International Journal for Parasitology: Parasites and Wildlife 3 (2014) 251–262

Contents lists available at ScienceDirect

International Journal for Parasitology: Parasites and Wildlife

journal homepage: www.elsevier.com/locate/ijppaw

Review

Wild and synanthropic reservoirs of *Leishmania* species in the Americas

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ARTICLE INFO

Article history:
Received 3 June 2014
Revised 19 August 2014
Accepted 21 August 2014

Keywords:
Leishmania spp
Reservoir
Wild mammals
Leishmaniasis

ABSTRACT

The definition of a reservoir has changed significantly in the last century, making it necessary to study zoonosis from a broader perspective. One important example is that of *Leishmania*, zoonotic multi-host parasites maintained by several mammal species in nature. The magnitude of the health problem represented by leishmaniasis combined with the complexity of its epidemiology make it necessary to clarify all of the links in transmission net, including non-human mammalian hosts, to develop effective control strategies. Although some studies have described dozens of species infected with these parasites, only a minority have related their findings to the ecological scenario to indicate a possible role of that host in parasite maintenance and transmission. Currently, it is accepted that a reservoir may be one or a complex of species responsible for maintaining the parasite in nature. A reservoir system should be considered unique on a given spatiotemporal scale. In fact, the transmission of *Leishmania* species in the wild still represents an complex enzootic "puzzle", as several links have not been identified. This review presents the mammalian species known to be infected with *Leishmania* spp. in the Americas, highlighting those that are able to maintain and act as a source of the parasite in nature (and are thus considered potential reservoirs). These host/reservoirs are presented separately in each of seven mammal orders – Marsupialia, Cingulata, Pilosa, Rodentia, Primata, Carnivora, and Chiroptera – responsible for maintaining *Leishmania* species in the wild.

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http://dx.doi.org/10.1016/j.ijppaw.2014.08.004

1. Introduction

Upon their arrival in the Americas, humans began be exposed to parasite species that circulate in the extant fauna (Araújo et al., 2013). Even now, though to a lesser extent, we are still exposed to the wild environment, its wildlife and their parasites. Habitat fragmentation, global warming, non-sustainable exploratory activities, expansion of agriculture and eco-tourism are some factors that contribute to intensifying this contact (Aguirre and Tabor, 2008; Alexander et al., 2012; Jones et al., 2008). Human infection by parasites that circulate in the wild is especially probable for multi-host parasites, i.e., those capable of infecting a wide range of mammalian and vector host species (Woolhouse et al., 2001). This is the case for some *Leishmania* species, including *L. infantum* (=syn. *L. chagasi*), *L. braziliensis, L. amazonensis* and *L. mexicana*, the most important etiological agents of human leishmaniasis in the Americas (Alvar et al., 2012). These trypanosomatids are characterized by high genetic heterogeneity and biological eclecticism, as evidenced in varied orders of mammals that they are able to infect. As a result, these protozoa species have complex transmission cycles with region-specific epidemiological characteristics (Ashford, 1996; Rotureau, 2006).

Cases of human leishmaniasis, which may present distinct infection patterns, are caused by more than 20 species of heteroxenic flagellates of the genus *Leishmania*. These parasites circulate among mammals belonging to seven orders and, in the Americas, are transmitted by sandflies of the genus *Lutzomyia* (Diptera: Psychodidae) (Alvar et al., 2012). The classification into visceral and cutaneous forms, observed in human disease, cannot be applied to the infection in other mammals. Dogs infected with *L. infantum* present viscero-dermic disease, where parasite isolation is common even from intact skin (Madeira et al., 2009). Moreover, *Leishmania* species associated with human cutaneous infection have been observed in rodent viscera since the 1950s (Nery Guimarães, 1951; Roque et al., 2010). We thus challenge the classical concept of tissue tropism of *Leishmania* species. This term comes from the Greek "tropos", a movement in a particular direction in response to an external stimulus. In *Leishmania* spp., however, the cells of the phagocytic mononuclear system represent the preferential niche. In ecological terms, the tissues where *Leishmania* species are found represent more favorable niches for permanent establishment (which may vary among mammalian hosts); preferential infection is not the result of a tropism for a given tissue.

Although the concepts and methods employed for the investigation of parasite reservoirs have changed significantly over time (Ashford, 1997; Haydon et al., 2002; Lainson et al., 1981a), most of the descriptions of *Leishmania* spp. reservoirs are still based on findings of natural infection, which do not provide information on the epidemiological importance of that host to parasite maintenance in the area. Considering the new definition of reservoirs, understanding the role of each mammalian host species in *Leishmania* transmission from secondary data demands a critical analysis of field and laboratory studies. Although knowledge of leishmaniasis has improved in recent decades (mainly concerning the cellular and molecular biology of the parasite, epidemiology and diagnosis of human infection), we still lack data on the transmission between their mammalian hosts and vectors. As a consequence, this disease presents an ongoing public-health problem and continues to expand its range (Alvar et al., 2012).

2. What defines a reservoir host?

As in any other host–parasite system, patterns of *Leishmania* infection in any mammalian host species are determined by host factors (species, concomitant infections/health, sex, age, behavioral patterns), parasite traits (generation time, dispersion strategies, molecular and biochemical characteristics of its sub-populations), exposure (inoculum size) and local environmental conditions (influenced, e.g., by stress and availability of natural resources) where the host–parasite encounter takes place (Chaves et al., 2007; De Tommasi et al., 2013). The influence of these factors shows that a given mammalian host species may not fill the same role in the transmission cycle in different localities and time periods (Desjeux, 2004; Mills and Childs, 1998). Furthermore, the competence to infect vectors (infectivity or transmissibility competence) is not homogeneously distributed in host populations, and transmission is assumed to be associated with only a minority of infected mammals in an ecological pattern known as the 20/80 rule (Miller and Huppert, 2013; Woolhouse et al., 1997). Parasite transmission nets are dynamic, thus it is likely that parasites are periodically extinguished in a particular host population and are re-introduced some time later (Mills and Childs, 1998).

Assuming that an infected mammal is a host, its importance in the transmission cycle will depend both on the dispersion strategy of the parasite and the peculiarities of this host–parasite interaction. The assemblage of these variables will determine the accessibility of the parasite to the external environment or to the intermediate host for transmission and thus for maintenance. These are the factors that determine the transmissibility competence of that host species; defining thus, its role as a reservoir host. Mainly based on studies by Ashford (1997) and Haydon et al. (2002), we consider a "reservoir" a system that includes one or more species of mammals that are responsible for maintaining the parasite in nature and should be considered as unique within a certain spatiotemporal scale (Jansen and Roque, 2010). Within this "reservoir system", each host species plays a distinct role in transmission in a certain time and space. Transmissibility competence is thus a trait that alters over the course of infection in given individual host, such that one species or individual may assume different roles in the epidemiology of a parasite during its lifespan. Here, we consider "maintenance hosts" to be those mammals that can be infected and maintain the infection and "amplifier hosts" to be those mammals that, in addition to maintaining the infection, display a characteristic that favors transmission (more parasites in the blood and skin for longer periods). These conditions are interchangeable, and maintenance hosts may be converted into amplifier hosts according to the host's health conditions for example, immune suppression and concomitant parasitic infections (Botero et al., 2013). A schema of the reservoir system should include the ecology/biology of that host (life area and explored habitats), the local population structure and the relative abundance and interaction of the host species with other mammals (Miller and Huppert, 2013; Noireau et al., 2009).

