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Review Article

Leishmaniasis: Complexities and Burden of a Vector-Borne Neglected Tropical Disease

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ABSTRACT

This review examines key dimensions of leishmaniasis, including its epidemiology, transmission dynamics, treatment options, and the major challenges and opportunities for control particularly through integration with other neglected tropical diseases. It highlights the complex interplay of biological, environmental, and socio-economic drivers that sustain transmission and hinder effective response. Although research and interventions have advanced, major barriers remain, notably emerging drug resistance and limited access to quality healthcare, compounded by conflict and environmental change. The review underscores the urgent need for sustained investment, strengthened collaboration, and committed political action to reduce and ultimately eliminate leishmaniasis as a public health threat. Addressing leishmaniasis alongside other neglected tropical diseases is essential to advancing health equity and supporting sustainable development.

Keywords: Drug resistance, Host interaction, Immunoregulatory Mechanism, Promastigotes, Sandfly.

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INTRODUCTION

Neglected tropical diseases are a diverse group of diseases that have historically got less attention than other diseases. Examples are Chagas disease, dengue, chikungunya, leishmaniasis, leprosy, rabies, human African trypanosomiasis and many more. These diseases are very common in the poorest regions of world with low-income populations. Mainly prevalent in tropical and subtropical areas, they affect impoverished, underserved communities.

Leishmaniasis is one of the most neglected tropical diseases worldwide that still stands as a testament to the intersection of poverty, tropical climates and restricted access to healthcare. This disease is caused by protozoan parasites of genus *Leishmania* which is transmitted through the bite of infected sandflies. Historical records can be traced back to regions from the Mediterranean basin to the Indian subcontinent (Torres-Guerrero *et al.*, 2017). However, its prevalence is still mainly seen in the poor areas of the tropics, where poor sanitation, high population density and limited access to disease control are the main contributors to its spread (Steverding, 2017).

This shows a global distribution of leishmaniasis and the following is an analysis of the situation, Leishmaniasis is a protozoan infection that affects communities in four continents globally. The areas with suitable environment for sandfly vectors include Africa, Asia, Latin America and the Mediterranean countries (Clare *et al.*, 2024). This is because different *Leishmania* species and sandfly vectors cause different clinical manifestations and thus make it difficult to come up with control measures. Although it is a major problem in areas of low economic development, the disease has not been given sufficient attention and research, surveillance, and control programs receive inadequate funding. Leishmaniasis is knowledge that is important to understand in order to combat it in affected populations. Along with the health outcomes, the disease has significant socioeconomic effects that sustain the intergenerational adversity in the affected regions. Also, the interface with conflict zones and displacement crises makes the vulnerable groups most prone to the disease, which makes it spread easily (Funna, 2020). Therefore, the fight against leishmaniasis has to be all-encompassing to include not only the specific biomedical aspects of disease control and cure but also the social and economic factors that contribute to its perpetuation.

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Furthermore, the challenge of leishmaniasis does not end with the impact on human health, but also impacts animal hosts and wildlife populations thus sustaining the cycle of transmission. Dogs, rodents and other mammals are the domestic hosts of *Leishmania* parasites and keep them active in the endemic areas and spread over to humans (Tazerji *et al*., 2022). This complex eco-epidemiological relationship points to the importance of One-Health approaches that consider the interlinked health of people, animals, and the environment. Leishmaniasis transmission is prevented and controlled more effectively by tackling the ecological determinants of the transmission and through the collaboration of public health, veterinary medicine and environmental protection it becomes possible to improve the surveillance and control of this Neglected Tropical Disease on humans and animals (Vlassoff *et al*., 2023).

This study may help knowledge dissemination by providing a systematic and integrated summary of a large number of studies. It assists in closing knowledge gaps by offering an overall view of leishmaniasis, which includes epidemiology, symptoms, and other causes. This is important for informing evidence-informed actions and management of limited health resources to where they are most critically needed. Also, the review reveals the extent of the leishmaniasis burden and its effects on vulnerable populations in low-resource settings. Through emphasizing the socio-economic factors that sustain the disease cycle, such as poverty, poor healthcare services and environmental degradation, it points to the need to address these fundamentals. This awareness can accelerate the advocacy and resource mobilization for improving the health care systems, increasing the treatment facilities and prevention measures. Moreover, by specifying its neglected status and the existing inequalities in research funding and interest versus other infectious diseases, it calls for increased investment in research, surveillance, and control. This includes sponsoring work on vaccine development, drug research, and new vector control methods suitable for the various Leishmaniasis endemic areas.

Etiology of parasites and vector-host interactions

Leishmania are protozoan parasites of the genus *Leishmania*, of the family Trypanosomatidae (Akhoundi *et al*., 2016). In terms of their morphology, they are easily recognizable by the presence of a flagellated form which is different from other parasitic protozoans. *Leishmania* has two main forms of the life cycle: promastigotes and amastigotes. Promastigotes are the flagellated form, which is cylindrical and is found in the sandfly vector's intestine, while amastigotes are round to oval in shape and are found in the phagolysosomes of the mammalian host cells (Chang *et al*., 2019). *Leishmania* parasites are classified according to their geographical distribution, clinical manifestations and genetic characteristics. More than 20 *Leishmania* species have been described so far, which differ in their ecology and pathogenicity (Mann *et al*., 2021). The major species of *Leishmania* include *Leishmania donovani, Leishmania infantum* and *Leishmania tropica* which are associated with visceral, cutaneous and mucocutaneous leishmaniasis, respectively. Leishmania taxonomy is still under development, and the new methods that help to understand the genetic profile of these organisms better have revealed a complex taxonomy of *Leishmania*.

The life cycle and the mode of transmission of *Leishmania* parasites are interwoven with the life history of their sandfly vectors and mammalian hosts (Jamal *et al*., 2020). It starts when a female sandfly takes a blood meal which may contain amastigotes from a mammalian host. Amastigotes taken in by the sandfly enter its midgut and change into promastigotes that multiply and move to the front gut to occupy the proboscis. The sandfly's method of feeding spreads promastigotes that are capable of infecting mammalian hosts, thus continuing the infection cycle.

