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# Leishmaniasis: A Review of Transmission, Pathogenesis and Diagnosis

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**Abstract:** *Leishmania* is an intracellular protozoan, belonging to the family Trypanosomatidae, documented across over 90 countries in the Middle East, Asia, South America along with Africa. Humans become infected with the *Leishmania* parasite through two source zoonotic source, where wild and domestic animals are important hosts and anthroponotic sources, in which humans act as the main hos of infection transmission. The sand fly is one of the most important vectors of the parasite, with 98 species of this genus recorded as being responsible for transmitting the disease, two of these species, *Phlebotomus* and *Lutzomyia*, have been confirmed to transmit the disease to humans. Approximately 53 species of the genus *Leishmania* was documented in various regions of the world, 14 species of *Leishmania* are transmitted from animals to humans. The severity of the leishmaniasis is affected by the parasite strain as well as efficiency of the hosts immune response, the infection is often asymptomatic, but in some cases it may develop into severe clinical manifestation that can be fatal if not treated appropriately. The Th1 response is a crucial factor in disease control, with both IFN-y and TNF-$\alpha$ stimulating macrophages, giving rise to parasite elimination or reduced replication.

**Keywords:** Leishmaniasis, Life cycle, *L. donovani, L. infantum*

## Introduction

*Leishmania* is an intracellular protozoan that causes leishmaniasis, the infection is transmitted when an infected sand flies fed on the blood of people [1], the gnus *Leishmania* includes 30 confirmed species, but 10 of these are considered important from a medical and veterinary perspective [2]. Three main types have been identified of *Leishmania*, the first type is called cutaneous leishmaniasis (CL) caused by a group of Leishmania species, *Leishmania tropica*, *Leishmania mexicana* and *Leishmania major*, second type is called visceral leishmaniasis (VL) the pathogen is *Leishmania donovani* and *Leishmania infantum* and the third type is known as mucocutaneous Leishmaniasis (MCL) associated with *Leishmania braziliensis* [3, 4].

Humans are infected with leishmaniasis through two main sources, zoonotic source, wild animals are an important reservoir host for the disease and domestic animals, anthroponotic source, where humans considered the major source of infection with Leishmaniasis [5], an estimated 350 million persons worldwide are susceptible to contracting Leishmaniasis, with an occurrence rate of between 0.7 and 1.2 million infection per year for CL, along with to about 0.2- 0.4 million infection with (syn. *L. chagasi*), which include different mammals species including dogs and human [6,7], dogs are infected with *L. infantum*, as dogs are main host for the parasite, invades internal viscera, include: bone marrow, liver and spleen, causing canine leishmaniasis, which is considered a serious systemic disease recorded across over 70 countries and also found in the South America and Mediterranean [7,8], in addition, *L. infantum* has been recorded in may mammalian hosts including cats, horses, red foxes, wolves and badgers [9,10,11].

## Life cycle

The biological life cycle of *Leishmania* sp. parasite consists of two primary main stage, amastigote and promastigote, the promastigote stage (Fig. 1) has a flagellum that enables it to move and reach the intestine of the sand fly [12].

