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Impact of different *Leishmania* reservoirs on sand fly transmission: perspectives from xenodiagnosis and other One Health observations

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Abstract

Leishmania has biologically adapted to specific phlebotomine sand flies through long co-evolution. The ability of *Leishmania* spp. to bind to sand fly midgut allows each *Leishmania* species to propagate and differentiate into infectious promastigotes and be transmitted. Sand fly feeding upon a mammalian host is the first step towards being infected and a host of *Leishmania*. Once deposited into the skin, host susceptibility to infection vs. ability to mount a sterilizing immune response predicts which hosts could be reservoirs of different *Leishmania* spp. Materials, in addition to parasites, are expelled during sand fly during feeding, including salivary antigens and other factors that promote local inflammatory responses. These factors aid visceralization of infection increasing the likelihood that systemic infection is established. Any environmental factor that increases sand fly biting of a particular host increases that host's role in *Leishmania* transmission. First descriptions of reservoir species were based on association with local human disease and ability to observe infected leukocytes on cytology. This approach was one pathogen for one reservoir host. Advances in sensitive molecular tools greatly increased the breadth of mammals found to host *Leishmania* infection. Visceralizing species of *Leishmania*, particularly *L. infantum,* are now known to have multiple mammalian hosts. *L. donovani,* long been described as

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an anthroponotic parasite, was recently identified through molecular and serologic surveys to have additional mammalian hosts. The epidemiological role of these animals as a source of parasites to additional hosts via vector transmission is not known. Current evidence suggests that dogs and other domestic animals either control infection or do not have sufficient skin parasitemia to be a source of *L. donovani* to *P. argentipes*. Further xenodiagnosis and characterization of skin parasitemia in these different hosts is required to more broadly understand which *Leishmania* spp. hosts can be a source of parasites to sand flies and which ones are dead-end hosts.

Keywords

Leishmania; reservoir; sand fly; vector

1. Introduction

1.1 *Leishmania* sand fly nexus

Leishmania are obligate intracellular protozoan parasites. The genus includes ~ 50 recognized species divided into five subgenera; *Leishmania*, *Viannia*, *Mundinia*, *Paraleishmania and Sauroleishmania* (Espinosa et al., 2018). Twenty of these, predominantly in the first three subgenera, are human pathogens. Sand flies are the biological vectors of *Leishmania* spp., implying that the parasite undergoes stage transformations within the sand fly gut and replicates there prior to transmission back to a mammal or reptile during blood feeding. Each *Leishmania* spp. has adapted to surviving in and transmitting through specific phlebotomine sand flies through long co-evolution, with fossil evidence of *Leishmania* from the early cretaceous period, 100 million years ago (Poinar and Poinar, 2004; Sacks and Kamhawi, 2001). Rodents are one of the oldest placental mammalian orders and represent more than 30% of mammals. It is not surprising that rodents are common reservoir spp. for *Leishmania* parasites.

The ability of *Leishmania* spp. to bind to the sand fly midgut establishes the ability of that *Leishmania* spp. to propagate and differentiate into infectious promastigotes and be transmitted during the next blood meal.(Kamhawi, 2006) It has been demonstrated for multiple parasite species that there is parasite stage adaptation to bind to particular sand fly guts, using digestive lectins and other receptors, providing sand fly host specificity (Ilg, 2000; Kamhawi et al., 2004). *Leishmania* transform through multiple stages while in the sand fly gut, with the nectomonad stage thought to bind via lectins to the gut epithelium and perhaps provide vector host specificity vs. permissivity to sand fly infection (Kamhawi et al., 2004; Turco and Sacks, 2003). These interactions have been shown to be dependent on the variable outer surface lipophosphoglycan (LPG), other glycans and proteoglycans on the parasite surface (Sacks et al., 2000) and additional digestive lectin receptors(Ilg, 2000; Kamhawi et al., 2004). After the blood meal is expelled, the parasite transforms into leptomonads and divides, beginning to transform into the predominant mammalian infectious form, metacyclic promastigotes(Kamhawi, 2006). More recent work has identified that a subsequent blood meal can augment the infectiousness of the sand fly and perhaps is an important means of promoting transmission in real life settings with multiple mammalian blood meal sources (Serafim et al., 2018).

