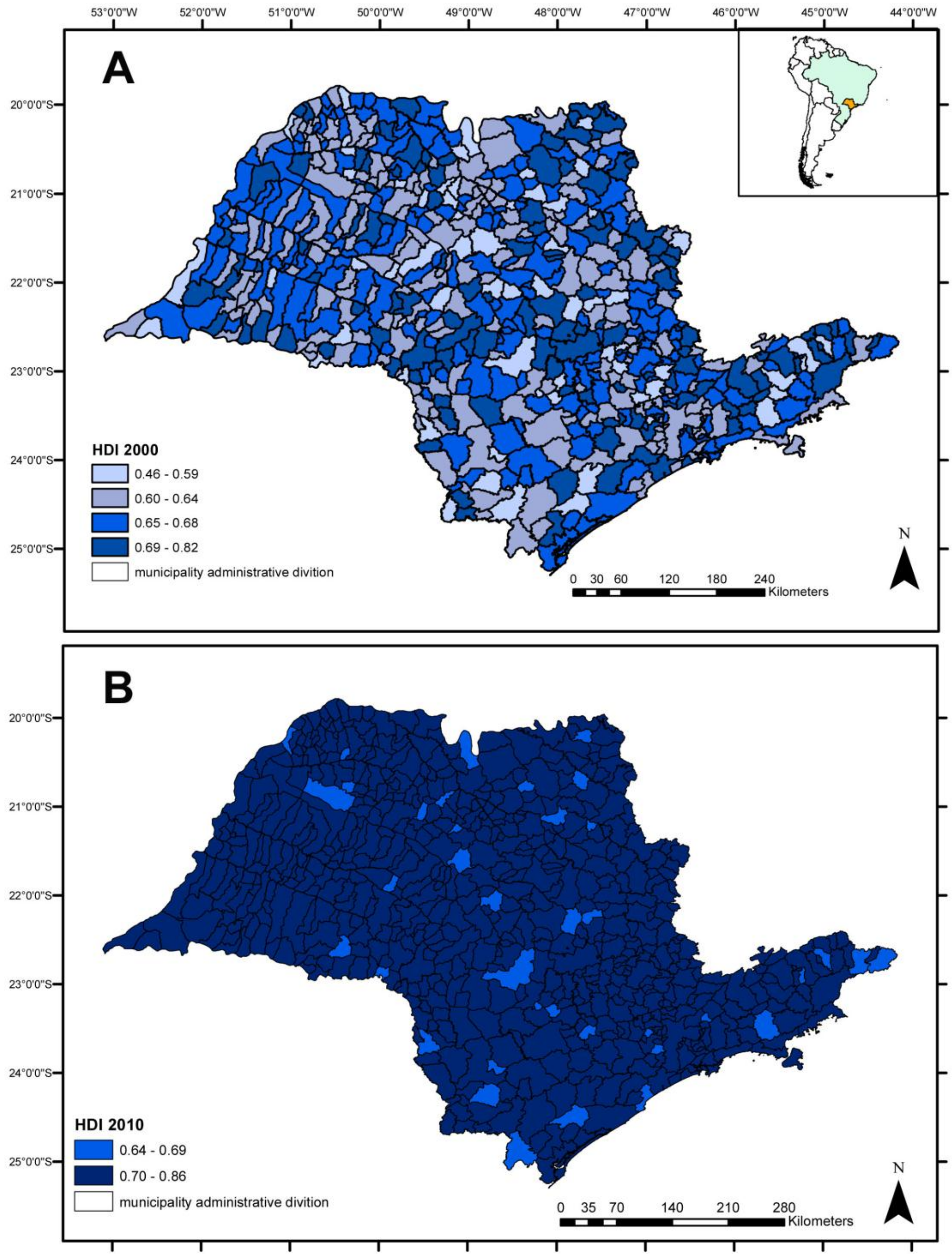

Fig. S3 Human Development Index (HDI) of 2000 and 2010 obtained from Brazilian Institute of Gegraphy and Statistics (IBGE).