Finally, a controversial point in the study of reservoirs is the assumption that a reservoir host must not show symptoms, as asymptomatic infection is usually associated with ancient host–parasite relationships (WHO, 1990). It is currently assumed, however, that not all ancient host–parasite interactions necessarily evolve into harmonic interactions because they may instead favor the transmissibility of the parasite. Transmission is crucial for parasite survival and is dependent on their reproductive strategy (Giorgio, 1995; Woolhouse et al., 2001). Indeed, virulence and pathogenicity may in some cases be considered fitness traits because both may improve parasite transmission and may, therefore, be positively selected.

3. Understanding the pattern of *Leishmania* spp. infection of mammalian hosts

Although they are enzootic parasites, there are few studies on the roles of different mammalian host species in the transmission of *Leishmania* spp. and "hosts" and "reservoirs" are usually treated as synonymous terms (WHO, 1990; Ashford, 1996). Studies considering long-lasting infection with these parasites in wild hosts are

scarce (Raymond et al., 2003; Travi et al., 2002). Understanding the role played by different mammalian species in the transmission of *Leishmania* spp. in nature requires an epidemiological investigation that includes an infection follow-up and a representative sampling of the potential host species and mammalian populations in the area. Equally important is the adoption of a broad methodological approach that should include the diagnosis of infection by direct and indirect parasitological tests to evaluate transmissibility competence. Additionally, whenever possible, experimental studies on potential wild reservoirs must be performed to assist the interpretation of the data obtained in field investigations (Roque et al., 2010).

Direct examination and blood-culture techniques are less effective for the detection of *Leishmania* spp. in wild mammals. Even in dogs infected by *L. infantum*, its sensitivity varies among different studies and mostly depends on parasite load, examined tissue and technical experience (Ikeda-Garcia and Feitosa, 2006). On the other hand, specificity is always 100%. The gold-standard methods are the cultures of punctures or fragments of hematopoietic tissues, but the positive result does not necessarily reflect the competence of that host to transmit the parasite. This competence is defined by the accessibility of parasites to vectors, which is correlated with the origin of the cultured material. Positive skin or blood cultures and xenodiagnosis suggest transmissibility. Direct visualization of parasites in skin fragments has lower sensitivity, but in combination with the confirmation of the etiologic agent, this technique also confirms viability and thus therefore, its transmissibility. Positive cultures always demonstrate the presence of viable parasites, but positive obtained from internal organs (liver, spleen, bone marrow, and lymph nodes) do not necessarily indicate infectivity to the vector.

Serological tests, among which the most used are the immunofluorescence (IFAT) and immunoenzymatic (ELISA) assays, demonstrate infection. Sensitivity and specificity of these tests range from 90% to 100% and 80% to 100%, respectively for IFAT (Mettler et al., 2005) and from 80% to 99.5% and 81% to 100%, respectively for ELISA (Mancianti et al., 1995; Marcondes et al., 2011). A host that is positive in serological but negative in parasitological tests has been exposed to *Leishmania* infection (expected to still be infected), but are not necessarily important for the maintenance of the parasite in nature, i.e., are not necessarily reservoirs of the parasite. Molecular diagnosis by polymerase chain reaction (PCR) can be considered a parasitological assay, because it detects constitutive parts of the parasites (fragments of DNA). This technique may reach sensitivity and specificity values near 100%, but these values may vary depending on the examined tissue (Ashford et al., 1995; Lachaud et al., 2002; Troncarelli et al., 2009). Despite certainly demonstrating the presence of the parasite, it does not allow us to indicate the integrity of that parasite (Silva et al., 2005). Concerning the parasite transmissibility, only recently it was demonstrated that the parasite load, especially in the skin, can be related to the infectiousness during natural infection (Courtenay et al., 2014). Although PCR is considered extremely sensitive, its use as the gold standard for diagnosis or therapeutic cure of human leishmaniasis remains a matter of debate (Mendonca et al., 2004; Salam et al., 2010). In wild and synanthropic animals, diagnosis by PCR is still a challenge, lacking standardization of techniques and species–specific molecular targets.

4. *Leishmania* hosts and putative reservoirs

Studies of host–parasite interaction among wild mammals and *Leishmania* species are rare because of the complexity of performing long-term field-work and the difficulties of maintaining captivity colonies of wild species for experimental infection. Moreover, an essential aspect of this type of study is the accurate taxonomic identification of the mammalian hosts. Identification is not trivial for taxa (e.g. rodents and bats) that comprise a great diversity of species, including several whose taxonomic position is still debatable and can be identified only by karyotyping and/or molecular analysis. Our aim in this review was to re-interpret the available data on *Leishmania* reservoirs using an ecological approach and to consider the transmissibility potential from that species. We also added data on characterization of parasite in wild hosts from the *Leishmania* sp. collection of the Oswaldo Cruz Institute (CLIOC/Fiocruz: clioc.fiocruz.br). Our main difficulties in this review involved: (i) access to the full text of some articles, especially the older articles, published in languages other than English and in journals that are not broadly distributed; and (ii) in some cases, identification of *Leishmania* species, as the numerous taxonomic revisions have repeatedly changed the nomenclature of some species.

In this context, we discuss some of the wild and synanthropic species known to be infected with *Leishmania* spp., distinguishing between “parasite hosts” and “potential reservoirs”, with the latter designation used only when the authors demonstrated the retention of infection or the potential to transmit the parasite to vectors (positive xenodiagnosis or cultures from skin or blood). As already noted, *Leishmania* reservoirs show regional and temporal variation, and only a local study including ecological and parasitological analysis can determine whether these “potential reservoirs” may serve as reservoir in a given environment.

4.1. Order Didelphimorphia

The autochthonous American order Didelphimorphia is the only marsupial order recognized in the Americas. Mammals from this order have a wide distribution, mainly due to their remarkable adaptability to different ecological niches, particularly to environments with a high degree of human activity. The genus *Didelphis* is the most widely dispersed on the continent, occurring from southeastern Canada to southern Argentina (Austad, 1988). *Didelphis* spp. are nomadic, solitary (mainly males), and excellent climbers that are mainly found in holes in trees and foliage. These animals can colonize ceilings of houses and other shelters in domestic and peridomestic areas, where they feed on human food garbage (Austad, 1988; Olifiers et al., 2005). Most likely due to its synanthropic character, this species is one of most studied regarding infection by *Leishmania* spp., although only a few of these studies included follow up on the natural or experimental infection (Travi et al., 1994, 1998b).

Didelphis marsupialis, a species distributed from Mexico to the Amazon region has been found to be infected with at least four *Leishmania* species (Arias et al., 1981; Corredor et al., 1989; Grimaldi et al., 1991) (Table 1). Its importance as a potential reservoir for *L. infantum* was demonstrated in a rural community from Colombia, where these animals were abundant, and displayed a high prevalence of positive cultures and high parasite loads (as observed in slide imprints), in the spleen (Corredor et al., 1989). Later studies also confirmed their importance elsewhere in Colombia and Venezuela (Quinnell and Courtenay, 2009; Travi et al., 1998a). Additionally, its importance as a reservoir was confirmed by the experimental infection by *L. infantum* of five specimens, which resulted in clinical signs suggestive of visceral leishmaniasis in one young female that presented amastigote parasites in the spleen, liver and lymph nodes. Parasites were re-isolated from all of these specimens, and three were also infective for *Lu. longipalpis* (Travi et al., 1998b).

