Parasite Biology: The Reservoir Hosts

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4.1 Introduction

Leishmaniases are parasitic diseases caused by protozoa belonging to the genus *Leishmania* (order Kinetoplastida, family Trypanosomatidae), which infects several mammal species, including humans. These parasites are primarily transmitted by the bite of an insect vector, the phlebotomine sand fly (order Diptera, family Psychodidae; subfamily Phlebotominae) of the genera *Phlebotomus* (Old World) and *Lutzomyia* (New World) (Killick-Kendrick 1999; WHO 2010; Maroli et al. 2013). Human leishmaniases have diverse clinical manifestations. Visceral leishmaniasis (VL) caused by parasites of the *Leishmania donovani* complex (*L. donovani* in the Old World and *L. infantum* in both the Old and New Worlds) is a severe disease of humans and other mammals, which leads to death if left untreated. A number of different *Leishmania* spp. cause localized cutaneous (LCL) or diffuse cutaneous (DCL) or mucocutaneous (MCL) leishmaniasis, which are responsible for considerable morbidity of a vast number of people in endemic foci. Leishmaniases are endemic in 98 countries on 4 continents, with more than 350 million people at risk. Published figures indicate an

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estimated incidence of 0.2–0.4 million VL cases and 0.7–1.3 million cutaneous leishmaniasis (CL) cases (WHO 2010; Alvar et al. 2012). These figures are, most probably, underestimated as official data and are often obtained through passive case detection, and the extent of underreporting in most leishmaniasis endemic countries (even in those where the disease is of compulsory notification) is substantial (Desjeux 2004; Dujardin et al. 2008; WHO 2010; Alvar et al. 2012).

Leishmaniases are dynamic diseases, and the circumstances of transmission are continually changing in relation to environmental, demographic and human behavioural factors. In most endemic regions, leishmaniases are characterized by a patchy distribution with discrete transmission foci due to microecological conditions that affect the vector, the parasite and the reservoir host. Changes in the habitat of the natural host and vector, immunosuppressive conditions (e.g. HIV infection or organ transplantation-associated therapies) and the consequences of military conflicts, all contribute to the changing leishmaniasis landscape, which can result in either an increase or a decrease in the incidence of the disease (Gramiccia and Gradoni 2005; WHO 2010; Alvar et al. 2012; Antoniou et al. 2013).

Leishmaniases can be grouped into two broad epidemiological categories according to the source of human infection: zoonotic leishmaniases, in which the reservoir hosts are wild or domestic animals and humans play a role of an accidental host, and anthroponotic leishmaniases, in which man is the sole reservoir host and source of vector's infection (Desjeux 2004; Gramiccia and Gradoni 2007; WHO 2010).

A reservoir host of leishmaniases is an animal in which an infectious agent survives persistently in a way that the animal may serve as a source of parasites to the vectors. The mere presence of the infection in a particular mammal species, even in large numbers, does not necessarily indicate that this mammal is a reservoir host. In order to incriminate a reservoir host formally, it is necessary to demonstrate that the parasite population depends on that particular mammal for its long-term maintenance (Ashford 1996; WHO 2010). A "good" reservoir should be susceptible to the parasites, live in close contact with man, and it should be a good source of parasites to the vectors. The proportion of individuals that become infected during their lifetime should be considerable, although the incidence can vary greatly with season. A good reservoir should provide a significant food source for the phlebotomine sand fly, and both should rest and breed in the same habitat. Infection should present a chronic evolution allowing the animal to survive at least until the next transmission season (Bray 1982; Ashford 1996; WHO 2010). *Leishmania* parasites identified in reservoir hosts must be biochemically and genetically the same as those in humans.

When more than one host species can be infected, they are often divided on epidemiological grounds into primary and secondary (or minor) reservoir hosts and accidental (or incidental) hosts: primary reservoir host is a host that is responsible for maintaining the parasite indefinitely in nature. In these hosts, the infection is normally without clinical signs; secondary reservoir host is a host that can transmit infection but cannot maintain parasite transmission in the absence of the primary host(s), while accidental host is a host that although infected plays no role in the

maintenance of the transmission cycle (Silva et al. 2005; WHO 2010; Quinnell and Courtenay 2009).

4.2 Anthroponotic Leishmaniases

Human beings are directly involved as a principal reservoir host in two forms of the disease: VL caused by *L. donovani* in Indian subcontinent (Bangladesh, India and Nepal) and East Africa (Djibouti, Ethiopia, Eritrea, Kenya, Somalia, South Sudan, Sudan and Uganda) and CL caused by *L. tropica* in semiarid subtropical regions from south-east Turkey to north-west of India. Small foci have also been described in Arabia, Ethiopia, Greece, Namibia, North Africa (Algeria, Egypt, Morocco and Tunisia) and in Central Asia (Gramiccia and Gradoni 2007; WHO 2010).

L. donovani-infected animals have been increasingly reported in several foci, despite the predominant anthroponotic transmission pattern, where post-kala-azar dermal leishmaniasis patients might constitute the main interepidemic reservoir host (WHO 2010). In certain districts of Sudan, rodents from the *Arvicanthis* genus (Hoogstraal and Heyneman 1969) and the Egyptian mongoose (*Herpestes ichneumon*) were suspected to be reservoir hosts of the parasite (Elnaiem et al. 2001). Anti-*Leishmania* antibodies have also been detected in donkeys, cows, goats and sheep in a kala-azar endemic region in Sudan, suggesting exposure of these animals to *L. donovani* infection (Mukhtar et al. 2000). In addition, canine leishmaniasis (CanL) seroprevalence between 42.9 and 74.3% and the same zymodemes were found in both humans and dogs in an endemic VL focus in Eastern Sudan (Dereure et al. 2000, 2003). However, in a more recent study performed in the same geographic region, a low number of dogs were found to have specific antibodies against *Leishmania* or to harbour parasites (Hassan et al. 2009).

In north-western Ethiopia, antibodies to and/or DNA of *L. donovani* complex have been detected in the blood of several domestic animals such as goats, sheep, cows, dogs and donkeys (Kalayou et al. 2011; Kenubih et al. 2015; Rohousova et al. 2015). *L. donovani* has also been molecularly amplified from the bone marrow of dogs (Bashaye et al. 2009) and from the spleen, bone marrow or liver of wild Ethiopian rodents (*Arvicanthis*, *Gerbilliscus* and *Mastomys* genera) (Kassahun et al. 2015a; Lemma et al. 2017). Finally, in the Indian subcontinent, *L. donovani* DNA has been detected in the blood of goats, cows and buffaloes in Nepal (Bhattarai et al. 2010), in goats (Singh et al. 2013) and domestic dogs (Jambulingam et al. 2017) in India and in stray dogs from Bangladesh (Akter et al. 2016).

