Leishmaniasis in the Americas

Julio Vladimir Cruz-Chan, Jesus Valenzuela, and Eric Dumonteil

Contents

Abstract Leishmaniasis is a neglected tropical disease caused by kinetoplastid protozoan parasites belonging to the *Leishmania* genus. Infection causes a wide diversity of clinical manifestations, ranging in severity from asymptomatic infections, self-healing cutaneous lesions (cutaneous leishmaniasis (CL)), mucocutaneous lesions (mucocutaneous leishmaniasis (MCL)), diffuse leishmaniasis, and visceral leishmaniasis (VL) which can be lethal when untreated. *Leishmania* parasites are transmitted to vertebrate hosts through the bite of female sandflies of the genus *Lutzomyia* in the New World. We review here some of the key aspects of leishmaniasis in Latin America and highlight some of the specificities of the disease in the American continent. The diversity of vector and parasite species poses

J.V. Cruz-Chan
Laboratorio de Parasitología, Centro de Investigaciones Regionales "Dr. Hideyo Noguchi", Universidad Autónoma de Yucatán, Ave. Itzaes #490 x 59, 97000 Mérida, Yucatán, Mexico

J. Valenzuela
Vector Molecular Biology Section, Laboratory of Malaria and Vector Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD, USA

E. Dumonteil (✉)
Laboratorio de Parasitología, Centro de Investigaciones Regionales "Dr. Hideyo Noguchi", Universidad Autónoma de Yucatán, Ave. Itzaes #490 x 59, 97000 Mérida, Yucatán, Mexico

Department of Tropical Medicine, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA, USA
e-mail: oliver@uady.mx; edumonte@tulane.edu

C. Franco-Paredes, J.I. Santos-Preciado (eds.), *Neglected Tropical Diseases - Latin America and the Caribbean*, Neglected Tropical Diseases,
DOI 10.1007/978-3-7091-1422-3_6

additional challenges compared to the situation in the Old World. Indeed, this diversity implies that most tools for disease surveillance and control, including diagnostics, vector control interventions, therapeutic treatments, and vaccines, need to be adapted to ensure their efficacy. Further research is thus needed to optimize leishmaniasis control and surveillance in the Americas.

Keywords *Leishmania* • Sand fly • *Lutzomyia* • Visceral leishmaniasis • Cutaneous leishmaniasis • New world

1 Introduction

Leishmaniasis is a neglected tropical disease caused by kinetoplastid protozoan parasites belonging to the *Leishmania* genus, which includes at least 35 species of which 20 are considered pathogenic to humans (Fraga et al. 2013; WHO 2010). Infection with *Leishmania* parasites causes a wide diversity of clinical manifestations, ranging in severity from asymptomatic infections, self-healing cutaneous lesions (cutaneous leishmaniasis (CL)), mucocutaneous lesions (mucocutaneous leishmaniasis (MCL)), diffuse leishmaniasis, and visceral leishmaniasis (VL) which can be lethal when untreated (WHO 2010). Leishmaniasis has a global geographic distribution in 98 countries, affecting about 12 million people worldwide, with a yearly incidence estimated at 0.2–0.4 million cases of VL and 0.7–1.2 million of CL (Alvar et al. 2012; Pigott et al. 2014). It is thus considered as one of the most important public health problem in these endemic countries.

CL is the most frequent clinical form of the disease, representing 75 % of leishmaniasis total cases, and 75 % of its global incidence is distributed in Colombia, Brazil, Peru, Costa Rica, Iran, Syria, Afghanistan, Algeria, Ethiopia, and Sudan (Pigott et al. 2014). CL is responsible for 2,356,000 Disability Adjusted Lost Years (DALYs) in men, and 946,000 in women (Murray et al. 2005). On the other hand, 90 % of all VL cases are reported in Brazil, Ethiopia, Sudan, South Sudan, India, and Bangladesh (Pigott et al. 2014).

Leishmania parasites are transmitted to vertebrate hosts through the bite of female sandflies of the genus *Phlebotomus* and *Lutzomyia* in the Old and New World, respectively. About 70 sand fly species from nearly 900 existing species have been incriminated in *Leishmania* transmission (Ready 2013). Several domestic and wild mammals are involved as host reservoirs, including dogs, sloths, anteaters, raccoons, and opossums, as well as some small rodent species (WHO 2010).

Given the diversity of parasite, vector, and host species, the epidemiology of leishmaniasis is complex, with urban and rural transmission cycles involving different species often in the same geographical area (Pigott et al. 2014, Ready, 2013; Shaw 2002; Lainson 2010). We review here some of the key aspects of leishmaniasis in Latin America and highlight some of the specificities of the disease in the American continent.

2 Epidemiology of Leishmaniasis in the Americas

Leishmaniasis is widely present in the Americas, and particularly relevant in the tropical and subtropical regions of the continent, ranging from the southern US and Mexico to northern Argentina and Chile. There were a total of 66,941 cases of CL/year reported in recent years in the American region, which, accounting for underreporting, corresponds to an estimated incidence of 187,000–307,800 cases of CL/year (Alvar et al. 2012). Similarly, 3,662 cases of VL/year have been reported in the region, corresponding to an estimated incidence of 4,500–6,800 cases of VL/year (Alvar et al. 2012). Thus, the American continent accounts for around 25–30 % of global CL and 1.5–2 % of global VL cases and burden.

The incidence of the disease is rather heterogeneous, with some countries showing a high incidence while others do not report cases (Fig. 1). Countries with the highest incidence are Brazil, Peru, and Colombia, while Canada and the United States do not present autochthonous cases.

Leishmaniasis has been extensively studied in Brazil over the past years, due to its very high incidence. Over 90 % of VL cases of the American continent occur in Brazil and 85 % of these cases are distributed in the northeast of the country (Harhay et al. 2011). Only in the Maranhao state, an epidemiological survey in children showed a prevalence of over 19 % of infection by *Leishmania infantum chagasi* (Nascimento Mdo et al. 2005). Similarly, in the other northeastern states of Piauí and Bahía, the affected population was around 14–16 % (Werneck et al. 2002; Felipe et al. 2011). In the Amazon rainforest in the state of Ceará, a prevalence of 4.6 % of VL was reported in children <11 years old, while in the state of Pará, a prevalence of 3.4 % was measured in a cohort study of 946 individuals living in endemic areas (Evans et al. 1992). Due to the high prevalence and incidence of VL in the country, Brazil has established a VL Control and Surveillance Program, in which all suspected and confirmed cases must be reported (de Araujo et al. 2012). CL is also very frequent, with an estimated yearly incidence of 26,000 cases (Fig. 1).

