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Review Article

Etiology, Clinical Spectrum, Epidemiology, Diagnosis, Public Health Significance and Control of Leishmaniasis: A Comprehensive Review

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Abstract

Leishmaniasis is the most neglected an intracellular protozoan disease caused by genus *Leishmania* and it has a geographic distribution in 98 countries in the world. Currently, over 350 million people are at risk of the infection; and about 60,000 deaths are estimated to occur from both cutaneous leishmaniasis and visceral leishmaniasis each year in the world. Infected female sand-fly genus *Phlebotomus* and *Lutzomyia* are responsible for transmission of leishmaniasis in the old and new worlds, respectively. The disease is occurring in a complicated variation in domestic and wild mammal reservoir hosts and sand fly as biological vector. The clinical manifestation of disease occurs in three main forms viz: cutaneous leishmaniasis, muco-cutaneous leishmaniasis, and visceral leishmaniasis. Laboratory techniques that include parasitological examination, immunological technique and molecular tools are imperative to establish an unequivocal diagnosis of leishmaniasis. A number of chemotherapeutic agents have been tried, however, treatment still remains challenging. Also the complex genetic and the population diversity of both the parasites and vectors make the control of this disease very difficult. Recently, leishmaniasis has been emerged or re-emerged in many geographical areas of the world. Thus globally coordinated more studies and assessment of the disease toward complexity chains in domestic and wild mammal reservoir hosts and the vector where leishmaniasis is endemic is recommended.

Keywords: Epidemiology; Leishmaniasis; Public Health; Reservoir Hosts; Sand-fly; Zoonotic Importance

Introduction

Leishmaniasis is a parasitic disease caused by the protozoa in the genus of *Leishmania*, which is transmitted by the bite of an infected female sand-fly; and has a significant clinical and epidemiological diversity [1-3]. This disease occurs as a global public health problem, and is one of the most neglected tropical diseases, with its existence in 98 countries of the world [4].

Leishmaniasis has a worldwide geographic distribution with the exception of Antarctica. The disease was endemic in tropical and sub-tropical regions, mainly in Africa, parts of Asia, the Middle

East, Latin America, and the Mediterranean region. Disease appears to be gradually spreading northward in Europe from its traditional foci in the south [5]. In recent times, disease has been emerged or re-emerged in different geographical areas, making global health and economic fears that could be implicated in humans, domestic animals, and wildlife [2,6,7].

About 53 species of the parasite have been described from diverse regions of the world; of these, 31 species are recognized to be parasites of mammals and 20 species are pathogenic for human beings [8,9]. Many human-infecting *Leishmania* species are zoonotic, with a wide range of domestic and wild mammal as reservoir hosts; others are anthroponotic, with human-to-human transmission in the presence of the vector [9].

The life cycle of *Leishmania* species involves final mammalian host and intermediate sand fly host [10]. The sand-fly vector gains *Leishmania* infection in the form of macrophages containing amastigotes during feeding on blood of infected mammal. In most cases, canids, especially the dogs, act as a reservoir of the disease, although hares, foxes, cats, rats and other wild animals may also serve as sylvatic reservoirs [11].

Depending on the species *Leishmania* involved, and the host's immunity, clinical manifestations of disease occurs in three main forms, namely cutaneous leishmaniasis, muco-cutaneous leishmaniasis and visceral leishmaniasis [12]. A number of diagnostic techniques for *Leishmania* diagnosis include parasitological examination, immunological technique and molecular diagnostics [13]. The prevention of leishmaniasis not only desirable but also necessary for both canine and human health because to its potential severity in dogs and zoonotic nature. For the reason that the infection to a receptive host take place through the bite of sand flies of the genus *Phlebotomus* and genus *Lutzomyia* [14]. The management of this disease is extremely complex [15]. In this regard, the prevention of the disease should include measures targeting the animals (at individual and population level) and the environment.