Similarly, and despite *L. tropica* is considered to depend on humans for its survival, at least in long-established endemic foci in urban settings (WHO 2010; Antoniou et al. 2013), in foci with few or sporadic cases, the disease is known or suspected to be zoonotic (Ashford 2000; WHO 2010). CanL due to *L. tropica* have been reported in Morocco (Dereure et al. 1991; Guessous-Idrissi et al. 1997), in Iran (Hajjaran et al. 2013; Bamorovat et al. 2015), in Israel (Baneth et al. 2014) and in Crete (Ntais et al. 2014). In addition, *L. tropica* promastigotes have recently been isolated from the blood of a young stray dog from Israel admitted to a veterinarian

hospital with a complaint of lethargy (Baneth et al. 2017). The isolation of the same zymodemes from dogs as those found in man in the same focus raised a potential role of dogs as reservoir hosts of this dermotropic *Leishmania* species. Nevertheless, the small number of canine cases and the short duration of the lesions in dogs make it difficult to define the precise role of this mammal in the epidemiological cycle (Dereure et al. 1991). In a broader geographical context of the Mediterranean region, several zoonotic foci have been described, with rock hyraxes (*Procavia capensis*) as reservoir hosts in Israel (Svobodova et al. 2006; Talmi-Frank et al. 2010) and the North African gundi (*Ctenodactylus gundi*) as probably serving as reservoir host of *Leishmania killicki* (synonym of *L. tropica*, Pratlong et al. 2009) in the area of Maghreb (Jaouadi et al. 2011; Bousslimi et al. 2012). In addition, *L. tropica* DNA has recently been detected in the spleen of wild rodents (*Acomys*, *Arvicanthis*, *Gerbillus* genera) (Kassahun et al. 2015a) and of one heart-nosed bat (*Cardioderma cor*) in Ethiopia (Kassahun et al. 2015b) as well as in the blood of stray cats from Izmir, Turkey (Can et al. 2016).

Despite these recent findings, more extensive studies to clarify the role of domestic animals in maintenance and transmission of *L. donovani* and *L. tropica* focusing on isolation and typing of the parasite and xenodiagnosis should be advocated.

4.3 Zoonotic Visceral Leishmaniasis

Leishmania infantum (synonymous of *L. chagasi*) is the etiological agent for zoonotic VL in several countries of Central and South America, the Mediterranean Basin, Middle East and Asia. The main vector in the New World is *Lutzomyia longipalpis*, while in the Old World, several species belonging to the subgenus *Phlebotomus* (*Larrossius*) (e.g. *Phlebotomus ariasi*, *Phlebotomus perniciosus*, *Phlebotomus tobbi*) are involved in *L. infantum* transmission (Maroli et al. 2013). Domestic dogs are the main domestic reservoir hosts for human infection.

In the Old and New Worlds, several indigenous wild mammal species have been found infected by or exposed to *L. infantum* (Table 4.1).

The role of foxes (*Vulpes* spp. and *Cerdocyon thous*), jackals (*Canis aureus*), wolves (*Canis lupus*) and raccoon dogs (*Nyctereutes procyonoides*) as sylvatic reservoir hosts has been suggested (Abranches 1989; WHO 2010). The existence of an autonomous or semi-autonomous sylvatic cycle in the Mediterranean Basin maintained by red foxes (*Vulpes vulpes*) has been proposed (Abranches et al. 1984), but the dependence level and the direction of parasite transmission (i.e. if foxes are inoculated with *L. infantum* through the bite of competent vectors that become infected after feeding on dogs harbouring parasites or vice versa) between these animal species were not evaluated. In fact, there is no strong evidence that wild carnivores are an important source of infection stressing the need of further quantitative studies to confirm their infectiousness to the vectors (Quinnell and Courtenay 2009). On the other hand, the ability to transmit infection has been confirmed by xenodiagnosis in black rats (*Rattus rattus*), hares and wild rabbits suggesting that they may represent a secondary reservoir host for *L. infantum*

Table 4.1 *Leishmania infantum* infection in wild animals in the Old and New Worlds (updated from Ashford 1996; Quinnell and Courtenay 2009; Savani et al. 2010; Millán et al. 2014; Chemkhi et al. 2015; de Oliveira et al. 2015; Ebani et al. 2016; Montoya et al. 2016; de Rezende et al. 2017; Pourmohammadi et al. 2017)

Order	Common name (scientific name)
Carnivora	Bush dog (*Speothos venaticus*)
	Common genet (*Genetta genetta*)
	Corsac fox (*Vulpes corsac*)
	Crab-eating fox (*Cerdocyon thous*)
	Egyptian mongoose (*Herpestes ichneumon*)
	European badger (*Meles meles*)
	European mink (*Mustela lutreola*)
	European pine marten (*Martes martes*)
	European wildcat (*Felis silvestris silvestris*)
	Fennec fox (*Vulpes zerda*)
	Golden jackal (*Canis aureus*)
	Grey wolf (*Canis lupus*)
	Hoary fox (*Lycalopex vetulus*)
	Iberian lynx (*Lynx pardinus*)
	Jaguar (*Panthera onca*)
	Least weasel (*Mustela nivalis*)
	Maned wolf (*Chrysocyon brachyurus*)
	Mediterranean monk seal (*Monachus monachus*)
	Polecat (*Mustela putorius*)
	Puma (*Puma concolor*)
	Raccoon dog (*Nyctereutes procyonoides*)
	Red fox (*Vulpes vulpes*)
	Stone marten (*Martes foina*)
Chiroptera	Broad-nosed bat (*Platyrrhinus helleri*)
	Common vampire bat (*Desmodus rotundus*)
	Flat-faced fruit-eating bat (*Artibeus planirostris*)
	Great fruit-eating bat (*Artibeus lituratus*)
	Pale spear-nosed bat (*Phyllostomus discolor*)
	Pallas's long-tongued bat (*Glossophaga soricina*)
	Pallas's mastiff bat (*Molossus molossus*)
	Seba's short-tailed bat (*Carollia perspicillata*)
	White-lined broad-nosed bat (*Platyrrhinus lineatus*)
Didelphimorphia	Black-eared opossum (*Didelphis aurita*)
	Common opossum (*Didelphis marsupialis*)
	Bennett's wallaby (*Macropus rufogriseus rufogriseus*)
Diprotodontia	Bennett's wallaby (*Macropus rufogriseus rufogriseus*)
Eulipotyphla	North African hedgehog (*Atelerix algirus*)
Lagomorpha	European hare (*Lepus europaeus*)
	European rabbit (*Oryctolagus cuniculus*)
	Iberian hare (*Lepus granatensis*)
Pilosa	Southern tamandua (*Tamandua tetradactyla*)

(continued)

Table 4.1 (continued)

Order	Common name (scientific name)
Primata	Black-fronted titi monkey (*Callicebus nigrifrons*)
	Black-headed night monkey (*Aotus nigriceps*)
	Brown howler (*Alouatta guariba*)
	Emperor tamarin (*Saguinus imperator*)
	Golden-bellied capuchin (*Sapajus xanthosternos*)
	Golden-headed lion tamarin (*Leontopithecus chrysomelas*)
	Vanzolini's bald-faced saki (*Pithecia vanzolinii*)
Rodentia	Algerian mouse (*Mus spretus*)
	Amazonian marsh rat (*Holochilus sciureus*)
	Azara's agouti (*Dasyprocta azarae*)
	Black rat (*Rattus rattus*)
	Brazilian porcupine (*Coendou prehensilis*)
	Broad-headed spiny rat (*Clyomys laticeps*)
	Brown rat (*Rattus norvegicus*)
	Colombian spiny rat (*Proechimys canicollis*)
	European wood mouse (*Apodemus sylvaticus*)
	Grey hamster (*Cricetulus migratorius*)
	House mouse (*Mus musculus*)
	Long-tailed climbing mouse (*Rhipidomys mastacalis*)
	Persian jird (*Meriones persicus*)
	Punaré (*Thrichomys laurentius*)
	South American water rat (*Nectomys squamipes*)
	Syrian hamster (*Mesocricetus auratus*)
	Tome's spiny rat (*Proechimys semispinosus*)

(Gradoni et al. 1983; Molina et al. 2012; Jiménez et al. 2014). The evidence that hares and, to a lesser extent, rabbits can play a role as reservoir hosts of *L. infantum* in a new focus in Fuenlabrada, Spain, linked to the urbanization of a sylvatic transmission cycle due to the creation of an urban periphery where both lagomorphs and phlebotomine sand fly vectors have the optimal conditions to increase in numbers, is an example that leishmaniasis can emerge due to environmental changes induced by man (Molina et al. 2012; Jiménez et al. 2014).