1.2 Sand fly and mammalian host dynamics for *Leishmania* transmission

Sand fly feeding upon a mammalian host is the first step towards being an infected host of *Leishmania*. Mechanisms of transmission are not completely understood. Perhaps the most important mechanism to induce transmission during feeding is the creation of a “blocked fly” from promastigote secretory gel (PSG) secretion by parasites in the anterior midgut. In order to take a bloodmeal, the sand fly has to regurgitate the PSG plug, resulting in the deposition of metacyclic promastigotes in the skin of a mammalian host. However other possible factors including damage to the sand fly stomodeal valve or parasite invasion into the salivary glands have also been proposed (Bates, 2007; Serafim et al., 2018).

Once deposited into the skin, it is then mammalian host susceptibility to infection vs. ability to mount a sterilizing immune response that predicts which hosts could be reservoirs of different *Leishmania* spp. Materials in addition to parasites are expelled during sand fly during feeding, including salivary antigens and other factors that promote local inflammatory responses and visceralization of infection increasing the likelihood that systemic infection is established (Courtenay et al., 2017; Dey et al., 2018).

There is robust evidence that multiple components in sand fly saliva are both inflammatory and antigenic, with demonstration that prior exposure to these components can prevent successful feeding and therefore infection (Collin et al., 2009; Oliveira et al., 2013; Xu et al., 2011). It has subsequently been demonstrated that the gut microbiome of sand flies changes dramatically during the period after blood meal feeding with *Leishmania* infection (Kelly et al., 2017). These sand fly bacterial gut microbiome contents then alter the infection and visceralization of parasites within the next mammalian blood meal source (Dey et al., 2018). An infectious sand fly bite liberates a limited number of promastigotes during the fairly rapid blood meal. These promastigotes are highly susceptible to local innate immune responses,(Hoover et al., 1985) particularly gp63 on the surface of the parasite mediates complement binding and lysis of the parasite (Wilson and Hardin, 1990; Yao et al., 2003). Components of a sand fly bite has additional effects as skin exposed to salivary antigens promotes a delayed-type hypersensitivity response with increased swelling and edema secondary to increased vasodilation hastening the time required to probe and feed when compared to feeding on naive skin (Belkaid et al., 2000).

In addition to sand fly factors, it has been shown that temperature and humidity also significantly increase transmission efficacy(Stamper et al., 2011), therefore the predominant hosts available to sand flies during optimal temperature and humidity conditions increases a host’s role in *Leishmania* transmission (Courtenay et al., 2017).

First descriptions of reservoir species were based on association with local human disease and ability to observe infected leukocytes on cytology (Forattini et al., 1970). This approach was one pathogen for one reservoir host. These original implications of a vector parasite relationship were based primarily on being found in the same or very close geographical distribution (Lainson and Shaw, 1972). Demonstration of a particular mammalian species as the reservoir were originally based on that mammalian species being demonstrability infected by cytological means of examination. These studies often used a perhaps incorrect idea stemming from viral/vector studies that there should be detectable infection of sand

flies in the same locations as highly infected yet still predominantly healthy reservoir animals. More recent studies indicated that animals with clinical signs could be more infectious than those without, indicating that there is not a highly parasitemic population of reservoir animals who are subclinical (Courtenay et al., 2002; Guarga et al., 2000). There are dogs who appeared to be parasite “super-shedders” and although clinical stage(s) were not defined through a clinical scoring system, these dogs had clinically observable disease and high skin vs. blood parasite burdens (Courtenay et al., 2014; Courtenay et al., 2017). These studies and others indicate that the role of parasitic load in the skin might be much more correlative to transmission than parasitemia (Courtenay et al., 2014).

Advances in sensitive molecular tools to detect parasites within blood and other fluids or tissues greatly increased the breadth of mammals found to host *Leishmania* infection, allowing a new perspective of the ecology and epidemiology of *Leishmania*. Both dermotropic and visceralizing forms of *Leishmania*, particularly *L. infantum,* are now known to have multiple mammalian hosts. *L. donovani,* long been described as an anthroponotic parasite, was recently identified through molecular and serologic surveys to have additional mammalian hosts. Similarly, *L. tropica* is also generally considered to be anthroponotic, but was shown to infect rodents, dogs and cats (Bousslimi et al., 2010; Tabbabi et al., 2011). In some countries, rodents are suspected to be a reservoir for *L. tropica*. The epidemiological role of these animals as a source of parasites to additional hosts via vector transmission is often not known. However, the outbreak of human visceral leishmaniasis (VL) due to *L. infantum* in Madrid demonstrated the possibility of non-traditional species beyond dogs or cats, specifically hares and rabbits, to be an active reservoir for human infection (Dominguez-Bernal et al., 2014). This has meant that the consideration of reservoirs for leishmaniasis has had to be thought of more broadly than just humans in settings previously thought to be anthroponotic, and beyond dogs or rodents, the traditional zoonotic reservoirs, elsewhere (Costa et al., 2000).