Leishmaniasis is a severe neglected zoonotic disease with one or more reservoir hosts preserving the disease. Among a restricted range of reservoir hosts for leishmaniasis, it includes dogs, hyraxes, rodents, wild canids and bats [16]. Leishmaniasis now has a larger geographic spread than it did previously, and it is considered a growing public health threat in various nations, including Ethiopia [16,17]. Furthermore, according to Amarasinghe and co-workers [18], the control of disease is difficult due to the parasites' and vectors' complex genetic and population diversity.

Thus the general objective of this review is to present the epidemiology and public health significance of leishmaniasis. In addition, it specifically describe the clinical features, diagnosis, prevention and control of leishmaniasis.

Etiology

Leishmaniasis is caused by a variety of protozoan parasites that belong to the Trypanosomatidae family and the genus *Leishmania* [19]. The parasite is flagellated and lives inside cells. A variety of morphological, immunological, biochemical, geographical, clinical, and behavioural characteristics distinguish *Leishmania* species. *Leishmania* has been identified in approximately 30 species, 20 of which are pathogenic to the mammals. Out of which, a total of 18 pathogenic *Leishmania* species have zoonotic potential [20,21].

There are two types of parasites: amastigotes and promastigotes. Small, round to oval bodies with no flagella are seen inside the monocytes, leucocytes/macrophages, and endothelial cells of infected vertebrate hosts. They are colorless, with a homogeneous cytoplasm and a pellicle around them. The nucleus is big, while the knetoplast is tiny. Sand flies have promastigotes in their digestive systems. They are 2.5 µm long and 1.5 to 3.5 µm wide [22].

Clinical spectrum

About 20 different species of the parasite *Leishmania* cause leishmaniasis, which has three clinical syndromes, such as visceral, cutaneous (CL), and mucocutaneous leishmaniasis. The cutaneous form is the most frequent type of the disease, with skin lesions and ulcers on exposed body areas as symptoms. Mucocutaneous leishmaniasis is a crippling form of leishmaniasis that causes soft tissue damage in the nose, mouth, and throat cavities. Visceral leishmaniasis (kala-azar) is the most dangerous of the three clinical forms of the illness, with devastating symptoms, such as swelling of the liver and spleen, extreme anemia, and recurrent bouts of fever. The infection is spread by female sandflies of the *Phlebotomus* and *Lutzomyia* genera in the Old World and *Lutzomyia* in the New World [23].

Leishmaniasis in dogs has a wide range of symptoms that might be mistaken for other disorders. The species *Leishmania infantum* is the well-studied. This organism can induce cutaneous, visceral, or both symptoms at the same time. Many infected dogs

are asymptomatic, with clinical instances ranging from moderate to severe. Lethargy, weight loss, a decreased appetite, anemia, splenomegaly, and local or systemic lymphadenopathy are all common visceral symptoms. Fever can be intermittent, and in certain situations, it is completely absent in humans. Chronic renal illness is a typical complication in dogs infected with *Leishmania infantum*; in some cases, it is the only symptom, and it is frequently fatal [5].

Epidemiology

Geographical distribution of leishmaniasis

Leishmaniasis has two major epidemiological entities: zoonotic, which includes animal reservoir hosts in the disease's transmission cycle, and anthroponotic, which considers humans to be the sand-fly vector's sole source of infection [24].

Leishmaniasis is endemic in 98 countries with greater than 350 million people at risk and an expected 700 000-1.2 million new cases of which, 600 000 to 1 million novel cases of CL, 50 000 to 90 000 new cases of VL and about 60,000 deaths from both CL and VL each year [2,25,26]. Of the whole current VL incidence reported, about 90% cases are from seven countries (Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan). In the same way, the prevalent of CL cases are endemic in only ten countries (Afghanistan, Algeria, Brazil, Colombia, Ethiopia, Iran, Pakistan, Peru, Saudi Arabia and Syria) [3,27,28]. East of Africa is the second prevalent VL centres after the Indian subcontinent, contributes to the worldwide burden with 30,000-40,000 new cases per year [29,30]. The global distribution of cutaneous and visceral leishmaniasis is shown in figure 1.

