Chapter

Epidemiology and Ecology of Leishmaniasis

Tonay Inceboz

Abstract

Leishmaniasis is the third most important vector-borne disease after malaria and lymphatic filariasis. It is common disease in all over the world. The vector for leishmaniasis is *Phlebotomus* and there have found around 20 different types of this vector. There are different clinical forms under the name of leishmaniasis such as kala-azar, dum-dum fever, white leprosy, espundia, pian bois, chiclero's ulcer, uta. Environmental factors leading to climate changes and global warming are major risk factors for the spreading of the disease. *Leishmania* spp. to prevent the spread of the definitive host and intermediate hosts is difficult compared to *Plasmodium* spp. Therefore; leishmaniasis disease will retain its importance for many years.

Keywords: leishmaniasis, neglected tropical diseases, vector-borne disease, epidemiology, ecology

1. Introduction

This fact is mainly due to the presence of many different species of *leishmania*, its vectors and hosts in different parts of the world. More than 20 pathologic species of *leishmania* and over 30 species of *Phlebotomus*—the vector- are known worldwide (**Figure 1**, **Table 1**).

On the other hand, deterioration of the eco-systems by human beings also contribute to the spread of the disease in the world.

Leishmaniasis has four clinical forms. These are cutaneous leishmaniasis (CL, local—LCL or diffuse—DCL), mucocutaneous leishmaniasis (MCL), visceral leishmaniasis (VL), post-kala-azar dermal leishmaniasis (PKDL), (**Table 1**).

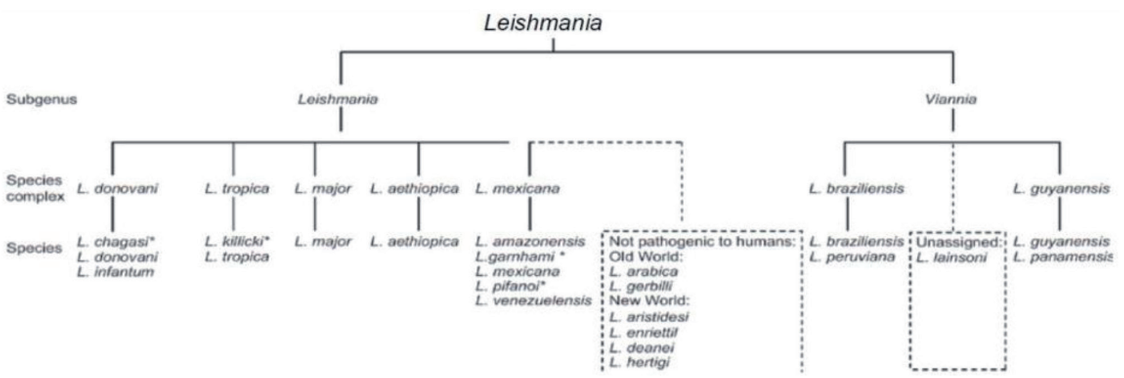

Figure 1.
Taxonomy of leishmania *family [1].*

Subgenus	*L.* (*Leishmania*)	*L.* (*Leishmania*)	*L.* (*Viannia*)	*L.* (*Viannia*)
Old World	*L. donovani*	*L. major*		
	L. infantum	*L. tropica*		
		L. killicki[a]		
		L. aethiopica		
		L. infantum		
New World	*L. infantum*	*L. infantum*	*L. braziliensis*	*L. braziliensis*
		L. mexicana	*L. guyanensis*	*L. panamensis*
		L. pifanoi[a]	*L. panamensis*	
		L. venezuelensis	*L. shawi*	
		L. garnhami[a]	*L. naïffi*	
		L. amazonensis	*L. lainsoni*	
			L. lindenbergi	
			L. peruviana	
			L. colombiensis[b]	
Principal tropism	Viscerotropic	Dermotropic	Dermotropic	Mucotropic

[a]*Species status is under discussion.*
[b]*Taxonomic position is under discussion.*

Table 1.
Leishmania *found in humans [1].*

In this section we aimed to reveal the epidemiologic analysis of different types of leishmaniasis in all over the world in every aspect.

2. Geographic distribution and incidence

Leishmaniasis, as being one of the world's most neglected diseases, affects mainly the poor, developing countries; 350 million people are thought to be at risk of contracting leishmaniasis. It is estimated that approximately 12 million men are ill and 2 million new cases occur annually [1, 2].

