Leishmania and Animal Reservoirs: A Major Challenge for Disease Control

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ABSTRACT

Leishmaniasis, caused by parasitic protozoans of the genus Leishmania, is a neglected tropical disease with significant global health consequences, particularly in regions lacking adequate healthcare infrastructure. The disease, transmitted by infected sandfly vectors, manifests in various clinical forms, ranging from self-healing skin ulcers to potentially fatal visceral infections. Animal reservoirs, including domestic and wild species, play a pivotal role in the perpetuation of Leishmania life cycles, acting as carriers without displaying any symptoms. The intricate interplay between Leishmania parasites, sandfly vectors, humans, and animal reservoirs poses a substantial challenge for effective disease control. The interaction between Leishmania and animal reservoirs exists, which emphasizes the challenges presented by the reservoirs for disease control. The geographical distribution of Leishmaniasis is linked to the presence and activity of animal reservoirs, influenced by environmental, biological, and ecological factors. Challenges in controlling Leishmaniasis via animal reservoirs include identification and monitoring, zoonotic transmission dynamics, resistance to conventional methods, limited therapeutics, heterogeneity among reservoirs, wildlife interactions, and resource constraints. The One Health approach, recognizing the interconnectedness of human, animal, and environmental health, emerges as a comprehensive strategy for addressing the complex challenges of Leishmaniasis. Surveillance and diagnostics for animal reservoirs are crucial components of control strategies, incorporating parasitological, immunological, molecular, and xenodiagnosis techniques. In conclusion, there is urgent need for a multidisciplinary, collaborative strategy to effectively address the challenges posed by animal reservoirs in Leishmaniasis control. From the complexities of surveillance to the risks of zoonotic transmission and the resistance to conventional control measures, it's clear that these reservoirs are not to be underestimated.

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1. INTRODUCTION

Leishmaniasis is a neglected disease of tropical and subtropical regions caused by intracellular parasitic protozoans of the genus *Leishmania* (Torres-Guerrero et al. 2017). Leishmaniasis, a poor man's disease, affects millions of people every year due to its vast geographic spread and varied clinical presentations, especially in areas with poor healthcare infrastructure and resources (Sasidharan and Saudagar 2021). Leishmaniasis is one of the seven most significant tropical diseases, and it poses a severe threat to global health due to its wide range of potentially lethal clinical symptoms. It is a vector-borne disease transmitted to human beings by the bite of an infected female sandfly, mainly *Phlebotomus* spp. (Torres-Guerrero et al. 2017). The parasite replicates after injection into the host's bloodstream, leading to a range of clinical outcomes, from self-healing skin ulcers to potentially fatal visceral infections (Mann et al. 2021).

Animal reservoirs are crucial for many *Leishmania* species to continue their life cycles. Various domestic and wild animals, from dogs and rodents to larger mammals, can serve as reservoirs for *Leishmania* parasites. These animals harbor the parasites without displaying obvious symptoms, contributing to the perpetuation of the disease in the environment (Alemayehu and Alemayehu 2017). The complexity of this leishmaniasis is amplified by the role of animal reservoirs in its transmission cycle, presenting a major challenge for effective disease control strategies. Understanding the interplay between *Leishmania* parasites, sandfly vectors, humans, and animal reservoirs is crucial for designing effective control strategies that target all components of the transmission cycle (Cecílio et al. 2022).

This chapter's aim is to explore the complex interaction between *Leishmania* parasites and animal reservoirs while highlighting the challenges these reservoirs present for disease prevention efforts. It also explores the biology of *Leishmania* parasites, the role of animal reservoirs in the transmission cycle, and the epidemiological impact of reservoir populations. The challenges of controlling animal reservoirs for the management of leishmaniasis will also be covered in this chapter, along with the shortcomings of present therapies and the possibilities for a One Health strategy. Through this exploration, this chapter will shed light on the complexity of Leishmaniasis transmission and inspire collaborative efforts to address this public health challenge from a multidisciplinary perspective.