In Colombia, both visceral and dermatropic clinical forms have been described, but cutaneous leishmaniasis is largely predominant in 99 % of total cases. There is an estimated incidence of over 17,000 CL cases/year. *Leishmania (Viannia) panamensis* is responsible for 54–80 % of cases in northern and southwestern Colombia. On the other hand, *L. (Viannia) braziliensis* is distributed in most of the country and is responsible for 10–30 % of CL cases. About 1–5 % of additional leishmaniasis cases are caused by *L. (Leishmania) mexicana* and *L. (Viannia) guyanensis* (Martinez et al. 2010). Peru also has a high incidence of CL, reaching about 6,500 estimated cases/year (Llanos-Cuentas et al. 2008) and the disease is present in over 70 % of the country.

Bolivia, Ecuador, Venezuela, and Central American countries show intermediate incidence rates (Fig. 1). Bolivia presents a predominance of CL, and only 10 cases of VL have been reported in the period of 1983–2006. In contrast, the incidence of CL was estimated in 2006 at 32.7/100,000 habitants (Garcia

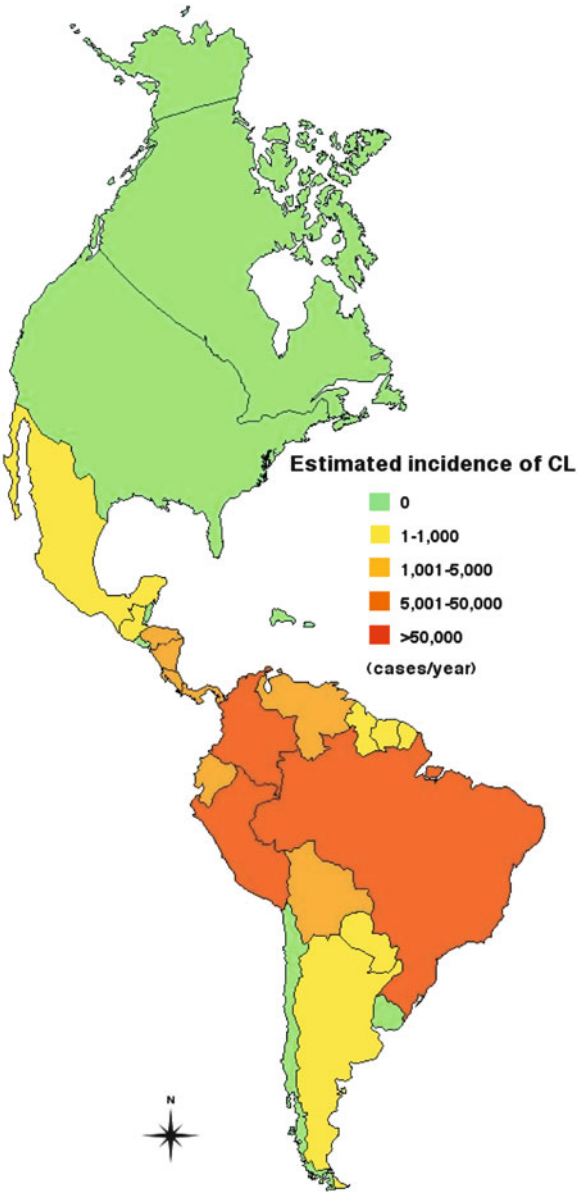

Fig. 1 Estimated incidence of CL in the Americas [Data were taken from Alvar et al. (2012)]

et al. 2009). Importantly, 90 % of cases were reported from only three of Bolivia's nine departments. The main causal agents involved were *L. (V.) braziliensis*, *L. (V.) amazonensis,* and *L. (V.) lainsoni*, with up to 85 % of total cases (Garcia et al. 2009).

In Ecuador, there is an estimated incidence of 3,000–4,500 cases of leishmaniasis per year, with CL found in most of the country, while MCL is rather restricted to the Amazon region (Calvopina et al. 2013).

VL is endemic in Venezuela, with an estimated yearly incidence of 0.2/100,000 people from 1995 to 2000, according to the National Registry of Leishmaniasis data (Feliciangeli et al. 2005; Convit et al. 2003; Zerpa et al. 2002). The main causative agent is *L. infantum chagasi*. The estimated incidence of CL is about 2,500 cases/year (Fig. 1).

Limited information is available for Central American countries. Cases have been described in patients from Guatemala and Belize, who present chronic ulcerative lesions characteristic of CL caused by *L. (L.) mexicana* (Blaylock and Wortmann 2012; Vinetz and Soong 2007; Demers et al. 2013). Panama seems to present the highest incidence, reporting up to 100 new cases/100,000 inhabitants per year, although incidence may still be underestimated (Miranda et al. 2009).

In spite of limited information, a significant incidence is also reported in the countries of Argentina, Paraguay, Guatemala, Mexico, Guyana, French Guiana and Suriname. In Mexico, both visceral and cutaneous leishmaniasis are present, mainly in the southern part of the country, but some cases have also been detected in northern states such as Sinaloa and Durango (Salazar-Mejia et al. 2010; Perez-Vega et al. 2009). Leishmaniasis is endemic in 22 of 31 Mexican states, but most cases have been found in the states of Veracruz, Tabasco, Chiapas, and in the Yucatan peninsula. Since 1995, only around 900 cases of both CL and VL have been reported per year (Bottazzi et al. 2011), but the epidemiology of the disease is poorly understood and controversial (Sanchez-Garcia et al. 2010; Andrade-Narvaez et al. 1990). VL is mostly present in the state of Chiapas, with 89 cases reported from the period of 1990–2006 (Pastor-Santiago et al. 2012).

In French Guiana, 100–350 CL cases/year have been reported in the past years, and the incidence appears to be significantly increasing, possibly in association with the development of ecotourism and mining in endemic forested areas (Rotureau 2006; Rotureau et al. 2007).

Uruguay, Chile, El Salvador, and Belize do not report any cases but are likely to have some disease present. For example, some sporadic cases have been described in Belize (Vinetz and Soong 2007), but the magnitude of *Leishmania* transmission to humans remains unknown. In the USA, canine leishmaniasis has been reported in several kennels, starting from an initial outbreak in 1999 in New York (Petersen and Barr 2009; Petersen 2009a), but there does not seem to have autochthonous human cases. The mechanisms of transmission of canine leishmaniasis in the USA remain largely unknown, although congenital transmission has been incriminated (Petersen 2009b; Boggiatto et al. 2011).