After being taken up by the mammalian host, *Leishmania* parasites subvert a number of cellular and immunological processes to sustain infection and counter host defenses. Promastigotes, when injected into the skin, are taken up by macrophages and change into amastigotes that multiply within the phagolysosomes of the host cell. This intracellular strategy allows *Leishmania* to avoid being recognized by the host immune system and also to subvert host cell signaling to facilitate its growth. Furthermore, *Leishmania* parasites can regulate host immune responses to proinflammatory and immunosuppressive types that are favorable for the parasites' survival (Inbar *et al*., 2017). The growth of amastigotes within cells results in formation of lesions characteristic of cutaneous leishmaniasis or, in the case of visceral leishmaniasis, spread to internal organs. Some species, including *L. braziliensis*, have metastatic spread of parasites to mucous membranes, resulting in mucocutaneous lesions in a small percentage of those infected (Falcão *et al*., 2019).

The dynamics of transmission of *Leishmania* parasites are influenced by factors such as the density of sandfly vectors and their feeding behaviour, susceptibility of the host and the local environment (Figure 1) (Courtenay *et al*., 2017). Transmission is most efficient where sandfly populations are high and where people and reservoir hosts come into contact with sandfly breeding sites (Pareyn *et al*., 2019; Falcão *et al*., 2016). Through this, it is important to know the dynamics of the transmission in order to design effective control strategies that can target the transmission cycles and decrease the burden of leishmaniasis to humans and animals. The pathogenesis of leishmaniasis is complex and the mechanism of the disease depends on the interaction between the parasite virulence factors, host immune responses and parasite specificity to the tissue (Gupta *et al*., 2022). *Leishmania* parasites also possess a number of virulence factors that are involved in the development and maintenance of the infection in the mammalian host organs (Gupta *et al*., 2022). These include surface antigens like Lipophosphoglycan (LPG) and Glycoprotein (gp63) that are involved in parasite adherence to host cells and regulation of host

immune responses. Furthermore, *Leishmania* parasites secrete proteases, lipases, and other enzymes that aid in invasion of tissue, immune evasion and nutrition (Reyes-López *et al*., 2023).

Immune responses of the host play the major role in determining the outcome of *Leishmania* infection and both innate and adaptive immunity are involved in defense (Elmahallawy *et al*., 2021). As primary targets of *Leishmania* infection, macrophages trigger antimicrobial responses like the generation of Reactive Oxygen Species (ROS) and proinflammatory cytokines to check the parasite growth (Basu *et al*., 2019; Kumari *et al*., 2022). However, *Leishmania* parasites have also learned how to evade these immune responses, including inhibition of macrophage activation and induction of anti-inflammatory cytokines that facilitate parasite survival. In chronic infections, the dysregulated immune responses may cause tissue damage, ulceration and dissemination of the parasites to the visceral organs (Costa-da-Silva *et al*., 2022).

Furthermore, the pathogenesis of leishmaniasis is determined by specific tissue interactions of *Leishmania* parasites with host cells in various anatomical sites. Cutaneous leishmaniasis is identified by skin lesions which are due to the multiplication of *Leishmania* parasites in macrophages and other immune cells at the point of contact (Gurel *et al*., 2020). Visceral leishmaniasis is characterized by the spread of the parasites to the internal organs, including the spleen, liver, and bone marrow, which causes systemic inflammation, organ failure, and death if not treated (Veras *et al*., 2023). Mucocutaneous leishmaniasis which is spread of the disease to mucous membranes of the nose, mouth, and throat, is characterized by destructive lesions and is due to metastatic spread of parasites from primary cutaneous lesions (De *et al*., 2021). Therefore, it is crucial to understand the mechanisms of pathogenesis in leishmaniasis in the effort to develop new therapeutic and vaccine options for this tropical disease.

Epidemiology

Leishmaniasis is found worldwide and is particularly rampant in the tropical and subtropical areas of four continents; Africa, Asia, Latin America and some parts of Europe and Middle East. The disease has a spatial pattern and the different *Leishmania* species, sandfly vectors and the clinical manifestations are specific to the endemic foci within these regions. Visceral leishmaniasis is caused by *Leishmania donovani* and is endemic in countries such as Sudan, Ethiopia, Kenya and Somalia in Africa (Scarpini *et al*., 2022). The endemicity of the disease is seen in Asia, especially in India, Bangladesh, Nepal and Iran where different *Leishmania* species cause both cutaneous and visceral leishmaniasis (Thakur *et al*., 2018). The highest burden of cutaneous and mucocutaneous leishmaniasis is seen in the countries of Brazil, Colombia, Peru, and Bolivia (Azami-Conesa *et al*., 2021). These leishmaniasis are caused by *Leishmania braziliensis* and *Leishmania mexicana*, respectively, and continue to be a significant public health problem in these endemic regions despite efforts to control the disease. Other factors that further exacerbate the situation include poverty, poor healthcare systems, and environmental changes. However, the emergence of hybrid and atypical strains of *Leishmania* organisms further illustrates the dynamic nature of *Leishmania* species distribution and thus the value of molecular epidemiology in elucidating transmission patterns and disease prevalence.

Climate change and deforestation are known to increase the sandfly habitats and their abundance thereby expanding their distribution to new areas and increasing transmission. *Leishmania* parasites have also spread to peri-urban and urban areas owing to human migration and urbanization, resulting in the reappearance of leishmaniasis in new settings and posing new challenges to disease control. Furthermore spatio-temporal variations in the disease burden may be attributed to differences in the surveillance systems, healthcare access, and SES. It is crucial to monitor and track these trends in order to inform the appropriate control measures that can be taken to detect outbreaks early on and properly allocate resources in order to reduce the effect of leishmaniasis on people's health.

