Current status and management of canine leishmaniasis in Latin America

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A R T I C L E   I N F O

A B S T R A C T

Latin America encompasses diverse geographical, cultural and socio-economic conditions, which are reflected in the challenges for infectious disease control in the region. One of the most significant regional infectious diseases for humans and domestic dogs is leishmaniasis, occurring as visceral leishmaniasis (VL) caused by *Leishmania infantum* (syn. *L. chagasi*) transmitted by sand flies (*Lutzomyia longipalpis*) and with a canine reservoir, and the more common cutaneous leishmaniasis (CL) involving multiple *Leishmania* spp. (particularly *L. braziliensis*), sand fly vectors and reservoir hosts. VL is spreading within Latin America for reasons related to mass migration of human and canine populations, with incursion into novel environments (e.g. related to deforestation) coupled with a background of poverty and poor public health infrastructure. The challenges for control of VL also include: (1) the accurate identification of infected dogs (particularly subclinically infected dogs) with the current reliance on serological rather than molecular diagnostic methods, (2) controversy surrounding the ethics and efficacy of culling of seropositive dogs, (3) the limited efficacy of currently available canine vaccines and their potential to interfere with interpretation of serological testing, (4) the expense associated with distribution of insecticidal dog collars, which may prove to be the most valuable control method, and (5) the cost and therefore accessibility of licensed medical treatment for canine leishmaniasis by the general population. Resolution of these issues will necessitate a 'One Health' approach to co-ordination of resources between human and veterinary healthcare.

1. Introduction

Latin America consists of sovereign states and territories located between the northern border of Mexico and the southern tip of South America, including the Caribbean Islands, whose inhabitants speak Latin languages such as Portuguese, Spanish or French. A small part of the population speaks other languages, e.g. English and Dutch. Latin America has an area of approximately 19,197,000 km^2, and a population that was estimated at > 639 million in 2016 (United Nations, 2017). Brazil is the largest country, followed by Argentina and Mexico. Most of Latin America is located within the tropical zone, with a climate ranging from hot and humid in the Amazon basin, to the dry and desert-like conditions of northern Mexico and southern Chile. Data on the incidence of leishmaniasis in Latin America do not closely reflect reality, since under-reporting is a major problem, particularly in Central America, where many areas lack an adequate system for registering epidemiological information, and do not have a surveillance and control programme (WHO, 2017).

Visceral leishmaniasis (VL) is the most severe form of leishmaniasis, and is caused in Latin America by *Leishmania infantum* (syn. *L. chagasi*).

Originally, the disease was limited to rural environments; however, over time, there was an epidemiological transition, with increasing incidences in urban areas, associated with sand fly colonization and the spread and adaptation of natural reservoir hosts to these domestic and anthropic environments (Fernández et al., 2010; González et al., 2014; Harhay et al., 2011; Oliveira et al., 2016; Paiva et al., 2010; Rangel and Vilela, 2008). The expansion of VL in Latin America has been associated with: (1) ecosystem destruction and modification of natural environments due to deforestation, establishment of rural settlements, industrialization and construction of roads, highways, the Bolivia–Brazil natural gas pipeline, mining camps, dams and hydroelectric plants; (2) urbanization, associated with mass migration of people from rural areas to the cities; (3) the concomitant migration of infected domestic dogs; (4) movement of dogs with canine visceral leishmaniasis (CanVL) to prevent them from being euthanized; (5) poverty and poor sanitation; and (6) ineffective or partially effective vector and disease control measures (Araújo et al., 2013; Fernández et al., 2010; González et al., 2014; Harhay et al., 2011; Lara-Silva et al., 2015; Salomón et al., 2015; Oliveira et al., 2016; Paiva et al., 2010; Rangel and Vilela, 2008; Romero and Boelaert, 2010).

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Table 1
Estimated annual incidence rate and number of reported cases of visceral and cutaneous leishmaniosis in 2015 in Latin American countries (WHO, 2017).

Country	Visceral leishmaniosis		Cutaneous leishmaniosis	
	Cases/year	Incidence rate/year (/100,000 inhabitants)	Cases/year per year	Incidence rate/year (/100,000 inhabitants)
Argentina	8	0.67	334	3.57
Bolivia	0	0	2231	30.1
Brazil	3289	2.54	19,395	15.3
Chile	NACR	NACR	NACR	NACR
Colombia	21	0.63	7541	33.6
Costa Rica	NACR[a]	NACR	1171	30.0
Cuba	NACR	NACR	NACR	NACR
Dominican Republic	NACR	NACR	ND	ND
Ecuador	NACR	NACR	1479	14.9
El Salvador	0	0	20	14.4
French Guyana	NACR	NACR	228	DNA[c]
Guatemala	2	1.9	564	18.2
Guyana	NACR[a]	NACR	132	23.8
Honduras	6	0.34	2040	35.7
Mexico	1	0.1	479	6.32
Nicaragua	0	0	1925	76.6
Panama	NACR	NACR	930	29.7
Paraguay	92	2.36	122	7.93
Peru	NACR	NACR	5459	23.0
Suriname	NACR	NACR	241	218.5
Uruguay	NACR[b]	NACR	NACR	NACR
Venezuela	37	0.34	2013	8.75

NACR: No autochthonous case reported, ND: No data.
[a] There are some reports of sporadic transmission.
[b] To date just reports of canine visceral leishmaniosis.
[c] DNA: data not available, the country reports directly to France.

VL is widespread from Mexico to Argentina, with autochthonous cases reported in many countries (Table 1). In 2015, a total of 3456 cases of VL and an incidence of 2.27 cases per 100,000 people were reported in Latin America, with 95.1% occuring in Brazil (WHO, 2017). In Brazil, VL was initially concentrated in poor rural areas in the northeast of the country, but since the 1980s epidemics have occurred in major cities, and reports of infected dogs and humans have gradually extended to the southeast and mid-west of the country. Since 2004, > 3000 new human cases are reported in the country each year (Brasil, 2017a). Until 2006, the south of Brazil, Argentina and Uruguay were considered non-endemic areas for VL. In 2006, after VL outbreaks in the city of Asunción, Paraguay, the first autochthonous urban human case of VL in Argentina was reported in Posadas, a city on the border of Paraguay, on the Parana River (Acardi et al., 2010; Salomón et al., 2008a, 2009; Salomón et al., 2010). Three years later the first outbreak of VL occurred in the south of Brazil, in São Borja, a city on the border of Argentina, 160 km from Posadas, with over 1200 sepositive dogs identified (Tartarotti et al., 2011). Since then, VL has expanded in the region (Grill and Zurmendi, 2017; WHO, 2017). Major traffic of stray and owned pet dogs across the border of Paraguay and Argentina may have further contributed to the expansion of canine and human VL in this part of Latin America (Salomón et al., 2009).