Figure 1: Global map showing distribution of cutaneous as well as visceral leishmaniasis Source [30].

Vectors of leishmaniasis

The only known vector of *Leishmania* is the small dipteran fly identified commonly as a "sand-fly." The vector shares the family *Psychodidae* with the non-vector, nonbiting moth flies, often seen around shower drains. The subfamily *Phlebotominae* is included of the bloodsucking sand fly vectors of leishmaniasis and other diseases [31]. Sand flies, like other real flies, go through a complete metamorphosis and have four life stages: egg, larva, pupa, and adult. In contrast to mosquitos, the immature stages do not require standing water to mature, however they do demand warm, wet surroundings. Because animal burrows typically offer these necessities, sand flies are frequently found around rodent habitations [32].

There are above 600 species of the sand flies grouped into five genera: *Phlebotomus* and *Sergentomyia* in the Old World and *Lutzomyia, Brumptomyia*, and *Warileya* in the New World [14,33,34]. Although human-biting sand flies occur in various genera, the only proven vectors of human leishmaniasis are species and subspecies of the genus *Phlebotomus* and *Lutzomyia* as indicated in table 1. Several *Phlebotomus* species in the Old World and *Lutzomyia* species in the New World are responsible for the transmission of leishmaniasis. Each sand fly species normally transmits only one parasite species, and each parasite causes a specific sickness [35,36].

Sand fly species	Geographical distribution
Phlebotomus papatasi, Phlebotomus dubosqi, Phlebotomus salehi	Central and West Asia, North Africa, Sahel of Africa, Central and West Africa
Phlebotomus sergenti	Central and West Asia, North Africa
Phlebotomus longipes, Phlebotomus pedifer	Ethiopia, Kenya
Phlebotomus argentipes, Phlebotomus orientalis, Phlebotomus martini	Indian subcontinent, East Africa
Phlebotomus ariasi, Phlebotomus perniciosus	Mediterranean basin, Central and West Asia
Lutzomyia longipalpis	Central and South America
Lutzomyia olmecaolmeca	Central America
Lutzomyia flaviscutellata	South America

Lutzomyia wellcomei, Lutzomyia complexus, Lutzomyia carrerai	Central and South America
Lutzomyia peruensis, Lutzomyia verrucarum	Peru
Lutzomyia umbratilis	South America
Lutzomyia trapidoi	Central America

Table 1: Sand flies transmitting most human leishmaniasis.

Source: [35].

Reservoirs of leishmaniasis

Animal reservoirs are significant for sustaining the life-cycle of many *Leishmania* species and hence, are very important for transmission of zoonotic and rural infection. Human leishmaniasis has two main causes: zoonotic leishmaniasis, which has wild animals, commensals, or domestic animals as reservoir hosts, and anthroponotic leishmaniasis, which has humans as reservoir hosts [36].

Several species of wild, domestic and synanthropic mammals have been recorded as hosts and reservoirs of *Leishmania* species in diverse parts of the world. Multi-host reservoirs for leishmaniasis transmission in various areas include rock hyraxes, rodents, mongooses, dogs, cats, foxes, jackals, wolves, bats, monkeys, armadillos, and other domestic animals [1,37,38]. However, *Leishmania* reservoirs are so complex that they show regional and temporal variations [39] and only a local studies involving ecological and parasitological analysis can determine whether these animals are playing a role as reservoir in a given environment [37].

Life cycle of the parasite (*Leishmania*)

The life cycle of *Leishmania* is shown in figure 2. *Leishmania* species have two basic life cycle stages. These are the extracellular stage with in the invertebrate host and then intracellular stage with in vertebrate host. The parasite exists in to two main morphological forms, the amastigote and the promastigotes, which are found in vertebrate and invertebrate hosts, respectively [40].

The life cycle begins when a female sand fly takes a blood meal from vertebrate host and injects the promastigotes in to the host circulation. After inoculation into vertebrate host, the promastigotes are phagocytosed by the host's macrophages. Then the parasite evolves into amastigote form which they reproduce by binary fission continuously with in macrophages [41].