Vector biology

Sand flies of the phlebotomine subgroup are important in the transmission of *Leishmania* parasites, acting as vectors that transport the pathogen between its mammalian hosts. These small flies are of the family *Psychodidae*, subfamily *Phlebotominae* and are found in the tropical and subtropical areas of the world. Females are bloodsuckers and require blood meals for the production of eggs while males feed on plant juices and nectar.

Sand flies are characterized by their specific habitat selection and feeding habits that are crucial in determining their relationship with the vertebrate hosts and hence the *Leishmania* transmission (Pérez-Cutillas *et al*., 2020). Insects of this kind are found in various ecotypes including forests, caves, burrows, and even houses and prefer specific sites for breeding and shelter. Sand flies are crepuscular or nocturnal feeders, and their activity is highest during the twilight period. The hosts are attracted by sensory stimuli such as heat, carbon dioxide, and skin odours (Coutinho-Abreu *et al*., 2022). When a sand fly approaches a potential host, the female fly takes a number of briefs, intermittent feeds from the host, which may result in the acquisition or transmission of *Leishmania* parasites.

The interactions between sand flies and their mammalian hosts are factors such as availability of hosts, species of hosts and the vector competence. Sand flies are generally opportunistic feeders and feed on a large number of vertebrate hosts including man, his domestic animals and wild animals. However, depending on the local ecological conditions and the vector species, there may be certain preferences for the hosts. Host seeking behaviour is controlled chemically and the attractancy and feeding effectiveness

differ among sand flies (Pinto *et al.*, 2022). Furthermore, the competence of the vector that is the ability of sand flies to support development and transmit parasites varies with species and populations and affects the *Leishmania* transmission within the endemic areas. Environmental factors greatly determine the distribution and abundance of the phlebotomine sand flies and therefore the transmission of leishmaniasis. These include temperature, humidity, rainfall, vegetation cover and land use which directly determine the availability of sand fly breeding places, shelter and hosts (Bates *et al.*, 2015). Sand fly larvae need certain microclimatic conditions and the temperatures of 20°C to 30°C and the humidity of more than 40% are optimal for their development and adult sand flies' life. Changes in climate related to the global warming and climate change can alter the distribution of sand fly vectors and change the disease distribution and create new focuses of transmission (Waitz *et al.*, 2019).

Additionally, changes in land use such as deforestation, urbanization, and expansion of agricultural land can alter the sand fly habitat and affect their population and geographical distribution. Deforestation and habitat destruction and degradation may affect sand fly breeding places and movement and therefore shift vector species composition and organization. Urbanization can lead to suitable conditions for sand fly population growth in the peri-urban and suburban areas and, therefore, increase the risk of disease transmission to humans. Agricultural activities including irrigation and cultivation of crops may lead to more breeding places for sand flies and therefore high vector population and enhanced *Leishmania* transmission. The role of environmental factors in the ecology of sand flies is complex; therefore, the knowledge of their relationships is crucial for the proper design of vector control measures and leishmaniasis control.

Clinical spectrum, immunopathogenesis and host immune response in Leishmaniasis

Leishmaniasis is a spectrum of clinical manifestations which is primarily divided into three main forms according to the involvement of the organism; cutaneous, mucocutaneous and visceral. Cutaneous leishmaniasis is the most frequent form that presents with skin lesions at the site of parasite injection (Scorza *et al.*, 2017). These lesions usually appear as painless papules or nodules which ulcerate to become painful and are followed by scar formation. Mucocutaneous leishmaniasis is a more severe form that produces destructive lesions on the nasal, oral and pharyngeal mucous membranes leading to severe disfigurement and functional impairment (Yadav *et al.*, 2023). Visceral leishmaniasis also referred to as kala-azar is the most dangerous form of the disease characterized by systemic infection and organ damage (Volpedo *et al.*, 2021). It is characterized by spleen, liver and bone marrow involvement and the patient has features of fever, weight loss, hepatosplenomegaly, pancytopenia and if left untreated can be deadly.

The symptoms and severity of the disease depend on several factors, including the species of *Leishmania*, the immunity of the host, and the region where the infection has occurred. Cutaneous leishmaniasis produces localized skin lesions that may subside on their own or become chronic, non-healing ulcers. The severity and duration of cutaneous lesions are diverse; some episodes clear up within a few months while others may persist for several years and cause a lot of suffering. Mucocutaneous leishmaniasis is a chronic disease that affects the mucous membranes, producing symptoms such as blocked nose, bleeding from the nose, difficulty in swallowing, and speech impairment. In the worst case, the mucocutaneous involvement may lead to disfigurement of the face and loss of function, which affects the quality of life greatly. Systemic symptoms of VL (Visceral Leishmaniasis) include fever, weight loss, fatigue, and hepatosplenomegaly, which are manifestations of parasitic spread to other organs. If untreated, visceral leishmaniasis can worsen and cause serious complications such as infection, bleeding, and failure of one or more organs, which can lead to death.

The pathogenesis of leishmaniasis is not well understood and is believed to be due to a combination of factors including the interaction between *Leishmania* parasites and the host immune system (Dos *et al.*, 2019). When the sandfly injects the *Leishmania* parasites into the skin, the first line of defence is innate immune cells, including macrophages, dendritic cells and neutrophils that have a crucial role in the initiation of the host immune response. Among these cells, macrophages are the main target cells for *Leishmania* infection during which the parasites remain inside the phagolysosomes to avoid being recognized by the host immune system. *Leishmania* infection induces a pro and anti-inflammatory cytokines production which determine the fate of the disease. Cell mediated immune responses of the Th1 (T helper 1) type characterized by production of cytokines IFN-γ and TNF-α is typically associated with protection against *Leishmania* and healing of the disease (Samant *et al.*, 2021). On the other hand, Th2 (T helper 2) type responses, which are characterized by the production of cytokines such as IL-4 and IL-10, are associated with susceptibility to the disease and the persistence of the parasites in the host (Mirzaei *et al.*, 2021). Tregs and other immunoregulatory mechanisms are also involved in the regulation of the host immune response to *Leishmania* infection (Ghosh *et al.*, 2021). The balance between pro and anti-inflammatory cytokines and the interplay among different immune cell populations determine the outcome of *Leishmania* infection and the extent of disease and its manifestations. Thus, understanding the immunopathogenesis of leishmaniasis is crucial for the development of new therapeutic and vaccination strategies against this tropical disease.