With new epidemics occurring in endemic areas and the spread of leishmaniasis to previously free areas because of migration, tourism, and military activities. Leishmaniasis is a disease of the poor, occurring mostly in remote rural villages with poor housing and little or no access to modern health-care facilities. In endemic areas, diagnosis of any form of leishmaniasis puts a huge financial strain on an already meagre financial resource at both the individual and community levels [3].

Visceral leishmaniasis: approximately 90% of new cases occur in the world's cases of India, Bangladesh, Nepal, Ethiopia, Sudan and Brazil are seen. The annual number of cases worldwide has been estimated to be visceral leishmaniasis, between 200,000 and 400,000. The two important causative agents of visceral leishmaniasis (VL), namely *Leishmania* (L) *donovani* and *L. infantum*, cause significant health problems [1, 4].

Visceral leishmaniasis (VL), also known as "kala azar," is caused by parasites of the *L. donovani* complex in some parts of the world. The *L. donovani* complex can be found throughout Asia, North Africa, Latin America and Southern Europe, affecting mostly vulnerable and uncared populations. As being the most severe form, VL is almost always fatal if left untreated. It is characterized by undulating fever, loss

of weight, splenomegaly, hepatomegaly and/or lymphadenopathies and anemia *L. infantum*, the other causative agent of VL, is found in Southern Europe, North Africa and West and Central Asia [1, 5].

Post-kala-azar dermal leishmaniasis (PKDL) is another clinical composition of kala azar and it is seen in all areas endemic for *L. donovani*. It especially comments in East Africa and on the Indian subcontinent with a prevalence of 50 and 10%, respectively [1, 6].

Cutaneous leishmaniasis: approximately 90% of the world's cases of Afghanistan, Pakistan, Sudan, Syria, Saudi Arabia, Algeria, Iran, Iraq, is seen in Brazil and Peru. The annual number of cases worldwide has been estimated to be visceral leishmaniasis, cutaneous leishmaniasis: between 700,000 and 1.2 million [1]. Old World species: *L. major*, *L. infantum*, and *L. tropica*, New World species, such as, *L. amazonensis*, *L. chagasi*, *L. mexicana*, *L. viannia* (V) *naiffi*, *L.* (V.) *braziliensis*, and *L.* (V.) *guyanensis* [6, 7]. Antroponotic cutaneous leishmaniasis (ACL) is caused by most *Leishmania* species, occur in most subtropical and tropical regions (for example, *L. major* from Africa and Asia, and *L. mexicana* from Central and South America), and by many species in the subgenus *Viannia*, which are limited to Latin America (for example, *L. (V) brasiliensis*) [6].

Old World cutaneous leishmaniasis caused by *L. tropica* (seen particularly in the Mediterranean Basin, the Middle East, Pakistan and India) and *L. infantum*, (found sporadically in the Middle East, South Russia, and rural regions of Africa). New World cutaneous leishmaniasis, caused by *L. brazilensis* and *L. mexicana* is seen in Mexica and South America. Leishmaniasis exists on every continent except Australia, the Pacific Islands and Antarctica. The parasites that cause leishmaniasis are found in 98 countries around the world [7].

L. tropica, *L. major*, *L. aethiopica* and *L. infantum* causes Old World cutaneous leishmaniasis. *Leishmania tropica* is mainly seen in urban areas and causes ACL. Related vectors are *Phlebotomus sergenti* and *Phlebotomus papatasii*. Lesions are generally dry and remain without ulceration. During the course lesions change to papules [1, 8].

L. tropica is found in urban areas. It causes ACL via the vectors *Phlebotomus sergenti* and *Phlebotomus papatasii*. The lesions are dry and stay for a long period of time without ulceration. Thereafter, painless lesions as papules, tubercles or nodules subside without scarring in 9–12 months [8].

L. major infections generally cause wet lesions in habitants of rural areas. Incubation period is less than 4 months. Lesions are usually seen on the legs. They start as acute papillary infection in the bite area and advances into pustular ulcers in 1–3 weeks. The infection is categorized as "zoonotic cutaneous leishmaniasis (ZCL)" due to the transmission to rodents, dogs via *Phlebotomus papatasi* [9].