Among reports on domestic animals recurrently found infected with *L. infantum*, those regarding cats deserve attention for the potential implications to public health. *L. infantum* infection has been reported in domestic cats from several endemic countries in Europe, the Middle East and Brazil (Ozon et al. 1998; Martín-Sánchez et al. 2007; Nasereddin et al. 2008; Hatam et al. 2010; Vides et al. 2011; Pennisi et al. 2012; Chatzis et al. 2014; Maia et al. 2014; Can et al. 2016; Attipa et al. 2017). Thus, an increasing trend to regard cats as a potential domestic reservoir host of *L. infantum* exists as they seem to be:

1. Naturally susceptible to infection by this species, normally without development of clinical signs (these, when present are usually cutaneous but systemic involvement has also been recorded)
2. A blood source for some *Leishmania* vectors

3. Present parasites in an available way to infect the vector
4. Among the most popular pet animals around the world, often present in areas where the peridomestic and domestic transmission cycles of the parasite occur (Colmenares et al. 1995; Maroli et al. 2007; Martín-Sánchez et al. 2007; da Silva et al. 2010; Maia et al. 2010; Vides et al. 2011; Pennisi et al. 2012; Chatzis et al. 2014)

In addition, parasites isolated from infected cats seem to be biochemically and genetically identical to the ones obtained from humans and dogs with leishmaniases (Maroli et al. 2007; Pennisi et al. 2012; Maia et al. 2015). Despite this evidence, the epidemiological importance of cats in leishmaniasis is still poorly understood (Gramiccia and Gradoni 2007; Gramiccia 2011; Maia and Campino 2011; Pennisi et al. 2015). Therefore, from an epidemiological and control perspective it would be very important to evaluate the proportion of transmission in endemic areas attributable to cats in order to clarify if these animals are reservoir hosts sustaining and spreading *Leishmania* infection (Maia and Campino 2011). The dependence level and the direction of parasite transmission (i.e. if cats are inoculated with *L. infantum* through the bite of competent vectors that become infected after feeding on dogs harbouring parasites or vice versa) between these animal species are also important issues (Maia and Campino 2011).

Antibodies to *L. infantum* or its DNA have also been detected in horses in endemic areas from the Old and New Worlds (Solano-Gallego et al. 2003; Rolão et al. 2005; Fernández-Bellon et al. 2006; Lopes et al. 2013; Soares et al. 2013; Gama et al. 2014; Aharonson-Raz et al. 2015) and in nonendemic areas (i.e. Switzerland and Germany) close to the border of the limit of leishmaniasis distribution in Southern Europe (Koehler et al. 2002). Clinical cases of equine leishmaniasis have been described as self-limiting nodular or ulcerated skin lesions, isolated or disseminated (Koehler et al. 2002; Portús et al. 2002; Rolão et al. 2005; Gama et al. 2014; Baneth et al. 2015). Previous experimental data did not identified *Equus asinus* as a *L. infantum* reservoir host since the lesions of the experimentally infected donkeys spontaneously disappeared and xenodiagnosis performed using the vector *L. longipalpis* was negative (Cerqueira et al. 2003). Nevertheless, the dogma that domestic equines seem to display clinical and immunological responses of the resistant type (Fernández-Bellon et al. 2006) has recently been challenged as the concomitant cutaneous and visceral *L. infantum* infection was described in three horses from Belo Horizonte, Brazil (Soares et al. 2013). In addition, in northern Israel, facial lesions due to *L. infantum* in two horses progressively proliferated and needed to be treated with intralesional injections of meglumine antimoniate (Baneth et al. 2015), which together with the presence of *L. infantum* DNA in *P. perniciosus* sand flies that fed on two parasitaemic subclinically infected horses from the same stable allowed the authors to suggest that horses may serve as secondary reservoir hosts for this *Leishmania* species. Nevertheless, more research is required to elucidate the role, if any, of horses in *L. infantum* epidemiology, namely, the isolation for a more refined genetic, biological and biochemical characterization of the parasites infecting horses and the infectiousness of horses to vectors from nature and in horse populations.

Epidemiological studies conducted worldwide in endemic areas of VL caused by *L. infantum* strongly suggest that asymptomatic human infections are common (Costa et al. 2002; Michel et al. 2011). Risk factors for progression to disease include age, malnutrition, HIV coinfection and other immunosuppressive conditions (Gramiccia and Gradoni 2007; Boelaert and Sundar 2014). Parasite transmission by blood transfusion has also been reported (Michel et al. 2011). Therefore and despite the very low parasitaemia level, at least in immunocompetent asymptomatic carriers, their potential role as reservoir hosts should be addressed (Michel et al. 2011). It would also be important to screen patients from endemic areas for *Leishmania* infection before starting an immunosuppressive treatment (Basset et al. 2005).

Leishmania siamensis (*nomen nudum*) is referred in literature as the causative agent of several recent human cases of VL and CL with and without other co-immunosuppressive states in Thailand (Sukmee et al. 2008; Suankratay et al. 2010; Bualert et al. 2012; Chusri et al. 2012) and Myanmar (Noppakun et al. 2014). A putative vector, *Sergentomyia gemmea*, has recently been proposed (Kanjanopas et al. 2013). This so-called species, which belongs to the *Leishmania enrietti* complex, has not been formally named and described and therefore is not taxonomically valid (Pothirat et al. 2014; Akhoundi et al. 2016). In fact, it was recently showed that the majority of the ITS-1 and RNAPolII sequences that have been previously identified as *L. siamensis* in Thailand may actually be *Leishmania martiniquensis* (Pothirat et al. 2014). The geographical distribution of these novel *Leishmania* strains seems to be wide, as sporadic autochthonous equine and bovine CL have been reported in Germany, in Switzerland and in the USA (Müller et al. 2009; Lobsiger et al. 2010; Reuss et al. 2012). The zoonotic potential of *L. siamensis* has been suggested, as its DNA was amplified from liver and spleen samples of two black rats collected from the affected geographical area where VL in Thai patients have been reported (Chusri et al. 2014).