Didelphis albiventris is abundant in central South America, from Colombia to northern Argentina, and is quite abundant in northeastern, central and southern Brazil. *L. infantum* isolation from this marsupial species was first described in Bahia, Brazil (Sherlock et al., 1984). Later, the same authors demonstrated its infectivity to vectors by xenodiagnosis (Sherlock, 1996), and others reported their natural

Table 1
Mammal host species described infected by different *Leishmania* species in the Americas.

Order	Host species	*Leishmania* species	Infection pattern	Country	References
Didelphimorphia	*Didelphis marsupialis*	*L. infantum*	Potential reservoir	CO, VE	Corredor et al., 1989; apud Quinnell and Courtenay, 2009
		L. amazonensis	Parasite host	BR	Grimaldi et al., 1991
		L. guyanensis	Potential reservoir	BR; FG	Arias et al., 1981; Dedet et al., 1989
		L. forattinii	Parasite host	BR	IOCL 0067
	D. albiventris	*L. infantum*	Potential reservoir	BR	Sherlock et al., 1984; Sherlock, 1996
		L. braziliensis	Parasite host	BR	Quaresma et al., 2011
		L. peruviana	Potential reservoir	PE	Llanos-Cuentas et al., 1999
	D. aurita	*L. infantum*	Parasite host	BR	Carreira et al., 2012
	Philander opossum	*L. amazonensis*	Parasite host	BR	Lainson et al., 1981a
	Marmosa cinerea	*L. amazonensis*	Parasite host	BR	Arias et al., 1981
	Marmosa sp	*L. (Viannia)* sp.	Parasite host	BR	Brandão-Filho et al., 2003
	Micoreus paraguayanus	*L. amazoensis*	Parasite host	BR	Quintal et al., 2011
		L. braziliensis	Parasite host	BR	Quintal et al., 2011
	Gracilinanus agilis	*L. braziliensis*	Parasite host	BR	Quaresma et al., 2011
	Marmosops incanus	*L. guyanensis*	Parasite host	BR	Quaresma et al., 2011
	Metachirus nudicaudatus	*L. amazonensis*	Parasite host	BR	Lainson et al., 1981a
	Monodelphis domestica	*L. (Viannia) sp.*	Parasite host	BR	Lima et al., 2013
Pilosa	*Choloepus didactylus*	*L. guyanensis*	Potential reservoir	FG; BR	Gentile et al., 1981; Lainson et al., 1981a
		L. shawi	Parasite host	BR	Lainson et al., 1989
	C. hoffmanni	*L. colombiensis*	Parasite host	PN	Kreutzer et al., 1991
		L. equatoriensis	Parasite host	EC	Grimaldi et al., 1992
		L. panamensis	Parasite host	PN	apud Ashford, 2000
	Bradypus tridactylus	*L. shawi*	Parasite host	BR	Lainson et al., 1989
	Tamandua tetradactyla	*L. guyanensis*	Parasite host	BR	Lainson et al., 1981a
		L. amazonensis	Parasite host	EC	Mimori et al., 1989
		L. infantum	Parasite host	BR	Araújo et al., 2013
Cingulata	*Dasypus novemcinctus*	*L. naiffi*	Potential reservoir	BR	Lainson and Shaw, 1989; Naiff et al., 1991
		L. guyanensis	Parasite host	BR	Lainson et al., 1979
Rodentia	*Proechimys* species	*L. amazonensis*	Potential reservoir	BR; FG	Arias et al., 1981; Dedet et al., 1989
		L. guyanensis	Parasite host	BR; FG	Dedet et al., 1989; Lainson et al., 1981b
	P. canicollis	*L. infantum*	Parasite host	CO	Travi et al., 1998a
	P. semispinosus	*L. panamensis*	Potential reservoir	CO	Travi et al., 2002
		L. infantum	Parasite host	CO	Travi et al., 2002
	Thrichomys apereoides	*L. braziliensis*	Parasite host	BR	Quaresma et al., 2011
		L. guyanensis	Parasite host	BR	Quaresma et al., 2011
		L. infantum	Parasite host	BR	Oliveira et al., 2005; Quaresma et al., 2011
		L. amazonensis	Parasite host	BR	Oliveira et al., 2005
	T. laurentius	*L. infantum*	Potential reservoir	BR	Roque et al., 2010
		L. braziliensis	Potential reservoir	BR	Roque et al., 2010
		L. naiffi	Parasite host	BR	Cássia-Pires, unpublished data
		L. shawi	Parasite host	BR	Cássia-Pires, unpublished data
	T. inermis	*L. shawi*	Parasite host	BR	Cássia-Pires, unpublished data
	T. pachyurus	*L. naiffi*	Parasite host	BR	Cássia-Pires, unpublished data
	Nectomys squamipes	*L. infantum*	Parasite host	BR	Dantas-Torres and Brandao-Filho, 2006
		L. braziliensis	Parasite host	BR	Peterson et al., 1988
	Rattus rattus	*L. infantum*	Parasite host	BR; VE	apud Quinnell and Courtenay, 2009
		L. braziliensis	Potential reservoir	BR; VE	Vasconcelos et al., 1994; De Lima et al., 2002
		L. mexicana	Parasite host	VE	De Lima et al., 2002
	Clyomys laticeps	*L. infantum*	Parasite host	BR	Cássia-Pires, unpublished data
	Dasyprocta azarae	*L. infantum*	Parasite host	BR	Cássia-Pires, unpublished data
	Dasyprocta sp.	*L. amazonensis*	Parasite host	BR	Lainson et al., 1981b
	Rhipidomys mastacalis	*L. infantum*	Parasite host	BR	Quaresma et al., 2011
	Coendu sp.	*L. lainsoni*	Parasite host	BR	IOCL 1058
		L. hertigi/L. deanei	Parasite host	PN; BR	Herrer, 1971; Silva et al., 2013
	Coendu prehensilis	*L. infantum*	Parasite host	BO	Le Pont et al., 1989
	Akodon arviculoides	*L. braziliensis*	Parasite host	BR	Forattini et al., 1972; Rocha et al., 1988
	Akodon sp.	*L. amazonensis*	Parasite host	BO	Telleria et al., 1999
	Necromys lasiurus	*L. braziliensis*	Potential reservoir	BR	Brandão-Filho et al., 2003; de Freitas et al., 2012
	Sigmodon hispidus	*L. braziliensis*	Potential reservoir	VE	De Lima et al., 2002
		L. mexicana	Potential reservoir	MX, VE	Van Wynsberghe et al., 2000; De Lima et al., 2002
	Holochilus scieurus	*L. infantum*	Parasite host	BR	Lima et al., 2013
	H. scieurus	*L. (Viannia) sp.*	Parasite host	BR	Brandão-Filho et al., 2003
	Cerradomys subflavus	*L. (Viannia) sp.*	Parasite host	BR	Lima et al., 2013
	Mus musculus	*L. braziliensis*	Parasite host	BR	de Freitas et al., 2012
	Oryzomys species	*L. amazonensis*	Parasite host	BO	Kerr et al., 2006
	O. melanotis	*L. amazonensis*	Potential reservoir	MX	Van Wynsberghe et al., 2000
	O. nigripes	*L. braziliensis*	Parasite host	BR	Forattini et al., 1972
	Oligoryzomys sp.	*L. amazonensis*	Parasite host	BO	Telleria et al., 1999
	Sciurus vulgaris	*L. amazonensis*	Parasite host	EC	Mimori et al., 1989
	S. granatensis	*L. equatorensis*	Parasite host	EC	Grimaldi et al., 1992
	Neotoma species	*L. mexicana*	Potential reservoir	US	Kerr et al., 1995; Raymond et al., 2003
	Ototylomys phyllotis	*L. mexicana*	Potential reservoir	BE; MX	Ashford, 1996; Van Wynsberghe et al., 2000
	Heteromys species	*L. mexicana*	Parasite host	BE; MX	Ashford, 1996; Van Wynsberghe et al., 2009
	H. dermarestianus	*L. panamensis*	Parasite host	CR	Zeledon et al., 1977