Figure 2: Life cycle of *Leishmania.*

Source: [41].

As many as so many around 200 amastigote may be present in the cytoplasm of enlarged cell, so that the macrophage ruptured and releases a large number of amastigotes into the circulation. Then they invade monocytes and macrophages of the pleen, liver, bone marrow, lymph node and other tissue of reticulo-endothelial cells [42]. Free amastigotes in the blood as well as intracellular amastigotes in the monocyte are ingested by the female sand flies. After a period of 6 to 9 days, the promastigotes migrate from the mid gut to the pharynx and buccal cavity of the sand fly. Consequently, it can be transmitted to other new host where these fly feed on blood meal [22].

Transmission

The disease is carried by the female sand flies that have been afflicted. The bite of blood-feeding female *Phlebotomine* sand flies is the main mode of transmission for *Leishmania* species [43]. Generally, the transmission of disease by the vector sand fly is dependent on the life cycle (stages of development of the parasite) and feeding habit of this fly on its hosts.

Except under certain canine husbandry conditions, transmission by non-sand fly vectors is anticipated to be unlikely. The United States of America foxhound outbreak could be explained by iatrogenic transmission (via blood transfusion or immunization), fighting, and sexual transfer, while a role for sand flies has not been

conclusively ruled out. On the other hand, the epidemiological significance of these non-sand fly transmission routes in most endemic areas will be low. Nonetheless, several studies have found that sexual and congenital transmissions are rather common in dogs. Sexual transmission was confirmed in 58% (7/12) of non-infected bitches mated to many infected dogs [44].

The main transmission areas for leishmaniasis are determined by micro-ecological factors that affect the vector population, the parasite, and the reservoir host. The incidence of visceral leishmaniasis can be affected by urbanization, domestication of the transmission cycle, and the invasion of agricultural farms and communities into wooded areas. Rainfall, ambient temperature, and humidity all have an impact on parasite dispersal (climate-sensitive disease). A variety of factors including the global warming and land degradation are projected to disrupt the epidemiology of leishmaniasis [45].

Predisposing factors for leishmaniasis

High risk is associated with a number of demographic characteristics. Adults are more vulnerable to infections than children because of their outside occupations, and infections are common among young adults [46,47]. Males suffer more than females [18]. Certain occupations are linked to a higher risk of infection. Increased cutaneous leishmaniasis transmission is linked to unmonitored livestock breeding and living near rice fields [48,49]. The majority of farmers in endemic areas wear clothing that just covers the bottom half of their bodies. As a result, the top region of the body is more exposed to the sand-fly bites than the lower part [50]. The infection risks are also increased by poor living conditions and house clustering. Insect bites are associated with an increased risk of infection when protective measures are not used [51].

Diagnosis

The parasitological examination (histopathology, microscopy, and parasite culture), serological technique, molecular diagnostics, and other new xenodiagnosis procedures have all been developed, with significant variations in diagnostic accuracy [13].

Parasitological methods of diagnosis

Parasitological diagnostic procedures are still the gold standard for detecting *Leishmania* infection [52] and are critical in eco-epidemiological research [53]. Direct inspection of amastigotes in Giemsa or Wright stained scraping smears, biopsies, or impression smears can be used in the laboratory to provide a diagnosis [1]. Aspirates of bone marrow or splenic fluid are the most commonly used samples for the diagnosis. Amastigotes, on the other hand, can be found in other samples such as the buffy coat of peripheral blood, lymph nodes, and liver biopsies [54].

Parasitological methods are most favoured and first line diagnostics for determining the disease. The parasitological approaches, on the other hand, have several drawbacks, including low sensitivity, the need for technical skill to carry out the procedure, and additional hazards associated with the testing [55].

Immunological methods of diagnosis

Immunological procedures were developed to overcome the limitations of parasitological methods of diagnosis. The presence of distinct humoral reactions is the basis for these approaches. The humoral immune response is quite low inmuco-cutaneous and cutaneous leishmaniais patients [56].