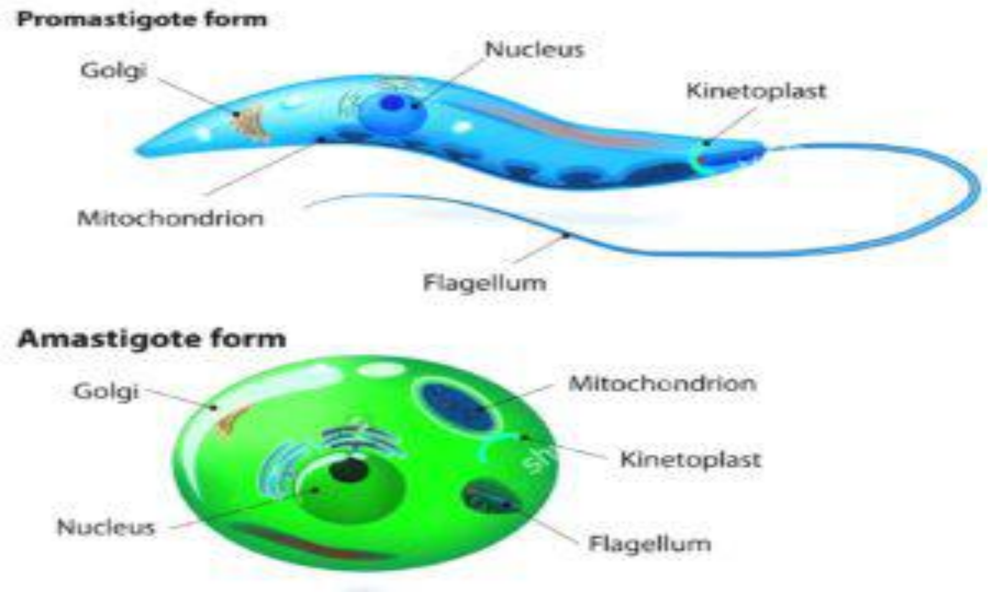

**Figure 1.** Morphological form for promastigote and amastigote [13].

According to the species of *Leishmania* parasaite, the biological cycle takes from 4-18 days inside the vector. The life cycle begins with the promastigote stage, which is a flagellated structure ranging in size from 12 to 20 μm, this stage is found in arthropods especially *Diptera*, which act as vectors of infection, as they ingest the parasite when they feed on the blood of vertebrate host [14]. As sandfly feeds, the transmission of the *Leishmania* parasite begins. It is the promastigote stage, equipped with a flagellum, which injects the parasite into the host skin outside the cell and is then engulfed by macrophages, the body's primary defense mechanism [15]. Within phagocytic cells, the ingested particles are digested, transforming the parasite from its flagellated form to a non-flagellated form (amastigotes), which is the amastigotes capable of replicative [16].

The biological cycle of all species in this genus is similar, with the amstigote reproducing within vertebrate host cells alternating with the promastigote stage, which grows and reproduces in the digestive tract of the insect vector. Sandflies, particularly those of genera *Phlebotomus* and *Lutzomya*, become infected with the parasite while feeding on infected animal or human reservoir. During the bite, the fly ingest blood and tissue containing the amastigotes within phagocytic cells, experimental studies have shown that natural vectors are highly susceptible to infection, even a single parasite or to may be enough to start an infection [17], species living in subtropical regions go through all stage of their life cycles in the warmer period, sandflies activity is associated with the nighttime period in a stealthy manner, often making it difficult for their prey to notice or detect their presence [18].