Advances and limitations in diagnosing leishmaniasis

Leishmaniasis is a vector-borne disease with diverse clinical manifestations; therefore, the diagnosis is based on laboratory and field techniques depending on the type of leishmaniasis and the area of distribution of the disease (Kumari *et al.*, 2021). Sampling of tissues, including scrapings, biopsies, or aspirates from sores or nodes is still widely used today. Another method is the use of light microscopy to visualize *Leishmania* parasites in tissue samples after staining with Giemsa or Wright stains (Garcia *et al.*, 2021). Other than microscopy, the cultures of the parasites in the suitable media can also give positive evidence of infection; however, it is time-consuming and requires experienced personnel and laboratory facilities. PCR assays are sensitive and specific and can detect and quantify the *Leishmania* DNA in clinical samples with high accuracy (Gow *et al.*, 2022). Immunoassays including ELISA and RDTs based on *Leishmania* antigens or antibodies are other strategies that can be used for diagnosis and are particularly useful in areas with limited access to molecular assays (Owen *et al.*, 2021).

The diagnosis of leishmaniasis is not easy; especially in the tropical and subtropical areas, where health care is poor and equipment and personnel are scarce. Microscopy is the most common method, but it has several drawbacks; it is labor-intensive, depends on the experience of the operator, and may be unresponsive, especially at low parasite densities or in co-infections. The culture methods are labor tedious and costly and hence not easily done in the mentioned regions. PCR assays are very sensitive and specific but are expensive and difficult to perform in resource-poor environments because they need sophisticated laboratory equipment. Some disadvantages of immunological diagnostic methods based on ELISA and RDTs are that they are less sensitive and specific and can give false positive results in areas of high *Leishmania* species complexity. In addition, leishmaniasis has many clinical forms, from cutaneous leishmaniasis with chronic ulcers to kala-azar with severe visceral involvement, which makes the diagnosis and the choice of therapy difficult (De *et al.*, 2020).

New diagnostic technologies have the potential to enhance the current methods of leishmaniasis diagnosis in terms of accuracy and availability. Some new techniques include molecular techniques like LAMP and NASBA (Nucleic Acid Sequence-Based Amplification) that are easier to use and more appropriate for field application as PCR alternatives with similar sensitivity and specificity (Becherer *et al.*, 2020). Serological assays using recombinant antigens or synthetic peptides are potentially fast and accurate in detecting the presence of *Leishmania* antibodies, especially in areas where the disease is not commonly seen and the clinician may not have a high level of suspicion (Kühne *et al.*, 2019). Ultrasound, CT (Computed Tomography) and MRI are currently used with increasing frequency in the diagnosis of visceral leishmaniasis, which can help to avoid invasive procedures and assess the involvement of organs and disease progression (De *et al.*, 2020). The combination of molecular, serological, and imaging techniques is potentially suboptimal for improving the accuracy of diagnosis and, thus, the targeting of treatment, which should lead to better patient outcomes and ultimately the reduction of the leishmaniasis burden in endemic areas (Table 1) (Thakur *et al.*, 2020).

Management strategies for leishmaniasis

Managing leishmaniasis calls for different strategies which are dependent on the type of leishmaniasis and its level of severity. Cutaneous leishmaniasis having its own tendency to heal on its own may need topical applications like antimonial creams, cryotherapy, or application of heat in the affected area. In case of more severe or widespread cutaneous lesions, systemic drugs like pentavalent antimonials, sodium stibogluconate or meglumine antimoniate is the first line of treatment but is accompanied by toxicity and increasing resistance to the drugs (Husein-ElAhmed *et al.*, 2020). Other drugs include oral drugs like miltefosine, an alkyl phosphocholine compound, or azole antifungals such as ketoconazole and itraconazole (Andrade-Neto *et al.*, 2021). Mucocutaneous leishmaniasis which has a tendency to involve the mucous membranes in a destructive manner usually needs systemic therapy with pentavalent antimonials accompanied by cryotherapy or intralesional injection of antimonials or amphotericin B (Aflatoonian *et al.*, 2016). Visceral leishmaniasis, the most dangerous manifestation of the disease, requires immediate and strong therapy to avoid death. The first-line therapies are parenteral antimonials, liposomal amphotericin B, or oral miltefosine, and these are often used in combination to increase effectiveness and prevent the development of resistance to drugs (Monge-Maillo *et al.*, 2018; Sundar *et al.*, 2019; Vakil *et al.*, 2015).

Along with the specific anti-leishmanial therapies, supportive care is important in the management of symptoms and the overall health of the patient with leishmaniasis. Symptomatic treatment can include pain medications, wound dressing, and nutrition support to help with pain and improve healing especially in cutaneous and mucocutaneous leishmaniasis. It is crucial to monitor and manage treatment complications to reduce morbidity and enhance treatment adherence. Tracking vital signs, lab values, and EKGs (Electrocardiograms) can assist with the identification and treatment of drug-related toxicities shortly (Mhatre *et al.*, 2024). Also, the psychosocial and mental health care is crucial for the patients with disfiguring lesions or chronic infections and is an essential component of the patient care (Bamorovat *et al.*, 2023). A multidisciplinary strategy including dermatologists, infectious disease specialists, tropical medicine experts, and mental health care gives the best results and improves the quality of life of people with leishmaniasis. Thus, healthcare workers can offer an all-encompassing and patient-centered care

for leishmaniasis with consideration of the disease itself and the patient's care needs.