As a result, immunological tests are rarely used in areas where cutaneous leishmaniais is prevalent because circulating antibodies are low and specificity can fluctuate in locations where cross-reacting parasites like *Trypanosoma cruzi* present. In visceral leishmaniais, however, excessive immune-globulinemia is seen. Many antibody detection approaches for leishmaniasis diagnosis have been developed based on this interaction between hosts and parasites [57]. The enzyme-linked immune sorbent assay (ELISA), western blot, indirect fluorescent antibody, and direct agglutination are some of these diagnostic procedures. It is mentioned that Dot-ELISA is a rapid method to diagnose visceral leishmaniasis [1].

The sensitivity of these immunological tests is mostly determined by the assay and methodology utilized, whereas specificity is determined by the antigen rather than the serological format [54].

Xenodiagnosis

The basic approach of assessing transmissibility from a host to an insect species with the goal of distinguishing infectious from non-infectious hosts is xeno-diagnosis [58].The infected lesion or tissues are exposed to the *Phlebotomine* vector in this method of diagnosis, and the vector's gut is later analyzed for the presence

of *Leishmania* flagellates [59]. Xenodiagnosis has a high sensitivity and is easier to use than other procedures, but it cannot distinguish between various *Leishmania* species. It is also a time-consuming procedure that would not be possible without the insect/animal [60].

Molecular methods

When it comes to diagnosing leishmaniasis, traditional parasitological and serological techniques have several limitations, which have led to the development of molecular methods [61]. Molecular approaches are preferred over traditional diagnostic procedures for cutaneous leishmaniasis because of their high accuracy and rapidity [62].

Molecular approaches can be used as a supplement or as a replacement to traditional diagnostic methods. The feasibility, safety, and reliability of molecular instruments are the primary reasons for their acceptance in ordinary laboratories around the world. In a study comparing microscopy and culture methods to distinguish *Leishmania* species based on internal transcribed spacers ITS-PCR, it was discovered that ITS-PCR is not only valid for species identification but also has a high sensitivity and specificity (98.8% and 100%, respectively) when compared to parasitological methods of diagnosing CL (79.6% and 86.2% sensitivity respectively) [63].

Nanomaterial-based detection of *Leishmania*

Biosensors are made up of a recognition element (antigen, antibody, oligonucleotide, or enzyme) and a signal transducer. The transducer provides a signal when the recognition element binds to the target [64].

Biosensors are classified as immune sensors, genosensors, or aptamer-based sensors based on the recognition element [65]. Antibodies are used as the recognition element in immune sensors. In this scenario, the transducer turns the antibody–antigen interaction into a physical signal that can be measured. Genosensors, on the other hand, are DNA biosensors that work by combining two complementary oligonucleotides in a hybridization reaction [66].

The optical, catalytic, electrical, and magnetic characteristics of nanomaterials are well-known. Many published studies have described the use of these unique physical and chemical properties of nanoparticles in the development of biosensors and other nano-based techniques for *Leishmania* detection [67].

Nanomaterials as nanoquenchers for fluorescent DNA tests were described by Pedro and co-investigators [84]. Through electron transfer processes, the generated nanostructure interacted with the fluorophore of a labelled DNA probe (*Leishmania infantum* specific), suppressing the fluorescence emission [68].

Public health significance of Leishmaniasis

Leishmaniasis is a major public health issue around the world. It affects over 98 nations and is native to Asia, Africa, and some regions of South America, Central America, and the Mediterranean. Leishmaniasis is one of the world's seven most dangerous tropical illnesses, as described by World Health Organization (WHO) [69].

Leishmaniasis in humans

Due to various limiting variables, such as a discontinuous distribution in endemic areas and a large number of misdiagnosed cases, human statistics underestimate the true frequency of the disease, as indicated by [11]. At least twenty species of *Leishmania* are responsible for the different clinical forms of the disease cutaneous leishmaniasis (CL), localized cutaneous (LCL) or diffuse cutaneous (DCL), muco-cutaneous (MCL) and visceral (VL).