Cutaneous leishmaniasis (CL) is the most common form of the disease, characterized by a spectrum of clinical manifestations in humans, ranging from localized dermal ulcers to mucocutaneous lesions. Although death from CL is rare, cutaneous lesions may generate psychological, social and economic problems (Santaella et al., 2011). The epidemiology of CL in the Americas is complex, with variations in transmission cycles, reservoir hosts, sand fly vectors, and multiple circulating *Leishmania* species in the same geographical area (WHO, 2017). The disease is endemic in 18 Latin American countries, with different transmission intensities (Table 1). The species of *Leishmania* that cause human CL in Latin America are presented in Table 2 (WHO, 2017). *Leishmania braziliensis* is the most widespread and is responsible for the greatest number of notified cases of CL in Latin America (Arjona-Jiménez et al., 2012; Davies et al., 2000; Steverding, 2017; WHO, 2017). Additionally, some hybrids, or intermediate variants, are reported in some Latin American countries (Davies et al., 2000). The incidence of human infection has increased, largely due to the factors described above for VL (Brasil, 2017b; WHO, 2017).

2. Canine leishmaniasis in Latin America

Domestic dogs are considered to be the main reservoirs of *L. infantum*, having an important role in the epidemiology of VL (Baneth et al., 2008; Brasil, 2006). The number of infected dogs in South America is estimated in millions, and there are high infection rates, especially in Brazil, where a high prevalence of canine infection is associated with a high risk of human disease (Baneth et al., 2008; Brasil, 2006; 2017a). However, it is difficult to estimate the real prevalence of CanVL in the Americas due to: (1) the limited number of publications from some countries, (2) limitations in the methodology used in reported studies, not allowing identification of the *Leishmania* spp. involved, (3) the overlapping of areas endemic for Chagas disease (reported in dogs from southern USA throughout the Americas) (Gürtler et al., 2006), CL and VL (Bastrenta et al., 2003; Guimarães-e-Silva et al., 2017; Maywald et al., 1996; Rosypal et al., 2007), which can lead to serological cross-reaction between parasites (Marcondes et al., 2011; Tolezano et al., 2007; Troncarelli et al., 2009; Umezawa et al., 2009; Zanette et al., 2014), (4) the fact that, like humans, dogs can also be co-infected by *L. infantum* and *L. braziliensis* (Dantas-Torres et al., 2010; Madeira et al., 2006; Pires et al., 2014; Quaresma et al., 2011), (5) the fact that most infected dogs (as evidenced by a positive polymerase chain reaction [PCR]) are apparently healthy and do not show clinical signs (Baneth et al., 2008; Miró et al., 2008).

The identification of subclinically infected dogs in a population is often a challenge. While seropositivity is found in 88–100% of clinically affected dogs, it is evident in only 30–66% of subclinically infected animals (Miró et al., 2008). Studies using PCR in endemic areas have confirmed that the prevalence of infection in dogs is much higher than the proportion that actually develops disease (Baneth et al., 2008; Coura-Vital et al., 2011). Although the development of sensitive molecular diagnostic techniques has improved the detection of clinically healthy infected dogs, those methods are not always available to researchers in Latin America; therefore, the real percentage of those dogs is difficult to estimate. A study conducted in the northeast of Brazil reported that 85.3% of seropositive dogs were considered subclinically infected; however, this prevalence may be lower, since clinical status was based only on physical examination (i.e. without clinicopathological evaluation, including haematological and serum biochemical analysis and urinalysis) and dogs presenting with just one clinical sign were categorized as subclinically infected (Dantas-Torres et al., 2006). Dogs with subclinical infection or clinically healthy infected dogs are defined as those that show no clinical signs on physical examination and have no clinicopathological abnormalities on the routine laboratory tests listed above, but have confirmed *L. infantum* infection (Solano-Gallego et al., 2009, 2011). A lower percentage of dogs with subclinical infection was reported by Lara-Silva et al. (2015), in an area endemic for VL in Southeastern Brazil. Among 1408 dogs evaluated serologically by indirect fluorescent antibody test (IFAT) and enzyme-linked immunosorbent assay (ELISA) for the presence of *L. infantum* antibodies, seroprevalence was 3.6% (51 dogs), and dogs with subclinical infection represented 45% of the seropositive animals. In a study of 1443 dogs from an area endemic for VL in Belo Horizonte, Southeastern Brazil, 230 (15.9%) animals were seropositive on ELISA, while 356 (24.7%) dogs were PCR positive, demonstrating that the prevalence of infection was higher when determined by PCR compared with serology. Only 60 (16.8%) of the PCR-positive dogs were seropositive (Coura-Vital et al., 2011). Despite the sensitivity of PCR for

Table 2

Geographical distribution of *Leishmania* species infecting people and dogs in Latin America, and respective proven/suspected vectors.