Vector management, surveillance and community engagement for leishmaniasis control

Vector control is very efficient in the control of leishmaniasis through the control of sand flies and breaking the parasite's life cycle. Several strategies have been adopted for sand fly control including environmental management, insecticide application and biological control strategies (Bates *et al*., 2015). Environmental management is changing or removing factors that encourage sand fly breeding such as still water and organic matter. This may involve changing the habitat, managing the waste and improving the water flow to minimize the availability of breeding places. Insecticide application through IRS (Indoor Residual Spraying) or ITNs (Insecticide-treated bed nets) affects the adult sand flies and limits their population and transmission (Kumar *et al*., 2017; Garlapati *et al*., 2021). Also, larvicidal treatments, which are applications made to the breeding places, can eliminate sand fly larvae (Balaska *et al*., 2021). Biological control strategies including the use of larvivorous fish or microbial control of sand fly larvae are environmentally friendly than the use of chemicals (Rawani, 2023). Thus, implementation of different control measures simultaneously can increase the effectiveness and the duration of effectiveness in the control of sand flies and leishmaniasis.

It is important to have effective case detection and surveillance in leishmaniasis control programs so as to determine the extent of the disease, detect trends, find outbreaks and, hence, inform better focused control efforts (Ferreira *et al*., 2022). Passive case detection is a method where health facilities are expected to notify public health officials of the leishmaniasis cases they have diagnosed (Dial *et al*., 2021). An example of active case detection includes door to door surveys, mobile clinics and community health workers (Rahi *et al*., 2022). This approach is useful in the detection of asymptomatic or subclinical cases that may not be detected in the normal course of disease management and can lead to further spread of the disease. Serological and molecular assays in conjunction with clinical evaluation help in accurate case definition and species differentiation in order to proceed with the right treatment and control measures. Moreover, entomological surveillance entails observing sand fly prevalence, exposure rates and vector competence to determine the risk of transmission and recommend vector control measures (Salomon *et al*., 2022). The use of epidemiological, clinical and entomological surveillance data provides a better understanding of leishmaniasis transmission and is used in the formulation of prevention and control strategies.

Leishmaniasis control programs rely heavily on the concept of community engagement and health education in order to involve the community, create awareness and change behaviour. Community members are involved in vector control activities such as environmental clean-up or larval source management which makes people become active in their health and the environment to find long-term solutions for sand fly breeding areas. Health education campaigns conducted through community meetings, schools, and media networks, provide knowledge on the disease, its mode of transmission, prevention and cure, thereby changing behaviour and encouraging people to avoid exposure and seek early treatment. Leishmaniasis control programs that adopt an integrated approach with vector control, case detection and health promotion are more likely to be effective in the control of leishmaniasis than focus on either the human or vector populations. Thus, leveraging the role of healthcare providers, researchers, policymakers, and other community leaders, integrated control programs can be optimized to achieve the greatest impact and greatest cost savings and duration of leishmaniasis control.

Zoonotic/anthroponotic transmission

Leishmaniasis has a complex life cycle of transmission through zoonotic and anthroponotic cycles which depend on the *Leishmania* species, sand fly vectors and reservoir hosts. In the zoonotic cycle, animals including wild or domestic are the host of *Leishmania* parasites and thus maintain the cycle in the sylvatic or peridomestic cycle. The *Leishmania* parasites can infect mammals, including rodents, canids and marsupials and help in the cycle of transmission of the disease (Brandão *et al*., 2020). Sand flies pick the infection from the blood of the infected reservoir hosts and then transfer the parasite to humans during blood meal. Zoonotic leishmaniasis is usually a disease of the rural or sylvatic cycle where people's activities bring them into contact with infected vectors and hosts (Kushwaha *et al*., 2022). By contrast, anthroponotic cycles are direct cyclic transmission of *Leishmania* parasites from man to man and man is the host and source of the parasite.

Hosts and domestic animals are very important in the transmission of leishmaniasis because they act as hosts of *Leishmania* parasites and help in the multiplication of the parasites. In the zoonotic cycles, the hosts of rodents, canids and other wild or domestic animals keep the parasite in the wildlife or peridomestic cycling and transmit the parasite to sand flies. Dogs are well known to act as domestic hosts for some *Leishmania* species including *L. infantum* the causative agent of visceral leishmaniasis (Medkour *et al*., 2019). Infected dogs may have no symptoms or may have clinical signs of the disease and, therefore, act as a source of sand fly infection and spread of the disease to humans. Moreover, other domestic animals like livestock can also be infected and pass the infection to sand flies but they are not very important in the overall transmission. Measures that have been recommended for the control of reservoir hosts and domestic animals include vector control, vaccination and treatment of infected animals, and these are important in the control of leishmaniasis and the break of transmission cycles. Further, changes in people's habits

such as urbanization, deforestation and climate change affect the prevalence of zoonotic transmission by altering the distribution, density and behaviour of sand flies, their hosts and people.

Challenges in leishmaniasis control

The ineffective use of drugs is a major problem in the control of leishmaniasis and affects the desired results. This paper has also shown that there is resistance to the first-line drugs like pentavalent antimonials and miltefosine in numerous foci. This has limited the choices for treatment and hence the need to consider other therapies (Ponte-Sucre *et al.*, 2017). Mechanisms of drug resistance in *Leishmania* parasites include changing the parasite's sensitivity to the drug through changing the way the drug is taken up, metabolized or binds to its target, and increased shedding of the drug from the parasite cells. Many side effects of leishmaniasis treatments include cardiotoxicity, hepatotoxicity, nephrotoxicity and gastrointestinal toxicity that make management difficult and may require dose alteration or treatment cessation (Roatt *et al.*, 2020). Moreover, genetic mutations and phenotypic alterations may lead to multi-drug resistance, which makes it difficult to select an appropriate treatment regimen and require the use of combination therapy to overcome the developed resistance (Sundar *et al.*, 2017). It is important to note that treatment failures may be associated with suboptimal dosing, incomplete treatment courses, non-compliance, or underlying immunosuppression, thus stressing on the need to follow the treatment guidelines and to closely watch the treatment effects. The formation of new drugs including the discovery of new drugs and the assessment of drugs already in the market is crucial in the fight against drug resistance and treatment of leishmaniasis (Paliwal *et al.*, 2021).