4.4 Zoonotic Cutaneous Leishmaniases

4.4.1 Old World

Leishmania aethiopica shows a geographical distribution limited to the highlands of East Africa (Ethiopia, Kenya and Uganda), and stable foci of low endemicity are maintained by hyraxes (*Procavia capensis* and *Heterohyrax brucei*) (Ashford et al. 1973; Saliba and Oumeish 1999; Tonui 2006; WHO 2010; Alvar et al. 2012). *Phlebotomus longipes*, *P. pedifer* and *P. sergenti* are the proven vectors (Killick-Kendrick 1999; Maroli et al. 2013; Akhoundi et al. 2016). Rock hyrax is also suspected of being the reservoir host of *L. aethiopica* in Saudi Arabia (Morsy et al. 1997; WHO 2010). Human LCL cases, and less frequently DCL or MCL, occur mostly in rural villages built on rock hills or river banks, associated with proximity to hyrax colonies. However, human cases have also been reported in and near Ethiopian urban centres, including Addis Ababa suggesting that this parasite is

probably not so uncommon at lower altitudes (Negera et al. 2008; Lemma et al. 2009). *L. aethiopica* has also been isolated from a goat in Kenya (Williams et al. 1991) and from a ground squirrel (*Xerus rutilus*) in Ethiopia (Abebe et al. 1990).

Sporadic cases of LCL due to *L. infantum* are seen throughout the Mediterranean Basin (WHO 2010). This parasite is the most frequent cause of CL in Southern Europe (Gramiccia and Gradoni 2007). As mentioned before, several phlebotomine sand flies of *Larrossius* subgenus are the proven vectors of this parasite, and dogs are the main reservoir hosts for human infection. Nevertheless, in the recent focus of VL and CL in Fuenlabrada, Spain, the role of lagomorphs as potential sylvatic reservoir hosts has been raised up (Molina et al. 2012; Jiménez et al. 2014).

Leishmania major is the main cause of zoonotic CL in an area that stretches from India through Central Asia, the Middle East, to North and West Africa (WHO 2010). CL due to this *Leishmania* species, which is transmitted by several *Phlebotomus* species of *Paraphlebotomus* and *Phlebotomus* subgenera (Killick-Kendrick 1999; Maroli et al. 2013; Akhoundi et al. 2016), is widely distributed in rural arid areas with proneness to epidemic pattern with seasonal occurrence of cases (WHO 2010; Aoun and Bouratbine 2014). Several rodent species have been identified as reservoir hosts: the great gerbil (*Rhombomys opimus*) in Central Asia, Northern Afghanistan and Iran, the Indian desert jird (*Meriones hurrianae*) in India, the fat sand rat (*Psammomys obesus*) and Sundevall's jird (*Meriones crassus*) in Northern Africa and Middle East, Libyan jird (*Meriones libycus*) in the Arabian Peninsula and Central Asia, the short-tailed bandicoot rat (*Nesokia indica*) in Iran and several rodent species (*Arvicanthis*, *Tatera*, *Mastomys* or *Xerus* spp.) in sub-Saharan Africa (Ashford 2000; Gramiccia and Gradoni 2005; Pourmohammadi et al. 2008; WHO 2010; Aoun and Bouratbine 2014; Chaara et al. 2014). The Shaw's jird (*Meriones shawi*) also seems to play an important role in the transmission of *L. major* in Morocco (Rioux et al. 1982) and Tunisia (Ghawar et al. 2011a). The voles of the species *Microtus tristrami* and *Microtus guentheri* have recently been implicated as *L. major* reservoir hosts in a CL focus in northern Israel (Faiman et al. 2013). The sympatric occurrence of both vector (*Phlebotomus papatasi*) and *M. guentheri* in Turkey, Central Asia and Southern Europe suggests a threat for the spread of *L. major* into these regions (Antoniou et al. 2013; Faiman et al. 2013).

Leishmania major DNA has also been detected in internal organs of North African hedgehogs (*Atelerix algirus*) collected in Algeria (Tomás-Pérez et al. 2014) and North-Western Tunisia (Chemkhi et al. 2015), in the liver and spleen of Baluchistan gerbils (*Gerbillus nanus*) and brown rats (*Rattus norvegicus*) (Motazedian et al. 2010) and in the ears of long-eared hedgehogs (*Hemiechinus auritus*) in Iran (Azizi et al. 2011; Rouhani et al. 2014). The parasite was also detected by molecular techniques in the spleen of a hairy slit-faced bat (*Nycteris hispida*) in Ethiopia (Kassahun et al. 2015b), in the blood of domestic cats in the Ege Region of Turkey (Paşa et al. 2015) and in two dogs with dermal lesions from Israel (Baneth et al. 2016, 2017). *L. major* was isolated from an ear ulcer of a dog in Saudi Arabia (Elbihari et al. 1987) and from the spleen of an emaciated dog and

from the blood of a dog with mild generalized alopecia, both from Egypt (Morsy et al. 1987). Isolation of parasites has also been made from cutaneous lesions in a vervet monkey (*Chlorocebus aethiops*) in Kenya (Binhazim et al. 1987) and in a least weasel (*Mustela nivalis*) in Tunisia (Ghawar et al. 2011b). In Kenya, specific antibodies to *L. major* have been reported in feral nonhuman primates: vervet monkeys, olive baboons (*Papio cynocephalus anubis*) and Sykes' Monkeys (*Cercopithecus albogularis*) (Gicheru et al. 2009). Nevertheless and despite the detection of this *Leishmania* species in a variety of mammals, most of them are probably accidental hosts as they are rarely infected.

4.4.2 New World

Most of *Leishmania* species responsible for CL in the Americas are native to tropical rainforests, where a variety of wild animal species and phlebotomine sand flies maintain the enzootic cycle (Table 4.2).

Leishmania amazonensis (syn. *Leishmania garnhami*) is endemic in Argentina, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, French Guyana, Peru, Suriname and Venezuela (Lainson 2010; WHO 2010; Alvar et al. 2012). The main clinical human forms are localized or DCL, although this last form of the disease, an anergic variant of LCL, as well as a visceralization of infection in immunocompetent people have also been documented (WHO 2010; Boelaert and Sundar 2014). *Lutzomyia flaviscutellata*, the major vector of this dermotropic *Leishmania* species, feeds predominantly on ground-dwelling rodents, the primary reservoir hosts of *L. amazonensis*. Several other wild mammals (Table 4.2) are suspected of being secondary reservoir hosts (Ashford 2000; Gramiccia and Gradoni 2005; Lainson 2010; WHO 2010). This parasite has also been documented in dogs and cats (de Souza et al. 2005; Tolezano et al. 2007; reviewed by Dantas-Torres 2009 and Pennisi et al. 2015; Ferreira et al. 2015; Ramirez et al. 2016; Sanches et al. 2017). In addition, *L. amazonensis* DNA has recently been detected in the skin and/or spleen of different species of insectivores, frugivorous or haematophagous bats captured in non-urban and urban areas of São Paulo state, Brazil (Savani et al. 2010; de Oliveira et al. 2015).

