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Fatores de risco ambientais e socioeconômicos associados com a leishmaniose

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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). Vector-borne diseases depend on complex interactions between pathogens, vectors, hosts and reservoirs (Fig. 1) occurring in a permissive environment (Reisen 2010). 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 animal reservoirs that maintain the cycle in the nature (Gubler 2009). Introduction of the cycle in human settlements often leads to disease emergence.

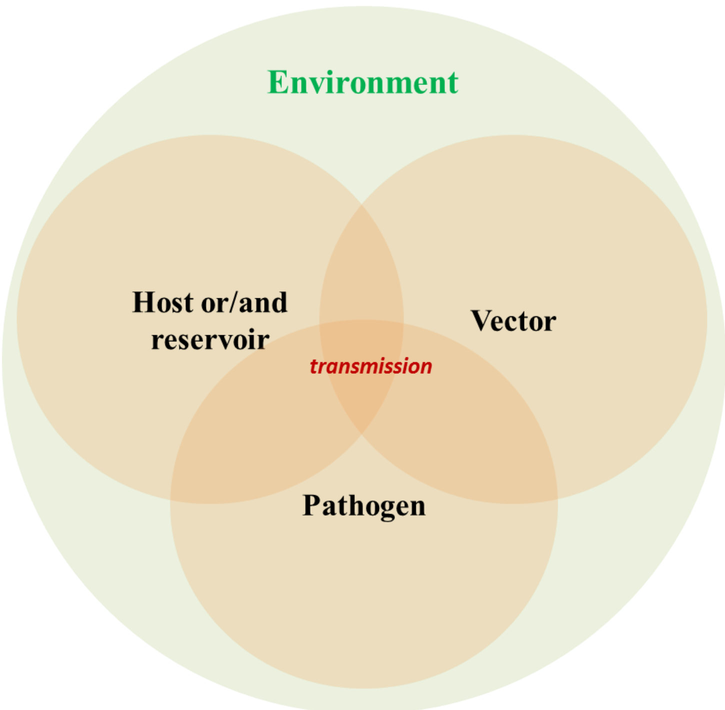

Figure 1. Transmission of vector-borne disease. Vector, host/reservoir, and pathogen populations intersect within a permissive environment to enable pathogen transmission. Adapted from (Reisen 2010).

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).

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 are hunted and eaten 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).

In domestic environments we found potential reservoir mainly for VL: (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 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 in the modification of the ecology of the parasite, 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 (L. M. R. 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 the 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. 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). Global mortality was estimated to be 20,000 to 40,000 leishmaniasis deaths per year, mainly attributed to VL (World Health Organization 2010).

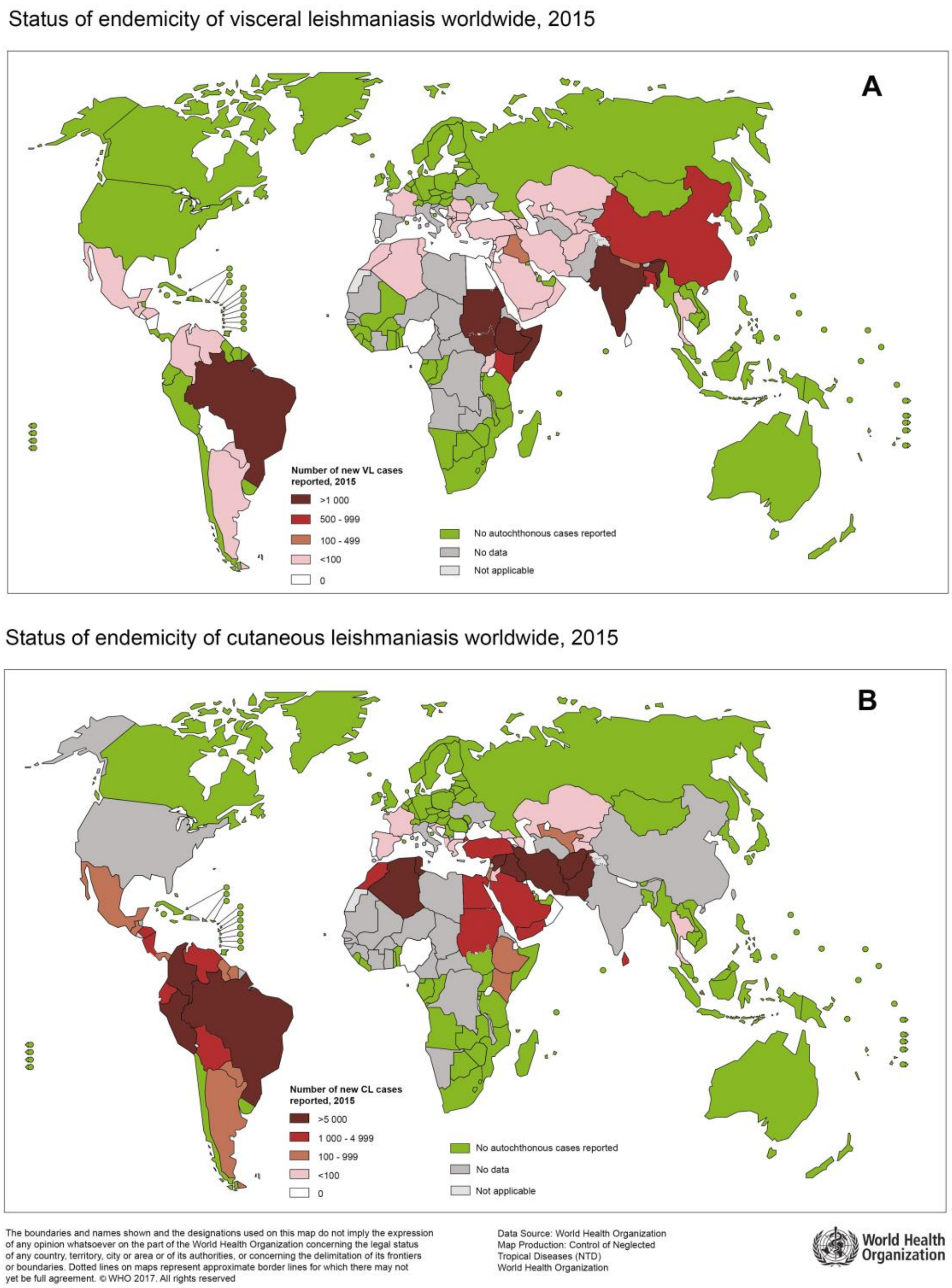

Figure 4. Number of new visceral **(A)** and cutaneous leishmaniasis **(B)** cases reported worldwide in 2015. Font: (WHO 2017)

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 28.7% of Brazilian GDP, it has marked socioeconomic inequalities with vulnerable populations in both rural areas and rapidly developing peri-urban areas in the Sao Paulo metropolitan region. Climate in the state also includes dry winters and marked rainy season in the summer, and average annual temperature above 18°C to 22°C, conditions favorable for the vectors (Alvares et al. 2013). 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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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. No precipitation variable increase 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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