Health care services and diagnostic equipment are generally not easily accessible in the endemic areas which further worsens the leishmaniasis prevalence and delays the diagnosis and treatment. In many resources constrained situations, the health care infrastructure is poor and there are shortages of personnel, laboratories and essential drugs. This means that many people who are affected do not have access to the tests such as microscopy, culture or molecular assays that are used to confirm the disease, thereby leading to failure in the beginning of treatment. In addition, the costs of the diagnostic tests and treatments may be unfeasible for the patients, especially for those from low-income households living in the informal settlements. Point-of-care diagnostic tools like RDTs (Rapid Diagnostic Tests) or LAMP (Loop-mediated isothermal amplification) assays are promising strategies for decentralized testing and early case detection in the remote or poorly accessed areas. Expanding access to health care, enhancing abilities of health systems to provide quality essential health services especially diagnostic and treatment services, and implementing community-based health care delivery systems are important steps towards the prevention and control of leishmaniasis incidence in the affected regions. Leishmaniasis transmission dynamics are worsened by conflict, displacement, and environmental changes, which increase the risk of disease and make control difficult (Grifferty *et al.*, 2021). Conflict and instability affect health care facilities, move people, and generate conditions that foster the spread of disease,

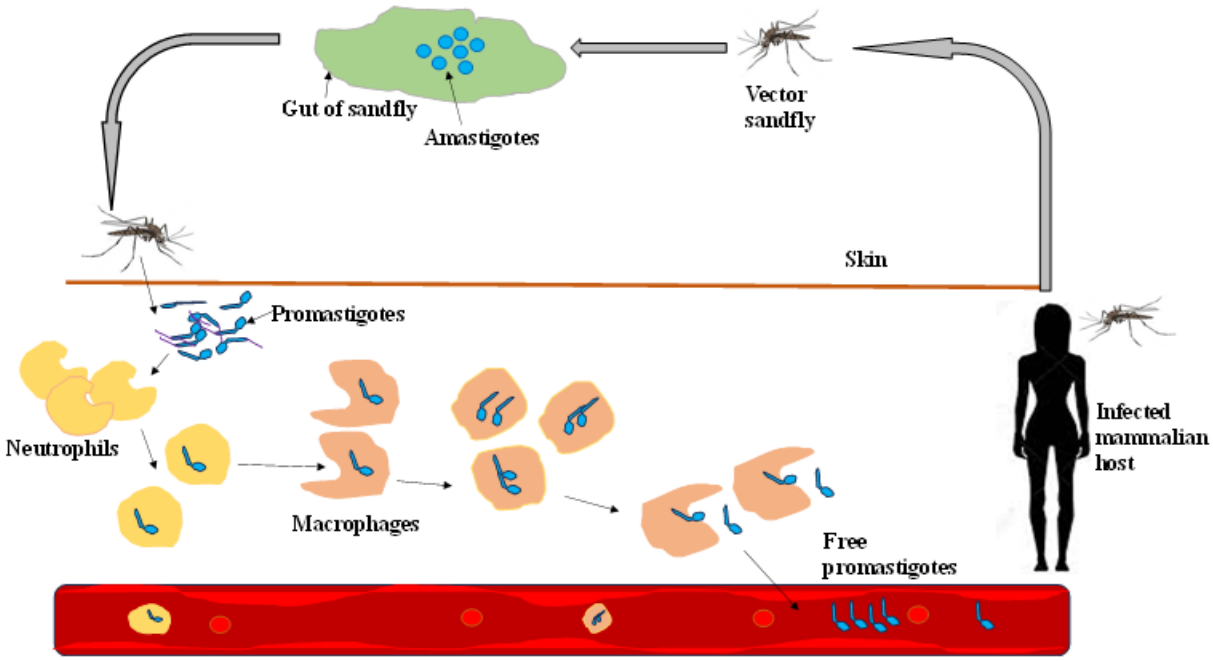

Figure 1: Displays components of sandfly saliva, bacteria, and parasites entering the skin, attracting neutrophils, and the survival of parasites within macrophages.

Table 1: Innovations and challenges in diagnosing leishmaniasis (include Molecular Diagnostics, Serological Assays, RDTs, Culture/Microscopy, and Imaging).

Diagnostic Method	Description	Advantages	Challenges	Examples of Use	References
Molecular Diagnostics	Utilizes PCR or other molecular techniques	High sensitivity and specificity	Requires specialized equipment and training	Detection of *Leishmania* DNA in clinical samples	(Gow *et al.*, 2022)
Serological Assays	Detects antibodies against *Leishmania* antigens	Non-invasive, can detect past exposure	Limited sensitivity in certain populations	Screening of at-risk populations for exposure	(Vijayakumar *et al.*, 2024)
Rapid Diagnostic Tests	Immunochromatographic tests for antigen detection	Simple, rapid results	Variable sensitivity and specificity	Point-of-care testing in resource-limited settings	(Chakraborty *et al.*, 2024)
Culture and Microscopy	Parasite isolation and visualization	Definitive diagnosis, species identification	Labor-intensive, time-consuming	Confirming diagnosis in research settings	(Basu *et al.*, 2021)
Imaging Techniques	X-rays, ultrasound, and MRI (Magnetic resonance imaging) for tissue visualization	Non-invasive, assesses disease extent	Limited availability in endemic areas	Assessing organ involvement in visceral leishmaniasis	(Matcuk *et al.*, 2024)

including high population density, poor sanitation, and restricted health care access. Leishmaniasis is a disease that affects displaced populations, including refugees and IDPs (Internally Displaced Persons), because they have poor living conditions, no access to clean water and sanitation, and limited health care. Changes in the environment such as deforestation, urbanization, and climate variability affect the vector habitats, host distributions, and transmission patterns, resulting in changes in the disease endemic and appearance of new focuses. Warmer temperatures, changed precipitation patterns, and extreme weather events can change vector numbers, behaviour, and pathogen development rates, leading to increased disease transmission in areas that were previously non endemic for the disease (Soni *et al.*, 2022). The impact of conflict, displacement, and environmental changes on leishmaniasis can only be addressed through multi sectoral strategies that combine humanitarian assistance, public health measures, and sustainable development approaches, with emphasis on enhancing health systems, standard living, and surveillance and control of disease.