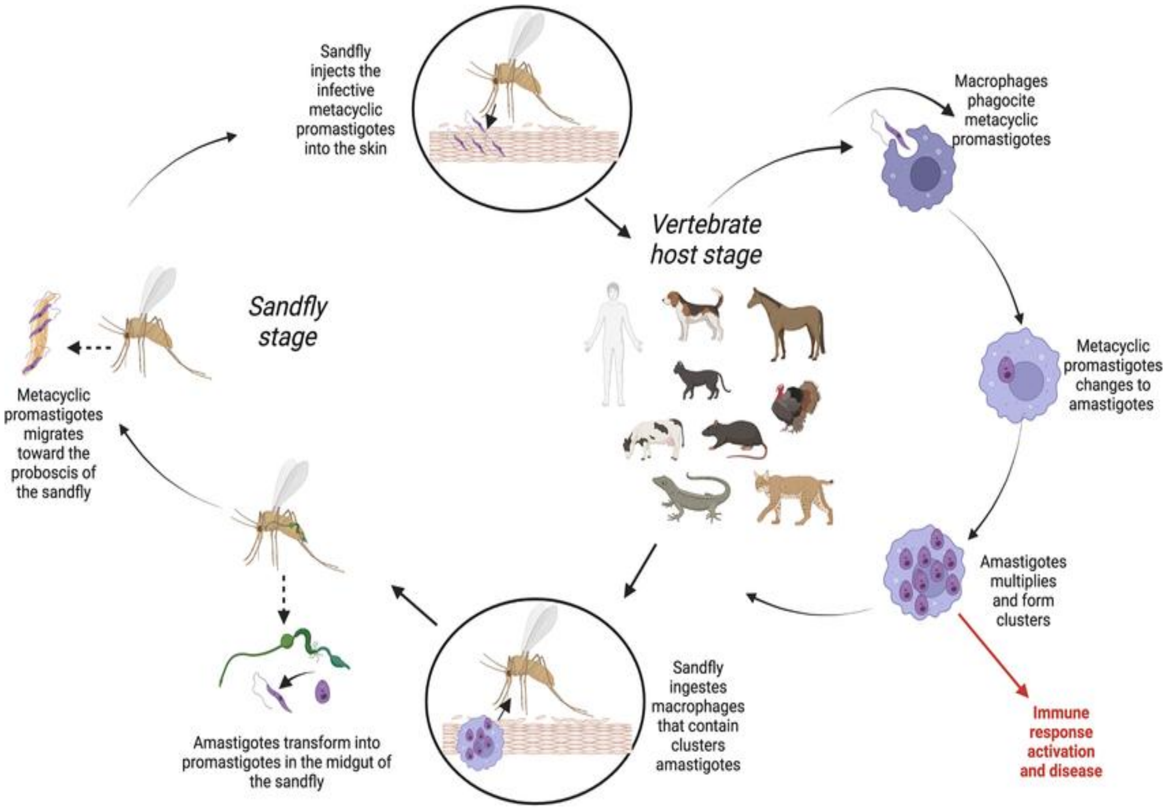

**Figure 2.** Illustration of *Leishmania* spp. transmission and life cycle [19]

**Epidemiology**

leishmaniasis has not received much attention, and it is widespread among disadvantaged people, affecting across over 90 countries in Asia, the Middle East, South America, along with Africa [20]. Leishmaniases is a vector-borne parasitic diseases arising from obligate intracellular protozoa of species of the genus *Leishmania*, which are endemic in tropical, Subtropical and Mediterranean basin, this includes people at risk of infection, with approximately 12 million cases, the annual incidence of CL is approximate at 0.7 -1.2 million infection worldwide and the number of cases of VL is approximate at 0.2 to 0.4 million [21].

The high prevalence of the disease may be attributed to two factors: firstly the climate is suitable for the growth and survival of *Leishmania* and its vector, and secondly, it may be attributed to the low level of economic development, which leads to low energy consumption, malnutrition among the population, and weak spending on healthcare. Wars, famines, and displacement also contribute significantly to increased rates of illness and death [22]. Many factors also influence the epidemiology of the *leishmania* parasite, including interconnected environmental relationships between human and reservoir source, species of both parasite and sandfly, the nature of the endemic areas, susceptibility of human and animal population to infection with the parasite and human behavior [23]. With regarding to dogs, it has long been known that dogs represent a source for the transmission of VL (zoonotic cycle), particularly in urban and peri-urban region [24], despite these cases showing that domestic cat may contributes significantly to the spread of Leishmaniasis, this role has received little attention remains a point of contention. The role of whether domestic cats, whether as a definitive, accidental or intermediate hosts is still unknown [25]. Dogs are considered important reservoir hosts, infection with *Leishmania* sp. has been documented in domestic cats living in urban areas, thus cats facilitate to the spread of the parasite in endemic [26].

The *L. donovani* complex consist Both *L. donovani* and *L. infantum*, the two species that are considered the primary etiological agents of VL. *L. infantum* is responsible for infection from an animal source (zoonotic) for VL, with dogs serving as the principal reservoir hosts within regions of the South America, Mediterranean, Asia, and The Middle East [27], in contrast, *L. donovani* is of human source (anthroponotic), is the causative agent of VL in the eastern Africa and Indian subcontinent [28]. A variety of DNA targets, including the mini-exon, hsp70gene, ITS-1 and ITS-2 regions were employed to investigate genetic diversity and phylogenetic relationship [29,30,11].

## Transmission

There are approximately 30 species belonging to the *Phlebotomus* and *Lutzomyia*, the two species identified as vectors for leishmaniasis. These diseases are caused by organisms belonging to the genus *Leishmania*, which are similar morphologically to the order kinetoplastida, family trypanosomatida. The disease is transmitted when a sandfly carrying the parasite ingests on the blood of a host [31]. The amastigote stage is transmitted from humans or infected mammalian hosts to the sandfly when it feeds on their blood in the insects gut, it transforms within about a week into promastigotes stage, which then multiplies and spreads towards mouthparts. When the fly bites a healthy human, it transmits promastigotes via the bloodstream, initiating the infection [32]. Appropriate environmental and climatic conditions enable for the reproduction and activity of the sandfly, which contributes to the spread of canine Leishmaniasis [33].