Species	Human cases reported	Dog reported cases	Vectors
L. (L.) amazonensis	Argentina, Bolivia, Brazil, Colombia, Ecuador, Peru, Suriname, Venezuela	Brazil	*Lu. flaviscutellata, Lu. longipalpis, Lu. nuneztovari anglesi, Lu. olmeca*
L. (V.) braziliensis	Argentina, Bolivia, Brazil, Colombia, Costa Rica, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Peru, Panama, Paraguay, Venezuela	Argentina[a], Bolivia, Brazil, Colombia, Mexico, Panama, Paraguay, Peru, Venezuela	*Lu. intermedia, Lu migonei, Lu. whitmani, Lu. nuneztovari, Lu. tejadai, Lu. youngi, Lu. neivai, Lu. ovallesi, Lu. panamensis, Lu. ylephiletor, Lu. fischeri, Lu. gomezi, Lu. longipalpis*
L. (V.) colombiensis	Colombia, Panama, Venezuela	Venezuela	*Lu. hartmanni*
L. (V.) equatoriensis	Ecuador		
L. (V.) guyanensis	Argentina, Bolivia, Brazil, Colombia, Guyana, Peru, Suriname, Venezuela	Colombia	*Lu. umbratilis, Lu. ayacuchensis, Lu. migonei*
L. (L.) infantum	Argentina, Bolivia, Brazil, Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua Paraguay, Venezuela	Argentina, Bolivia, Brazil, Colombia, French Guyana, Mexico, Paraguay, Uruguay, Venezuela	*Lu. Longipalpis, Lu. cruzi, Lu evansi, Lu. migonei, Lu. forattinii, Lu. almerioi, Lu. whitmani, Lu. fischeri*
L. (V.) lainsoni	Brazil, Bolivia, Peru, Suriname		*Lu. ubiquitalis*
L. (V.) lindenberg	Brazil		*Lu. antunesi*
L. (L.) mexicana	Colombia, Costa Rica, Ecuador, Guatemala, Mexico, Venezuela	Colombia, Ecuador, Mexico	*Lu. migonei, Lu. ovallesi, Lu. gomezi, Lu. cruciata, Lu. panamensis, Lu. olmeca Lu. shannoni, Lu. ylephiletor*
L. (V.) naiffi	Brazil, Ecuador		*Lu. ayrozai*
L. (V.) panamensis	Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama	Colombia, Ecuador, Panama	*Lu. trapidoi, Lu. gomezi,*
L. (V.) peruviana	Peru	Peru	*Lu. peruensis, Lu. ayacuchensis Lu. verrucarum*
L. (V.) pifanoi	Venezuela	Ecuador	*Lu. flaviscutellata*
L. (V.) shawi	Brazil		*Lu. whitmani*
L. (L.) venezuelensis	Venezuela		*Lu. olmeca*

[a] Species isolated from dogs were not characterized, but were from the same area of human cases of CL caused by L. *braziliensis.*

identifying *Leishmania* infection, this technique is time consuming and expensive for routine use in surveillance programmes (Gomes et al., 2007). In areas endemic for VL, clinically healthy infected dogs can be a source of infection to sand fly vectors (Alvar et al., 2004; Borja et al., 2016; Costa-Val et al., 2007; Laurenti et al., 2013; Magalhães-Junior et al., 2016; Michalsky et al., 2007).

Among all of the Latin American countries where *L. infantum* has been isolated from dogs (Fig. 1), Brazil, Argentina and Paraguay show the greatest evidence of expansion of CanVL. The seroprevalence of CanVL in endemic areas of Brazil ranges from 3.1% to 36.0%, depending on the region, the population evaluated, the year and the serological method employed (Ashford et al., 1998; Belo et al., 2017; França-Silva et al., 2003; Lara-Silva et al., 2015; Lopes et al., 2010; Pacheco et al., 2013; Rondon et al., 2008; Rosypal et al., 2007; Tolezano et al., 2007). Results must be interpreted with caution, since many serological studies were conducted in areas with overlap between VL and CL (Tolezano et al., 2007). The number of registered cases of VL and CanVL has increased significantly in recent years in Paraguay, with seroprevalences of CanVL ranging from 23% to 32% from 2005 to 2016 (Canese et al., 1999; Miret et al., 2010; Portillo et al., 2011). Most cases are concentrated around the capital of the country. In the Asunción area, where urban transmission is of high concern, the seroprevalence of CanVL ranged from 3.1% to 11.8% until 1999 (Canese, 2000), was estimated to be 58% in 2006 (Cousiño, 2006), and reached values of 69% in stray dogs in 2010 (Miret et al., 2011). In 2006, when the first case of CanVL was reported in Posadas, Argentina, the prevalence of CanVL (based on serology and/or PCR) was 57.3% (Cruz et al., 2010). From Posadas, CanVL began to gradually spread throughout the province and to other areas, with > 7000 cases of CanVL found 350 km south of Posadas up to 2010 (Barrio et al., 2012), finally reaching Puerto Iguazú, on the border of Brazil and Paraguay (Salomón et al., 2015, 2016). In 2013, seroprevalence in Puerto Iguazú was 7.2% (Costa et al., 2015).

In 2010, the presence of *Lutzomyia longipalpis*, the main sand fly vector of *L. infantum* in Latin America, was recorded for the first time in Uruguay, in a city located near the Argentinian border, across the Paraná River, where a focus of CanVL was reported in 2009 (Salomón et al., 2011). The environmental conditions, the presence of the vectors, the occurrence of canine and human leishmaniasis in border countries, and the movement of individuals and dogs along the border, have made
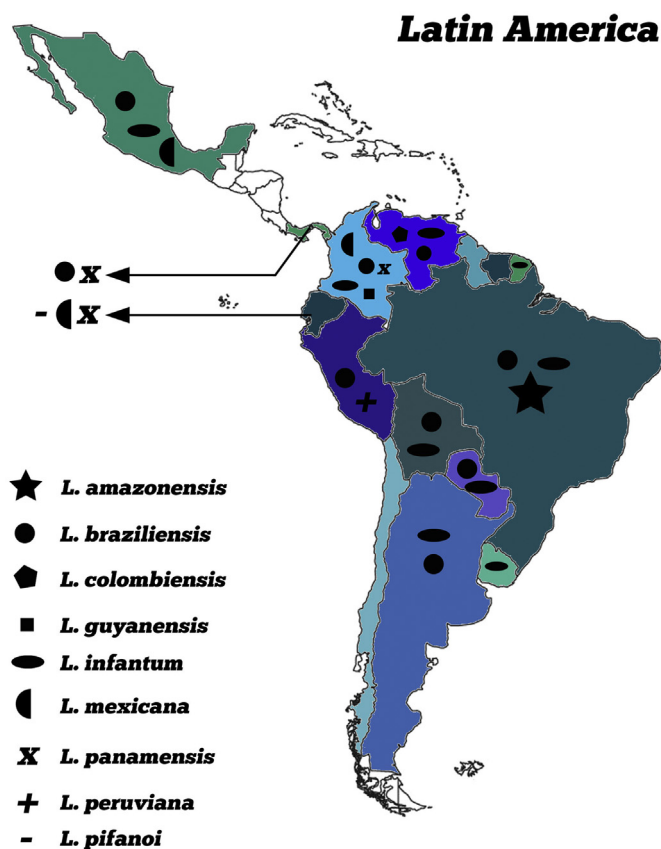

Fig. 1. Geographical distribution of *Leishmania* species infecting dogs in Latin America.