2.0 Geographic description of *Leishmania* spp. and mammalian hosts

2.1 Europe/Mediterranean basin

Leishmania major is the most predominant dermotrophic *Leishmania* spp. in the Mediterranean basin. *L. major* is found across vast areas of North Africa and the Middle East as well as Central Asia (Chajbullinova et al., 2012). *Phlebotomus papatasi* is the main vector in North Africa and the Middle East. *Leishmania major* is also present in sub-Saharan Africa where the main vector is *P. duboscqi*. The predominant reservoirs of *L. major* are rodents, frequently from the subfamily *Gerbillinae* and less so *Sciuridae* (Akhavan et al., 2010). In some areas 100% of gerbils are infected and infection is lifelong. Sand flies of the genus *Phlebotomus* readily feed on rodents, both in captivity (Figure 1) and in the wild. Some *L. major* outbreaks of cutaneous leishmaniasis were believed to involve primarily human reservoirs,(Khosravi et al., 2017) a concept still under debate (Sunyoto et al., 2018). *L. major* infection has also been suggested to occur in dogs, as the parasite was isolated from cutaneous and splenic canine samples (Baneth et al., 2016; Morsy et al., 1987). Three other *Leishmania* parasites genetically similar to *L. major*, considered subspecies, have been

identified from rodents and a dog (Peters et al., 1986). These are *L. gerbilli, L. turanica,* and *L. arabica,* isolated from the dog. These species are rarely found to infect people.

Leishmania tropica is the second most common agent of human cutaneous leishmaniasis in old world. *L. tropica* is widely distributed across central Asia and more localized areas in north and east Africa,(Peters et al., 1986) as well as Greece. *P. sergenti* as the most common vector for *L. tropica*. Other species can be the main vector in particular locations, for instance *P. guggisbergi* in Kenya. *L. tropica* is mainly considered to be anthroponotic. However, an animal reservoir could exist and even be predominant in some areas. Rock hyraxes (*Procavia capensis or P. jonhnstoni*) have been described as reservoirs for *L. tropica* in several zoonotic foci (Sang et al., 1992a; Sang et al., 1992b; Svobodova et al., 2006). Dogs have been also reported to be infected and could be reservoirs or accidental hosts of *L. tropica*. Multiple descriptions were made mainly based on morphology and epidemiology (Dereure et al., 1991; Gramiccia and Gradoni, 2007), without genetic identification of strains, in locations where this could also be *L. infantum*. The sheer number of observations in the dog could support the hypothesis that dogs contribute to the overall pool *of L. tropica*, although this requires further investigation. Perhaps then, terming *L. tropica* a cause of "anthroponotic cutaneous leishmaniasis" may not be appropriate. Two other species are genetically very similar to *L. tropica*; *L. killicki* and *L.aethiopica*. *L. killicki* has been described in Tunisia, Yemen, and Namibia, isolated from hyraxes and vectored by *Phlebotomus rossi*. *L. aethiopica* seems to have a limited distribution to Southern Ethiopia and Kenya with hyraxes again as reservoirs with *Phlebotomus longipes* and *P. pedifer* as vectors (Ashford, 1970; Sang et al., 1994; Sang et al., 1992b). Human cases have been found areas with hyraxes. Experimental infections under laboratory conditions identified that only *P. papatasi* and *P. sergenti,* allow maturation of *L. major* and *L. tropica*, respectively.