(*continued on next page*)

Table 1 (*continued*)

Order	Host species	*Leishmania* species	Infection pattern	Country	References
	Peromyscus yucatanicus	*L. mexicana*	Potential reservoir	MX	Van Wynsberghe et al., 2000
	Nyctomys sumichrasti	*L. mexicana*	Parasite host	HN	Lainson and Strangways-Dixon, 1964
	Reithrodontomys gracilis	*L. mexicana*	Parasite host	HN	Disney, 1968
	Agouti paca	*L. lainsoni*	Potential reservoir	BR	Silveira et al., 1991
	Phyllotis andinum	*L. peruviana*	Parasite host	PE	Llanos-Cuentas et al., 1999
	Cavia porcellus	*L. enriettii*	Parasite host	BR	Machado et al., 1994
Carnivora	*Cerdocyon thous*	*L. infantum*	Potential reservoir	BR	Deane and Deane, 1955; Courtenay et al., 1996
		L. amazonesis	Parasite host	BR	apud Rotureau, 2006
	Speothos venaticus	*L. infantum*	Potential reservoir	BR	Figueiredo et al., 2008; Lima et al., 2009
	Pseudalopex vetulus	*L. infantum*	Parasite host	BR	Curi et al., 2006; Luppi et al., 2008
	Chrysocyon brachyurus	*L. infantum*	Parasite host	BR	Curi et al., 2006; Luppi et al., 2008
	Puma concolor	*L. infantum*	Parasite host	BR	Dahroug et al., 2010
	Panthera onca	*L. infantum*	Parasite host	BR	Dahroug et al., 2010
	Nasua nasua	*L. shawi*	Parasite host	BR	Lainson et al., 1989
	Potos flavus	*L. guyanensis*	Parasite host	FG	Pajot et al., 1982
		L. amazonensis	Parasite host	EC	Kreutzer et al., 1991
	Conepatus chinga	*L. amazonensis*	Parasite host	BO	Telleria et al., 1999
		L. braziliensis	Parasite host	BO	Buitrago et al., 2011
Primata	*Cebus apella*	*L. shawi*	Potential reservoir	BR	Lainson et al., 1989
	Cebus xanthosternos	*L. infantum*	Parasite host	BR	Malta et al., 2010
	Chiropotes satanas	*L. shawi*	Potential reservoir	BR	Lainson et al., 1989
	Saguinus geoffroyi	*L. amazonensis*	Potential reservoir	PN	Herrer et al., 1973
	Aotus trivirgatus	*L. braziliensis*	Potential reservoir	PN	Herrer and Christensen, 1976
	Aotus azarai	*L. (Viannia) sp.*	Parasite host	AR	Acardi et al., 2013
	Aotus nigriceps	*L. infantum*	Parasite host	BR	Malta et al., 2010
	Callicebus nigrifrons	*L. infantum*	Parasite host	BR	Malta et al., 2010
	Alouatta guariba	*L. infantum*	Parasite host	BR	Malta et al., 2010
	Leonthopitecus crysomelas	*L. infantum*	Parasite host	BR	Malta et al., 2010
	Pithecia irrorata	*L. infantum*	Parasite host	BR	Malta et al., 2010
	Saguinus imperator	*L. infantum*	Parasite host	BR	Malta et al., 2010
	Ateles paniscus	*L. amazonensis*	Parasite host	BR	Lima et al., 2012a
Chiroptera	*Carollia perspicillata*	*L. infantum*	Potential reservoir	VE	De Lima et al., 2008
	Molossus molossus	*L. infantum*	Parasite host	BR	Savani et al., 2010
		L. amazonensis	Parasite host	BR	Savani et al., 2010
		L. (Viannia) sp.	Parasite host	BR	Shapiro et al., 2013
	M. rufus	*L. amazonensis*	Parasite host	BR	Savani et al., 2010
	Glossophaga soricina	*L. infantum*	Parasite host	BR	Savani et al., 2010
		L. amazonensis	Parasite host	BR	Savani et al., 2010
		L. (Viannia) sp.	Parasite host	BR	Shapiro et al., 2013
	Nyctinomops laticaudatus	*L. amazonensis*	Parasite host	BR	Savani et al., 2010
	Eumops glaucinus	*L. amazonensis*	Parasite host	BR	Savani et al., 2010
	E. auripendulus	*L. amazonensis*	Parasite host	BR	Savani et al., 2010
	Artibeus literatus	*L. amazonensis*	Parasite host	BR	Savani et al., 2010
	Sturnira lilium	*L. amazonensis*	Parasite host	BR	Savani et al., 2010
	Myotis nigricans	*L. amazonensis*	Parasite host	BR	Savani et al., 2010

Countries: AR – Argentine, BR – Brazil, CL – Chile, CO – Colombia, VE – Venezuela; FG – French Guiana; PE – Peru; PN – Panama; EC – Ecuador; BO – Bolivia; US – United States of America; BE – Belize; MX – Mexico; HN – Honduras; CR – Costa Rica.
IOC L*: Characterized Strains deposited in the *Leishmania* sp. Collection of the Oswaldo Cruz Institute (www.clioc.fiocruz.br). The number refers to the deposit number in CLIOC Catalogue.

infection detected by PCR (Humberg et al., 2012; Santiago et al., 2007). The other *Leishmania* species found infecting *D. albiventris* are *L. braziliensis* (Quaresma et al., 2011) and *L. peruviana* (Llanos-Cuentas et al., 1999) (Table 1).

L. infantum has also been detected in *D. aurita* (Carreira et al., 2012), and another study also strongly suggests such infection in the periphery of urban areas (Santiago et al., 2007). Although its role as a reservoir has not yet been demonstrated, it has strong potential to act as a reservoir due to the great phylogenetic proximity among the *Didelphis* species (Jansa et al., 2014). A unique study on a marsupial species able to explore distinct forest strata, the opossum *Philander opossum*, described its infection by *L. amazonensis* (Lainson et al., 1981a). The *Leishmania* species found infecting other marsupial species are described in Table 1 (Quintal et al., 2011).

Apart from the *Didelphis* species, which are proven as potential *Leishmania* reservoirs, other marsupial species are poorly studied. These ancient mammals are perhaps the very first *Leishmania* spp. hosts in the Americas, although their role in transmission net remains to be defined.