2. THE BIOLOGY OF *LEISHMANIA*

Leishmania is a vector-borne parasitic disease. Phlebotomine sand flies and 98 species of the genera are responsible for transmitting *Leishmania* parasites through bites. The two proven or potential human leishmaniasis vectors include *Phlebotomus* and *Lutzomyia* (Steverding 2017). This parasite exhibits a digenetic life cycle that alternates between insect vectors and mammalian hosts. The *Leishmania* life cycle is restricted to the sand fly's digestive system outside of the vertebrate host (Dostálová and Volf 2012). When a mammalian host is fed on by an infected female sandfly, promastigote forms of the *Leishmania* parasite are introduced into the host's circulation. The immune cell-type macrophages engulf the promastigotes after they have entered the host. The parasite's intracellular form, amastigotes, develops from promastigotes inside the macrophages. As the amastigotes develop inside the host cells, the cells eventually burst, releasing additional parasites into the circulation. The cycle can be continued by the freshly released amastigotes infecting more macrophages. When an uninfected sandfly bites an infected animal and consumes the amastigote-rich macrophages, the cycle is completed. The amastigotes change back into promastigotes inside the sandfly's gut. When the sandfly feeds again, these promastigotes travel to the proboscis, where they are prepared to infect another mammalian host (Serafim et al. 2021).

Leishmania parasites are remarkably diverse, with over 20 species known to cause various forms of Leishmaniasis. Leishmaniasis exists in three general forms i.e. cutaneous, visceral, and mucosal (Goncalves et al. 2020). Cutaneous leishmaniasis can be caused by *Leishmania major, L. mexicana, L. amazonensis,* or *L. braziliensis* in the arid regions, whereas *L. donovani* causes visceral Leishmaniasis in parts of Africa and Asia (Kbaich et al. 2017, Özbilgin et al. 2017).

Sandflies, as the vectors of *Leishmania* parasites, are influenced by climatic conditions, habitat types, and breeding sites. Changes in these factors can alter the distribution and behavior of sandfly populations, subsequently impacting parasite transmission (Shymanovich et al. 2019). Similarly, there are different animal species that vary in their susceptibility to *Leishmania* infection (Pérez-Cabezas et al. 2019). Some species, such as domestic dogs, may be highly susceptible and serve as effective reservoirs, while others may exhibit resistance to infection (Campino and Maia 2018). There are several other factors that influence the transmission of *Leishmania* parasites among animals and humans which include socioeconomics, climatic, and environmental variables (Valero and Uriate 2020).

3. ANIMAL RESERVOIRS OF LEISHMANIASIS

Leishmaniasis has a strong zoonotic potential, meaning that the disease can be transmitted from animals to humans, as shown in Fig. 1. Zoonotic transmission can result in diverse clinical manifestations in humans, ranging from cutaneous to visceral forms. This zoonotic transmission is influenced by factors such as the species of *Leishmania*, the vector species, and the genetic compatibility between parasites from animal and human hosts (Montaner-Angoiti and Llobat 2023). The implications of zoonotic potential for human health are considerable. Outbreaks among humans can be triggered by increases in reservoir populations or changes in environmental conditions that favor vector proliferation (Baker et al. 2022). Animal reservoirs significantly contribute to the complex epidemiology of Leishmaniasis. Identifying these reservoirs, understanding their roles, and assessing their zoonotic potential are crucial steps in devising effective control strategies (Pal et al. 2022).

Reservoirs are defined as living host that harbor the parasite without exhibiting apparent symptoms of the disease (Roque and Jansen 2014). Understanding the role of the reservoir species in disease transmission is made easier by longitudinal study when paired with ecological and genetic studies (Blanchong et al. 2016). Dogs are among the domesticated animals that serve as the disease's main reservoir hosts. Infected dogs serve as a reservoir for sandflies that bite them, subsequently transmitting the parasite to humans (Campino and Maia 2018). Cats and livestock can also contribute to the reservoir, though their role may be less significant compared to dogs (Maia and Campino 2011). This close proximity between humans and domestic animals increases the risk of zoonotic transmission (Keesing and Ostfeld 2021). Aside from domestic animals, wild animals like wolves, foxes, and jackals have also been connected to diverse areas' reservoirs of pathogens. These species frequently occupy a variety of ecological niches, which helps the disease's global spread (Campino and Maia 2018). These interactions between wild and domestic reservoirs can lead to complex transmission dynamics (Alexander et al. 2012).