3 Clinical Forms and *Leishmania* Species

In Latin America, the clinical forms of leishmaniasis include CL and VL as mentioned above, but also disseminated, atypical cutaneous and mucocutaneous leishmaniasis. This diversity of clinical forms of the disease is strongly associated with the diversity of *Leishmania* parasite species. Indeed, while leishmaniasis is caused by only five species of *Leishmania* in the old world (*L. aethiopica,*

Table 1 Main *Leishmania* species and their common clinical manifestations

Genus	Subgenus	Species	Clinical manifestations
Leishmania	*(Leishmania)*	***donovani***	VL
		infantum	VL
		infantum chagasi	VL
		major	CL
		tropica	CL
		aethiopica	CL
		mexicana	CL (VL[a])
		amazonensis	CL, ADCL
	(Viannia)[b]	***braziliensis***	CL, MCL
		guyanensis	CL, MCL
		panamensis	CL, MCL
		naiffi	CL
		peruviana	CL
		colombiensis	CL
		shawi	CL

[a]Mostly in immunocompromized patients. Bold fonts indicate species for which the genome sequence is available
[b]The *Viannia* subgenus is exclusively present in the Americas

L. donovani, L. infantum, L. major, and *L. tropica*), a key characteristic of the American continent is the presence of a much greater diversity of parasite species, which include both the *Leishmania* and *Viannia* subgenus (Table 1). Species from the *Viannia* subgenus are endemic only in the new world. This diversity of species has important implications for disease epidemiology, control, and patient care. Indeed, it complicates vector control as well as diagnosis and treatment of patients in the Americas.

The species status of *L. chagasi* has been debated for many years, but recent molecular studies provided very strong evidence indicating that it should be considered as a subspecies of *L. infantum*, hence denominated *L. infantum chagasi*. Phylogeographic analysis indeed suggests a recent introduction of *L. infantum chagasi* in the new world, potentially from infected dogs brought to the Americas from Europe around 500 years ago during colonization (Marcili et al. 2014). This introduction was associated with a major bottleneck signature in *L. infantum chagasi* in the New World and a dramatic 1,000-fold reduction in the genetic diversity of this subspecies compared to *L. (L.) infantum* in the Old World.

CL can result from the infection with most of the species, including *L. (L.) mexicana, L. (L.) venezuelensis, L. (L.) amazonensis* as well as *L. (V.) braziliensis, L. (V.) guyanensis, L. (V.) panamensis, L. (V.) shawi, L. (V.) naiffi, L. (V.) lainsoni, L. (V.) lindenbergui,* and *L. (V.) peruviana* (Shaw 2002; WHO 2010). Localized cutaneous lesions are usually characterized by a unique or a few round-to-oval well-delimited ulcerated lesions with elevated borders, which can persist for months or even years, leaving a scar which can have severe social implications according to its severity (Banuls et al. 1999, 2011; Guimaraes et al. 2009). There are important geographic variations in the frequency of the different *Leishmania* species found. For example, *L. (L.) mexicana* is the most frequent species present in southern

Mexico. In Panama, the most frequent species is *L. (V.) panamensis* while other species such as *L. (V.) amazonensis*, *L. (V.) colombiensis, and L. (L.) mexicana* are less frequent (Miranda et al. 2009). In Peru, *L. (V.) peruviana, L. (V.) guyanensis,* and *L. (V.) braziliensis* are the most frequent species infecting humans, although *L. (V.) guyanensis* is also present in the Andean region. The identification of *Leishmania* species is important for the diagnosis and treatment, as treatment failure with pentavalent antimonials can be very frequent, particularly in infections with *L. (V.) peruviana* and *L. (V.) braziliensis* (Llanos-Cuentas et al. 2008; Adaui et al. 2011). *Leishmania* species identification can be achieved using monoclonal antibodies, but these methods have now largely been replaced by PCR-based molecular approaches based on a variety of molecular targets (Tsukayama et al. 2009, 2013; Valencia et al. 2012; Fraga et al. 2012).

Atypical manifestations of cutaneous leishmaniasis have been reported in Bahia, Brazil, where 1,396 cases between 2005 and 2006 were studied and 1.3 % patients without other morbidities resulted with vegetative, verrucous, crusted, and lupoid lesions. *L. (V.) braziliensis* was isolated and responsible for atypical leishmaniasis in 8 of these patients (Guimaraes et al. 2009). In Costa Rica and Nicaragua, some patients infected with *L. infantum chagasi* also showed atypical cutaneous cases (Convit et al. 2005).

Disseminated leishmaniasis appears as multiple pleomorphic lesions in at least two separated parts of the body and it is characterized by limited T cell responses to *Leishmania* antigens and a high number of phagocytized parasites within macrophages (Turetz et al. 2002). Disseminated leishmaniasis is rather rare, as it occurred in 1.9 % of 2,206 cutaneous leishmaniasis cases reported from 1992 to 1998, and patients showed an initial and isolated ulcer lesion, which developed into >10 up to hundreds of acneiform, nodular, papular, and ulcerated lesions over the following days. The principal causal agent of disseminated leishmaniasis is *L. (V.) braziliensis* (Turetz et al. 2002) and it has been observed mainly in northeastern Brazil, but some cases have been reported in other countries where this species is present (Table 1).

More than a clinical form, the mucocutaneous or mucosal leishmaniasis is the involvement of the mouth, pharynx, and larynx following the extension of cutaneous lesions. MCL is characterized by early nose block and bleeding. Patients can show a septal perforation after days or months postinfection, nose skin can be thickened and hyperemic, with deformation of the nasal pyramid. Metastasis can occur in mucosal tissues of the mouth and the upper respiratory tract, resulting in severe mutilation and difficulties for feeding or breathing (WHO 2010; Lessa et al. 2012). Also known as "espundia," mucosal leishmaniasis occurs in 3 % of CL cases in Bahia, Brazil. In the Amazon region of Brazil, mucosal leishmaniasis cases are often caused by *L. (V.) braziliensis* in 2/3 of the cases, while *L. (V.) guyanensis* is responsible for 1/3 of the cases (Guerra et al. 2011). Mucosal leishmaniasis has also been reported in Bolivia and Peru (WHO 2010; Lessa et al. 2012).

The visceral form (VL) is exclusive of *L. infantum* infection in the new world and its subspecies *L. infantum chagasi*. It is characterized by liver and spleen

involvement, and it is often fatal if not treated. The main symptoms associated with an unfavorable prognosis of VL include jaundice, thrombocytopenia, hemorrhage, diarrhea, severe neutropenia, and dyspnea, and the associated factors are HIV co-infection, age <5 and age >40–50 years, and bacterial infections (Belo et al. 2013). Tubuloglomerular dysfunction and renal inflammation have also been observed in some VL patients, suggesting that renal damage may also be part of the clinical evolution of VL (Silva Junior et al. 2014). Although Brazilian government efforts are directed toward early diagnosis and treatment, the fatality rate reported for VL was estimated to be 7 %, and in Belo Horizonte, Mina Gerais, it reached 12.6 % during the years 2002–2009 (de Araujo et al. 2012). HIV co-infection is also a growing concern, as it leads to a much more severe VL outcome (van Griensven et al. 2014; Lindoso et al. 2014). Other species such as *L. (L.) mexicana* can also cause VL, particularly in patients with low immune status (Ramos-Santos et al. 2000).