4.2. Order Pilosa

This order is composed of anteaters and sloths, which, along with armadillos (order Cingulata), compose the superorder Xenarthra (odd joints), previously known as Edentata (Moller-Krull et al., 2007). Together with the marsupials, these ancient *Leishmania* hosts are also native American fauna and present a peculiar blood–vessel structure that allows an extremely low metabolic rate, sparing energy (Bugge, 1979). Since the Tertiary Period, many representatives of this taxon have become extinct, and the extant genera constitute only a small proportion of the order. Mammals from this order have a long co-evolutionary history with trypanosomatids, including several *Leishmania* and *Trypanosoma* species, as well as the poorly studied genus *Endotrypanum* (Rotureau, 2006).

Sloths are arboreal inhabitants of tropical regions of Central and South America and are represented by two genera, *Bradypus* (Bradypodidae family) and *Choloepus* (Magalonichidae family). Sloths have reduced muscle mass and move slowly between trees by traveling directly through the arboreal strata, descending only weekly

to defecate (Miranda and Costa, 2006). The two-toed sloth (*Choloepus didactylus*) is a potential reservoir of *L. guyanensis*, as demonstrated by the high rates of parasite isolation from intact skin (as well as viscera), which vary from 35% to 47% in French Guiana (Dedet et al., 1989; Gentile et al., 1981) and reach up to 46% in Brazil (Lainson et al., 1981a).

L. shawi was described infecting the two-toed sloth and the pale-throated sloth (*Bradypus tridactylus*), both in Brazil (Lainson et al., 1989). In Panama, *L. colombiensis* was isolated from the viscera of Hoffmann's two-toed sloth (*Choloepus hoffmanni*) (Kreutzer et al., 1991), while *L. equatorensis* was found infecting the same species in Ecuador (Grimaldi et al., 1992). Finally, *L. panamensis*, a species closely related to *L. guyanensis*, has been described in *Choloepus hoffmanni* from Panama (Ashford, 2000) (Table 1).

The anteaters constitute a single family (Myrmecophagidae) that are mainly arboreal, but that may also explore the terrestrial strata. The isolation of *Leishmania* was described in only one species, the lesser anteater *Tamandua tetradactyla. L. guyanensis* (Lainson et al., 1981a), *L. amazonensis* (Mimori et al., 1989), and *L. infantum*, this last in mixed infection with *T. cruzi* and *T. rangeli* (de Araujo et al., 2013), were found infecting the lesser anteater (Table 1).

The diversity of *Leishmania* species already known to infect sloths and anteaters suggests that these mammals may be important hosts for parasite species that are transmitted in the arboreal strata. In fact, most of the *Leishmania* species found infecting these hosts are transmitted by vectors associated with the arboreal strata, such as *Lu. umbratilis* and *Lu. whitmani*.

4.3. Order Cingulata

Armadillos, together with didelphid marsupials and Pilosa, are also among the oldest mammal groups from the Americas. They are also the most primitive of the xenarthrans. Members of the family Dasypodidae are the only surviving species in the order and are found from the southern United States to the Straits of Magellan (Miranda and Costa, 2006). So far, the nine-banded armadillo (*Dasypus novemcinctus*) is the only non-human host from which *L. naiffi* has been isolated (from blood, liver and spleen) (Lainson and Shaw, 1989; Naiff et al., 1991). *L. guyanensis* is another species already detected in *D. novemcinctus* from Brazil (Lainson et al., 1979). In some rural areas, armadillos are commonly observed invading chicken pens, searching for eggs, and frequenting peridomestic areas (personal observations), where it is possible that they can be a source of *Leishmania* infection for sandflies in this environment.

Armadillos, sloths and anteaters are hunted and eaten in some areas of South America, such as the Amazon. People commonly care for the young in their backyards after having killed the mothers during a hunt. The young are kept until they reach adulthood and we cannot exclude the possibility of they become sources of infection in the peridomestic environment.

4.4. Order Rodentia

Rodents are the most diverse and widespread order of mammals and include several cryptic species that can only be separated by karyotyping (Bonvicino et al., 2002). The first rodents (Hystricognathi – caviomorphs) arrived in the Americas (along with primates) from Africa approximately 45 million years ago. The second wave of rodent migration to the Americas (Sciurognathi – cricetids) was much more recent and included an initial establishment in North America (Flynn and Wyss, 1998). Since their arrival, rodents have diversified widely and may be found in desert, adapted to aquatic media, digging long and interconnected tunnels, and in forest canopies (Wilson and Reeder, 2005). This taxon is most likely the most studied in terms of infection by *Leishmania* spp. in both natural and experimental conditions; however, excepting a few studies, experimental infections have been conducted in laboratory mouse lineages, which are not representative of the wild *Mus musculus*.

After the Pilosa, Marsupialia and Cingulata, caviomorphs (suborder Hystricognathi) are most likely the most ancient hosts of *Leishmania* spp. Moreover, their arrival in the Americas is related to the entry of some species from the sub-genus *Leishmania* into the continent (Thomaz-Soccol et al., 1993). Caviomorphs from the genus *Proechimys* were already found to be infected by various *Leishmania* species. These rodents are characterized by their longevity (more than 3 years in captivity) and high abundance in most localities where they are found in tropical forests of Central and South America (Ashford, 1996). Various *Proechimys* species have been identified as potential reservoirs of *L. amazonensis* in Brazil and French Guiana, as demonstrated by the frequent skin parasitism confirmed by tissue culture (Arias et al., 1981; Dedet et al., 1989). In French Guiana, for example, this infection was observed in two sympatric species, *P. cuvieri* and *P. guyanensis* (Rotureau, 2006). Other reports of natural infection in the skin of these rodents include: *L. infantum* in *P. canicollis* from Colombia (Travi et al., 1998a), and *L. guyanensis* in *Proechimys* sp. from French Guiana (Dedet et al., 1989), and Brazil (Lainson et al., 1981a) (Table 1).

P. semispinosus from Colombia experimentally infected with *L. panamensis* developed self resolving non-ulcerated lesions (from which parasites could be re-isolated, and which were demonstrated to be highly infective to vectors in the initial phase of infection (Travi et al., 2002). This host–parasite interaction exemplifies a temporal reservoir competence in one host species, passing from an amplifier host (in the beginning of infection) to a maintenance host, in which transmissibility competence is lower. In contrast, the same rodent species experimentally infected with *L. infantum* developed only subclinical infection and was not infective to vectors, although the authors re-isolated the parasites from the spleen of some rodents during necropsy (Travi et al., 2002). Other authors have detected no infection in laboratory-bred specimens of another species, *P. guyannensis*, after inoculation with promastigotes or amastigotes of *L. infantum* (Lainson et al., 2002). This difference may be due to many variables related to the host and the parasite, such as the intra-specific heterogeneity of both taxa and/or the size and route of the inoculum.