Recent advances in Leishmaniasis study

Recent research efforts in leishmaniasis have led to the development of new drugs and vaccine candidates which are a significant advancement towards better prevention and treatment of this neglected tropical disease. In the drug development domain, the researchers have focused on finding new drug targets and finding new uses for existing drugs to address the problem of drug resistance. These include high-throughput screening assays, target-based drug design, and structure-activity relationship studies that have helped in the identification of lead compounds with high anti-leishmanial activity (Gopu *et al.*, 2023). These efforts have resulted in the identification of new chemical entities that act on parasite enzymes such as kinases, proteases and metabolic processes as well as known drugs with anti-parasitic activity (Imran *et al.*, 2022; Gupta *et al.*, 2023). Moreover, nanotechnology-based drug delivery systems including liposomes, nanoparticles and micelles are novel drug delivery systems that can be used to improve the solubility, stability and bioavailability of drugs to improve the therapeutic effect and decrease the side effects (Abpeikar *et al.*, 2023). Furthermore, leishmaniasis treatment by combination therapies which include synergistic drug combinations or drug repurposing has been found to be effective in the management of drug resistance and improve the overall treatment results (Kumari *et al.*, 2021).

Vaccines are also improving in leishmaniasis, both prophylactic and therapeutic, in an effort to create better vaccines that will help the immune system fight the disease. Preventive vaccines that are administered before the contact with the pathogen with the aim of inducing long term immunity and avoiding initial infection are *Leishmania* antigen based or whole parasite vaccines which may be live attenuated or killed (Solana *et al.*, 2022). The recombinant protein subunit vaccines, DNA vaccines and viral vector-based vaccines are some of the candidates currently being explored and many of them have shown potential in preclinical and early-stage clinical trials (Duthie *et al.*, 2022). Therapeutic vaccines that are used to enhance the immune system and support the elimination of the disease can be used as adjunctive treatment for people

with an active disease. These vaccines are designed to modify the host immune response, improve antigen presentation and induce effector T cell responses against *Leishmania* parasites. Despite the current challenges in vaccine formulations, adjuvant selection and immunization schedules, the current advances in vaccine technology, immunology and adjuvant development are promising for the development of safe and efficacious vaccines against leishmaniasis. There is therefore the need for further collaboration between the academia, industry and public health agencies to fast track the implementation of these research findings into practical solutions to prevent and control leishmaniasis worldwide.

Genomics and molecular epidemiology of parasites and their role in understanding their diversity and transmission dynamics of leishmaniasis have changed the previous concepts about this complicated disease (Santi *et al*., 2022). Genetic studies based on genomic data have given unique information on the genetic structure, virulence, drug resistance, and host-parasite interactions of *Leishmania* parasites. A large number of clinical isolates from different geographical regions have been sequenced fully to reveal a high level of genetic diversity within *Leishmania* species, in their adaptation to various ecological habitats and host systems. Comparative genomic analyses have been used to detect genetic determinants that are specific to a given species for virulence, tissue tropism, and drug sensitivity which may help in the development of diagnostic and therapeutic measures for the control of the disease (Talimi *et al*., 2024). Moreover, population genomic analyses including GWAS (Genome-Wide Association Studies) and phylogenetic analysis have helped in understanding the genetic determinants of parasite adaptation, transmission and disease epidemiology and, therefore, the identification of high-risk populations and transmission foci.

Epidemiology molecular complements genomic analyses by offering information on the spread and transmission of *Leishmania* parasites in humans and animals (Pal *et al*., 2022). This section discusses the application of PCR (Polymerase Chain Reaction), DNA sequencing and microsatellite genotyping in the characterization of parasite strains and their distribution in the focus areas. The terms used in this article for molecular typing techniques, including Multilocus Sequence Typing (MLST) and Multilocus Microsatellite Typing (MLMT), describe the phenotypic markers that enable the distinction of parasite genotypes and the description of transmission networks. Outbreak investigation and disease surveillance require the knowledge of the movement of the parasite strains and the sources of infection, and thus, molecular epidemiology helps in this regard. Furthermore, as molecular markers of drug resistance, mutations in the target genes or in the gene expression profiles allow for the detection of drug resistance patterns and, therefore, the implementation of evidence-based treatment approaches. The role of genomics and molecular epidemiology has been revisited to understand the Leishmaniasis transmission dynamics as a complex interplay of parasite genetics, vector biology, host immunity, and the environment. These approaches are, therefore, used to inform the development of new, more efficient control strategies, including vector control interventions, surveillance programs, and targeted treatment regimens, based on the understanding of the factors that control parasite diversity and transmission. Leishmaniasis is a devastating disease, and with the advancement of genomic technologies and their availability for leishmaniasis research, these hold a great promise to eliminate this disease.