As the climate undergoes change and sand flies expand their territory, other permissive sand fly spp. with broad vectorial competence could have epidemiological importance in new leishmaniasis foci (Antoniou et al., 2013). One instance of new foci of leishmaniasis is the recent introduction of *L. donovani* to the island of Cyprus (Antoniou et al., 2008; Koliou et al., 2008). *L. donovani* is responsible for "anthroponotic VL" on the Indian subcontinent as will be discussed in more detail later, as well as being demonstrated in Turkey and East Africa. In Cyprus, *L. donovani* was also found infecting a dog (Mazeris et al., 2010) and could be found in rats (Psaroulaki et al., 2010).

Leishmania infantum is the most important agent of visceralizing leishmaniasis/ leishmaniosis in humans and animals of the Mediterranean basin. In humans, visceral leishmaniasis due to *L. infantum* predominantly causes disease in immunocompromised individuals in Europe and those with poor living conditions similar to other highly endemic areas where human leishmaniases occur. The first description of VL in Mediterranean basin was soon after identification of *Leishmania (L. donovani)* in India in the 1900s. Dogs were considered reservoir after the first description by Charles Nicolle in Tunisia (Nicolle and Comte, 1908). *Leishmania infantum* is found throughout the Mediterranean basin. In this region there are nine proven or potential *Phlebotomus* vectors of the subgenus *Larroussius* with two to four present in each country. *Phlebotomus perniciosus* is present all around Mediterranean Basin*; Phlebotomus ariasi* is found from Portugal to Italy and from Morocco

to Tunisia. *P. perfiliewi, P. neglectus, P. tobbi* are found from Italy across the Balkan peninsula to Greece. *P. perfiliewi* is additionally found from Tunisia to Morocco. *P. tobbi* is also present in Turkey and *P. neglectus* in Romania, Slovenia, Turkey and Ukraine. *P. langeroni* is a proven vector in Egypt and found across North Africa and across the Straits of Gibraltar, Spain. *P. longicuspis* has also been found infected in North Africa (From Libya to Morocco and Spain). A vectorial role was not proven for each of these species in each country (Mhaidi et al., 2018; Ready, 2010). Over the last few decades there has been an extension of vector distribution to Northern areas traditionally considered non-endemic. In northern Italy, *P. perniciosus* and *P. neglectus have* expanded to the foot of the Alps with associated *Leishmania* transmission (Bourdeau et al., 2014; Maroli et al., 2013).

Dogs are highly susceptible to *L. infantum*. Canine infection represents both a public health threat and a veterinary problem. The role of dogs in the ecology of *L. infantum* infection has been reinforced by research of infection using serology and microscopy techniques which failed to demonstrate infection in other domestic or wild mammals. The infection in cats was rediscovered in areas where canine leishmaniosis (CanL) is present although a first description of infection made in 1912 associated to the first human case of VL in Algeria (Sergent et al., 1912). Many European epidemiological studies based on serology or PCR have revealed significant canine *Leishmania* infection prevalence often above 25% of tested animals. Cats also suffer from leishmaniosis, which is less severe disease than CanL (Pennisi et al., 2015). The use of molecular tools and sometimes serology helped to detect *Leishmania* in both clinically healthy and seronegative animals. This was done not only on dogs (or cats) but also in a number of other domestic/peridomestic mammal species including rats (*Rattus rattus:* black rat, *Rattus norvegicus: brown* rat)(Zanet et al., 2014), mice (*Mus musculus:* domestic mouse; *Mus spretus* : Algerian mouse), *Apodemus sylvaticus* (European wood mouse), *Eliomys quercinus* (dormouse), *Ctenodactylus gundi* (gundi) and others. The abundance of rodents and their longevity through sand fly season makes them possible candidates for genus *Leishmania* dispersion in both the Old and New World including *L. infantum* (Schenk et al., 2013). Many carnivoran species were found to be infected *L. infantum* including Mustelidae: *Meles meles* (European badger), *Martes martes* (European pine marten) *Martes foina* (stone marten), *Mustela nivalis* (weasel), *Mustela putorius (polecat), Mustela lutreola (European mink), Genetta genetta* (common genet), Herpestidae: *Herpestes ichneumon* (Egyptian Mongoose) (Millan et al., 2014; Sobrino et al., 2008) and in other canids including red fox (*Vulpes vulpes*)(Rioux et al., 1968), jackals (*Canis aureus*) and wolves (*Canis lupus lupus*).