Considered monospecific until 2002, caviomorphs from the genus *Thrichomys* comprise at least five cryptic species distributed across different biomes in Brazil (Bonvicino et al., 2002). *T. apereoides* were found to be infected with *L. braziliensis, L. guyanensis, L. infantum* and *L. amazonensis* in leishmaniasis-endemic areas in Minas Gerais, Brazil (Oliveira et al., 2005; Quaresma et al., 2011). Recently, we also detected infection by various *Leishmania* species in these rodents: *L. infantum, L. naiffi, L. braziliensis* and *L. shawi* in *T. laurentius, L. shawi* in *T. inermis* and *L. naiffi* in *T. pachyurus* (Cássia-Pires et al., unpublished data). Moreover, *T. laurentius* experimentally infected with *L. infantum* and *L. braziliensis* were able to maintain the infection and parasite re-isolation was achieved up to 12 months after infection. *Leishmania* DNA was detected in all experimental groups and in all tissues sampled, independent of the *Leishmania* species inoculated (Roque et al., 2010).

In addition to *Proechimys* spp. and *Thrichomys* spp., *L. infantum* has been diagnosed in *Clyomys laticeps, Dasyprocta azarae, Nectomys squamipes, Holochilus sciureus* and *Rhipidomys mastacalis* from Brazil (Cássia-Pires et al., unpublished data; Dantas-Torres and Brandão-Filho, 2006; Quaresma et al., 2011; Lima et al., 2013;) and *Rattus rattus* from Brazil and Venezuela (Quinnell and Courtenay, 2009). Natural infection of *Coendu prehensilis*, used as sentinels in Bolivia, has been parasitologically confirmed in the liver and spleen (Le Pont et al., 1989).

Regarding *L. braziliensis*, if we consider only studies that confirmed the identity of the etiological agent (not considering the

ancient *L. braziliensis* sensu lato), the following rodent species have been described to be naturally infected: *Akodon arviculoides, Mus musculus, Nectomys squamipes, Necromys* (=*Bolomys*) *lasiurus, Oryzomys nigripes, Rattus rattus* and *Sigmodon hispidus* (Brandão-Filho et al., 2003; de Freitas et al., 2012; De Lima et al., 2002; Forattini et al., 1972; Peterson et al., 1988; Rocha et al., 1988; Vasconcelos et al., 1994). In other cases, the authors confirmed infection by the subgenus *Leishmania* (*Viannia*) sp. (*Holochilus scieurus* and *Cerradomys subflavus*) (Brandão-Filho et al., 2003; Lima et al., 2013) or tentatively identified the etiological agent through the biological pattern of in vitro growth (*Rhipidomys leucodactylus* and *Proechimys guyannensis*) (Lainson et al., 1981b).

Rodents are also usually considered as the main reservoirs of *Leishmania* from the *L. mexicana* complex (*L. mexicana* and *L. amazonensis*). *L. amazonensis* was described in rodents from the following genera: *Akodon, Dasyprocta Oligoryzomys, Oryzomys, Proechimys, Thrichomys* and *Sciurus* (Arias et al., 1981; Kerr et al., 2006; Lainson et al., 1981b; Mimori et al., 1989; Oliveira et al., 2005; Telleria et al., 1999). None of these studies, however, included follow-up of the infection or demonstrated competence to infect vectors.

L. mexicana has been isolated from various species of *Neotoma*, including a specimen of *N. floridana* with a large lesion in the ear from which the parasite could be isolated (Kerr et al., 1995; McHugh et al., 2003). This finding was informative, suggesting that this rodent species may be infective for the vector and an important reservoir of *L. mexicana. Ototylomys phyllotis* from Belize should be considered as a possible reservoir of *L. mexicana* because of its relative abundance, prevalence of infection and attraction to *Lu. flaviscutellata*, the most important vector in the region. Curiously, the same author failed to reproduce this infection under experimental conditions (Ashford, 1996), possibly due to factors occurring only in nature, such as stress and concomitant infections, which may be important for the establishment of *Leishmania* infection. This situation highlights the importance of the studies of naturally infected specimens and the difficulties of adopting potential reservoir hosts as alternative models for leishmaniasis studies. Moreover, these findings attest to the hazards of applying conclusions based solely on experimental models to natural systems.

The persistence of *L. mexicana* infection in wild rodents was demonstrated twice. The first such finding occurred in Mexico, where 29 naturally infected rodents were maintained in captivity and tested monthly for parasites for up to 2 years. In that study, the authors demonstrated persistent infection, including symptomatic infections, in *Sigmodon hispidus, Oryzomys melanotis, Ototylomys phyllotis* and *Peromyscus yucatanicus*, the latter two being the most important because of their high relative abundance in local fauna and longer life spans (Van Wynsberghe et al., 2000). Second, in the United States, during a 19-month mark–release–recapture study of *Neotoma micropus*, the authors reported the persistence of *L. mexicana* infection for up to 1 year (Raymond et al., 2003). *Heteromys, Nyctomys* and *Reithrodontomys* were also found infected with *L. mexicana* (Ashford, 1996; De Lima et al., 2002; Disney, 1968; Lainson and Strangways-Dixon, 1964; Van Wynsberghe et al., 2009).

Leishmania lainsoni was isolated from fragments of intact skin from pacas (*Agouti paca*) in the Brazilian state of Pará (Silveira et al., 1991) and from *Coendu* sp. (Table 1). *Leishmania panamensis* was isolated from naturally infected *Heteromys dermarestianus* from Costa Rica (Zeledon et al., 1977), while a squirrel *Scirus granatensis* was found to be infected with *L. equatorensis* in Ecuador (Grimaldi et al., 1992). *Leishmania peruviana*, a species suggested to be a synonym of *L. braziliensis*, was isolated from the Peruvian *Phyllotis andinum* (Llanos-Cuentas et al., 1999). Finally, *L. hertigi/L. deanei* and *L. enriettii*, species taxonomically more similar to *Endotrypanum* than to *Leishmania* have been described, respectively, in porcupines *Coendu* spp. (Herrer, 1971; Silva et al., 2013) and in the guinea pig *Cavia porcellus* (Machado et al., 1994).

Taken together, a broad diversity of *Leishmania* species naturally infect this mammal group, most likely reflecting the diversity of ecological niches occupied by the hosts. The differences observed among the rodent species include the forest strata they occupy and their reproductive strategies (seasonality, gestation time and number of offspring), and these traits should be considered evaluations of the importance of a rodent species as a *Leishmania* reservoir. Moreover, as expected for every host–parasite interaction, this heterogeneous mammalian taxon shows a spectrum of competence to maintain and transmit *Leishmania* from high susceptibility with high transmissibility competence to quick control of infection.

4.5. Order Carnivora

The mammals from this order also comprise a very heterogeneous group, including strict carnivores, such as ocelots (*Leopardus pardalis*) and tayras (*Eira barbara*) and species that supplement their diet with insects and fruits, such as coatis (*Nasua nasua*) and maned wolves (*Chrysocyon brachyurus*). Most have a large biomass and large range, important aspects of parasite dispersion (Rocha et al., 2013). Moreover, some species such as raccoons and tayras are found both on the ground and in the canopy, favoring the dispersion of parasites among forest strata. Unfortunately, carnivores require large ranges and, because of their potential to predate on livestock (mainly chickens and cattle), are heavily hunted, placing some carnivore species at risk of extinction (Silva and Adania, 2007).