Following the sequencing of *L. (L.) major* genome in 2005 (Ivens et al. 2005), the complete genomes of 17 additional *Leishmania* species and strains are now available, including for *L. (L.) donovani, L. (L.) infantum, L. (L.) mexicana, L. tarentolae, L. (V.) panamensis,* and *L. (V.) braziliensis*. It is expected that these sequences and databases will allow a large variety of studies to further understand the pathogenesis and biology associated with the different species of *Leishmania* (Table 1).

4 Sand Fly Vectors of *Leishmania* Parasites in the Americas

A large diversity of sand fly vectors is present in the Americas, and they have adapted to a variety of habitats throughout the continent. Most species are associated with sylvatic habitats, but some have adapted to peridomestic habitats as well. Figure 2 summarizes the major sand fly species that have been incriminated as vectors of *Leishmania* in the Americas.

In contrast to the rather good knowledge of vectors in the Old World, much less is known about *Leishmania* vectors in the New World. For example, while a few vector species have been established for the transmission of *L. (L.) mexicana*, *L. (L.) infantum*, *L. (V.) braziliensis*, *L. (V.) guyanensis,* and *L. (L.) amazonensis*, the sandfly species associated with *L. peruviana*, *L. panamensis*, *L. shawi*, *L. Lainsoni*, *L. colombiensis*, *L. naiffi,* and *L. venezuelensis* transmission are still not clearly established (Ready 2013). A number of sand fly species are suspected vectors, but many await confirmation.

As can be seen, *Lu. longipalpis* is the most widespread and predominant vector of *Leishmania* (Fig. 2). It is considered the main vector for *L. infantum* in Brazil, where it has been able to adapt to the peridomestic habitat, possibly in association with environmental changes (Lainson and Rangel 2005). *Lu. Longipalpis* is also

Fig. 2 Diversity of sand fly vectors of *Leishmania* in the Americas. Only demonstrated vectors are indicated. Bold fonts indicate the most epidemiologically relevant species. Additional species of sandflies are also suspected to contribute to *Leishmania* transmission but are not indicated

present in Bolivia, Colombia, Venezuela, various parts of Central America, and to a lesser extent in Mexico. In some instances, such as in Panama, *Lu. longipalplis* has been found but no case of VL has been reported (Miranda et al. 2009). *L. infantum* infection rate can be up to 19 % for *Lu. Longipalpis,* but other sand fly species such as *Nyssomiya intermedia* and *Ny. Whitmani* also present high *L. infantum* infection

rates in Brazil (Saraiva et al. 2010), and *Lu. pseudolongipalpis* has also been proposed as a vector for *L. infantum* (Feliciangeli et al. 2005).

Important vector species for dermotropic *Leishmania* parasites include *Lu. ovallesi*, which is widely distributed in Guatemala, Belize, Panama, Colombia, and Venezuela (Fig. 2). It presents anthropophilic habits and shows high susceptibility to parasite infection, and it is considered the main vector of *L. (V.) braziliensis* in Venezuela (Nieves et al. 2012). *Lu. olmeca* and *Lu. cruciata* are the principal vectors of *L. (L.) mexicana* in Mexico and America Central (Pech-May et al. 2010). *Lu. panamensis*, *Lu. trapidoi*, *Lu. ylephileptor*, *Lu. gomezi,* and *Lu. sanguinaria* are incriminated in *L. panamensis* transmission. In the USA, *Lu. shannoni* and *Lu. vexator* are present, but seem to participate only in zoonotic transmission cycles.

This extensive diversity of sand fly species involved in parasite transmission to humans in the Americas has important implications. First it makes vector control very challenging, given the diversity of ecological niches and habitats implicated for the different sand fly species. Second, it also complicates the study of the role of sand fly saliva in Leishmania pathogenesis. Indeed, following pioneering studies with *L. (L.) major* and *Phlebotomus papatasii*, an Old World vector (Belkaid et al. 1998; Kamhawi et al. 2000), it is now clearly established that while the primary role of salivary proteins is to facilitate sand fly blood feeding, an important secondary property is to modulate the host immune response and the outcome of *Leishmania* infection (Kamhawi et al. 2000, 2014). Protection against *Leishmania* may be obtained following exposure with specific sand fly salivary proteins, and these have thus been proposed as a vaccine component against *Leishmania* parasites. In the Americas, most studies have focused on *Lu. longipalpis*, given its epidemiological relevance (Kamhawi et al. 2014), and some studies have highlighted some level of antigenic variability in key salivary proteins such as maxadilan (Milleron et al. 2004). The immune response to salivary proteins may also be used as a biological marker of exposure to sand fly bites in epidemiological studies (Souza et al. 2010). However, much less is known about the repertoire of salivary proteins from other species and their biological properties, although recent studies are beginning to unravel some information on the saliva of a variety of sand fly species, including *Lu. intermedia* (Weinkopff et al. 2014) and *Lu. ovallesi* (Nieves et al. 2012).

5 Reservoir Hosts of *Leishmania* in the Americas

A reservoir host is considered to be responsible for the long-term maintenance of circulating *Leishmania* parasites. Humans are rather considered to be incidental hosts, who may in some cases be involved in parasite transmission, but are not considered essential to complete transmission cycles.

In southern Texas *Neotoma micropus* is one of the most common rodent species which is associated with cactus vegetation where *Lu. anthophora* is present, and at least 9 % of the rodents are found positive to *L. (L.) mexicana* (Ashford 1996). In

Mexico, small rodents such as *Ototylomys phyllotis* and *Peromyscus yucatanicus* have been incriminated as reservoirs for *L. (L.) mexicana* parasites (Van Wynsberghe et al. 2009). Sloths and anteaters have been reported to be infected with *L. (V.) guyanensis* and *L. (V.) panamensis*, and may serve as reservoirs for these species, as well as opposums for *L. (V.) guyanensis*, *L. (L.) infantum,* and *L. (V.) peruviana*; and raccoons may serve as reservoirs for *L. (V.) panamensis* parasites (WHO 2010).