4. EPIDEMIOLOGY OF LEISHMANIASIS: FOCUS ON RESERVOIRS

The geographical distribution of Leishmaniasis is intimately tied to the presence and activity of animal reservoirs, which are hosts that harbor the parasite and serve as a source of infection for humans and sandflies (Dvorak et al. 2018; Roque and Jansen 2014). Leishmaniasis is endemic in 98 countries around the world, including parts of Latin America, Africa, Asia, and the Mediterranean (Pal et al. 2022). The presence of reservoir species frequently coincides with the presence of the disease. For instance, canine Leishmaniasis seems to be more common in South America, where dogs are important reservoirs (Alemayehu and Alemayehu 2017). Different *Leishmania* species are linked to particular geographic regions and reservoir hosts. This leads to regional variations in disease prevalence and clinical manifestations (Jagadesh et al. 2021). *Leishmania* infection and transmission rates differ across various animal reservoirs. The capacity of reservoir animals to spread the parasite to sandflies might vary. Some animals may have higher parasitemia, making them more infectious to sandfly vectors. Certain reservoir species may have a stronger attraction for sandfly vectors, leading to higher transmission rates (Bourdeau et al. 2020).

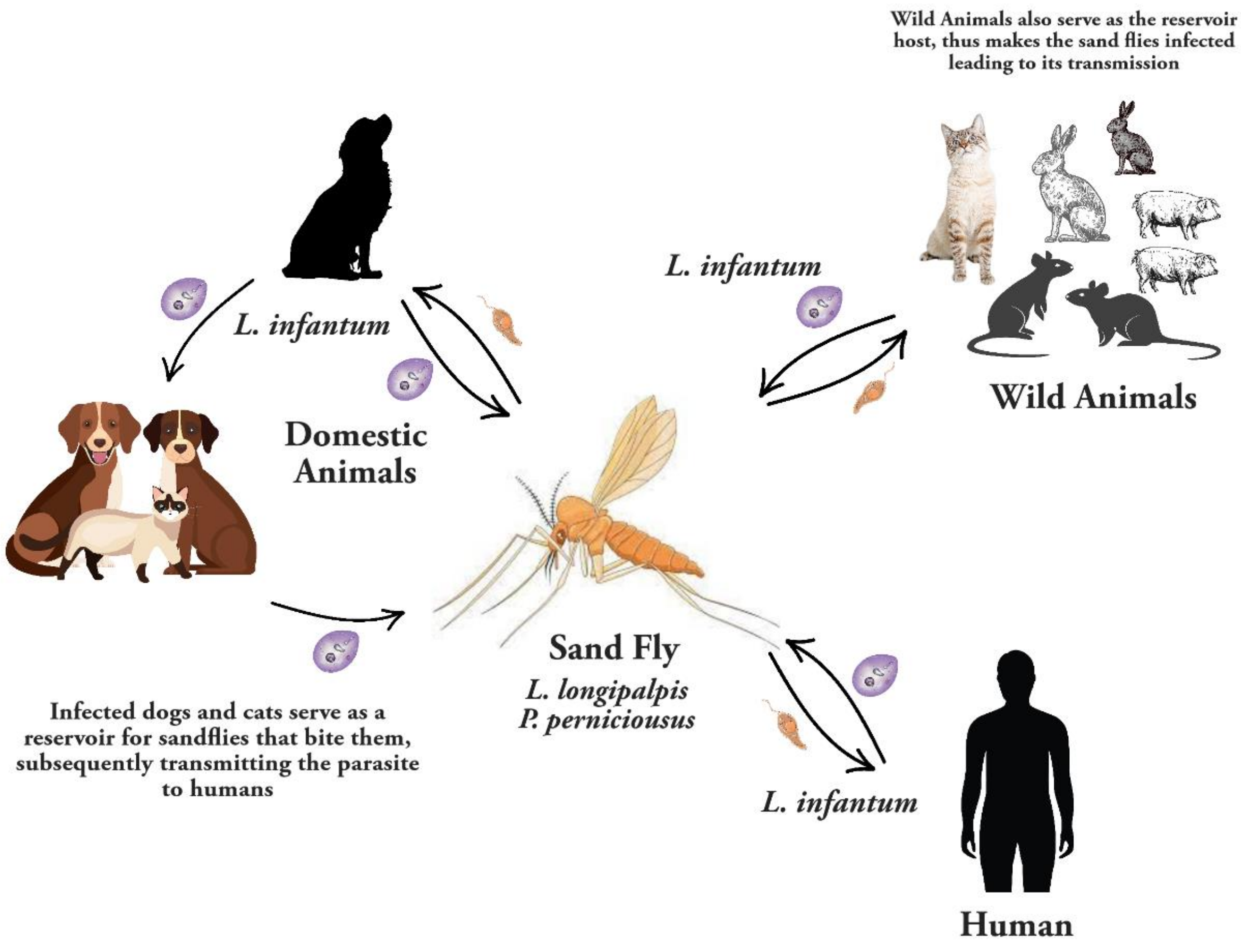

Fig. 1*:* Zoonotic Transmission of Leishmaniasis.

The presence and abundance of animal reservoirs are influenced by environmental, biological, and ecological factors. According to Ghatee et al. (2018), these variables are crucial in determining the composition of animal reservoir populations for leishmaniasis. These variables affect the distribution, abundance, and behavior of the reservoir species and the disease-carrying vectors, which has an effect on the dynamics of the disease's transmission (Eder et al. 2018). The distribution and density of both sandfly vectors and reservoir animals are directly influenced by the local climatic variables, including temperature, humidity, and the amount of vegetation (Ghatee et al. 2018). Changes in climate can alter the range of Leishmaniasis, shifting disease transmission zones (Semenza and Suk 2018). Seasonal changes in temperature and rainfall can also influence both sandfly and reservoir populations, leading to fluctuations in disease transmission rates, often peaking during specific seasons (Karmaoui 2020). Additionally, the seasonal or migratory behavior of some reservoir species can impact the spatial distribution of Leishmaniasis and introduce the disease to new areas (Charrahy et al. 2022). Human activities such as deforestation and urbanization can fragment natural habitats, disrupting the habitats of reservoir species and affecting