Two carnivore species are closely linked to humans: dogs and cats. Dogs are the most important reservoirs of *L. infantum* throughout South America, although they can be infected with at least six other *Leishmania* species (Dantas-Torres, 2009). Recently, the importance of cats in *Leishmania* epidemiology has also been suggested (Pennisi et al., 2013). Among the wild carnivore hosts of *L. infantum*, the first description of infection was in the crab-eating fox *Cerdocyon thous*, although the authors inaccurately reported the host as *Lycalopex vetulus* (Courtenay et al., 1996; Deane and Deane, 1955). Since then, many studies have confirmed *L. infantum* infection in *C. thous* by parasitological, serological and/or molecular assays. Notably, these animals sometimes develop serious symptoms of the disease and present with amastigotes in intact skin, as also described in domestic dogs. Their prevalence of infection may range from 42% (by parasitological tests) to 78% (by serology) (Lainson et al., 1990; Quinnell and Courtenay, 2009; Silva et al., 2000). The vector infectivity was proven by xenodiagnosis, although the infection rate of vectors is reported to be lower than that observed for domestic dogs (Courtenay et al., 2002; Quinnell and Courtenay, 2009).

Apart from *C. thous*, another wild carnivore that is a potential reservoir of *L. infantum* is the bush dog *Speothos venaticus*. An individual kept in a zoo in Rio de Janeiro, Brazil, is the only wild canid, except for *C. thous*, from which *L. infantum* was isolated (Figueiredo et al., 2008). Infection in bush dogs was also confirmed by direct visualization, PCR and serology in two females with clinical signs of visceral leishmaniasis and maintained in other Brazilian zoos (Lima et al., 2009; Souza et al., 2010). Other wild canid species found to be infected, albeit only by PCR and/or serology, were the hoary fox *Pseudalopex vetulus* and the maned wolf *Chrysocyon brachyurus* (Curi et al., 2006; Luppi et al., 2008) (Table 1).

Some authors have investigated *Leishmania* infection in captive wild carnivores. Five of 15 wild canids belonging to the four native species mentioned earlier were found to be infected in a zoo in Belo Horizonte, Brazil. Of these, one bush dog and one hoary fox developed clinical signs of visceral leishmaniasis (Luppi et al., 2008). Among the wild felines, five pumas (*Puma concolor*) and one jaguar (*Panthera onca*) in a zoo from Cuiabá, Brazil, were PCR-positive in lymph-node puncture biopsy, *L. infantum* was specifically identified by the digestion of the amplified products with restriction

enzymes (Dahroug et al., 2010). Later, the same authors demonstrated *L. infantum* infection in one lion, a non-native felid species, kept in the same zoo (Dahroug et al., 2011).

In addition to *L. infantum*, at least four other *Leishmania* species were found in wild carnivores: *L. shawi* in coatis *Nasua nasua* (Lainson et al., 1989); *L. guyanensis* in the kinkajou *Potos flavus* (Pajot et al., 1982); *L. amazonensis* in kinkajous, crab-eating foxes and skunks *Conepatus chinga* (Kreutzer et al., 1991; Rotureau, 2006; Telleria et al., 1999); and *L. braziliensis* in one Bolivian skunk (Buitrago et al., 2011) (Table 1).

Contrary to the numerous reports of infection in dogs and cats, much remains to study in terms of the putative roles of wild carnivores as *Leishmania* reservoirs. As in all host–parasite interactions, the infection patterns display regional and even individual peculiarities (Rocha et al., 2013). If we consider that in some biomes ("Pantanal or Chaco", "Cerrado", and "Pampa") carnivore species are abundant and represent a huge biomass, any study of *Leishmania* reservoirs must include carnivores, including their *Leishmania* infection pattern, density and population structure in the area. Despite its inherent difficulties, the study of wild carnivores, especially in the areas where their relative abundance is high, is of fundamental importance to improve understanding of *Leishmania* ecology.

4.6. Order Primata

Nonhuman primates can be divided in two groups: the catarrhines (infraorder Catarrhini), from Africa, Europe and Asia (Old World Primates) and the platyrrhines (Platyrrhini) from the Americas (New World or Neotropical Primates). The main difference between them is that the catarrhines have upside-down nostrils on a long snout, while platyrrhines have laterally-faced nostrils on a shorter snout (Verona and Pissinatti, 2007). The different species of neotropical primates are included in the families Cebidae (tamarins) and Callitrichidae (marmosets), although some classifications also recognize three other families: Aotidae, Pithecidae and Atelidae. The neotropical primates occupy distinct arboreal strata and consume diverse diets, including species that feed on fruits, invertebrates and even small mammals (Verona and Pissinatti, 2007).

To date, few studies have described natural infection by *Leishmania* parasites in neotropical primates. Infection by *L. shawi* was described in the tufted capuchin monkey *Cebus apella* and the bearded saki *Chiropotes satanas* (Lainson et al., 1989), while infection by *Leishmania* (*Viannia*) sp. was recently demonstrated in four Argentinean owl monkeys *Aotus azarai* (Acardi et al., 2013). In Panamá, Geoffroy's tamarin *Saguinus geoffroyi* and the owl monkey *Aotus trivirgatus* were found to be infected with *L. amazonensis* and *L. braziliensis*, respectively (Herrer and Christensen, 1976; Herrer et al., 1973). In a Brazilian zoo, one black-fronted titi *Callicebus nigrifrons* from Belo Horizonte/MG presented with a fatal disease that resembled visceral leishmaniasis. Histological and immunohistochemical examinations, as well as a PCR specific for parasites from the *L. donovani* complex, confirmed infection with *L. infantum* (Malta et al., 2010). The other primate species that had PCR-positive blood samples in the same study were *Alouatta guariba, Cebus xanthosternos, Leonthopitecus crysomelas, Aotus nigriceps, Pithecia irrorata* and *Saguinus imperator* (Malta et al., 2010). In the zoo in Bauru/SP, *Leishmania amazonensis* was detected by PCR-RFLP in a spider monkey *Ateles paniscus* from the endemic Amazon region (Lima et al., 2012b) (Table 1).

Leishmania species that circulate in the Americas have been demonstrated to infect other neotropical primates, but only under experimental conditions. Most of these studies focused on the immune response to different drug treatments or on vaccine development. For many years, black-tufted marmosets *Callithrix penicillata* were used in experimental studies with *L. braziliensis* and *L. amazonensis* (Cuba et al., 1990; Cuba-Cuba and Marsden, 1993). Experimental infection of the common squirrel monkey *Saimiri sciureus* resulted in non-ulcerated skin lesions from which *L. braziliensis* and/or *L. panamensis* could be re-isolated (Pung et al., 1988). Owl monkeys *Aotus trivirgatus* developed localized cutaneous lesions after experimental infection with *L. braziliensis, L. mexicana* and *L. panamensis* (Christensen and de Vasquez, 1981; Lujan et al., 1986). *Cebus apella* developed skin lesions after experimental infection with *L. lainsoni, L. amazonensis, L. braziliensis, L. mexicana* and *L. guyanensis* (Garcez et al., 2002; Grimaldi, 2008). Conversely, *Cebus nigrivittatus* developed fatal disease when experimentally infected with *L. infantum* (Vouldoukis et al., 1986).