This long list of potential reservoir hosts identified through molecular testing illustrates the frequent and nonspecific infection of wild mammals without proximity to dogs as an indirect source. This also demonstrates that sand flies bite transmits *Leishmania* between a rich diversity of mammals. Frequently positive xenodiagnoses were obtained on apparently healthy animals suggesting long persistence and impact as a reservoir even if an individual parasite load was limited(Gramiccia and Gradoni, 2007). Considering these data, one may hypothesize that sylvatic populations can maintain a permanent parasite circulation in endemic areas without dogs.

The best example of wild fauna as reservoir was illustrated recently in the southwestern Madrid region of Spain. Between 2009 and 2013 human cases increased 20%. Cases were localized around a park where hares and rabbits were abundant. There was no increase in prevalence in dogs or cats while *Leishmania* was detected by PCR in 29% of hares. Xenodiagnosis proved that *P. perniciosus* could be infected by feeding on apparently healthy hares. *Leishmania* sequence homology between hares and human isolates was identical (Gonzalez et al., 2017; Jimenez et al., 2014; Molina et al., 2012). This was the first evidence that hares could be a predominant reservoir of *L. infantum* in Europe, suggesting the existence of a rural/sylvatic transmission cycle linked to the urban cycle and direct causal influence of humans on environmental change. Such human influence could also explain the high variability from low to very high prevalence of infection in red foxes through hunting in many areas and their predation on rabbits/hares.

Non vectorial circulation amongst the numerous infected mammalian hosts only increases the complexity of circulation of *Leishmania* within the reservoir host population. In the future, the comparison of parasite isolates from humans, dogs and wildlife, xenodiagnosis studies in wild carnivores, and the study of other vertebrate taxonomic groups will help determine the current role of European wildlife in the epidemiology of leishmaniosis. While the role as reservoir of wild carnivores has not been fully demonstrated, black rats, wild rabbits and hares might contribute to maintaining *L. infantum* circulation in some areas of southern Europe (Millan et al., 2014). The criteria to define a reservoir have now been verified for many interacting host species (abundance, attractiveness to sand flies, infectiousness to sand flies; evidence of long-term infection at individual or species level) and their categorization as primary, secondary, or accidental reservoir need to be precise and adapted to local ecological and epidemiological conditions independently of the presence or not of dogs. In such context dogs would appear as « sentinel » species with variable contribution to the reservoir of *Leishmania infantum*.

2.2 South America/Brazil

Due to the great ecological diversity presented by the Amazon river basin and other major river systems in South America, a great many species of phlebotomine sand flies have been described and vectorial competence demonstrated for many (Rangel and Lainson, 2009). This ecological diversity resulted in a number of species of parasites identified in human cutaneous lesions belonging to *Leishmania* subgenera *(L. mexicana L.venezuelensis, L. amazonenesis)* or the *Vianna* subgenus *(L. guyanensis, L.panamensis, L. peruviana)* or mucocutaneous cases of leishmaniasis *(L.V. braziliensis).*

For each of them specific wildlife reservoir was identified and for most, apart humans, infection in dogs or cats was also mentioned. These species will not be presented here in detail. *Lutzomyia intermedia* was the first described vector species in the state of Minas Gerais in 1912 (Lainson and Shaw, 1972), and has been shown to have adapted well to peri-domestic environments and to be attracted to dogs and horses, causing infestations in kennels and stables and observation of cutaneous lesions caused by *L. braziliensis* in these domestic animals as well as people (Aguilar et al., 1989; McIntyre et al., 2017; Oliveira-Neto et al., 1988).

The most common vector for *L. infantum chagasi* infection in multiple areas of Brazil and South America is *Lu. longipalpis* (Forattini et al., 1970). This vector species has a broad ability to be infected by *Leishmania* species and as such has been used to demonstrate vector transmission for multiple mammalian host and parasite parings that may not naturally occur (Pech-May et al., 2018). A handful of studies have targeted prevention of sand fly feeding through use of collars and other prevention methods (Kazimoto et al., 2018; Leite et al., 2018; Lopes et al., 2018). The purpose of these studies has been to demonstrate that instead of other means currently subscribed by federal policy in Brazil, particularly dog culling (Costa, 2011; Courtenay et al., 2002; Esch et al., 2012; Moreira et al., 2004; Nunes et al., 2008; Nunes et al., 2010; Reithinger et al., 2004; Seva et al., 2016), prevention of sand fly bites, particularly of the predominant reservoir dogs, would likely have a more positive impact. The role of vaccination in controlling existing infection,(Lopes et al., 2018; Seva et al., 2016; Toepp et al., 2018) and more particularly skin parasite burden, is poorly understood and should be the focus of future studies to establish to what extent vaccination might prevent transmission.