Uruguay susceptible to the disease. In 2015, a survey in Salto, a city on the border of Argentina and Uruguay, found 22% seroprevalence for *Leishmania* spp., with confirmation of infection in some dogs by direct parasitologial diagnosis in lymph node biopsy samples and bone marrow aspirates, and by *L. infantum* PCR and sequencing (Satragno et al., 2017). Studies on the seroprevalence of CanVL in Mexico,

Venezuela and Colombia have reported levels between 1.7% and 15.7% (Arjona-Jiménez et al., 2012; López-Céspedes et al., 2012), 5.6% and 40.0%, (Delgado et al., 1998; Feliciangeli et al., 2005; Zerpa et al., 2000, 2001, 2003) and 1.6% and 36.0% (Cortés, 2006; Fernández et al., 2002; Paternina-Gómez et al., 2013; Rosypal et al., 2007), respectively. CanVL is comparatively rare in Bolivia relative to CL, but dogs can be infected by *L. infantum* (García et al., 2009; Lepont et al., 1989). Although French Guyana has no reported autochthonous case of VL in humans up to now, the first autochthonous case of CanVL was described in 2005 (Rotureau et al., 2006).

Dogs with clinical leishmaniasis present with a spectrum of clinical signs and clinicopathological abnormalities (Baneth et al., 2008; Paltrinieri et al., 2010; Solano-Gallego et al., 2009). Co-infections of *L. infantum* and other canine vector-borne pathogens have been reported in Latin America, and may confound clinical presentation, making diagnosis more challenging (Andreotti et al., 2006; Cardinot et al., 2016; Gennari et al., 2006; Ikeda et al., 2005; Sousa et al., 2013). The presence of infected dogs has been widely identified as a risk factor for the occurrence of human VL in Latin America (Belo et al., 2013a; Camargo-Neves et al., 2001; Carneiro et al., 2004; González et al., 2014). A multilevel approach used to evaluate the effect of canine infection and environmental and socio-economic factors on the incidence rates of VL in the city of Teresina, Northeastern Brazil, revealed that an increasing prevalence of canine infection predicted a higher incidence of human VL, and that poor socio-economic conditions and increased vegetation were also associated with a higher incidence of human VL (Werneck et al., 2007). Studies conducted in the city of Belo Horizonte, Southeastern Brazil, also showed a correlation between the prevalence of canine infection and the incidence of human VL (Araújo et al., 2013; Borges et al., 2009; Margonari et al., 2006; Oliveira et al., 2001).

3. Canine cutaneous leishmaniasis in Latin America

Leishmania spp. isolated from dogs in Latin America are presented in Fig. 1 and Table 2. Results of studies on the prevalence of canine cutaneous leishmaniasis (CanCL) in Latin America should be interpreted with caution, since there is considerable variation between study protocols and sample sizes, and most were based on serological surveys, in areas where VL and CL overlap (Nunes et al., 1991). The most widespread aetiological agent of CanCL in South America is *L. braziliensis*. Originally associated with forested areas, the transmission cycle of CL has now adapted to the domestic environment due to deforestation and urbanization (Serra et al., 2003). In Brazil, the prevalence of canine infection with *Leishmania* spp. associated with CanCL ranges from 3.2% to 50.3%, depending on the area and methods used (Aguilar et al., 1989; Barbosa et al., 1999; Castro et al., 2007; Dantas-Torres et al., 2010; Falqueto et al., 1986; Leça Junior et al., 2015; Oliveira-Neto et al., 1988; Passos et al., 1996; Serra et al., 2003; Soccol et al., 2009). In Argentina, the prevalence of CanCL in an area where *L. braziliensis* and *Leishmania amazonensis* were previously isolated from human patients was 27.4% (Padilla et al., 2002), and the yearly incidence of seroconversion and of the appearance of ulcerative lesions, in dogs living in an area endemic for *L. braziliensis*, were 22.7% and 13.5%, respectively (Marco et al., 2001). The increase in the number of cases of CanCL in Colombia is related to the high number of trained guard dogs accompanying soldiers into forested areas, because of the armed conflict in the country and in the fight against drug trafficking (Santaella et al., 2011; Vélez et al., 2012). Dogs are mainly infected by *L. braziliensis* and *Leishmania panamensis* (Travi et al., 2006; Vélez et al., 2012), but can also be infected by *Leishmania mexicana* (López-Céspedes et al., 2012) and *Leishmania guyanensis* (Santaella et al., 2011). Venezuela has also reported clinical cases of CanCL, with prevalences ranging from 5.0% to 7.0% (Aguilar et al., 1984, 1989) and a seroprevalence in dogs of 2.8% (Delgado et al., 1993). Among *Leishmania* species identified in Ecuador, there are reports of dogs infected by *L. mexicana* (Hashiguchi and Gomez Landires, 1991), *L. panamensis* (Dereure et al., 1994) and

Leishmania pifanoi (Reithinger and Davies, 1999). In Mexico, canine seroprevalence for *L. mexicana* and *L. braziliensis* ranged from 7.5% to 30.2% (Arjona-Jiménez et al., 2012; López-Céspedes et al., 2012). There are reports of CanCL caused by *L. panamensis* (Dereure et al., 1994) and a prevalence of CanCL of 3.3% was found during 1968–1973, with *L. braziliensis* isolated from some dogs, in Panama (Herrer and Christensen, 1976). *Leishmania peruviana* is the principal aetiological agent of CL throughout much of the Peruvian Andes, although *L. braziliensis* is also endemic in Peru (Llanos-Cuentas et al., 1999; Reithinger et al., 2000, 2003a). The prevalence of *Leishmania* infection in areas where both parasites are endemic was found to be 8.1%, with parasites detected in 7.6% of subclinically infected dogs (Reithinger et al., 2000). Another study, conducted over a 3-year period found a cumulative prevalence of 26% of canine infection (Reithinger et al., 2003a). In Paraguay and Bolivia, only *L. braziliensis* has been identified as the agent of CL in dogs (Chena et al., 2012; Lepont et al., 1989).