The most common clinical form of cutaneous leishmaniasis is a single skin ulcer (oriental sore), which can self-resolve depending on the host's immunological features [70].

Cutaneous leishmaniasis

Localized cutaneous leishmaniasis

Lewis and Cunningham were the first to describe pure cutaneous leishmaniasis in the Old World in 1876 *Leishmania tropica* is to blame. It affects areas of the body susceptible to insect bites; the most commonly affected areas are the ears (helix and anti-helix), nose, upper lip, cheeks, legs, hands and forearms, and ankles, in decreasing order of frequency [71].

The incubation time ranges from 1 to 4 weeks, although it can persist for years. It is characterized by a localized rise in temperature as well as oedema. Although pruritus may be present, an erythematous asymptomatic papule forms at the biting site. The

diameter of the beads varies from 1 to 10 mm. After two days, it transforms into a vesicle, then a pustule, and when it breaks, either spontaneously or as a result of scratching, it creates a spherical ulcer with nodular or thick borders, sharp and peaked edges, and nodular or thick borders. In rare circumstances, excessive secretion results in the formation of an adhering crust as indicated in figure 3 [69].

Figure 3: Figures of localized cutaneous leishmaniasis (Early ulcer on the forearm with meliceric crust (A), Ulcer on the upper limb with crusts and raised borders (B) and Atrophic stage of chiclero's ulcer with deforming scarring of the ear (C). Source: [69].

Diffuse cutaneous leishmaniasis

Anergy is a characteristic of this type (that is, lack of cellular immune response to parasite antigens). This allows for spread through tissue, lymph, and blood routes, resulting in lesions in the majority of the skin (excluding the scalp) and occasionally mucous membrane involvement. Central America, Amazonian Brazil, Venezuela, Ethiopia, and Kenya have all experienced it. It usually begins with reddish-brown infiltrative smooth or verrucous plaques and firm erythematous nodules. The latter may or may not ulcerate, and they begin on the face before spreading to the extremities, buttocks, and mucous membranes, and in some cases, the entire skin surface look as shown in figure 4. Lymphedema, lymphadenopathy, poor general health, and fever are all possible symptoms [72].

Muco-cutaneous Leishmaniasis

After 5 years of healing, the LCL form of leishmaniasis progresses into mucocutaneous leishmaniasis in 1 to 10% of individuals in endemic locations in South America. The causal species of this

Figure 4: Diffuse cutaneous leishmaniasis (anergic clinic form). Source: [69].

clinical form belong to the complex *Leishmania braziliensis*, which includes *Leishmania braziliensis, Leishmania guyanensis,* and *Leishmania panamensis*. It causes invasion and destruction of the nasopharyngeal mucosa [73]. Invasion occurs gradually, causing little initial discomfort and so allowing the mucosal injury to go unnoticed; in some situations, it only causes mild itching and swelling [74,75]. As shown by figure 5, lesions usually begin in the nasal mucosa and extend to the oral and pharyngeal mucosa, the larynx, and the nose and lip skin.

Figure 5: Muco-cutaneous leishmaniasis. Source: [69].

Visceral leishmaniasis/kala-azar (black fever)

Kala-azar (black fever) is a febrile infectious disease that affects children and adults in a wide section of south and East Asia (primarily India and China), as well as a big part of Africa, the

Mediterranean, and South America (where children are affected). It is caused by *Leishmaniadonovani* (India and Eastern Africa), *Leishmania infantum* (Mediterranean area), and *Leishmania chagasi, Leishmania amazonensis,* and *Leishmania tropica* in South America [74]. The incubation phase lasts somewhere between 3 and 8 months. Preschool children, as well as immune-compromised and malnourished people, are among those at danger.