All neotropical primates are included in the list of the "Convention on International Trade in Endangered Species of Wild Fauna and Flora" (CITES), indicating that all are vulnerable to some degree (Verona and Pissinatti, 2007). For this reason, many species such as the golden lion tamarin *Leonthopitecus rosalia* are included in conservation programs. These programs often include exchange, translocation and re-introduction of animals without consideration of their parasite fauna, here including *Leishmania* and other trypanosomatids. Data from naturally infected primates demonstrate that these mammals may be involved in the maintenance of *Leishmania* in the wild, especially considering their ecology, species transmitted in the canopy. Taking into account the transmission cycle of these parasites, a lack of knowledge regarding the health status of the relocated primates may result in the introduction of infected mammals into a given area, promoting the establishment of new transmission cycles (Lisboa et al., 2006).

4.7. Order Chiroptera

Bats are nocturnal mammals and the only able to fly (sometimes associated with seasonal migration), an important trait that can result in the dissemination of parasite species. Their dispersion capacity is due to the ability to do true flapping flight (apparently evolved differently among bat lineages) and the sophisticated echolocation system that allows them to identify the environment (Jones and Teeling, 2006). Despite their known diversity, bats are still considered as a monophyletic group (Bishop, 2008; Bisson et al., 2009).

Bats are commonly infected with several trypanosomatid species, mainly from the *Trypanosoma* genus: *T. cruzi, T. vespertilionis*, and *T.* (*Megatrypanum*) sp., among others (Lima et al., 2012a). There is only one report of the isolation of *Leishmania* parasites (*L. infantum*) from the blood of a short-tailed fruit bat *Carollia perspicillata* in Venezuela (De Lima et al., 2008) (Table 1). Before that, Lampo et al. had demonstrated that bats could be sources of blood for *Lutzomyia longipalpis* in Venezuelan caves (Lampo et al., 2000).

In Brazil, two *Leishmania* species were identified in macerated fragments of spleen and liver from bats using a nested PCR followed by sequencing of the amplified products. *Molossus molossus* and *Glossophaga soricina* were found to be infected with *L. infantum* and *L. amazonensis*, and the latter was also found in *Molossus rufus, Nyctinomops laticaudatus, Eumops glaucinus, E. auripendulus, Artibeus literatus, Sturnira lilium* and *Myotis nigricans* (Savani et al., 2010). Recently, *Leishmania* (*Viannia*) sp. was detected in a skin lesion from *Glossophaga soricina* and blood from *Molossus molossus* (Shapiro et al., 2013) (Table 1). In this article, although the authors have described infection with *L. braziliensis*, PCR-RFLP using primers b1 and b2 (Schonian et al., 2003) does not allow for differentiation among other species from the same subgenus, such as *L. guyanensis*.

Bats should not be excluded as potential reservoirs of *Leishmania* sp. because of the lack of studies involving *Leishmania* and bats. Chiroptera represents 39% of the 560 mammal species reported in South American rainforests, it is the most common mammal group in terms of diversity and biomass (Emmons and Feer, 1997; Rotureau, 2006). These flying mammals are found in wild, domestic and

synanthropic environments, being able to colonize different habitats in different ecotypes. Their refuges include hollow trees, the canopies of palm trees and ceilings of human houses and other rural buildings. Their high abundance and adaptability to peri-domestic environment reinforce the importance of investigating bats, already recognized as reservoirs of other trypanosomatids (Jansen and Roque, 2010), in the transmission cycles of *Leishmania* species.

5. Conclusions and perspectives

Many decades have passed since the description of *Leishmania* parasites, but their epidemiology is still not well understood in part because of the human-health focus of most studies. Only recently, influenced by the "one health" approach has the epidemiology of leishmaniasis started to be evaluated from a broader perspective (Palatnik-de-Sousa and Day, 2011).

In the case of human visceral leishmaniasis caused by *L. infantum*, the idea that dogs are the only reservoir of the parasite has led health authorities to direct the eradication of seropositive dogs on the basis that this action was the only way to control this zoonosis. In fact, several studies have demonstrated that dogs are epidemiologically important as reservoirs in different localities (reviewed by Lainson and Rangel, 2005; Dantas-Torres, 2009; Quinnell and Courtenay, 2009). Nevertheless, the participation of other infected mammals, rather than dogs, in the transmission cycle of *L. infantum* in urban areas, was already proposed for cats and opossums, for example (Pennisi et al., 2013; Santiago et al., 2007). The low effectiveness of dog culling program in Brazil is probably due to an assemblage of factors, most of them related to the lack of a structured surveillance system, and include the high interval between tests and between the positive result and dog elimination, the rapid replacement of susceptible dogs when an infected dog is euthanized, and the resistance of owners to euthanize their infected dogs (Costa et al., 2013; Grimaldi et al., 2012; Nunes et al., 2008). Some of these localities are very close to sylvatic areas, and the possibility that wild mammals may serve as a source of infection to vectors in peridomiciliary areas has been ignored. The putative participation of these mammals is an important additional factor to be considered in the proposition of measures to control this zoonosis. This review highlights species from distinct orders that may maintain and serve as a source of infection to phlebotomine sand fly vectors, providing a constant source of re-infection to a peridomestic transmission system.

The reservoirs of the *Leishmania* species responsible for the cutaneous forms of human leishmaniasis are still unknown most likely because research has focused on the search for a specific reservoir host, as observed for dogs and *L. infantum*. These species may be maintained in the wild by a different strategy, as by a few "hot species" with high transmissibility competence or, most likely, through a reservoir system, an assemblage of mammals with distinct and transient degrees of transmissibility competence throughout infection. This hypothesis agrees with the reservoir definition proposed by Ashford (1997), almost 20 years ago. This system involves a tradeoff that could explain the evolutionary success of these parasite species: several individuals are infected, but each is competent for transmission for only a limited time, while retaining the infection for long periods of time. The sum of multiple short periods of infectivity in numerous infected mammals guarantees the maintenance and transmission of these *Leishmania* species.

All the links in the epidemiological chain must be clarified as a prerequisite for effective control strategies (Abdussalan, 1959; Palatnik-de-Sousa and Day, 2011; Shaw, 2007). We are still far from understanding the maintenance of different *Leishmania* species in nature. In this sense, the follow-up of naturally infected animals and experimental studies using potential reservoirs are essential to improving understanding of the mechanisms of maintenance of these parasites in their natural hosts. In the field, the studies should not be restricted to previously described infected hosts, but should be carried out using an integrated ecological approach to understand the role of each host species in the maintenance and amplification of *Leishmania* parasites. Priorities include the identification of the factors that influence the transmissibility competence of the individual mammalian hosts and understanding how environmental management could decrease infections in humans living close to sylvatic.

Over the last century, the scientific community has shown that different and several wild mammal species can become infected with *Leishmania* species. The focus must change to identify species that may serve as sources of infection to vectors and amplify enzootic foci, constituting a risk for human transmission. To this end, a paradigm shift in research and surveillance of wild reservoirs of *Leishmania* is urgently needed. This change will depend, among other factors, on understanding reservoir systems and acknowledging the importance of understanding the role each mammal species plays in maintaining these parasites in nature. The factors involved in the amplification of enzootic foci are temporally and regionally specific, and understanding some of these factors may support the development of effective and sustainable strategies for leishmaniasis surveillance.

Acknowledgements

AMJ is a "Cientista do Nosso Estado", provided by FAPERJ and is financially supported by CNPq ("Bolsista de Produtividade, nível 1", CNPq). ALRR is a "Jovem Cientista do Nosso Estado" provided by FAPERJ. The authors have declared that no competing interests exist.

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