VL which causes *L. infantum*, is spread via *Ph. Perfiliewi* and ph. perniciosus, While cutaneous leishmaniasis, which causes L. major and *L. tropica* is spread by *Ph. Papatasi* and *Ph. Sergenti* respectively [34]. However, in the old world, the most important vectors associate with *Euphlebotomus*, *Larroussius* and *Synphlebotomus* to the subgenera of the sand fly, in the New World, subgenus of *Lutzomyia* flies act as the primary vector of the disease [35,36]. Untreated parasite hosts such as cattle and companion animals, may contribute to parasite breeding and transmission, and the proximity of sandflies to human further increases the likelihood of infection and its spread [37]. A sandfly can be a vector for zoonotic diseases if following factors are present: it must meet five conditions, It prefers to feed on human (anthropophilic), it relies on reservoir hosts for its nutrition within cycles of zoonotic infection, to be exposed in nature to the same type of *Leishmania* that infects humans, The parasite development is completed inside the insect until it reaches the stage capable of causing infection and The insect can transmit the parasite while feeding on the host blood [(38]. However, the sandfly that transmits disease becomes a carrier of the parasite, when it feed on the blood of diseased person or a vertebrate animals such as, dogs or rodents [39], sandflies are among the most important vectors of Leishmaniasis with 98 species of this genus documented as responsible for transmitting the disease via bites. Two species have been confirmed transmit the disease to human, *Phlebotomus* and *Lutzomyia* [40]. A number of factors influence the transmission of the parasite from animal the humans, including the type of vector, *Leishmania* species, in addition the degree of genetic compatibility between parasites strain found in animal and those that infect humans [19].

Canids of both domestic and wild breeds are constitute the primary reservoir for *Leishmania* parasite, ensuring the continued spread of *L. chagasi* across the New World, while *L. infantum* is prevalent in the Old World, in particularly Europe. Canine visceral Leishmaniasis is of particular importance from a public health and veterinary pharmaceutical perspective, as it is a severe chronic disease characterized by viscerocutaneous manifestation [41].

## Pathological

Approximately 53 species of the genus *Leishmania* have been documented in several region around the world, 31of these species are found in mammals, and 20 of them cause disease in human [21].There are 14 species of Leishmaniasis that are zoonotic (transmitted from animal to human), these species belong to two subgenus *Leishmania* in the Americas, *Leishmania* (*Vianna*) and *Leishmania* (*Leishmania*).The subgenus *Vianna* includes 10 species, 9 of which are transmitted from animal to humans, the subgenus *Leishmania* included 7 species, 5 of which are zoonotic [42], in addition, the majority of *Leishmania* species that cause infection in human are zoonotic, meaning they are transmitted from animal to human. However, no animal other than humans has been documented as a reservoir for the *L. donovani*, although some studies in India suggest that mongooses and domestic dogs might also be potential reservoirs [43]. *Leishmania* infection in mammals begins once the metacyclic promastigotes is injected into the dermis through sandfly bites, a blood–sucking insect belonging to the order Diptera. Once inside the skin, the parasite is rapidly taken up by resident phagocytes cells or those summoned to the bite site, particularly dendritic cells, neutrophils and macrophages [44]. In the New and Old World, infection with *L. donovani* and *L. infantum* leads to VL, which is potentially fatal without treated [45]. In the majority of individuals, leishmaniasis does not develop into a clear clinical signs, as studies in highly endemic areas indicate that approximately 30% of those infected remain without apparent symptoms [46], the clinical spectrum of leishmaniasis encompasses a wide array of symptoms, including mucosal, CL, MCL and VL, the severity of the illness varies determined by parasite strain and the efficiency of the immune response host [47].

*L. infantum* is classified as a zoonosis and the main cause of canine Lishmaniasis in dogs, leading to a wide ranging from asymptomatic infection to severe and fatal cases [48], in dogs, *L. infantum* infection can lead to severe systemic disease that is often fatal, coinciding with clinical signs comprising lethargy, weight loss and generalized lymphadenomegaly, after infection, diverse pathological manifestation may develop, involving the skin, eyes, vascular system and nervous system. In majority of cases, pathological clinical disorders consistent with this disease are observed [49].The *L. infantum* colonizes and multiplies residing macrophages in the bone marrow, spleen, along with liver, in cases of VL in human, approximately 90% of infected person show no obvious symptoms or experience only mild symptoms, exhibiting active of cellular immunity with a positive delayed-type hypersensitivity reaction to parasite antigens [50].