These opportunities for combining leishmaniasis control with other NTD initiatives may be a promising way to improve the effectiveness and efficiency of public health interventions, use resources to the maximum, and tackle the interrelated issues that affect people in the affected communities. Several other NTDs including lymphatic filariasis, soil transmitted helminthiasis, schistosomiasis and Chagas disease, among others have geographical distributions and risk factors that greatly overlap with those of leishmaniasis (Chimfwembe *et al*., 2024). The consequences of co-endemicity of these diseases are that the at-risk populations are usually overlapping and the environmental determinants are shared, which makes integrated control strategies not only feasible but also advantageous. The benefits of integrating leishmaniasis control with existing NTD programs are seemed to be streamlined service delivery, cost savings and better health outcomes. By using the existing infrastructure such as community health platforms, diagnostic facilities, and treatment programs, integration can enhance the coverage and delivery of health care interventions in resource constrained settings. Co-administration of interventions, including MDA (Mass Drug Administration) campaigns or vector control measures, can help optimize the use of resources and increase the overall impact in reducing the disease burden (Fimbo *et al*., 2024).

Furthermore, integration makes it possible to develop integrated strategies for disease control, fighting the organizational causes and mechanisms of the spread of several NTDs at the same time. For instance, measures that are directed towards the control of vector populations such as the use of insecticide treated bed nets or indoor residual spraying can prevent the spread of many vectors borne diseases at the same time including leishmaniasis, malaria and dengue fever (Montenegro-Quiñonez *et al*., 2024). In the same way, community interventions aimed at improving Water, Sanitation and Hygiene (WASH) can prevent the spread of sTHs and certain forms of leishmaniasis (World Health Organization, 2022). Furthermore, the integrated management of NTDs (Neglected Tropical Diseases) contributes to the development of integrated and participatory approaches to health, which involve the combination of different interventions and partners to address the determinants of health and promote health equity. This way, it is possible to share knowledge, build capacity and

advocate for the continued funding of NTD (Neglected Tropical Diseases) control and elimination efforts across different sectors. However, the integration of leishmaniasis control into other NTD programs needs to be approached with caution, and stakeholders should be involved in the process, and the strategies adapted to the local epidemiological and socio-economic context. Important aspects include synchronization of programmatic actions, the establishment of unified surveillance and evaluation tools, and the coordination of funding sources to support integrated strategies. However, community engagement, social organisation and health promotion are vital aspects of integrated NTD control strategies, which empower communities to manage their health.

FUTURE DIRECTIONS

To fight leishmaniasis more effectively, we need to move from current control approaches to precision public health strategies that focus on local transmission patterns. Improving measurement is essential, which means building better surveillance systems that combine human case data with information about sand flies and animal reservoirs. This will help address under-reporting and hidden cases. New diagnostic tools should be reliable and easy to use in remote areas, such as point-of-care tests and biomarkers to confirm whether treatment is working. We also need targeted solutions for managing reservoir states, such as Post-Kala-Azar Dermal Leishmaniasis (PKDL). This includes gathering better data on how infectious these cases are, improving case-finding methods, and developing safer treatments. For vaccines, it is important to define what protection means and ensure they are relevant to local needs. This broad approach supports the WHO roadmap for neglected tropical diseases and encourages countries to take the lead and be accountable.

CONCLUSION

Leishmaniasis has to be addressed with continued investment and effort for it to be eliminated as a public health issue. Despite improvements in knowledge of disease patterns, some hurdles remain, including drug resistance, poor healthcare seeking, and ecosystem factors. Research, multisectoral collaboration, and political will must still be invested in and maintained to continue to implement integrated control strategies and to mobilize resources. This is not only the right thing to do from a moral point of view, but also the smart thing to do from the point of view of health equity and sustainable development: This is why we prioritize neglected tropical diseases on global health agendas. By partnering with one another, by looking at the big picture and by tackling the root causes of the disease, we can fast track the improvement of the Sustainable Development Goals and actually create a world without these neglected tropical diseases.

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ABBREVIATIONS

LPG: Lipophosphoglycan; **Gp63:** Glycoprotein; **ROS:** Reactive oxygen species; **MLST:** Multilocus sequence typing; **MLMT:** Multilocus microsatellite typing; **WASH:** Water sanitation and hygiene; **GWAS:** Genome-Wide Association Studies; **NTD:** Neglected Tropical Diseases; **PCR:** Polymerase Chain Reaction; **RDTs:** Rapid diagnostic tests; **LAMP:** Loop-mediated isothermal amplification; **IRS:** Indoor residual spraying; **ITNs:** Insecticide-treated bed nets; **MRI:** Magnetic resonance imaging; **NASBA:** Nucleic acid sequence-based amplification; **CT:** Computed Tomography; **RH:** Running Head; **VL:** Visceral Leishmaniasis; **SES:** Socioeconomic Status; **IDPs:** Internally Displaced Persons; **EKGs:** Electrocardiograms; **Th1:** T helper 1; **Th2:** T helper 2; **MDA:** Mass Drug Administration; **PKDL:** Post-kala-azar dermal leishmaniasis; **ELISA:** Enzyme-linked immunosorbent assay; **STHs:** Soil-transmitted helminthiasis; **IFN-γ:** Interferon-gamma; **TNF-α:** Tumor Necrosis Factor-alpha; **IL-4:** Interleukin-4; **IL-10:** Interleukin-10; **Tregs:** Regulatory T cells.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Mohammed Tarique conceived and supervised the study and drafted the manuscript. Mohiuddin Khan Warsi and Mohd Imtiaz Nawaz contributed to data analysis, and interpretation. Osama Ali Almuzaini and Mahjabeen Rahmani assisted in literature review, and manuscript editing. Mohammad Azhar Kamal critically reviewed, and approved the final manuscript. All authors read and approved the final version.

GENERATIVE AI STATEMENT

The author declares that Generative AI (Artificial Intelligence) tools, including, Grammarly, and QuillBot, was used to enhance the language and clarity of this work. I take full responsibility for the accuracy and integrity of the content.

SUMMARY

Leishmaniasis remains a severe public health issue that needs ongoing investment and collaboration. Challenges like drug resistance, determinate access to care, and environmental factors indicate why research and collaboration are still needed.

Addressing neglected tropical diseases can improve health equity and support sustainable development, moving us closer to eliminating them.

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