Leishmania braziliensis is reported in almost all countries of Central and South America (WHO 2010; Alvar et al. 2012). The usual clinical form caused by the parasite is a localized CL, although diffused CL has also been reported. In addition, about 5% of the patients evolve towards a severe mucocutaneous disease (WHO 2010; Alvar et al. 2012). Visceralizing disease has also been reported for *L. braziliensis* in HIV coinfected patients (Boelaert and Sundar 2014) and in dogs coinfected with *Hepatozoon canis* (Morgado et al. 2016). Several *Lutzomyia* species of the *Lutzomyia*, *Nyssomyia*, *Psathyromyia*, *Psychodopygus* and *Verrucarum* subgenera are implicated in its transmission (Killick-Kendrick 1999; Maroli et al. 2013; Akhoundi et al. 2016). Albeit *L. braziliensis* is primarily associated to tropical forests and several bats, edentates, marsupials, opossums and wild rodents have been found infected (Table 4.2), this parasite has adapted to human-modified environments, being frequently found in the peridomestic

Table 4.2 *Leishmania* spp. causing CL in the New World and their proven/putative wild hosts (updated from Grimaldi and Tesh 1993; Lainson and Shaw 2005; Brandão-Filho et al. 2011; Marcelino et al. 2011; Shapiro et al. 2013; Roque and Jansen 2014; Kipp et al. 2016; Caldart et al. 2017; Carreira et al. 2017; de Castro Ferreira et al. 2017)

Leishmania	Order	Common name (scientific name)
L. amazonensis	Carnivora	Crab-eating fox (*Cerdocyon thous*)
		Hog-nosed skunk (*Conepatus chinga*)
		Kinkajou (*Potos flavus*)
	Chiroptera	Black bonneted bat (*Eumops auripendulus*)
		Black mastiff bat (*Molossus rufus*)
		Black myotis (*Myotis nigricans*)
		Broad-eared free-tailed bat (*Nyctinomops laticaudatus*)
		Common vampire bat (*Desmodus rotundus*)
		Flat-faced fruit-eating bat (*Artibeus planirostris*)
		Great fruit-eating bat (*Artibeus lituratus*)
		Little yellow-shouldered bat (*Sturnira lilium*)
		Pallas's long-tongued bat (*Glossophaga soricina*)
		Pallas's mastiff bat (*Molossus molossus*)
		Wagner's bonneted bat (*Eumops glaucinus*)
		White-lined broad-nosed bat (*Platyrrhinus lineatus*)
	Didelphimorphia	Brown four-eyed opossum (*Metachirus nudicaudatus*)
		Common opossum (*Didelphis marsupialis*)
		Grey four-eyed opossum (*Philander opossum*)
		Linnaeus's mouse opossum (*Marmosa murina*)
		Tate's woolly mouse opossum (*Marmosa paraguayana*)
		White-eared opossum (*Didelphis albiventris*)
		Woolly mouse opossum (*Marmosa demerarae*)
	Pilosa	Southern tamandua (*Tamandua tetradactyla*)
	Primata	Geoffroy's tamarin (*Saguinus geoffroyi*)
		Red-faced spider monkey (*Ateles paniscus*)
		Three-striped night monkey (*Aotus trivirgatus*)
	Rodentia	Black-eared rice rat (*Oryzomys melanotis*)
		Black-rumped agouti (*Dasyprocta prymnolopha*)
		Bolivian Hylaeamys (*Hylaeamys acritus*)
		Common punaré (*Thrichomys apereoides*)
		Cuvier's spiny rat (*Proechimys cuvieri*)
		Elegant rice rat (*Oryzomys nitidus*)
		Elegant-spined Atlantic spiny rat (*Trinomys setosus*)
		Hairy-tailed bolo mouse (*Necromys lasiurus*)
		Large-headed rice rat (*Hylaeamys megacephalus*)
		Red-tailed squirrel (*Sciurus granatensis*)
		Spiny rat (*Proechimys guyanensis*)
		Trinidad spiny pocket mouse (*Heteromys anomalus*)

(continued)

Table 4.2 (continued)

Leishmania	Order	Common name (scientific name)
L. braziliensis	Carnivora	Hog-nosed skunk (*Conepatus chinga*)
	Chiroptera	Flat-faced fruit-eating bat (*Artibeus planirostris*)
		Pallas's long-tongued bat (*Glossophaga soricina*)
		Pallas's mastiff bat (*Molossus molossus*)
		White-lined broad-nosed bat (*Platyrrhinus lineatus*)
	Didelphimorphia	Agile Gracile mouse opossum (*Gracilinanus agilis*)
		Common opossum (*Didelphis marsupialis*)
		Tate's woolly mouse opossum (*Marmosa paraguayana*)
		White-eared opossum (*Didelphis albiventris*)
		Woolly mouse opossum (*Marmosa demerarae*)
	Pilosa	Linnaeus's two-toed sloth (*Choloepus didactylus*)
	Primata	Three-striped night monkey (*Aotus trivirgatus*)
	Rodentia	Atlantic bamboo rat (*Kannabateomys amblyonyx*)
		Azara's agouti (*Dasyprocta azarae*)
		Black rat (*Rattus rattus*)
		Brown rat (*Rattus norvegicus*)
		Diminutive akodont (*Akodon arviculoides*)
		Dusky rice rat (*Melanomys caliginosus*)
		Common punaré (*Thrichomys apereoides*)
		Hairy-tailed bolo mouse (*Necromys lasiurus*)
		Hispid cotton rat (*Sigmodon hispidus*)
		House mouse (*Mus musculus*)
		Large-headed rice rat (*Hylaeamys megacephalus*)
		Lowland paca (*Cuniculus paca*)
		Natterer's Oecomys (*Oryzomys concolor*)
		Punaré (*Thrichomys laurentius*)
		South American water rat (*Nectomys squamipes*)
		White-footed climbing mouse (*Rhipidomys leucodactylus*)
L. colombiensis	Pilosa	Hoffman's two-toed sloth (*Choloepus hoffmanni*)
L. equatoriensis	Pilosa	Hoffman's two-toed sloth (*Choloepus hoffmanni*)
	Rodentia	Red-tailed squirrel (*Sciurus granatensis*)
L. guyanensis	Carnivora	Kinkajou (*Potos flavus*)
	Cingulata	Nine-banded armadillo (*Dasypus novemcinctus*)
	Didelphimorphia	Common opossum (*Didelphis marsupialis*)
		Grey slender mouse opossum (*Marmosops incanus*)
	Pilosa	Linnaeus's two-toed sloth (*Choloepus didactylus*)
		Southern tamandua (*Tamandua tetradactyla*)
	Rodentia	Common punaré (*Thrichomys apereoides*)
		Guyenne spiny rat (*Proechimys guyanensis*)
L. lainsoni	Rodentia	Lowland paca (*Cuniculus paca*)
L. lindenbergi		Unknown

Table 4.2 (continued)