their population distribution and dynamics. Anthropogenic activities, such as irrigation projects, can create new breeding sites for sandflies, increasing the likelihood of disease transmission, while land use practices that reduce vegetation cover can disrupt sandfly habitats (White and Razgour 2020). The spread of *Leishmania* parasites can be impacted by the degree of biodiversity in a certain habitat. By lowering the frequency of interaction between vulnerable hosts and infected sandflies, high biodiversity can reduce the incidence of leishmaniasis in reservoir populations, while low biodiversity regions may see more concentrated transmission (Kocher et al. 2023). The number of reservoir hosts is intimately related to the ecology of sandfly vectors, particularly their nesting locations and accessibility to blood meals (Dvorak et al. 2018). The range and density of reservoir populations are impacted by changes in sandfly ecology, which can affect disease transmission (Oryan and Akbari 2016).

5. CHALLENGES IN CONTROLLING LEISHMANIASIS VIA ANIMAL RESERVOIRS

Globally, leishmaniasis control has significant challenges. Leishmaniasis is one of the hardest diseases to manage or eradicate since each of its characteristics presents particular challenges (Kamhawi 2017). Some of the challenges posed are;

5.1. IDENTIFICATION AND MONITORING

The identification and monitoring of reservoir populations is one of the major obstacles. Animals do not often exhibit overt symptoms in the same way that humans do, making it difficult to identify infected animals. Reliable surveillance techniques can lessen fatalities and further transmission by identifying, monitoring, and treating reservoirs (Prakash Singh et al. 2016).

5.2. ZOONOTIC TRANSMISSION DYNAMICS

Zoonotic transmission dynamics are the consequence of the intricate interactions between humans and animal reservoirs, which frequently occur in the same habitat (Borlase et al. 2021). This complexity can complicate control efforts, as the disease can cycle between animals and humans, making it challenging to break transmission chains (Cable et al. 2017).

5.3. RESISTANCE TO CONVENTIONAL METHODS

Leishmania parasites are susceptible to developing resistance to traditional controls, including pesticides used to kill sandfly vectors. Moreover, the treatment of infected animals is often less effective than in humans, further complicating control strategies (Alvar and Arana 2018).

5.4. LIMITED THERAPEUTICS OPTIONS

Unlike human Leishmaniasis, there are limited vaccines and treatment options available for animals. Developing effective vaccines and treatments for animals is an ongoing challenge, as it requires consideration of diverse reservoir species (Volpedo et al. 2021).