General conclusions

Leishmaniasis is a vector-borne disease whose magnitude of risk depends on the environmental and socioeconomic conditions of the region affected. This work emphasized the conditions that influence the two main clinical forms of leishmaniasis: visceral leishmaniasis (VL) and cutaneous leishmaniasis (CL), first analyzing the disease transmission around the world, and then focusing on tropical regions where leishmaniasis is considered a neglected tropical disease, because the environmental conditions that favor the transmission worsen with economic inequalities.

In the first chapter, we reviewed the characteristics of environmental and socioeconomic conditions that affect leishmaniasis in tropical, arid and Mediterranean regions. The preference of climatic conditions by sand fly vectors among regions differed in the amount of precipitation, but was similar in the preference of warmer temperatures (Pace 2014). Landscape conditions were important for the transmission cycle considering the wild origin of this zoonosis. Dense vegetation areas provide shelter to vectors and reservoirs in undisturbed environments, rural and peri-urban areas in tropical regions and surrounding vegetation of urban areas in Mediterranean regions also played an important role in the transmission (Elnaiem et al. 2003; Cerbino Neto et al. 2009; Gomez-Barroso et al. 2015). Altitude related to climate conditions and soil types that retain humidity were important, especially in arid regions where the vegetation cover is smaller (Bhunia et al. 2011; Seid et al. 2014). In Mediterranean regions, cutaneous and visceral leishmaniasis are considered re-emergent diseases due to vector adaptation to urban environments (Steffens 2010). In tropical and arid regions the transmission cycle of CL remains in rural, forest and peri-domestic areas, but the transmission cycle of VL presented an urban adaptation (Nasser et al. 2009; Kariyawasam et al. 2015). Socioeconomic conditions influence the incidence of both leishmaniasis worldwide. In developing countries of arid and tropical regions socioeconomic vulnerability of population, as poor housing and health conditions create an ideal environment that favors the transmission (Alvar et al. 2006). Therefore, in these regions an outbreak of leishmaniasis can be more serious than in developed countries of Mediterranean regions where living conditions and health systems are better (Faucher et al. 2012).

Considering the reviewed above, the second chapter was focused on São Paulo state, the wealthiest state of Brazil, and also a state with reduced native vegetation cover and marked climate seasonality. On the one hand, São Paulo state has a history of cutaneous leishmaniasis transmission and CL related in the last century to modification of native vegetation cover areas which modified its epidemiology (Tolezano 1994). Nowadays, CL is present in 70% of the state and the SE of the state present the highest incidence of CL in municipalities with high vegetation cover. Vegetation areas favor the transmission of CL because several suspected *Leishmania* spp. vectors of CL and potential reservoirs depend on vegetation areas. On the other hand, the transmission of visceral leihsmaniasis in state is recent, because in 1999 were reported the first urban VL cases in human and dogs (Cardim et al. 2013). The transmission of VL was associated with migratory movement of people and dogs infected from Mato Grosso do Sul, where the disease was presented, prompted by the construction of the first stage of Gasbol (Bolivia – Brazil) pipeline and dispersed in the following years by the adjacent municipalities (Antonialli et al. 2007; Cardim et al. 2015). As a consequence, the actual distribution of VL is aggregated in the NW of the state in municipalities with low vegetation cover and until 2015 was not present in other municipalities of SE of São Paulo state. The transmission of VL in São Paulo state is mainly urban due to the presence of *Lutzomyia longipalpis* the main vector of *Leishmania infantum* and because the main reservoir is the dog . Therefore, we analyzed the CL and VL cases from 1998 to 2015 in the 645 municipalities of São Paulo state and fitted two separated models for each clinical form, one that allowed us to analyze the conditions that influence the occurrence of leishmaniasis cases and another one that analyzed those conditions that influenced the number of cases.