Leishmania	Order	Common name (scientific name)
L. mexicana	Chiroptera	Commissaris's long-tongued bat (*Glossophaga commissarisi*)
		Common vampire bat (*Desmodus rotundus*)
		Godman's long-tailed bat (*Choeroniscus godmani*)
		Great fruit-eating bat (*Artibeus lituratus*)
		Highland yellow-shouldered bat (*Sturnira ludovici*)
		Jamaican fruit bat (*Artibeus jamaicensis*)
		Little yellow-shouldered bat (*Sturnira lilium*)
		Pale spear-nosed bat (*Phyllostomus discolor*)
		Pallas's long-tongued bat (*Glossophaga soricina*)
		Pygmy fruit-eating bat (*Dermanura phaeotis*)
		Southern long-nosed bat (*Leptonycteris curasoae*)
		Sowell's short-tailed bat (*Carollia sowelli*)
		Texas mouse (*Peromyscus attwateri*)
		Wagner's moustached bat (*Pteronotus personatus*)
	Didelphimorphia	Common opossum (*Didelphis marsupialis*)
		Mexican mouse opossum (*Marmosa mexicana*)
		Robinson's mouse opossum (*Marmosa robinsoni*)
	Rodentia	Big-eared climbing rat (*Ototylomys phyllotis*)
		Black-eared rice rat (*Handleyomys melanotis*)
		Black rat (*Rattus rattus*)
		Desmarest's spiny pocket mouse (*Heteromys desmarestianus*)
		Eastern woodrat (*Neotoma floridana*)
		Hispid cotton rat (*Sigmodon hispidus*)
		Slender harvest mouse (*Reithrodontomys gracilis*)
		Southern plains woodrat (*Neotoma micropus*)
		Sumichrast's vesper rat (*Nyctomys sumichrasti*)
		Yucatan deer mouse (*Peromyscus yucatanicus*)
		White-throated woodrat (*Neotoma albigula*)
L. naiffi	Cingulata	Nine-banded armadillo (*Dasypus novemcinctus*)
	Rodentia	Paraguayan punaré (*Thrichomys pachyurus*)
		Punaré (*Thrichomys laurentius*)
L. panamensis	Carnivora	Northern olingo (*Bassaricyon gabbii*)
		Kinkajou (*Potos flavus*)
		South American coati (*Nasua nasua*)
	Didelphimorphia	Brown four-eyed opossum (*Metachirus nudicaudatus*)
		Common opossum (*Didelphis marsupialis*)
	Pilosa	Brown-throated sloth (*Bradypus variegatus*)
		Brown-throated three-toed sloth (*Bradypus griseus*)
		Hoffman's two-toed sloth (*Choloepus hoffmanni*)
	Primata	Geoffroy's tamarin (*Saguinus geoffroyi*)
		Northern night monkey (*Aotus trivirgatus*)
	Rodentia	Black rat (*Rattus rattus*)
		Tome's spiny rat (*Proechimys semispinosus*)
		Desmarest's spiny pocket mouse (*Heteromys desmarestianus*)

(continued)

Table 4.2 (continued)

Leishmania	Order	Common name (scientific name)
L. peruviana	Didelphimorphia	Andean white-eared opossum (*Didelphis pernigra*)
	Rodentia	Andean pericote (*Phyllotis andium*)
L. shawi	Carnivora	South American coati (*Nasua nasua*)
	Pilosa	Linnaeus's two-toed sloth (*Choloepus didactylus*)
		Pale-throated three-toed sloth (*Bradypus tridactylus*)
	Primata	Black bearded saki (*Chiropotes satanas*)
		Tufted capuchin (*Cebus apella*)
	Rodentia	Highlands punaré (*Thrichomys inermis*)
		Punaré (*Thrichomys laurentius*)
L. venezuelensis		Unknown
L. waltoni		Unknown

environment of rural houses. In these settings, domestic animals (i.e. horses, donkeys, mules, dogs and cats) may act not only as blood sources to phlebotomine sand flies but might also participate in the transmission cycle (Bonfante-Garrido et al. 1981, 1992; Aguilar et al. 1984; Passos et al. 1996; Schubach et al. 2004; Madeira et al. 2006; Vedovello et al. 2008; Rougeron et al. 2011; Santaella et al. 2011; Truppel et al. 2014). Nevertheless, their role as reservoir hosts is still considered circumstancial (Reithinger and Davies 1999; Dantas-Torres 2007; Truppel et al. 2014; Pennisi et al. 2015). In order to prove that these animals can act as domestic reservoirs in the peridomestic environment, it will be necessary to conduct infectivity tests on phlebotomine sand flies and perform the isolation and characterization of the parasites from samples accessible to the vectors. In addition, insights derived from recent research suggest that humans might be important domestic reservoir hosts of *L. braziliensis*, at least during outbreaks (Dantas-Torres 2007; WHO 2010).

Leishmania colombiensis, which is responsible for single or multiple cutaneous lesions, is endemic in Colombia, Panama and Venezuela (WHO 2010; Alvar et al. 2012). *Lutzomyia gomezi*, *Lutzomyia hartmanni* and *Lutzomyia panamensis* are the proven or suspected vectors, and the Hoffmann's two-toed sloth (*Choloepus hoffmanni*) is the reservoir host in Panama (Killick-Kendrick 1999; Lainson 2010; WHO 2010; Maroli et al. 2013; Akhoundi et al. 2016). This parasite has also been isolated from the bone marrow of a dog in Venezuela (Delgado et al. 1993).

Leishmania guyanensis is responsible for LCL, and less frequently by DCL, being endemic in Argentina, Bolivia, Brazil (Acre, Amapá, Amazonas, Pará and Roraima states), Colombia, Ecuador, French Guiana, Guyana, Peru, Suriname and Venezuela (Lainson 2010; WHO 2010; Alvar et al. 2012). Transmission is associated with activities in forests (WHO 2010). The parasite can cause mucocutaneous lesions in a small proportion of cases (WHO 2010). The main vector is *Lutzomyia umbratilis* (Lainson 2010). Linnaeus's two-toed sloth (*Choloepus didactylus*) is a major reservoir host of *L. guyanensis* in Brazil and in French Guiana maintaining the zoonosis in the forest canopy (Table 4.2). The southern

tamandua (*Tamandua tetradactyla*) has been suggested as responsible for dispersal of the parasite due to its nomadic behaviour (WHO 2010). Occasional infections in rodents and opossums have been documented (Ashford 2000; Lainson 2010; WHO 2010). The DNA of the parasite has also been detected in one dog from Colombia (Santaella et al. 2011), but the contribution of domestic dogs in the life cycle of *L. guyanensis* seems limited.

Leishmania lainsoni causes CL, usually presenting as a single ulcer. The disease is found in Bolivia (subtropical areas), Brazil (Acre, Amapa, Pará and Rondônia states), Ecuador, French Guiana, Peru (tropical areas) and Suriname (Silveira et al. 1987; WHO 2010; Alvar et al. 2012; Kato et al. 2016). The vectors are *Lutzomyia ubiquitalis* in Brazil and Peru and *Lutzomyia nuneztovari anglesi* in Bolivia (Silveira et al. 1991a; Killick-Kendrick 1999; WHO 2010; Maroli et al. 2013; Akhoundi et al. 2016). The lowland paca (*Cuniculus paca*) is said to be the reservoir host (Silveira et al. 1991b; WHO 2010).

Leishmania lindenbergi causes CL in Brazil (Pará state) (Silveira et al. 2002; Lainson 2010; WHO 2010; Alvar et al. 2012). The suspected vector is *Lutzomyia antunesi*, and the reservoir host remains unknown (Silveira et al. 2002; WHO 2010; Maroli et al. 2013; Akhoundi et al. 2016).