However, domestic dogs (*Canis familiaris*) are considered the most important domestic reservoir of *Leishmania* parasites in most of its geographic distribution, including the Americas. Dogs have been found infected with *L. infantum*, *L. tropica*, *L. major*, *L. (L.) mexicana,* and *L. (V.) braziliensis* (Ashford 1996). Canine infection with *Leishmania* spp., as in humans, can thus lead to VL or CL clinical forms, although many animals may remain asymptomatic as well. In peridomestic transmission cycles, dogs play a major role in attracting sandflies around human dwellings as demonstrated in southern Brazil, where the presence of infected dogs increases the risk of human infection 4.39 times (CI: 1.37–13.45) (Membrive et al. 2012). *L. infantum chagasi* infection rates can be very high in dogs, reaching nearly 50 % in Maranhao, or even 67 % in Sao Luis, Brazil (Felipe et al. 2011). While it is clearly established that dogs are the main reservoirs of *L. infantum chagasi* in many regions (Moreno and Alvar 2002; Baneth et al. 2008), their role in the transmission of cutaneous *Leishmania* species is not well understood. The observation of long-lasting skin ulcer lesions and a high susceptibility of dogs from Argentina suggests that they could act as reservoirs for other *Leishmania* parasites species (Padilla et al. 2002; Cruz-Chan et al. 2014). This has important implications for the definition of epidemiological control measures of this important reservoir. Indeed, the massive euthanasia of infected dogs in Brazil has been strongly discussed and has had a questionable efficacy to reduce infection rate in humans (Moreira et al. 2004; Grimaldi et al. 2012). Thus, alternative control strategies, including dog vaccination still need to be considered (Otranto and Dantas-Torres 2013; Palatnik-de-Sousa 2012). A few canine vaccines against VL are available in some countries, such as Brazil, and while they are highly immunogenic, their protective potential is still debated (Fernandes et al. 2014; Wylie et al. 2014). Further evaluation of these vaccines, as well as their improvement, is thus needed for an optimal control of canine leishmaniasis, and as for a human vaccine, these need to take into account the diversity of *Leishmania* species circulating in the region.

6 Concluding Remarks

Leishmaniasis remains a significant neglected disease in the Americas, with a rather high incidence in many regions and countries. Importantly, the diversity of vector and parasite species poses additional challenges compared to the situation in the Old World where leishmaniasis is also highly endemic. Indeed, this diversity

implies that most tools for disease surveillance and control, including diagnostics, vector control interventions, therapeutic treatments, and vaccines, need to be adapted to the species involved to ensure their efficacy. Further research is thus needed to optimize leishmaniasis control and surveillance in the Americas.

References

Adaui V, Maes I, Huyse T, Van den Broeck F, Talledo M, Kuhls K, De Doncker S, Maes L, Llanos-Cuentas A, Schonian G, Arevalo J, Dujardin JC (2011) Multilocus genotyping reveals a polyphyletic pattern among naturally antimony-resistant *Leishmania braziliensis* isolates from Peru. Infect Genet Evol 11(8):1873–1880. doi:10.1016/j.meegid.2011.08.008

Alvar J, Velez ID, Bern C, Herrero M, Desjeux P, Cano J, Jannin J, den Boer M (2012) Leishmaniasis worldwide and global estimates of its incidence. PLoS ONE 7(5):e35671. doi:10.1371/journal.pone.0035671

Andrade-Narvaez FJ, Simmonds-Diaz E, Rico-Aguilar S, Andrade-Narvaez M, Palomo-Cetina A, Canto-Lara SB, Garcia-Miss MR, Madera-Sevilla M, Albertos-Apulche N (1990) Incidence of localized cutaneous leishmaniasis (chiclero's ulcer) in Mexico. Trans R Soc Trop Med Hyg 84:219–220

Ashford RW (1996) Leishmaniasis reservoirs and their significance in control. Clin Dermatol 14 (5):523–532

Baneth G, Koutinas AF, Solano-Gallego L, Bourdeau P, Ferrer L (2008) Canine leishmaniosis - new concepts and insights on an expanding zoonosis: part one. Trends Parasitol 24 (7):324–330. doi:10.1016/j.pt.2008.04.001

Banuls AL, Hide M, Tibayrenc M (1999) Molecular epidemiology and evolutionary genetics of *Leishmania* parasites. Int J Parasitol 29:1137–1147

Banuls AL, Bastien P, Pomares C, Arevalo J, Fisa R, Hide M (2011) Clinical pleiomorphism in human leishmaniases, with special mention of asymptomatic infection. Clin Microbiol Infect 17(10):1451–1461. doi:10.1111/j.1469-0691.2011.03640.x

Belkaid Y, Kamhawi S, Modi G, Valenzuela J, Noben-Trauth N, Rowton E, Ribeiro J, Sacks DL (1998) Development of a natural model of cutaneous leishmaniasis: powerful effects of vector saliva and saliva preexposure on the long-term outcome of *Leishmania major* infection in the mouse ear dermis. J Exp Med 188(10):1941–1953

Belo VS, Werneck GL, Barbosa DS, Simoes TC, Nascimento BW, da Silva ES, Struchiner CJ (2013) Factors associated with visceral leishmaniasis in the americas: a systematic review and meta-analysis. PLoS Negl Trop Dis 7(4):e2182. doi:10.1371/journal.pntd.0002182

Blaylock JM, Wortmann GW (2012) A case report and literature review of "Chiclero's ulcer". Travel Med Infect Dis 10(5–6):275–278. doi:10.1016/j.tmaid.2012.08.005

Boggiatto PM, Gibson-Corley KN, Metz K, Gallup JM, Hostetter JM, Mullin K, Petersen CA (2011) Transplacental transmission of *Leishmania infantum* as a means for continued disease incidence in North America. PLoS Negl Trop Dis 5(4):e1019. doi:10.1371/journal.pntd.0001019

Bottazzi ME, Dumonteil E, Valenzuela JG, Betancourt-Cravioto M, Tapia-Conyer R, Hotez PJ (2011) Bridging the innovation gap for neglected tropical diseases in Mexico: capacity building for the development of a new generation of antipoverty vaccines. Bol Med Hosp Infant Mex 68(2):130–138

Calvopina M, Martinez L, Hashiguchi Y (2013) Cutaneous leishmaniasis "chiclero's ulcer" in subtropical Ecuador. Am J Trop Med Hyg 89(2):195–196. doi:10.4269/ajtmh. 12-0690

Convit J, Ulrich M, Zerpa O, Borges R, Aranzazu N, Valera M, Villarroel H, Zapata Z, Tomedes I (2003) Immunotherapy of American cutaneous leishmaniasis in Venezuela during the period 1990–99. Trans R Soc Trop Med Hyg 97(4):469–472

Convit J, Ulrich M, Perez M, Hung J, Castillo J, Rojas H, Viquez A, Araya LN, Lima HD (2005) Atypical cutaneous leishmaniasis in Central America: possible interaction between infectious and environmental elements. Trans R Soc Trop Med Hyg 99(1):13–17. doi:10.1016/j.trstmh.2004.02.005