Reptiles are infected by various species of parasite belonging to the subgenus *Sauroleishmania*, some of which, such as *L. adleri*, can infect mammals [51]. Leishmaniasis can present with different clinical signs according to the species, the host response and geographical area [52], leishmaniasis is regarded as a major global health problem, as it contributes significantly to morbidity rates among communicable diseases and is a major causes of death associated with tropical diseases [53].

## Immunity

When the amastigotes form enters the hos cells, the parasite will continue to multiply and persist in spreading triggering a type 1 immune response that largely on mediation by NK cells and $CD4^+$ T lymphocytes, leads to the stimulation of macrophage via a specific reaction and release of cytokines among others IFN–y and TNF [54]. leishmaniasis is traditionally described as resulting from an imbalance in the immune reaction between Th1 cytotoxic T lymphocytes and Th2 $CD4^+$ helper cell, which act as antibody-presenting cells against foreign antigens [55], pro-inflammatory cytokines among other IFN- y, TNF-a are formed by the Th1 cellular response [56], an increases in cytokines by Th1 lymphocytes, like IL-12, TNF-a, IL-2 in addition INF-y, leads to macrophage activation and consequently to inhibition or reduction of the Th2 population [57]. In fact, the Th1-type response, driven by proinflammatory cytokine namely TNF-a, IL-12 and IFN-y, contributes to the activation of macrophage and increases their ability to fight the disease, thus limiting the development of infection and reducing the extent of clinical manifestations. But, Th2-type response mediated via anti-inflammatory cytokines such as IL-6, IL-4 and IL-1o can inhibit macrophage creating a favorable environment for parasite to survival and leading to severe clinical signs [58].The release of proinflammatory cytokines is essential for limiting parasite multiplication, but complete eradication of *Leishmania* parasite is not achieved. Furthermore, over activation Th1 response may lead to acute inflammation and the development of serious illnesses [59]. Other immune mechanisms, furthermore, the immune responses of both Th1 and Th2 types play fundamental to directing the progression of the disease, both in terms of its control and its progression, according to the species of parasite and the animal model used in the study, elevated level of both interleukin-17and interleukin-10 were recorded in individuals with MCL and CL [60].

## Diagnosis

Improving the accuracy of identifying pathogenic *Leishmania* species and their vector requires the use of modern and advanced techniques, most notably polymerase chain reaction [61]. Nucleic acid–based molecular techniques demonstrate a greater degree of sensitivity and specificity compared to currently available diagnostic tests [62]. There are several challenges that affect the diagnosis of Leishmaniasis, including the types of parasites causing the infection, genetic characteristics, and immune system effectiveness. In addition, the Th2 response which produces interleukin-10 and transforming growth factor β (TGF β), is a participates in factor to the persistence and exacerbation of the disease [63], diagnosing leishmaniasis is also a major challenge when relying solely on medical history, clinical examination, and laboratory and test results [64].

The ITS-rDNA gene is one of the most appropriate genetic markers for studying the evolutionary relationships among different *Leishmania* species and confirming their scientific classification in the old world, situated between the 18s and 5.8s rRNA genes, this gene is characterized by its conserved regions and a suitable degree of polymorphism, making it an effective tool for differentiating between different species

[65]. Various regions of ribosomal RNA (rRNA) gene, collectively known as ribosomal DNA (rDNA), are among the most prominent targets used at the chromosomal DNA level. *Leishmania* cell contain tens or even hundreds of copies rDNA unit, ensuring high and sufficient sensitivity for analyzing DNA extracted from clinical samples [66]. Studies have been conducted to evaluate the efficiency of PCR-based techniques using various samples, the internal transcribed spacer (ITS) region, among several gene, has been shown to exhibit variation in length and nucleotide sequence between different species, making it a suitable molecular marker for detecting and tracking *Leishmania* species in canine hosts. [67].

## Control

The geographical spread of leishmaniasis depends on several factors, including the availability and activity of animal reservoirs, this spread is also influenced by environmental, ecological and biological factors [68].The challenges associated with combating the disease, which relies on animal reservoirs, include the difficulty of identifying and monitoring these reservoirs, understanding the dynamics of transmission from animal to human, the increasing resistance of the parasite to traditional methods, the limited treatment options available, the varying nature of animal reservoirs wildlife interactions [68].