Leishmania mexicana (syn. *Leishmania pifanoi*) is endemic in Belize, Colombia, Costa Rica, Ecuador, Guatemala, Mexico, Southern USA and Venezuela (WHO 2010; Alvar et al. 2012). Localized CL is the most common clinical form in humans, although diffuse CL has also been reported (WHO 2010). Many species of sylvatic ground-dwelling rodents (*Heteromys*, *Neotoma*, *Nyctomys*, *Ototylomys* and *Sigmodon* spp.) and marsupials have been implicated in the transmission cycle of *L. mexicana* (Table 4.2). In Texas, USA, cases of feline CL due to parasites belonging to the *L. mexicana* complex have been reported in the same areas where human cases occurred (Craig et al. 1986; Barnes et al. 1993; Trainor et al. 2010). *L. mexicana* DNA has also been detected in skin biopsies taken from a stray dog in Texas (Kipp et al. 2016) and in different tissues (i.e. heart, liver, skin and spleen) of several species of bats collected in six states of Mexico (Berzunza-Cruz et al. 2015). This dermotropic species has also been isolated from the liver aspirate of a dog from Ecuador (Hashiguchi et al. 1991). *Lutzomyia olmeca olmeca* is the main vector, and various other species are suspected to be involved in the life cycle of the parasite (Killick-Kendrick 1999; Lainson 2010; WHO 2010; Maroli et al. 2013; Akhoundi et al. 2016).

Leishmania naiffi causes a single, small, self-limiting lesion. It is found in Brazil (Rondônia state), Ecuador, Suriname and French Guiana (WHO 2010; van Thiel et al. 2010; Alvar et al. 2012; Kato et al. 2013). The proven vector is *Lutzomyia ayrozai*, while several other species are suspected to be involved in the transmission (Killick-Kendrick 1999; Maroli et al. 2013; Akhoundi et al. 2016); the reservoir host is the nine-banded armadillo (*Dasypus novemcinctus*) (Lainson and Shaw 1989; Naiff et al. 1991; WHO 2010).

Leishmania panamensis is responsible for LCL with some patients developing diffuse or mucocutaneous disease. This species is endemic in Colombia, Costa Rica, Ecuador (Pacific littoral), Guatemala, Honduras, Nicaragua and Panama

(WHO 2010; Alvar et al. 2012). The major vector is considered to be *Lutzomyia trapidoi*, but several other species (e.g. *Lutzomyia gomezi* and *Lutzomyia panamensis*) have also been found to be naturally infected (Killick-Kendrick 1999; Maroli et al. 2013; Akhoundi et al. 2016). *Lutzomyia trapidoi* prefers to feed in the canopy, on arboreal mammals, such as sloths, which are the primary hosts of *L. panamensis*. Various wild mammalian species, including monkeys and several rodent species (Table 4.2), have been found to be infected, but their role as possible reservoir hosts is poorly known. According to WHO (2010), humans seem to play a reservoir role in some outbreaks caused by this *Leishmania* species. Dogs have also found infected with *L. panamensis*, but there is no evidence that they can play a role as reservoir hosts (Dereure et al. 1994; Vélez et al. 2012; Ramírez et al. 2016).

Leishmania peruviana distribution is limited to the Peruvian Andes, confined to areas with scant vegetation of the Western slopes between 800 and 3000 m altitude (Lainson 2010; WHO 2010). The clinical form is a localized ulcerative CL, and *Lutzomyia ayacuchensis*, *Lutzomyia peruensis* and *Lutzomyia verrucarum* are the proven vectors (Killick-Kendrick 1999; Maroli et al. 2013; Akhoundi et al. 2016). The natural reservoir hosts are probably wild marsupials and rodents (Table 4.2). Dogs are reputed to be the principal peridomestic reservoir hosts (Llanos-Cuentas et al. 1999). This assumption is based on a positive correlation observed between the risk of human CL and CanL prevalence in Huanuco, Peru. However, the scarcity of parasites in cutaneous lesions together with the high serorecovery rates suggest that dogs are able to control infection and thus may not be the main reservoir host of the parasite (Reithinger et al. 2003). Therefore, the role of dogs as reservoir hosts of *L. peruviana* should be confirmed by experimental transmission studies (Dantas-Torres 2007).

Leishmania shawi found in Brazil (Atlantic Forest of Pará state) causes localized CL (WHO 2010). In primary forest, the vector is *Lutzomyia whitmani* (Lainson et al. 1989; Killick-Kendrick 1999; Maroli et al. 2013; Akhoundi et al. 2016). The sylvatic reservoir hosts are monkeys, coatis and sloths (Lainson et al. 1989) (Table 4.2).

Leishmania venezuelensis is responsible for localized and DCL in Venezuela (Bonfante-Garrido et al. 1996; WHO 2010). *Lutzomyia olmeca bicolor* is suspected of being the vector (Killick-Kendrick 1999; Lainson 2010; Maroli et al. 2013; Akhoundi et al. 2016), while domestic cats are suspected to be the reservoir hosts (Bonfante-Garrido et al. 1991).

Leishmania waltoni is a recently described species associated with cases of DCL in humans in Dominican Republic (Shaw et al. 2015). This species belongs to the *L. mexicana* complex, and its reservoir hosts and vectors are still unknown.

4.5 Control of Reservoir Hosts

In 2010, a WHO Expert Committee defined that control strategies of leishmaniases should combine case management, integrated vector control and, in the case of zoonotic transmission, animal reservoir host control (WHO 2010).

For the control of anthroponotic leishmaniasis, an effective strategy for active case detection, surveillance and effective treatment of patients with clinical forms of leishmaniasis, accompanied by measures for preventing reinfection, should reduce or eliminate the parasite load and reduce transmission (WHO 2010). In fact, better tools have been made available to developing countries, such as: improvement of VL diagnosis (e.g. recombinant antigen (K39)-dipstick tests for in-field diagnosis), (ii) affordable VL treatment (e.g. the first oral antileishmanial drug, miltefosine; short course of therapy) and (iii) a more efficient phlebotomine sand fly control for both anthroponotic VL and CL (e.g. long-lasting insecticide-treated bed nets) (Desjeux 2004; Gramiccia and Gradoni 2005).

Control of reservoir hosts has been recommended for zoonotic VL and CL. Due to the exophilic habit of the phlebotomine vectors and the sylvatic nature of the reservoir hosts, the control of the zoonotic CL forms in both the Old and New Worlds is not easy and may even not be feasible, as it would require expensive environmental management difficult to implement and sustain (Gramiccia and Gradoni 2005; WHO 2010; Boelaert and Sundar 2014). As there is currently no vaccine for human use, the ways to protect individuals from contracting the infection include avoiding intrusion in natural zoonotic foci as well as the adoption of personal protective measures against phlebotomine sand fly bites with repellents and other devices (WHO 2010; Boelaert and Sundar 2014).