Treatment, prevention and control of leishmaniasis

Treatments of leishmaniasis

Numerous drugs, such as antimony sodium gluconate, berberine sulphate, megalumine antimoniate, pentamidine isothionate, stiboogluonate sodium and others have been tried for the treatment of leishmaniasis [1]. One Indian study covering 45 patients of cutaneous leishmaniasis due to *L. tropica* were treated with 2% berberine sulphate solution. The drug was injected intra-lesionally at weekly intervals for 4 to 8 occasions. The treatment was found very effective (97.77%) as 44 patients were cured with 2% berberine sulphate solution. During this study, it was interesting to note that 70% of human cases with cutaneous leishmaniasis were cured after 4 and 5 intralesional injections [76]. Pentavalent antimoniate was the most effective medicine with good outcomes when it was originally launched 60 years ago. Pentavalent antimoniate, such as sodium stibogluconate, is administered at a dose of 20 mg/kg body weight, and these medications can be taken together or separately [77].

The widespread incidence of leishmaniasis and the emergence of medication resistance high lights the need for new, less toxic, and more promising therapeutic techniques to be developed and tested. Drug combinations can be used to fight drug resistance generated by monotherapy in the treatment of visceral leishmaniasis. It can extend the spectrum, improve the medication's efficacy through additive or synergistic action, reduce the length and dosage, reduce side effects, reduce treatment costs, and prevent drug resistance [78].

Prevention and control

Early detection and treatment are currently used as control methods [1]. Some sand-fly management programs are only carried out when there is an epidemic in endemic areas. Because biochemical studies indicated acetylcholinesterase and esterase-based pesticide resistance pathways in sand-flies, sand-fly control strategies should be implemented with caution. As a result, insect control with organophosphorus and carbamate pesticides may already be in jeopardy [79].

Because of the infection's potential severity in dogs and its zoonotic nature, prevention is not only desirable but also necessary for both dog and human health. Because the illness is transmitted to a receptive host by sand flies of the genera *Phlebotomus* and *Lutzomyia* [14]. The management of this disease is extremely complex. In this regard, the prevention of canine leishmaniasis should include measures targeting animals (at individual and population level) and the environment [80].

The other is to raise public knowledge of *Leishmania* infection through health education and monitoring [1]. The prevalence of disease will be reduced by raising public knowledge about changing clothing habits and being mindful of insect bites. A large study should be conducted to determine which demographic features and behaviours enhance the chance of contracting leishmaniasis [75]. It is pertinent to mention that transmission of *L. tropica and L. donovani* can be decreased by treating the affected persons [81].

Conclusions

Leishmaniasis is an intracellular parasitic protozoan disease caused by *Leishmania* that has a worldwide geographic distribution in 98 countries with greater than 350 million people at risk. Disease represents a significant global zoonotic health problem pronounced as one of the seven most important tropical diseases including Ethiopia.

The disease is occurring in a complicated variation in domestic and wild mammal reservoir hosts and sand fly as biological vector. Also the complex genetic and the population diversity of both the parasites and vectors make the control of this disease very difficult.

Biochemical assays revealed using acetylcholinesterase and esterase-based insecticides made resistance in sand-flies and insect control by organophosphorus and carbamate insecticides may have already been compromised.

In addition, drug case management could not decrease incidences of leishmaniasis due to mammalian reservoir hosts are responsible for maintaining infectious agent in a population.

Thus the following recommendations are forwarded.

- Globally coordinated additional research studies and assessment of the disease in more detail going on complication chain in domestic and wild mammal reservoir hosts and biological vector (sand fly) where leishmaniasis is endemic, is recommended.
- The occurrence of chemical resistance in sand-flies and other compromised insecticides to control the sand fly vector needs other new biotechnological interventions.
- Creating social awareness in all stakeholders and communities about the detail of ways of controlling sand fly vector and breaking the chain of the disease in mammalian host reservoirs should be taken.
- Leishmaniasis is a complex disease that poses challenges in diagnosis and treatment. Hence, advances in vaccine development, diagnosis, reporting, and treatment could prevent substantial morbidity and mortality from this emerging protozoon disease.

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Consent for Publication

The authors have full agreement for this review article for its publication.

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Competing Interests

The authors declare that they do not have any conflict of interest.

Authors' Contributions

All the authors contributed equally. They read the final version, and approved it for the publication.

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