Controlling disease globally is considered an achievable goal, however, it faces substantial challenges due to the complexity of *Leishmania* transmission, which arises from a multi-faceted biological interplay involving, human as the host, animal reservoirs, sandfly vectors and the different of parasite species. In addition, transmission dynamics are affected by several factors such as deforestation, climate change, and armed conflicts, this challenge is further compounded by the presence of asymptomatic and paucisymptomatic infections, as undiagnosed individuals become hidden reservoir of the parasite,thereby leading to increased transmission and the persistence of Leishmaniasis foci [69]. However, important aspects of combating the disease in areas where Leishmaniasis is prevalent include conducting epidemiological investigation, evaluating effectiveness, taxonomic and genetics surveys, identifying parasite species and studying genetic variation [70].

## Methodology

This scientific article was conducted through a review of scientific publication related to the parasite *Leishmania*, using databases relevant to the article topic, including PubMed, Scopus, Science Direct and Google Scholar. The study included scientific research addressing the life cycle of *Leishmania* parasite, pathological, methods transmission, immunity and control. Scientific articles and previous studies were selected using keywords related to Leishmaniasis, species of *Leishmania* and immunity.

## Result

Previous reviewed studies and articles have shown that Leishmaniasis is considered one of the health problems affecting people in tropical and subtropical regions. The disease is caused by protozoan parasites of the genus *Leishmania* and transmitted when a sandfly carrying the parasite ingests on the blood of a host two of these species, *Phlebotomus* and *Lutzomyia*, have been confirmed to transmit the disease to humans.

Three different clinical forms of *Leishmania* were identified, including CL caused by a group of Leishmania species, *L. tropica*, *L. mexicana* and *L. major*, VL the pathogen is *L. donovan* and *L. infantum* and MCL associated with *L. braziliensis*.

Studies have shown that the clinical spectrum of leishmaniasis encompasses a wide array of symptoms, and the severity of the illness varies determined by parasite strain and the efficiency of the immune response host. the immune responses of both Th1 and Th2 types play fundamental to directing the progression of the disease, both in terms of its control and its progression.

## Discussion

Leishmaniases is a vector-borne parasitic diseases arising from obligate intracellular protozoa of species of the genus *Leishmania* [37]. Leishmaniasis continues to represent a major public health challenge, particularly in developing, which are endemic in tropical, Subtropical and Mediterranean basin, with approximately 12 million cases, the annual incidence of CL is approximate at 0.7 -1.2 million infection worldwide and the number of cases of VL is approximate at 0.2 to 0.4 million. The widespread prevalence of the disease may be attributed to the favorable climate for the growth and survival of *Leishmania* and its vector in addition to the low level of economic development, malnutrition among the population, and weak healthcare expenditure. As well as, Untreated parasite hosts such as cattle and companion animals, may contribute to parasite breeding and transmission, and the proximity of sandflies to human further increases the likelihood of infection and its spread. Another factor contributing to the increased spread of the disease, is that majority individuals infected with leishmaniasis does not develop into a clear clinical signs. Studies conducted in highly endemic areas indicate that approximately 30% of those infected remain without apparent symptoms.

At least 53 species of the genus *Leishmania* have been documented in several region, 31of these species are found in mammals, and 20 of them cause disease in human, the spread disease depends largely on the diversity of *Leishmania* parasite species and variety of insect vectors that transmit the disease. There are numerous *Leishmania* parasite species that differ in their virulence and ability to cause various clinical forms of the disease, such as CL, VL and MCL. Furthermore, the diversity of vector species and their varying adaptations to environmental and climatic conditions increase the chances of disease spread in tropical and subtropical regions. Moreover, domestic dogs and cats may contribute to the spread of *Leishmania*.The challenges associated with controlling this disease include the difficulties in identifying and monitoring reservoirs host, understanding the dynamics of transmission from animal to human, the increasing resistance of the parasite to conventional control method, and the limited availability of treatment options.On the other hand, the diagnosis of the disease is influenced by several factors, including the different parasite species, genetic characteristics, as well as the efficiency and response of the host immune system. Therefore, the use of modern tools for diagnosing parasite species is required, including PCR techniques *Leishmania* species, vectors, and reservoir hosts, as well as studying genetic variation.

## Conclusion

Leishmaniasis is a significant a common health problem in countries worldwide due to its widespread prevalence, multiple animal reservoir, and the difficulty in controlling the vector. There are many species of *Leishmania* that cause the disease, and their clinical manifestation vary, including CL, VL, and MCL, depending on the species of parasite and the host immune response.

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