Our results show that the occurrence of CL in São Paulo state increased in municipalities with larger native vegetation cover and low socioeconomic conditions, and was not associated with rural areas or agricultural activities. However, these characteristics did not influence the increase of the number of CL cases. Thus, our results suggest a possible urbanization of cutaneous leishmaniasis transmission related to peri-urban areas with surrounding vegetation where settlements of population with low socioeconomic status exist. For VL the occurrence increased in municipalities with high socioeconomic conditions and was not related with vegetation cover and rural areas. In addition, the presence of larger vegetation cover had a negative influence in the number of cases of VL so characterized municipalities with urban areas and low vegetation cover where the cycle does not depend on the amount of vegetation. Furthermore, *Lutzomyia longipalpis* tolerate areas with low vegetation cover and not depend to survive on surrounding vegetation.

Regarding climate conditions, considering each *Leishmania* spp. vector of CL and VL responds to different annual and seasonal climate variables the probability of occurrence of both visceral and cutaneous leishmaniasis were mainly related to high temperature and seasonal precipitation conditions. In addition, the only factors which increased the number of cases in the state for both clinical forms were high annual mean temperatures, thus show that São Paulo state have the adequate temperature conditions for CL and VL transmission. Precipitation variables decrease the number of cases for CL, probably because during the years with more incidence of CL the amount of precipitation decrease due to EL Niño Southern Oscillation (warm ENSO conditions) and also because the suspected *Leishmania* spp. vectors of CL prefer warm temperature and are abundant during dry season. High mean fall precipitation also influence the increase of VL cases, because *Lutzomyia longipalpis* is abundant during the rainy season (summer and early fall), so suitable conditions of temperature and extended rainy season (summer and fall) could increase transmission of VL in the state in the years of more incidence.

This thesis shows that São Paulo state presents an urbanization of both VL and CL transmission. VL is mainly urban, whereas CL prevails in the peri-urban areas because its vectors still depend on surrounding vegetation. This transmission pattern was observed in developed regions as Mediterranean regions where the transmission is mainly urban and outbreaks of leishmaniasis depend of climate variability. Nevertheless, the peri-urban settlement and the transformation of rural areas into urban areas can increase the socioeconomic inequalities of São Paulo state (Torres et al. 2007) which, summed with its tropical climate variability, increase the risk of leishmaniasis. These results suggest that, in tropical regions, despite the urbanization and the economic development of a region, the transmission cycle of *Leishmania* spp. is able to adapt to novel conditions of the environment (Salomón et al. 2015). Therefore, the main risk is related to some species of vectors of leishmaniasis, which are able to adapt to urban environments and increase their abundance during climate oscillations. Without adequate entomological surveillance, vigilance of possible peri-domestic reservoirs, and an adequate health care system, leishmaniasis can affect urban population, especially immunosuppressed people (e.g., children, elderly and people with other diseases).

We hope our results contribute to a better understanding of the environmental and socioeconomic factors that influence the transmission of leismaniasis. Our findings may be useful in guiding public health policymaking, not only in São Paulo state, but also in other regions with similar characteristics. In addition, given the characteristics of leishmaniasis transmission, the disease could increase in municipalities of São Paulo with low incidence and arrive at other areas where it is not present, especially for VL that is present only in 15% of the state. Therefore, it is necessary to continue the entomological and peri-domestic mammal surveillance to identify other possible vectors of *Leishmania* and potential reservoirs and also encourage the education about the disease. Leishmaniasis is a disease that will not disappear in urban environments with low amount of vegetation, instead, could increase under favorable climate conditions, especially in areas with socioeconomic vulnerabilities. In addition, given the relevance of climate conditions to the transmission of leishmaniasis, it is necessary to analyze the risk of transmission under scenarios of future climate change, not only in São Paulo, but also in other endemic regions of Brazil, especially in areas where the population can still continue to modify the landscape (e.g. Amazon region) and the sylvatic transmission cycle is present.

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