Clinical signs of CL in dogs include chronic single or multiple ulcerative lesions affecting the ears, nasal planum, scrotum, face or other areas of the skin; erosive mucocutaneous lesions in the mouth and nasal mucosa; depigmentation and inflammation of the nostrils and lymphadenomegaly (Herrer and Christensen, 1976; Leça Junior et al., 2015; Pirmez et al., 1988). Multiple lesions can be the result of repeated exposures to sand fly bites, or may also result from the dissemination of the parasite via the blood or lymphatic route, as suggested for human infection (Madeira et al., 2005). *Leishmania* spp. DNA can sometimes be detected in blood and bone marrow of infected dogs, suggesting haematogenous dissemination (Reithinger et al., 2000). However, since the parasite is not always found in blood, if blood dissemination occurs, it may be an eventual or intermittent phenomenon (Madeira et al., 2005). Depending on the species of *Leishmania* involved, some dogs can heal spontaneously months after the appearance of the lesions, with complete clinical and serological recovery. However, lesions, accompanied by seroconverion, can relapse (Marco et al., 2001; Reithinger et al., 2003a; Reithinger and Davies, 1999). Infected dogs can be clinically healthy (Leça Junior et al., 2015). The proportion and epidemiological significance of CanCL-resistant dogs in natural populations is unclear (Reithinger and Davies, 1999).

Although viewed with controversy, some studies have suggested that dogs may act as reservoirs of *L. braziliensis* and other aetiological agents of CL (Aguilar et al., 1987; Davies et al., 2000; Castro et al., 2007; Falqueto et al., 1986, 1991; Madeira et al., 2005; Padilla et al., 2002; Reithinger et al., 2000, 2003b), while others have shown little evidence for this, suggesting that dogs do not play an important role in transmission of CL and are more likely to be incidental hosts, since they probably suffer the same pressure as humans when there is an epidemic outbreak (Castro et al., 2007; Dantas-Torres, 2007; Soccol et al., 2009; Travi et al., 2006). Since the transmission cycle of *L. braziliensis* is primarily forest-based and is frequently associated with human penetration into forests or regions of vegetation, sylvatic mammals such as rodents and opossums (family Didelphidae) are the most likely reservoirs of *L. braziliensis* and *L. mexicana* complexes in some Latin American countries (Brandão-Filho et al., 2003; Lima et al., 2013; Marcelino et al., 2011; Oliveira et al., 2005; Quaresma et al., 2011). However, with CL now established in rural and urbanised areas, the transmission cycle in these places appears to be maintained through the participation of synanthropic or even domestic reservoirs. Considering that domestic dogs are not the principal reservoir hosts of the aetiological agents of CL, it remains to be determined which mammals play this role in rural and urban areas (Quaresma et al., 2011).

Current evidence that domestic dogs act as reservoir hosts for the domestic transmission of CL is circumstantial, and comes from the fact that some *Leishmania* strains isolated from dogs and humans are indistinguishable, and on the detection of a high prevalence of CanCL in dogs surveyed in endemic areas (Davies et al., 2000; Reithinger and Davies, 1999). Nevertheless, the identification of infected dogs does not determine whether dogs are accidental or reservoir hosts of the agent.

The presence of infected dogs in households with CL patients indicates that humans and dogs are exposed in the same way to the sand fly vector, but is not evidence for dogs being reservoirs (Reithinger and Davies, 1999). While some authors found no evidence that people who own dogs are at any greater risk of acquiring CL or that villages with higher dog densities have a greater population risk (Reithinger and Davies, 1999), others observed a clear relationship between the presence of infected dogs and the occurrence of new human cases of the disease (Falqueto et al., 1986).

4. Vectors of *Leishmania* parasites in Latin America

Leishmania parasites are mainly transmitted by the bite of infected phlebotomine sand flies of the genus *Lutzomyia* in Latin America, and approximately 56 species are supposed, or have been proven, to be involved (Guimarães et al., 2016; Maroli et al., 2013; Steverding, 2017). The main vector of *L. infantum* in Latin America is *Lutzomyia longipalpis*, distributed from Mexico to Argentina (Bravo et al., 2013; Feliciangeli et al., 2003; Fernández et al., 2010; Guimarães et al., 2016; Guimarães-e-Silva et al., 2017; Lainson and Rangel, 2005; Rangel and Vilela, 2008). Although already displaying an extensive geographical distribution, it appears that this vector is undergoing further territorial expansion in Brazil and in Argentina and Uruguay (Bravo et al., 2013; Salomón et al., 2011; Salomón and Orellano, 2005; Rangel and Vilela, 2008). Formerly associated with forested and rural areas, the epidemiological profile of leishmaniasis has changed and VL vectors now appear to be present also in urban and periurban areas of Latin America, including large cities in Brazil (Bejarano et al., 2001; Oliveira et al., 2016; Saraiva et al., 2009). Although *Lu. longipalpis* is found in Latin America over the whole year, there is evidence that sand fly density increases during or soon after the rainy season (Amóra et al., 2010; Barata et al., 2004; Harhay et al., 2011; Margonari et al., 2004; Resende et al., 2006; Oliveira et al., 2008).

The occurrence of VL in areas from which the usual VL vector, *Lu. longipalpis*, is absent, as well as the finding of other sand flies naturally infected with this agent have suggested that there are other vectors in Latin America (Table 2) (de Araújo-Pereira et al., 2010; Belo et al., 2013b; Bejarano et al., 2001; Carvalho et al., 2010; Feliciangeli et al., 1999; Galvis-Ovallos et al., 2017; González et al., 2014; Guimarães et al., 2016; Lainson and Rangel, 2005; Missawa et al., 2011; Moya et al., 2015, 2017; Paternina-Gómez et al., 2013; Pita-Pereira et al., 2008; Rodrigues et al., 2016; Romero and Boelaert, 2010; Salomón et al., 2010; Travi et al., 1990; Zerpa et al., 2003); however, for only some of them has vectorial capacity been proven (Saraiva et al., 2009, 2010).

The impact of environmental changes on the behaviour of vectors of CL in Latin America has been found to be crucial to the establishment of some *Lutzomyia* species in the domestic environment, changing the epidemiological profile of the disease (Maroli et al., 2013). Table 2 presents some of the proven or suspected vectors of CL in Latin America, based on data found in the literature (Aguilar et al., 1984; Brilhante et al., 2015; Camargo-Neves et al., 2002; Calvopina et al., 2004; Córdoba-Lanús et al., 2006; Feliciangeli et al., 1994; Guimarães-e-Silva et al., 2017; Kato et al., 2005; Lana et al., 2015; Lara-Silva et al., 2015; Llanos-cuentas et al., 1999; Maroli et al., 2013; Martinez et al., 1999; Moya et al., 2017; Nunes et al., 1991; Paiva et al., 2010; Pech-May et al., 2010; Pita-Pereira et al., 2005, 2009, 2011; Rabinovich and Feliciangeli, 2004; Rangel and Lainson, 2009; Rêgo et al., 2015; Reithinger and Davies, 1999; Rowton et al., 1991, 1992; Salomón et al., 2008b; Saraiva et al., 2009; Soccol et al., 2009; Vélez et al., 2012; Vexenat et al., 1986). It is interesting to note that some *Lutzomyia* spp. are supposed to transmit more than one *Leishmania* spp., e.g. *Lutzomyia migonei* has been found to be infected with *L. braziliensis*, *L. guyanensis*, *L. mexicana* and *L. infantum*, while *Lutzomyia whitmani* is supposed to be a vector of *L. braziliensis* and *Leishmania shawi* and *Lu. longipalpis* of *L. amazonensis* and *L. infantum* (Maroli et al., 2013). The occurrence of *Lu.*