2.3 Indian sub-continent

Phlebotomus argentipes is the only proven vector involved in the transmission of visceral leishmaniasis (VL) caused by *Leishmania donovani* in the Indian subcontinent. Vector control programs using indoor residual spraying (IRS) applied against mosquitoes have also affected sand flies, resulting in declines of VL incidence(Muniaraj, 2014). Although recent IRS campaigns have made considerable progress in India, Nepal and Bangladesh in the reduction of VL, they fell short of the 2015 elimination target and are not currently on track for the new deadline based on the London declaration on neglected tropical disease (signed in 2012) for 2020 (Le Rutte et al., 2017; Le Rutte et al., 2016). The goal for the 2020 version of elimination is defined as less than 1 case of kala-azar in 10,000 people in endemic areas at the block (India) or upazila (Bangladesh) levels. Notably, insecticide resistance is increasingly becoming a problem and threatens the goal of elimination(Coleman et al., 2015).(Coleman et al., 2015). Due to the declining effectiveness of DDT in sand fly control, synthetic pyrethroids are being used as an alternative in the second phase of IRS (WHO, 2015).(WHO, 2015). However, the substantial increase in the use of pyrethroids for vector control will likely lead to increased resistance as it has elsewhere and in other vectors (Fawaz et al., 2016).(Fawaz et al., 2016). Thus, the elimination effort will require careful monitoring of insecticide resistance in field populations of *P. argentipes,* the development of biomarkers that will help to quickly identify resistant populations, and studies to identify which insecticides remain effective for control of vector populations collected across VL endemic areas.

L. donovani infection has long been considered an anthroponotic disease based on studies indicating that high levels of infection within people and indoor dwelling of sand flies with these infected people led to continued infection (Malaviya et al., 2011; Stauch et al., 2011). (Malaviya et al., 2011; Stauch et al., 2011). Since these studies a decade ago, evidence indicates that IRS has altered *P. argentipes* behavior from endophilic (indoor resting) to exophilic (outdoor dwelling)(Cameron et al., 2016; Hasker et al., 2012).(Cameron et al., 2016; Hasker et al., 2012). If this is true, it is probable that sand flies are feeding on animals

found predominantly outdoors. Alternative blood sources for exophilic *P. argentipes* beyond outdoor-sleeping humans may include cattle, goats, dogs, rodents and others. Recent studies of the potential impact of sand fly feeding on other domestic species in Nepal found PCR evidence of infection in cattle, water buffalo and goats(Bhattarai et al., 2010). Similarly, *Leishmania* DNA was detected in one stray dog from a VL-endemic area of Bangladesh (Alam et al., 2013). Furthermore, there are several reports of *L. donovani* infection in sick dogs in Sudan (Shamboul et al., 2009). Based on different resting behaviors of sand flies as a consequence of IRS, sand flies are adapting to other sources of blood meals,(Poche et al., 2018) including cattle, goats, water buffalo, dogs and rodents, and that one or more of these species of animals may emerge as a reservoir important for *L. donovani* transmission within Bihar state.

Studies of live caught sand flies from villages around Muzaffarpur in 2015 identified that 30 % of flies had fed on cattle, and 16% had fed on dogs based on cytochrome c analysis of blood meals (Tiwary et al unpublished data). It is not known to what extent these animals currently serve as a host that can promote or sustain *Leishmania* transmission within the overall local ecology of disease, and what their role(s) will be as elimination goals are reached within Bihar. Xenodiagnosis is well established as the best way to determine the transmissibility of a specific host/reservoir to sand fly spp. and can be applied to investigate the role of non-human reservoirs in the shifting ecology of *L. donovani* transmission in Bihar (Figure 2).