5.5. HETEROGENEITY OF RESERVOIR

Leishmaniasis-carrying animals come in a vast variety of species, each with its own distinct traits. While certain reservoirs may have high parasite burdens, others could show signs of infection resistance. Tailoring control measures to address this heterogeneity is a challenge (Alemayehu and Alemayehu 2017).

5.6. WILDLIFE INTERACTION

Wildlife can be the source of newly emerging transmissible diseases that impact both humans and cattle. Several wild animals, including foxes, can act as reservoir hosts. In regions where wildlife serves as reservoirs, interactions between domestic animals and wildlife can complicate disease management. A thorough understanding of the ecology and behaviour of animals is necessary to control leishmaniasis in such environments (Hailu et al. 2016).

5.7. RESOURCE CONSTRAINTS

Leishmaniasis is especially prevalent in developing countries. Effective control measures might be hindered by a lack of resources, both financial and logistical, especially in resource-scarce endemic locations. Significant expenditures are needed to coordinate multifaceted treatments including humans, animals, and vectors (Wijerathna et al. 2017).

5.8. ENVIRONMENTAL FACTORS

Environmental changes, such as urbanization and deforestation, might affect disease transmission by changing the habitat distribution of reservoirs and sandfly vectors. Predicting and adapting to these changes is a persistent challenge (White and Razgour 2020).

6. ONE HEALTH APPROACH FOR LEISHMANIASIS

In recognition of the interdependence of human, animal, and environmental health, the One Health method is a comprehensive and team-based strategy (Mackenzie and Jeggo 2019). Examples of effective one-health initiatives include those used to combat the rabies, Ebola, and Zika virus outbreaks (Ryu et al. 2017, Acharya et al. 2020). Potential pandemics have been successfully averted because of this strategy (Kelly et al. 2020). Similarly, the One Health strategy offers a strong foundation for tackling the complex problems brought on by leishmaniasis and its animal reservoirs. By integrating human, animal, and environmental health efforts, this complex disease can better be understood, detected, and controlled, ultimately working towards its elimination and improved public health outcomes (Webster et al. 2016). Leishmaniasis transmission involves a triad of hosts (humans, animals and sandflies) and their shared environment. Early diagnosis of Leishmaniasis outbreaks is made possible by cooperation among human health specialists, veterinary professionals, entomologists, and ecologists. Combining resources and expertise from multiple disciplines optimizes the allocation of limited resources, thereby enhancing the efficiency of control measures (Turkson 2020). Due of the growing impact of humans on the environment, Leishmaniasis is re-emerging in endemic regions and emerging in non-endemic regions. The One Health strategy must be used in order to effectively control the disease, taking into consideration the complexity of the condition (Hong et al. 2020).

7. SURVEILLANCE AND DIAGNOSTICS FOR ANIMAL RESERVOIRS

Surveillance and diagnostics for animal reservoirs are critical components of Leishmaniasis control strategies. Effectively identifying and monitoring reservoir populations are essential for managing the disease's transmission dynamics (Prakash Singh et al. 2016). In spite of recent improvements in diagnostic methods, detecting leishmaniases still poses significant difficulties in the rural regions of endemic nations worldwide. Additionally, identifying the relevant *Leishmania* species is essential for disease management and treatments due to the disease's intricate transmission cycle, which involves several biological entities (Hong et al. 2020). Numerous diagnostic techniques have been developed, with significant differences in their accuracy of diagnosis, including molecular diagnostics, serological approach, and parasitological examination (histopathology, microscopy, and parasite culture) (Thakur et al. 2020).

7.1. PARASITOLOGICAL DIAGNOSES

For diagnosing leishmaniasis, parasitological techniques continue to be the gold standard (de Vries et al. 2015). In order to make a parasitological diagnosis, a suspected case of visceral leishmaniasis is subjected to tissue aspirations from the spleen, bone marrow, lymph nodes, peripheral blood, or skin biopsies/smears from ulcers/lesions. If parasites are present in samples, they can either be immediately observed using optical microscopy or cultivated in the proper culture medium and then viewed under a microscope later (in vitro culture) (WHO 2010). It is also possible to inoculate parasites into laboratory animals such mice, guinea pigs, hamsters, or rats (Ready 2014), although this approach is not regarded as a first method of diagnosis because it takes them several weeks to show signs of being infected with parasite (Thakur et al. 2020). By injecting the parasites into animals that are susceptible and then performing an in vivo culture, it is possible to determine viability of parasite (Hong et al. 2020). It is the most preferred and initial line of diagnostics for identifying the disease. However, the limited sensitivity of parasitological techniques, the need for technical skill to perform the operation, and additional hazards related to the examinations are drawbacks of the strategy (Reithinger 2008).