longipalpis naturally infected by *L. braziliensis*, *L. amazonensis*, *L. mexicana*, *L. shawi*, *L. guyanensis* and *L. lainsoni* or *L. naiffi*, in an area that is higly endemic for leishmaniasis in Brazil, was also reported (Guimarães-e-Silva et al., 2017). Regarding the seasonality of proven and suspected vectors of CL in Latin America, differences in sand fly densities according to the season of the year have been noted among different species and in different regions of Latin America (Rangel and Lainson, 2009).

5. Control of canine leishmaniasis in Latin America

5.1. Culling of seropositive dogs

To control the spread of VL, Latin American countries (i.e. Argentina, Brazil, Paraguay and Uruguay) have instituted measures including early diagnosis and treatment of human cases, vector control by residual insecticide spraying and identification and culling of seropositive dogs (Echenique, 2010; Brasil, 2006; Paraguay, 2011; Uruguay, 2016). During the 3rd Meeting of the National Programmes of Leishmaniasis of the Priority Countries of the Americas, promoted by the Pan American Health Organization (PAHO), held in Colombia in 2015, the recommendation for surveillance and control of *Leishmania* spp. reservoirs was maintained, including dog euthanasia (PAHO, 2015). This measure is controversial and the Brazilian experience has shown that widespread culling (i.e. the elimination of 176,000 seropositive dogs during 1990–1997) has not been associated with a reduction in the number of human and canine cases of disease and infection (Coura-Vital et al., 2014; Courtenay et al., 2002; Dietze et al., 1997; Grimaldi et al., 2012b). In contrast, the total number of human cases in the country has increased and the disease has become a serious public health problem in several Brazilian states (Brasil, 2017a; Costa, 2011). The lack of effectiveness of eliminating infected dogs is related to: (1) the high incidence of infection and infectiousness in areas of endemicity (Costa et al., 2013); (2) the lack of sufficient sensitivity and specificity of serological methods to accurately identify all infected dogs (Coura-Vital et al., 2014; Courtenay et al., 2002; Moreira Jr. et al., 2004); (3) the delay between detecting a seropositive dog and culling of 80–180 days (Coura-Vital et al., 2014; Courtenay et al., 2002; Grimaldi et al., 2012b); (4) the tendency to replace infected dogs with susceptible puppies (Coura-Vital et al., 2014; Moreira Jr. et al., 2004), some of them by two or more dogs and in a mean time of 4 months, leading to a younger population that might be more susceptible to CanVL (Nunes et al., 2008). Nonetheless, some authors found that euthanasia of infected dogs, associated with other current control measures, can reduce the incidence of canine and human cases of VL (Ashford et al., 1998; Costa et al., 2007; Nunes et al., 2010).

Most of the studies conducted in Latin America to evaluate serological tests used to diagnose CanVL were performed in Brazil. The sensitivity and specificity of ELISA using crude antigens varied from 72% to 100%, and from 77.8% to 100%, respectively (Almeida et al., 2005, 2017; Arruda et al., 2013; Figueiredo et al., 2010; Laurenti et al., 2014; Lira et al., 2006; Silva et al., 2013); while for IFAT, sensitivity and specificity varied from 22.2% to 100%, and from 65.5% to 100%, respectively (Almeida et al., 2005; Figueiredo et al., 2010; Laurenti et al., 2014; Lira et al., 2006; Silva et al., 2013), demonstrating the lack of consistency in the results obtained between different studies (Peixoto et al., 2015). Among all Latin American countries, Brazil has the highest incidence and distribution of CanVL. Until 2011, the screening and confirmatory tests adopted by the Brazilian Ministry of Health (BMH) in canine serological surveys for VL were, respectively, an ELISA (EIE-LVC kit; Bio-Manguinhos/Fiocruz, Rio de Janeiro, Brazil), and an IFAT (IFI-LVC kit; Bio-Manguinhos/Fiocruz, Rio de Janeiro, Brazil), both using antigens of promastigotes of *Leishmania major*-like species (Lira et al., 2006). Besides being considered innacurate, another problem with this protocol was a prolonged period (of around 60 days), between sampling and release of the results (Belo et al., 2017). When those tests were

carried out in series (i.e. the result is considered positive only when both tests are positive), the sensitivity was 48.0% and the specificity 100%, whereas when carried out in parallel (i.e. only one test needs to be positive), sensitivity was 92.0% and specificity 75.0% (Lira et al., 2006). Arruda et al. (2013), evaluating whether the antigen used (*L. major*-like) could interfere with the performance of the serological test, demonstrated sensitivities of 91.84% and 89.80%, and specificities of 83.75% and 82.69% for ELISA-*L. major* and *L. infantum*, respectively, suggesting that there was no need to change the antigen composition of the ELISA used in Brazil for the diagnosis of CanVL.