Cruz-Chan JV, Aguilar-Cetina Adel C, Villanueva-Lizama LE, Martinez-Vega PP, Ramirez-Sierra MJ, Rosado-Vallado ME, Guillermo-Cordero JL, Dumonteil E (2014) A canine model of experimental infection with *Leishmania (L) mexicana*. Parasit Vectors 7:361. doi:10.1186/1756-3305-7-361

de Araujo VE, Morais MH, Reis IA, Rabello A, Carneiro M (2012) Early clinical manifestations associated with death from visceral leishmaniasis. PLoS Negl Trop Dis 6(2):e1511. doi:10.1371/journal.pntd.0001511

Demers E, Forrest DM, Weichert GE (2013) Cutaneous leishmaniasis in a returning traveller. CMAJ 185(8):681–683. doi:10.1503/cmaj.120694

Evans TG, Teixeira MJ, McAuliffe IT, Vasconcelos I, Vasconcelos AW, Sousa Ade A, Lima JW, Pearson RD (1992) Epidemiology of visceral leishmaniasis in northeast Brazil. J Infect Dis 166(5):1124–1132

Feliciangeli MD, Delgado O, Suarez B, Chiurillo MA (2005) The burden of the *Leishmania chagasi/infantum* infection in a closed rural focus of visceral leishmaniasis in Lara state, west-central Venezuela. Trop Med Int Health 10(5):444–449. doi:10.1111/j.1365-3156.2005.01408.x

Felipe IM, Aquino DM, Kuppinger O, Santos MD, Rangel ME, Barbosa DS, Barral A, Werneck GL, Caldas Ade J (2011) *Leishmania* infection in humans, dogs and sandflies in a visceral leishmaniasis endemic area in Maranhao, Brazil. Mem Inst Oswaldo Cruz 106(2):207–211

Fernandes CB, Junior JT, de Jesus C, Souza BM, Larangeira DF, Fraga DB, Tavares Veras PS, Barrouin-Melo SM (2014) Comparison of two commercial vaccines against visceral leishmaniasis in dogs from endemic areas: IgG, and subclasses, parasitism, and parasite transmission by xenodiagnosis. Vaccine 32(11):1287–1295. doi:10.1016/j.vaccine.2013.12.046

Fraga J, Veland N, Montalvo AM, Praet N, Boggild AK, Valencia BM, Arevalo J, Llanos-Cuentas A, Dujardin JC, Van der Auwera G (2012) Accurate and rapid species typing from cutaneous and mucocutaneous leishmaniasis lesions of the New World. Diagn Microbiol Infect Dis 74(2):142–150. doi:10.1016/j.diagmicrobio.2012.06.010

Fraga J, Montalvo AM, Van der Auwera G, Maes I, Dujardin JC, Requena JM (2013) Evolution and species discrimination according to the *Leishmania* heat-shock protein 20 gene. Infect Genet Evol 18:229–237. doi:10.1016/j.meegid.2013.05.020

Garcia AL, Parrado R, Rojas E, Delgado R, Dujardin JC, Reithinger R (2009) Leishmaniases in Bolivia: comprehensive review and current status. Am J Trop Med Hyg 80(5):704–711

Grimaldi G Jr, Teva A, Santos CB, Ferreira AL, Falqueto A (2012) The effect of removing potentially infectious dogs on the numbers of canine *Leishmania infantum* infections in an endemic area with high transmission rates. Am J Trop Med Hyg 86(6):966–971. doi:10.4269/ajtmh. 2012.12-0040

Guerra JA, Prestes SR, Silveira H, Coelho LI, Gama P, Moura A, Amato V, Barbosa M, Ferreira LC (2011) Mucosal Leishmaniasis caused by *Leishmania (Viannia) braziliensis* and *Leishmania (Viannia) guyanensis* in the Brazilian Amazon. PLoS Negl Trop Dis 5(3):e980. doi:10.1371/journal.pntd.0000980

Guimaraes LH, Machado PR, Lago EL, Morgan DJ, Schriefer A, Bacellar O, Carvalho EM (2009) Atypical manifestations of tegumentary leishmaniasis in a transmission area of *Leishmania braziliensis* in the state of Bahia, Brazil. Trans R Soc Trop Med Hyg 103(7):712–715. doi:10.1016/j.trstmh.2009.04.019

Harhay MO, Olliaro PL, Costa DL, Costa CH (2011) Urban parasitology: visceral leishmaniasis in Brazil. Trends Parasitol 27(9):403–409. doi:10.1016/j.pt.2011.04.001

Ivens AC, Peacock CS, Worthey EA, Murphy L, Aggarwal G, Berriman M, Sisk E, Rajandream MA, Adlem E, Aert R, Anupama A, Apostolou Z, Attipoe P, Bason N, Bauser C, Beck A, Beverley SM, Bianchettin G, Borzym K, Bothe G, Bruschi CV, Collins M, Cadag E, Ciarloni L, Clayton C, Coulson RM, Cronin A, Cruz AK, Davies RM, De Gaudenzi J, Dobson

DE, Duesterhoeft A, Fazelina G, Fosker N, Frasch AC, Fraser A, Fuchs M, Gabel C, Goble A, Goffeau A, Harris D, Hertz-Fowler C, Hilbert H, Horn D, Huang Y, Klages S, Knights A, Kube M, Larke N, Litvin L, Lord A, Louie T, Marra M, Masuy D, Matthews K, Michaeli S, Mottram JC, Muller-Auer S, Munden H, Nelson S, Norbertczak H, Oliver K, O'Neil S, Pentony M, Pohl TM, Price C, Purnelle B, Quail MA, Rabbinowitsch E, Reinhardt R, Rieger M, Rinta J, Robben J, Robertson L, Ruiz JC, Rutter S, Saunders D, Schafer M, Schein J, Schwartz DC, Seeger K, Seyler A, Sharp S, Shin H, Sivam D, Squares R, Squares S, Tosato V, Vogt C, Volckaert G, Wambutt R, Warren T, Wedler H, Woodward J, Zhou S, Zimmermann W, Smith DF, Blackwell JM, Stuart KD, Barrell B, Myler PJ (2005) The genome of the kinetoplastid parasite, *Leishmania major*. Science 309(5733):436–442

Kamhawi S, Belkaid Y, Modi G, Rowton E, Sacks D (2000) Protection against cutaneous leishmaniasis resulting from bites of uninfected sand flies. Science 290(5495):1351–1354

Kamhawi S, Aslan H, Valenzuela JG (2014) Vector saliva in vaccines for visceral leishmaniasis: a brief encounter of high consequence? Front Public Health 2:99. doi:10.3389/fpubh.2014.00099

Lainson R (2010) The neotropical *Leishmania* species: a brief historical review of their discovery, ecology and taxonomy. Rev Pan-Amaz Saude 1(2):13–32