In the case of zoonotic CL caused by *L. major*, where the reservoir hosts are peridomestic rodent species, their elimination could be achieved by the destruction of the burrow systems by deep ploughing followed by planting. Another approach is by poisoning the colonies of rodents with wheat grains mixed with zinc phosphide along with the prior treatment of burrows with the anticoagulant dicoumarol (Saliba and Oumeish 1999; Ashford 2000; WHO 2010; Boelaert and Sundar 2014). This method of control may be effective against *Rhombomys* and *Meriones* rodents that feed on grains but not against *Psammomys obesus*. Because zinc phosphide is very toxic to man and other animals, care should be taken during its application (Saliba and Oumeish 1999; WHO 2010). The removal of chenopod plants, the only ones that *P. obesus* feed on, from areas close to inhabitants would also lead to the reduction of their numbers (Desjeux 1996; Saliba and Oumeish 1999; WHO 2010). Transmission of zoonotic CL due to *L. aethiopica* could also be reduced by controlling hyraxes around villages. Elimination of hyraxes within 1 km of settlements is thought to be effective in reducing transmission. As reinvasion is likely, control must be continuous. In some countries, hyraxes are protected animals, and their control is illegal and prohibited (Saliba and Oumeish 1999; Ashford 2000; WHO 2010).

In the New World, where most of *Leishmania* cycles are maintained by edentates, procyonids, arboreal or ground sylvatic rodents, an integrated environmental management approach, combining clearance of primary forest around villages and spraying of the cleared areas with insecticides to remove both the reservoir hosts and the vector, thus creating a "vector- and reservoir-free" zone around villages, might be effective for the control of zoonotic CL (WHO 2010). However, even clearing forest around villages may not reach the objective, as various *Leishmania*

species (e.g. *L. braziliensis*) have proved to be remarkably adaptable to environmental degradation leading to peridomestic transmission rather to the elimination of the infections (Brandão-Filho et al. 1999; Ashford 2000; Boelaert and Sundar 2014).

Regarding zoonotic VL, infection in the canine domestic reservoir host should be monitored, and the management of infected dogs should be treatment or elimination (WHO 2010). Albeit test-and-treat strategies are performed in several Mediterranean countries, treating infected dogs alone may not be an effective control measure as relapses are frequent, and because despite clinical cure, dogs can recover infectivity weeks after treatment (Gradoni et al. 1987; Alvar et al. 1994; Miró et al. 2011); therefore, the use of repellents on dogs during and after treatment is imperative. In addition, the widespread use of the available anti-*Leishmania* drugs for both canine and human treatment might contribute to the generation and spread of drug-resistant parasites (Campino and Maia 2012). On the other hand, and despite culling dogs infected with *L. infantum* has been recommended by WHO, the implementation of this measure in countries where dogs are considered part of the family is impracticable. In Brazil, seropositive dogs are eliminated as part of a control programme, although its effectiveness in the control of infection is not clear-cut and it has not been tested in trials measuring clinical disease (González et al. 2015). Failure may occur due to several reasons (e.g. poor sensitivity of diagnostic methods, delay between diagnosis and culling and rapid replacement of culled dogs by new susceptible animals).

Leishmania life cycle can be interrupted through the use of impregnated dog collars and topical application of insecticide with repellent effect against phlebotomine sand flies (Killick-Kendrick et al. 1997; Mencke et al. 2003; Liénard et al. 2013; Dumont et al. 2015; Franc et al. 2015). In fact, a significant decrease in the incidence of zoonotic VL in children (Gavgani et al. 2002) and dogs has been observed in areas where most dogs used deltamethrin collars or have been treated with permethrin-based spot-on formulations (Maroli et al. 2001; Manzillo et al. 2006; Courtenay et al. 2009; Otranto et al. 2010). The impact of this type of control measure is dependent on the correct application and frequency of reapplication of the topical insecticides and in the loss rate of collars. In addition, the application of insecticides/repellents would have less impact on disease transmission if not integrated with stray dog control (Gramiccia and Gradoni 2005). Additional measures to control phlebotomine sand flies include reducing microhabitats favourable to them in the vicinity of the house and in other locations where dogs spend time, housing pets at dusk and indoor insecticide spraying of homes and animal shelters (Alexander and Maroli 2003; Maroli et al. 2010; Solano-Gallego et al. 2011).

Vaccination could be another strategy to reduce both CanL and the incidence in humans (Alvar et al. 2004). An effective vaccine would control both infection progression and the parasite transmissibility via the vector (Gradoni 2015). In Brazil, two canine vaccines (Leishmune® and Leishtec®) have been commercialized. Leishmune® was shown to induce a significant, long-lasting and strong protective effect against CanL in phase III of clinical trials (Silva et al. 2000; Borja-Cabrera et al. 2002). Although this vaccine was also proposed to be used as immunotherapeutic in infected dogs and as a transmission-blocking vaccine (Borja-Cabrera et al. 2004; Saraiva et al. 2006), in 2014

the Brazilian Ministry of Agriculture, Livestock and Food Supply suspended its commercialization due to non-compliance with all the requirements for phase III studies (http://www.agricultura.gov.br/assuntos/politica-agricola/arquivos/nota-tecnica-dfip-38-14-leishmune.pdf/view). Leish-Tec® conferred a significant reduction in the number of cases of CanL with an efficacy of 71.4% estimated according to parasitological results (i.e. imprinting, culture, or histopathology of dog tissues) (Regina-Silva et al. 2016). The infectiousness to reared *L. longipalpis* of vaccinated dogs presenting antibodies against the A2 antigen was 46.6% lower in comparison with non-vaccinated animals (Regina-Silva et al. 2016). In Europe, a vaccine consisting of purified excreted-secreted proteins of *L. infantum* and with QA-21 saponin as adjuvant (CaniLeish®) has provided a significant reduction in the risk of progressing to active infection or overt disease, with a clinical efficacy of 68% (Oliva et al. 2014). In vaccinated dogs that developed disease and that were exposed to the bites of reared *P. perniciosus*, the reduction in parasite transmission was found significant when compared to matched controls (Bongiorno et al. 2013). More recently (in 2017), a second vaccine (Letifend®) consisting of a recombinant Protein Q from *L. infantum* MON-1 has been commercialized in Europe. According to the product information available at the European Medicines Agency, a vaccinated dog has five times less risk to develop clinical disease than a non-vaccinated dog (https://ec.europa.eu/health/documents/communityregister/2016/20160420134483/anx_134483_en.pdf).

In last years, CanL expanded northwards in Europe, mainly due to movement of infected dogs from endemic to previously nonendemic areas (Maia and Cardoso 2015). Therefore, control of CanL should also include the compulsory certification by veterinarians of the non-infective state of animals moving from one place to another to avoid the introduction of infected dogs in areas previously nonendemic, especially in those having competent vectors which might result in the persistence of *L. infantum* (WHO 2010; Maia and Cardoso 2015).

4.6 Final Remarks

The development of efficient tools for reservoir host control depends on proper understanding of the local epidemiology of leishmaniasis (including whether transmission is anthroponotic or zoonotic). Apart from the proven reservoir hosts, *Leishmania* parasites have been found in a variety of wild and domestic animals around the world, but their role in sustaining the life cycle of the parasite is unknown. In some instances, the parasites have been isolated and formally characterized, but in many cases, the infection status and parasite species have been inferred based on the detection of DNA fragments of the parasite through PCR-based tools. Therefore, it would be crucial to isolate and formally identify *Leishmania* parasites infecting any suspected reservoir host. As in many cases, information about food sources, breeding season, movement and migration activities and longevity of the potential reservoir host(s) is lacking; further work along these lines should also be performed.

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