In December 2011, due to the limitations of these techniques, the Brazilian public health authorities replaced the methods used to diagnose CanVL (ELISA and IFAT) by a rapid immunochromatographic Dual Path Platform immunoassay (DPP®; Bio-Manguinhos, Fiocruz, Rio de Janeiro, Brazil), based on a recombinant protein (rk28) derived from expression of a plasmid containing genes encoding the *L. infantum* k9, k26 and k39 proteins. This assay is used as a screening test and positive results are confirmed by ELISA (Brasil, 2011), in an effort to increase the specificity, reliability and speed (results given in 15 days) of the diagnosis of CanVL (Belo et al., 2017; Fraga et al., 2016; Regina-Silva et al., 2014). This new protocol has been shown to be better for the serodiagnosis of CanVL (Coura-Vital et al., 2014; Fraga et al., 2016). In serological surveys conducted in Brazil, ELISA and IFAT were peformed using blood samples dried onto filter paper with subsequent extraction of serum protein from the filter. Changing this to liquid serum or plasma samples has been recommended; however, this has not yet been widely adopted by all health departments of the municipalities located in many endemic areas, because of operational difficulties (Brasil, 2011; Coura-Vital et al., 2014). The DPP® has a sensitivity ranging from 82.3% to 91.0% and a specificity between 70.2% and 96.0% (Almeida et al., 2017; Alves et al., 2012; Laurenti et al., 2014). Although the kit has the advantage of simplicity, speed (result within 15 min) and flexibility in the type of biological samples used (whole blood, serum or plasma), the use of DPP® as a screening test is controversial, and it has been proposed that it should be used as a confirmatory rather than a screening test (Coura-Vital et al., 2014). Laurenti et al. (2014), investigating the performance of the DPP®, demonstrated that it was equally sensitive as ELISA (BioManguinhos); however, the specificities were 95.1% and 84.3%, respectively, which resulted in a higher positive likelihood ratio (18.3 vs 4.1), higher positive predictive value (95.1% vs 81.1%) and higher accuracy (92.7% vs 84.3%) for DPP®, suggesting its potential to be used as a confirmatory and a screening test. Lopes et al. (2017), evaluating dogs from an area endemic for VL in Brazil by DPP®, ELISA and real-time PCR (qPCR) on blood and lymph node aspirates, showed that 19.6% (174/887) of DPP®-seronegative dogs were classified as infected by molecular tests. A systematic review and meta-analysis of serological diagnosis of CanVL in Brazil has demonstrated that ELISA using crude antigens and DPP® tests have moderate accuracy (sensitivity and specificity for ELISA 89% and 87%, respectively, and for DPP® 83% and 73%, respectively) for the diagnosis of CanVL (Peixoto et al., 2015).

Another limitation of serological tests used for the diagnosis of CanVL is the possibility of false-positive results due to cross-reactivity with other infectious agents reported in Latin America, e.g. *Trypanosoma cruzi, Trypanosoma caninum, Babeisa canis, Ehrlichia canis, Toxoplasma gondii* and *Neospora caninum*, especially when serological titres to *Leishmania* spp. are near the cut-off value (Alves et al., 2012; Laurenti et al., 2014; Lira et al., 2006; Marcondes et al., 2011; Rosypal et al., 2005, 2007; Silva et al., 2011; Troncarelli et al., 2009; Zanette et al., 2014). Silva et al. (2011), evaluated 155 seroreactive dogs (i.e. titre > 40 by IFAT on blood collected onto filter paper) that had been culled by the Brazilian control programme, by IFAT, ELISA, parasitological culture (from cutaneous lesions, intact skin and spleen) and PCR (from intact skin). They found that 91 (59.0%) dogs were negative for all four techniques, five (3.2%) dogs were infected by *L. braziliensis*, seven (4.5%) by *T. caninum* and one animal was co-infected by *L.*

infantum and *L. braziliensis*. A study comparing the use of serum and blood samples eluted from filter paper for the routine diagnosis of leishmaniasis in dogs showed that the sensitivity of IFAT using eluate and serum (cut-off titre of 40) were, respectively, 22.2% and 100% (Figueiredo et al., 2010), supporting calls for the use of filter paper to be discontinued. Serological tests have a low sensitivity for the detection of subclinically infected dogs (Grimaldi et al., 2012a; Lira et al., 2006; Peixoto et al., 2015; Porrozzi et al., 2007), and some dogs may not have seroconverted at the time of blood sampling, despite being infected (Alvar et al., 2004). To try to minimize these limitations, recombinant antigens have been developed to diagnose CanVL, and these have demonstrated sensitivity and specificity ranging from 70% to 100% and from 85 to 100%, respectively (Coelho et al., 2016; Faria et al., 2015; Peixoto et al., 2015; Porrozzi et al., 2007; Rosário et al., 2005; Venturin et al., 2015).

Although knowledge of the *Leishmania* spp. is particularly important in regions where both VL and CL are prevalent, serological diagnosis is inadequate for species discrimination (Gomes et al., 2007; Tolezano et al., 2007); however, other techniques such as DNA sequencing or use of PCR followed by restriction fragment length polymorphism analysis (PCR-RFLP) (Andrade et al., 2006) are not always available. Madeira et al. (2005), evaluating dogs with CL lesions caused by *L. braziliensis,* found seropositivity in 78.9% of the dogs by ELISA using soluble *L. braziliensis* antigen and in 73.7% by the official IFAT kit used by the BMH, demonstrating that, if diagnosis had been based only on serological tests, the dogs could have been culled. These results highlight the necessity for the use of more than one test to diagnose CanVL.

5.2. Dog vaccination

In 2003, the Brazilian Ministry of Agriculture, Livestock, and Food Supply (MAPA) granted a license for Leishmune®, originally marketed by Fort Dodge Animal Health and later by Zoetis, the first commercially available vaccine aginst CanVL, consisting of a purified fraction (fucose–mannose ligand; FML) from promastigotes of *Leishmania donovani* adjuvanted with saponin. However, in 2014 the vaccine was withdrawn from the market, since it did not fulfill the phase III requirements regarding evaluation of vaccine efficacy (MAPA, 2014). In 2006, another vaccine was launched onto the Brazilian market, Leish-Tec® (Hertape Calier), consisting of the recombinant protein A2, expressed in the amastigote stage of *Leishmania* parasites, adjuvanted with saponin, currently the only vaccine against CanVL sold in Brazil (Campos et al., 2017). Vaccination as a measure to control VL, has not been adopted by the BMH, due to lack of scientific evidence regarding its efficacy in reducing the incidence of the disease in dogs and humans (Travi, 2014). Recently, a vaccine consisting of culture supernatant of *L. infantum* promastigotes (LiESAp), composed of a 54 kDa excreted protein of *L. infantum* with muramyl dipeptide (MDP), CaniLeish® (Virbac Animal Health), licensed for use in Europe since 2011 (Wylie et al., 2014), was licensed in Paraguay and Argentina. One of the concerns of the BMH, was the possible seroconversion of vaccinated dogs, interfering with seroepidemiological investigations and removal of infected animals from endemic areas, since infected dogs may be not differentiated from vaccinated animals. A study evaluating the three serological tests officially adopted by the BMH for the diagnosis of CanVL (ELISA, IFAT and DPP®) and an 'in-house' ELISA, showed that dogs vaccinated with Leishmune® could be seropositive for up to 6 months after the first dose of vaccine, with a higher percentage of positive dogs observed with the 'in-house' ELISA, followed by the official IFAT, official ELISA and DPP®. Six months after the first vaccine dose, 88.8%, 33.3%, 11.1% and 5.5% of the dogs remained seropositive by the 'in-house' ELISA, official ELISA, DPP® and official IFAT, respectively, and these animals may have been mistakenly diagnosed and culled (Marcondes et al., 2013). In contrast, dogs vaccinated with Leish-Tec® and monitored for up to 14 months after the first dose of vaccine did not seroconvert as measured by ELISA or DPP®, except by for one animal (1.42%) that became