Lainson R, Rangel EF (2005) *Lutzomyia longipalpis* and the eco-epidemiology of American visceral leishmaniasis, with particular reference to Brazil: a review. Mem Inst Oswaldo Cruz 100 (8):811–827. doi: /S0074-02762005000800001

Lessa HA, Lessa MM, Guimaraes LH, Lima CM, Arruda S, Machado PR, Carvalho EM (2012) A proposed new clinical staging system for patients with mucosal leishmaniasis. Trans R Soc Trop Med Hyg 106(6):376–381. doi:10.1016/j.trstmh.2012.03.007

Lindoso JA, Cota GF, da Cruz AM, Goto H, Maia-Elkhoury AN, Romero GA, de Sousa-Gomes ML, Santos-Oliveira JR, Rabello A (2014) Visceral leishmaniasis and HIV coinfection in Latin America. PLoS Negl Trop Dis 8(9):e3136. doi:10.1371/journal.pntd.0003136

Llanos-Cuentas A, Tulliano G, Araujo-Castillo R, Miranda-Verastegui C, Santamaria-Castrellon-G, Ramirez L, Lazo M, De Doncker S, Boelaert M, Robays J, Dujardin JC, Arevalo J, Chappuis F (2008) Clinical and parasite species risk factors for pentavalent antimonial treatment failure in cutaneous leishmaniasis in Peru. Clin Infect Dis 46(2):223–231. doi:10.1086/524042

Marcili A, Speranca MA, da Costa AP, Madeira Mde F, Soares HS, Sanches Cde O, Acosta Ida C, Girotto A, Minervino AH, Horta MC, Shaw JJ, Gennari SM (2014) Phylogenetic relationships of Leishmania species based on trypanosomatid barcode (SSU rDNA) and gGAPDH genes: taxonomic revision of *Leishmania (L.) infantum chagasi* in South America. Infect Genet Evol 25:44–51. doi:10.1016/j.meegid.2014.04.001

Martinez LP, Rebollo JA, Luna AL, Cochero S, Bejarano EE (2010) Molecular identification of the parasites causing cutaneous leishmaniasis on the Caribbean coast of Colombia. Parasitol Res 106(3):647–652. doi:10.1007/s00436-009-1712-6

Membrive NA, Rodrigues G, Gualda KP, Bernal MV, Oliveira DM, Lonardoni MV, Teodoro U, Teixeira JJ, Silveira TG (2012) Environmental and animal characteristics as factors associated with American cutaneous leishmaniasis in rural locations with presence of dogs, Brazil. PLoS ONE 7(11):e47050. doi:10.1371/journal.pone.0047050

Milleron RS, Mutebi JP, Valle S, Montoya A, Yin H, Soong L, Lanzaro GC (2004) Antigenic diversity in maxadilan, a salivary protein from the sand fly vector of American visceral leishmaniasis. Am J Trop Med Hyg 70(3):286–293

Miranda A, Carrasco R, Paz H, Pascale JM, Samudio F, Saldana A, Santamaria G, Mendoza Y, Calzada JE (2009) Molecular epidemiology of American tegumentary leishmaniasis in Panama. Am J Trop Med Hyg 81(4):565–571. doi:10.4269/ajtmh. 2009.08-0265

Moreira ED Jr, Mendes De Souza VM, Sreenivasan M, Nascimento EG, Pontes De Carvalho L (2004) Assessment of an optimized dog-culling program in the dynamics of canine *Leishmania* transmission. Vet Parasitol 122(4):245–252

Moreno J, Alvar J (2002) Canine leishmaniasis: epidemiological risk and the experimental model. Trends Parasitol 18(9):399–405

Murray HW, Berman JD, Davies CR, Saravia NG (2005) Advances in leishmaniasis. Lancet 366 (9496):1561–1577

Nascimento Mdo D, Souza EC, Silva LM, Leal Pda C, Cantanhede Kde L, Bezerra GF, Viana GM (2005) Prevalencia de infeccao por *Leishmania chagas*i utilizando os metodos de ELISA (rK39 e CRUDE) e intradermorreacao de Montenegro em area endemica do Maranhao, Brasil. Cadernos de saude publica 21(6):1801–1807

Nieves E, Sanchez Y, Sanchez H, Rondon M, Gonzalez N, Carrero J (2012) Sandfly saliva of *Lutzomyia ovallesi* (Diptera: Psychodidae) as a possible marker for the transmission of *Leishmania* in Venezuela Andes region. J Vector Borne Dis 49(1):8–14

Otranto D, Dantas-Torres F (2013) The prevention of canine leishmaniasis and its impact on public health. Trends Parasitol 29(7):339–345. doi:10.1016/j.pt.2013.05.003

Padilla AM, Marco JD, Diosque P, Segura MA, Mora MC, Fernandez MM, Malchiodi EL, Basombrio MA (2002) Canine infection and the possible role of dogs in the transmission of American tegumentary leishmaniosis in Salta, Argentina. Vet Parasitol 110(1–2):1–10

Palatnik-de-Sousa CB (2012) Vaccines for canine leishmaniasis. Front Immunol 3:69. doi:10.3389/fimmu.2012.00069

Pastor-Santiago JA, Chavez-Lopez S, Guzman-Bracho C, Flisser A, Olivo-Diaz A (2012) American visceral leishmaniasis in Chiapas, Mexico. Am J Trop Med Hyg 86(1):108–114. doi:10.4269/ajtmh. 2012.10-0561

Pech-May A, Escobedo-Ortegon FJ, Berzunza-Cruz M, Rebollar-Tellez EA (2010) Incrimination of four sandfly species previously unrecognized as vectors of *Leishmania* parasites in Mexico. Med Vet Entomol 24(2):150–161. doi:10.1111/j.1365-2915.2010.00870.x

Perez-Vega JH, Lopez-Moreno CY, Lopez-Valenzuela JA, Rendon-Maldonado JG, Lopez-Moreno HS (2009) Leishmaniasis cutanea causada por *Leishmania mexicana* en Durango, México. Informe del primer caso clínico. Gac Med Mex 145(5):433–435

Petersen CA (2009a) Leishmaniasis, an emerging disease found in companion animals in the United States. Top Companion Anim Med 24(4):182–188. doi:10.1053/j.tcam.2009.06.006

Petersen CA (2009b) New means of canine leishmaniasis transmission in North America: the possibility of transmission to humans still unknown. Interdisc Perspect Infect Dis 2009:802712. doi:10.1155/2009/802712

Petersen CA, Barr SC (2009) Canine leishmaniasis in North America: emerging or newly recognized? Vet Clin North Am Small Anim Pract 39(6):1065–1074, vi. doi:10.1016/j.cvsm.2009.06.008