7.2. IMMUNOLOGICAL DIAGNOSIS

Immunological diagnostic techniques were developed to address the shortcomings of parasitological techniques (Singh and Sundar 2015). These techniques are based on the existence of certain humoral reactions (Elmahallawy et al. 2014). The Leishmanin Skin Test (LST), also known as the Montenegro Skin Test (MST), the Complement Fixation Reaction (CFR), the Direct Agglutination Test (DAT), the Indirect Immunofluorescence Antibody Test (IFAT), various ELISAs, Western blotting, the Immunochromatographic Test (ICT), and the rK39 antigen-based immunochromatographic test are among the available techniques. These immunological tests' sensitivity mostly rely on the assay and its technique, although their specificity is more influenced by the antigen than by the particular serological format (Elmahallawy et al. 2014). Immunological diagnoses provide rather high diagnostic precision, particularly during the acute stage of

Visceral Leishmaniasis. Contrarily, they are not frequently utilized for Cutaneous Leishmaniasis because of their poor sensitivity and erratic specificity, as cutaneous lesions frequently exhibit lower amounts of antibodies (Hong et al. 2020).

7.3. MOLECULAR DIAGNOSTICS

Leishmaniasis may be diagnosed by traditional parasitological and serological methods, but these approaches have certain limitations (de Paiva-Cavalcanti et al. 2015). As a result, molecular approaches have been developed (Tlamcani 2016). Molecular methods are used as a complement to traditional diagnostic procedures as well as a substitute. The practicality, safety, and dependability of molecular instruments is the primary justification for the acceptance of molecular methods in normal laboratories across the world. Although other molecular diagnostic techniques, including pulse-field gel electrophoresis and multilocus enzyme electrophoresis, have been developed, tests based on polymerase chain reactions currently serve as the primary molecular diagnostic tool for practitioners and researchers. (Thakur et al. 2020). In epidemiological studies, pairing PCR with other methods including Restriction Fragment Length Polymorphism (RFLP) analysis and gene sequencing has aided in the confirmation of several species (Wang et al. 2011).

7.4. XENODIAGNOSES

This technique of diagnosis involves exposing the infected lesion or tissues to the phlebotomine vector, then afterwards examining the gut of the vector to check for the presence of *Leishmania* flagellates (Sadlova et al. 2015). In a study by Sadlova et al. (2015), *L. donovani* was administered intradermally to the ear pinna of BALB/c mice. This work shown that even a small number of mouse parasites can result in a huge infection in the vector *Phlebotomus orientalis*, making it an ideal laboratory animal for xenodiagnoses. Although Xenodiagnosis is considerably easier to use than other procedures and has great sensitivity, it is unable to distinguish between various *Leishmania* species. Additionally, it takes a lot of time and is impossible without the insect or animal (Akhoundi et al. 2017).

8. CONCLUSION

In conclusion, it's essential to reflect on the challenges that animal reservoirs pose in efforts to control Leishmaniasis. This chapter's investigation has shown the complex web of elements that contribute to the disease's persistence, emphasizing the crucial part that animal reservoirs play in the dynamics of the disease's transmission. From the complexities of surveillance to the risks of zoonotic transmission and the resistance to conventional control measures, it's clear that these reservoirs are not to be underestimated. In order to properly manage leishmaniasis, they demand consideration, comprehension, and creative techniques. The way forward is a call to action—an urgent call for a multidisciplinary, collaborative strategy. The issue of leishmaniasis cannot be resolved on its own. It requires experts from a range of disciplines, including human health, veterinary medicine, entomology, ecology, and more, to combine their knowledge, resources, and experience. Only by working together will we be able to address the complexities of leishmaniasis. With a deep understanding of the intricate transmission dynamics between animals and humans, precise and context-specific interventions can be crafted. These measures are not only successful in lowering the disease burden, but they also successfully stop the spread of leishmaniasis from animals to people, which is a crucial step on the path to ultimate disease eradication.

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