Current Leishmania transmission studies implicate that post-Kala Azar dermal Leishmaniasis (PKDL) as a major source of parasites, perhaps particularly in immunocompromised people (Kamhawi and Serafim, 2017). In areas beyond the Indian subcontinent, it seems that there is a special relationship between canine skin and *Leishmania* parasites(Courtenay et al., 2014), with wide-spread skin parasitemia even without initial sand fly-borne transmission(Schaut et al., 2015). To what extent this unique relationship exists between *L. donovani*-infected dogs, skin parasitemia and transmission to *P. argentipes* is yet to be determined, but studies are underway (Figure 3). It will be critical to establish whether these animals can contribute to the burden of infection for maintenance of elimination efforts (Kamhawi, 2017; Kamhawi and Serafim, 2017). In areas beyond the Indian subcontinent, it seems that there is a special relationship between canine skin and *Leishmania* parasites(Courtenay et al., 2014), with wide-spread skin parasitemia even without initial sand fly borne transmission(Schaut et al., 2015). To what extent this unique relationship exists between *L. donovani*-infected dogs, skin parasitemia and transmission to *P. argentipes* is yet to be determined.

3.0 Conclusions

The intimate relationship between sand fly spp. as the biological vector of *Leishmania* infection drives the extent of infection found in the blood meal sources for these sand flies. Multiple components excreted and secreted during sand fly feeding can augment or otherwise alter the outcome of mammalian *Leishmania* infection. Xenodiagnosis studies of dogs, the predominant reservoir host of *L. infantum* infection indicates that it is skin more than blood parasite burden that predicts transmissibility of any one animal to sand flies, and

therefore its contribution to the infectious pool that could infect people. Current evidence may suggest that dogs and other domestic animals may either control infection or do not have sufficient skin parasitemia to be a source of *L. donovani* to *P. argentipes*. Further xenodiagnosis and characterization of skin parasitemia and understanding the dermatologic immunology that influences transmission in these different hosts is required to more broadly understand which *Leishmania* hosts can be sources and which ones are dead-end hosts.

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Highlights

- Lectin receptor interactions dictate *Leishmania*/sand fly vector competence, with additional factors augmenting or dampening the likelihood of *Leishmania* transmission and spread.
- Traditionally each geographic region was found to have one *Leishmania* vector sand fly species and one reservoir.
- Molecular assays revealed that there are multiple mammalian species infected with *Leishmania*.
- The role of less traditional reservoirs in transmission is often not known due to complexities of xenodiagnosis on sylvatic species and inability of different sand fly species to be colonized.
- Overall multiple mammals are frequent blood meal sources for sand flies in any geographic region which may serve as important reservoir species for *Leishmania* transmission.

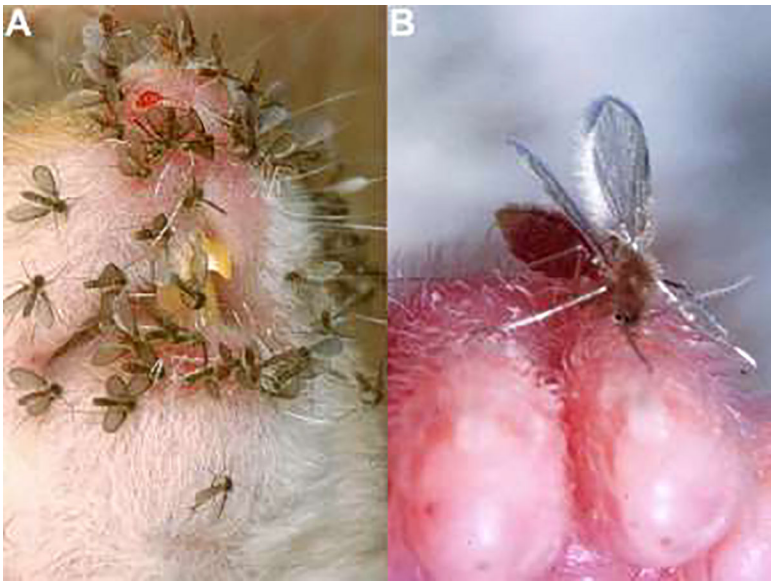

Figure 1.
Sand flies feeding on an anesthetized Syrian golden hamster, A. face and nose, B. foot.

Figure 2.

Field xenodiagnosis of *Rattus rattus*, water buffalo (*Bubalus bubalis)* and goats (*Capra aegagrus hircus*) using *Phlebotomus argentipes* in Bihar state, India.

Figure 3.
Field xenodiagnosis of domestic, but often feral, dogs *(Canis familiaris)* using *Phlebotomus argentipes* in Bihar state, India.