Pigott DM, Bhatt S, Golding N, Duda KA, Battle KE, Brady OJ, Messina JP, Balard Y, Bastien P, Pratlong F, Brownstein JS, Freifeld CC, Mekaru SR, Gething PW, George DB, Myers MF, Reithinger R, Hay SI (2014) Global distribution maps of the leishmaniases. eLife 3. doi:10.7554/eLife.02851

Ramos-Santos C, Hernandez-Montes O, Sanchez-Tejeda G, Monroy-Ostria A (2000) Visceral leishmaniosis caused by *Leishmania (L.) mexicana* in a Mexican patient with human immunodeficiency virus infection. Mem Inst Oswaldo Cruz 95(5):733–737

Ready PD (2013) Biology of phlebotomine sand flies as vectors of disease agents. Annu Rev Entomol 58:227–250. doi:10.1146/annurev-ento-120811-153557

Rotureau B (2006) Ecology of the *Leishmania* species in the Guianan ecoregion complex. Am J Trop Med Hyg 74(1):81–96

Rotureau B, Couppie P, Nacher M, Dedet JP, Carme B (2007) Les leishmanioses cutanées en Guyane française. Bull Soc Pathol Exot 100(4):251–260

Salazar-Mejia PG, Tejeda-Aguirre CR, Lopez-Moreno HS (2010) Reacción de antígenos de *Leishmania (Leishmania) mexicana* con sueros de pacientes con leishmaniosis cutanea de Sinaloa, México. Salud Publica Mex 52(2):165–169

Sanchez-Garcia L, Berzunza-Cruz M, Becker-Fauser I, Rebollar-Tellez EA (2010) Sand flies naturally infected by *Leishmania (L.) mexicana* in the peri-urban area of Chetumal city, Quintana Roo, Mexico. Trans R Soc Trop Med Hyg 104(6):406–411. doi:10.1016/j.trstmh.2010.01.010

Saraiva L, Andrade Filho JD, Silva Sde O, Andrade AS, Melo MN (2010) The molecular detection of different *Leishmania* species within sand flies from a cutaneous and visceral leishmaniasis sympatric area in Southeastern Brazil. Mem Inst Oswaldo Cruz 105(8):1033–1039

Shaw J (2002) New World Leishmaniasis: the ecology of leishmaniasis and the diversity of Leishmanial species in Central and South America. In: Farrel JP (ed) Leishmania, vol 4, World class parasites. Kluwer Academic, Norwell, pp 11–31. doi:10.1016/j.pt.2013.05.003

Silva Junior GB, Barros EJ, Daher Ede F (2014) Kidney involvement in leishmaniasis–a review. Braz J Infect Dis 18(4):434–440. doi:10.1016/j.bjid.2013.11.013

Souza AP, Andrade BB, Aquino D, Entringer P, Miranda JC, Alcantara R, Ruiz D, Soto M, Teixeira CR, Valenzuela JG, de Oliveira CI, Brodskyn CI, Barral-Netto M, Barral A (2010) Using recombinant proteins from *Lutzomyia longipalpis* saliva to estimate human vector exposure in visceral Leishmaniasis endemic areas. PLoS Negl Trop Dis 4(3):e649. doi:10.1371/journal.pntd.0000649

Tsukayama P, Lucas C, Bacon DJ (2009) Typing of four genetic loci discriminates among closely related species of New World *Leishmania*. Int J Parasitol 39(3):355–362. doi:10.1016/j.ijpara.2008.08.004

Tsukayama P, Nunez JH, De Los SM, Soberon V, Lucas CM, Matlashewski G, Llanos-Cuentas A, Ore M, Baldeviano GC, Edgel KA, Lescano AG, Graf PC, Bacon DJ (2013) A FRET-based real-time PCR assay to identify the main causal agents of New World tegumentary leishmaniasis. PLoS Negl Trop Dis 7(1):e1956. doi:10.1371/journal.pntd.0001956

Turetz ML, Machado PR, Ko AI, Alves F, Bittencourt A, Almeida RP, Mobashery N, Johnson WD Jr, Carvalho EM (2002) Disseminated leishmaniasis: a new and emerging form of leishmaniasis observed in northeastern Brazil. J Infect Dis 186(12):1829–1834. doi:10.1086/345772

Valencia BM, Veland N, Alba M, Adaui V, Arevalo J, Low DE, Llanos-Cuentas A, Boggild AK (2012) Non-invasive cytology brush PCR for the diagnosis and causative species identification of American cutaneous leishmaniasis in Peru. PLoS ONE 7(11):e49738. doi:10.1371/journal.pone.0049738

van Griensven J, Carrillo E, Lopez-Velez R, Lynen L, Moreno J (2014) Leishmaniasis in immunosuppressed individuals. Clin Microbiol Infect 20(4):286–299. doi:10.1111/1469-0691.12556

Van Wynsberghe NR, Canto-Lara SB, Sosa-Bibiano EI, Rivero-Cardenas NA, Andrade-Narvaez FJ (2009) Comparison of small mammal prevalence of Leishmania (Leishmania) mexicana in five foci of cutaneous leishmaniasis in the State of Campeche, Mexico. Rev Inst Med Trop Sao Paulo 51(2):87–94. doi:S0036-46652009000200006 [pii]

Vinetz JM, Soong L (2007) *Leishmania mexicana* infection of the eyelid in a traveler to Belize. Braz J Infect Dis 11(1):149–152

Weinkopff T, de Oliveira CI, de Carvalho AM, Hauyon-La Torre Y, Muniz AC, Miranda JC, Barral A, Tacchini-Cottier F (2014) Repeated exposure to *Lutzomyia intermedia* sand fly saliva induces local expression of interferon-inducible genes both at the site of injection in mice and in human blood. PLoS Negl Trop Dis 8(1):e2627. doi:10.1371/journal.pntd.0002627

Werneck GL, Rodrigues L, Santos MV, Araujo IB, Moura LS, Lima SS, Gomes RB, Maguire JH, Costa CH (2002) The burden of *Leishmania chagasi* infection during an urban outbreak of visceral leishmaniasis in Brazil. Acta Trop 83(1):13–18

WHO (2010) Control of the leishmaniasis: report of a meeting of the WHO committee on the control of the Leishmaniasis. WHO technical report series

Wylie CE, Carbonell-Antonanzas M, Aiassa E, Dhollander S, Zagmutt FJ, Brodbelt DC, Solano-Gallego L (2014) A systematic review of the efficacy of prophylactic control measures for naturally-occurring canine leishmaniosis, part I: vaccinations. Prev Vet Med. doi:10.1016/j.prevetmed.2014.06.015

Zerpa O, Ulrich M, Benitez M, Avila C, Rodriguez V, Centeno M, Belizario D, Reed SG, Convit J (2002) Epidemiological and immunological aspects of human visceral leishmaniasis on Margarita Island, Venezuela. Mem Inst Oswaldo Cruz 97(8):1079–1083