L. infantum often causes small (0.5–1 cm), solitary ulcers on the face [10].

L. aetropica lesions are seen in the mouth and nose with local or wide spread dermal involvement. Lesions rarely become ulcerated. Healing may take 1–3 years or more [11].

L. braziliensis, *L. mexicana*, *L. amazoensis*, *L. guyanensis*, *L. panamensis* and *L. peruviana* cause New World cutaneous leishmaniasis [8, 12].

The disease caused by *L. braziliensis* is named "espundia." The infection leads to metastatic lesions, damages and deformation of the cartilage and soft tissues by affecting buccal and nasal mucosa [13].

L. mexicana causes usually solitary, painless lesions in the pinna. It leads to chronic lesions in the pinna called "chiclero's ulcer" [14].

L. guyanensis infection is consisted of flat ulcerative plaques with leakage in whole body. The lesion is called "pianbois" in Uruguay and Venezuella [15].

L. amazonensis causes solitary or multiple lesions with rarely spontaneous remission. It is rare in humans [8].

L. peruviana infection causes solitary or multiple painless dermal lesions they usually subsided spontaneously in 4–5 months. This infection is called uta [16].

Lesions of *L. panamensis* are ulcers without spontaneous improvement the reservoirs are dogs and monkeys [12].

L. venezuelensis generally causes solitary painless nodular lesion. [12, 17].

L. garnhami usually causes solitary or multiple lesions and may spontaneously be healed in 6 months [12].

The Eastern Hemisphere (Old World): leishmaniasis is found in some parts of Asia, the Middle East, Africa (especially in the tropical region and North Africa), and Southern Europe.

The Western Hemisphere (New World), leishmaniasis is found in some parts of Mexico, Central America, and South America. It is not found in Chile or Uruguay.

Leishmaniasis is seen in most tropical and subtropical regions with climate, mainly in South and Central America, Africa, Asia, and Southern Europe. The leishmaniasis is considered as one of the neglected tropical diseases (NTD) (**Figures 2** and **3**) [18].

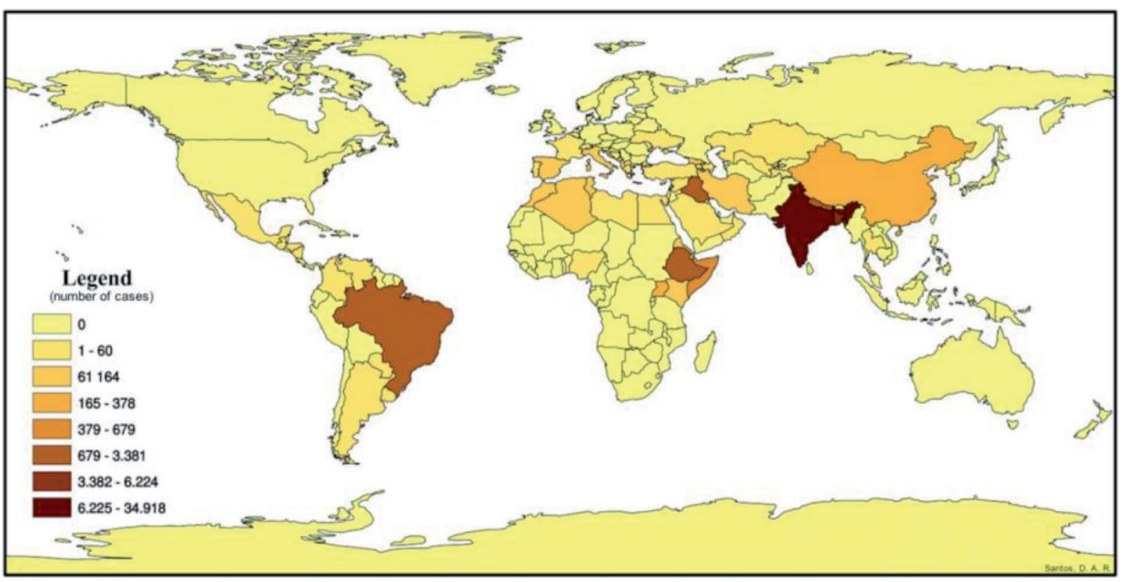

Figure 2.
World VL distribution in the last 10 years [19].