seropositive by ELISA (Testasicca et al., 2014). In another study, Leish-Tec® induced seroconversion in 30.9% of vaccinated dogs up to 11 months after the first vaccine dose (Fernandes et al., 2014). A previous history of vaccination does not exclude CanVL in dogs with clinical signs or clinicopathological abnormalities suggestive of the disease. In the Veterinary Teaching Hospital of São Paulo State University, in Araçatuba, São Paulo, Brazil, an area endemic for CanVL, sporadic cases of seropositive vaccinated dogs with clinical disease have been identified (data not shown).

The use of vaccines, from an epidemiological point of view, aims to reduce or interrupt the transmission of *L. infantum*. Evaluation of the potential infectiousness of vaccinated dogs (by xenodiagnosis) reported that 5.1% (2/39; one dog was symptomatic and the other was not) of dogs vaccinated with Leishmune® and 5.4% (2/37; both dogs were symptomatic) of dogs vaccinated with Leish-Tec® were infectious to sand flies (Fernandes et al., 2014). Another field study showed a reduction in the number of cases of CanVL in dogs vaccinated with Leish-Tec® when compared with the placebo group (7.4% vs 17.7%), as measured by parasitological examination plus xenodiagnosis (no information was provided on clinical status in this study). However, although these authors stated that there was a reduction in transmission to sand flies from vaccinated dogs with anti-A2 positive serology, there was no statistically significant difference between the prevalence of positive sand fly pools that fed on dogs from the placebo (44.2%) and vaccinated (35.7%) groups, when they were compared independently of serology (Regina-Silva et al., 2016). Further field studies are needed in order to evaluate whether vaccination of dogs against leishmaniasis may be a useful tool in disease control.

5.3. Vector control

The use of topical insecticides, especially collars, can reduce the risk of *L. infantum* infection in dogs, representing a tool that could be integrated into control programmes for VL (Dantas-Torres, 2009; David et al., 2001; Miró et al., 2008; Otranto and Dantas-Torres, 2013; Reithinger et al., 2004). However, in order to achieve a significant epidemiological impact on the transmission of CanVL, high rates of dog collar coverage are essential (Reithinger et al., 2004). This may not be feasible due to the cost of the collars and the poor socio-economic condition of dog owners, particularly those living in rural and suburban areas, unless such programmes are supported by the local public health authorities (Dantas-Torres, 2009; Reithinger et al., 2004). In order to evaluate the efficacy of insecticide-impregnated collars in the control of VL, the BMH has been distributing deltamethrin-impregnated collars in selected municipalities. In Campo Grande, the capital and largest city of the state of Mato Grosso do Sul, with an estimated population of 112,000 dogs, 110,000 collars were distributed by the BMH between 2009 and 2010 (data not shown). A mathematical model used to compare the efficacy of control measures for VL (i.e. vaccines, euthanasia of seropositive dogs and use of insecticide-impregnated collars) has shown that the three measures, at different coverages, were each associated with a decrease in the prevalence of infection in dogs and people. However, the use of insecticide-impregnated collars had the highest level of efficacy. When used at a coverage of 90%, insecticide-impregnated collars were able to decrease the prevalence of seropositive dogs and humans to zero (Sevá et al., 2016).

5.4. The 'One Health' approach to the control of canine leishmaniasis

It is clear from the above discussion that the control of canine leishmaniasis in the Latin American setting is complex and multifactorial, involving elements such as diagnostic identification of infected dogs and the use of topical insecticides supported by vaccination. This disease also poses a perfect 'One Health' challenge as it involves environmental effects (e.g. deforestation and movement of human communities into novel geographical areas, control of the sand fly

vector), a canine reservoir of the pathogen and zoonotic human infection. Therefore, the most valuable and cost-effective approach to control of the disease would be through multispecialist collaborations of field workers (e.g. public health officials, veterinarians and human physicians), researchers and laboratory diagnosticians (e.g. microbiologists, parasitologists, immunologists) and policy makers at local, national and regional level (e.g. politicians, civil servants and health economists). The One Health approach to control of leishmaniasis has been discussed in an earlier review (Palatinik-de-Souza and Day, 2011).

6. Treatment of canine leishmaniasis in Latin America

In Latin America, treatment of dogs with leishmaniasis is not usually performed, mainly due to the recommendation that seropositive dogs be culled in most countries. In Brazil, in 2008 the BMH and MAPA prohibited the treatment of CanVL with drugs for human use or drugs not licensed by MAPA (Brasil, 2008). Despite this, many veterinarians obtained court authorization to treat dogs, and many owners who refused to send their animals for euthanasia opted to treat their dogs with imported or second-line drugs. In September 2016, MAPA granted a license for the sale of Milteforan® (miltefosine; Virbac Animal Health), the first veterinary drug for the treatment of CanVL in Brazil, which was launched onto the Brazilian market in January 2017. However, the recommendation for euthanasia still remains for dogs whose owners cannot pay for treatment with Milteforan®.

7. Conclusions

It is clear that leishmaniasis represents one of the major infectious disease threats within Latin America and that the disease is spreading geographically to affect new canine and human populations. As discussed above, there are numerous socio-economic and scientific challenges that impede the successful control and prevention of this disease. The most effective means of overcoming these challenges would be to adopt a 'One Health' approach to the control of leishmaniasis (Palatinik-de-Souza and Day, 2011). One Health necessitates the coordinated activity of human and veterinary healthcare professionals, public health officers and basic scientists (including in this context environmentalists, ecologists, parasitologists, microbiologists and immunologists, among others) together with politicians, administrators and budget holders. As a zoonotic infectious disease with a canine reservoir, VL provides the perfect opportunity for implementation of a One Health approach to disease control.

Conflict of interest

The authors do not haave any potential conflicts of interest to declare.

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