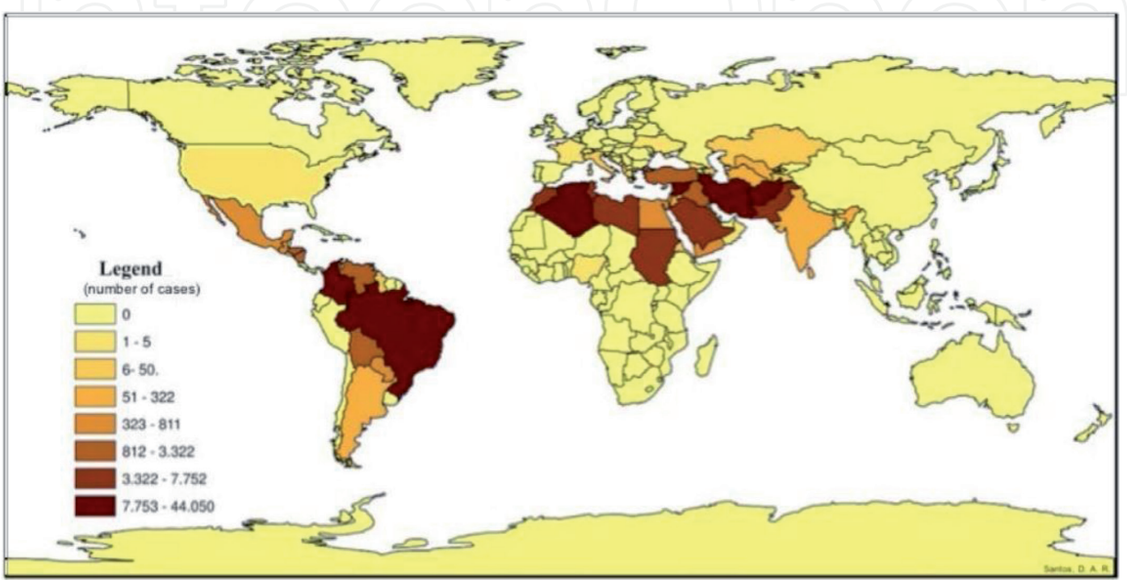

Figure 3.
World CL distribution in the last 10 years [19].

3. Epidemiology of leishmaniasis according to vector

a. *Phlebotomus* spp. (sandfly). (Old World).

b. *Lutzomyia* spp. (New World).

Humidity and moisture, whether from rainfall or in the soil, have often been identified as important for the sandfly, with humidity influencing breeding and resting [6].

Sandflies belonging to either *Phlebotomus* spp. (Old World) or *Lutzomyia* spp. (New World) are the primary vectors; domestic dogs, rodents, sloths, and opossums are amongst a long list of mammals that are either incriminated or suspected reservoir hosts [1, 21, 22]. Most of its foci in the Old World have a Mediterranean climate and sand fly vectors, usually *Phlebotomus* (Larroussius) species, *Phlebotomus* species (*P. papatasi*, *P. sergenti*, *Phlebotomus alexandri*, *P. tobbi*, *Phlebotomus syriacus*, *Phlebotomus neglectus*, *Phlebotomus perfiliewi*, *Phlebotomus galilaeus*, *Phlebotomus transcaucasicus*, and *Phlebotomus halepensis*) two *Sergentomyia* species (*Sergentomyia theodori* and *Sergentomyia dentata*), (*Phlebotomus ariasi* and *Phlebotomus perniciosus*, *Phlebotomus longicuspis*) can diapauses for human visceral leishmaniasis [21–24].

In contrast to malaria, there is little evidence for the effect of vector control in leishmaniasis because terrestrial habitat of *Phlebotomus* is mostly unknown.

4. Host

4.1 Human

Leishmania species are transmitted to human via vectors, blood transfusion, organ transplantation or vertically via transplacental route. Other factors that cause the transmission of the disease are contact with contaminated materials or needle stick injuries in the labs [25–27].

Leishmania-infected humans especially in poor socioeconomic conditions play a pivotal role as a reservoir in transmission of the agent to vectors or to other hosts. In another words, one can say that human beings contribute the disease transmission by themselves [26, 27]. Poor living conditions in adobe, wooden houses, barns create a tendency towards an increase of vectors [27–29].

In all three clinical types of *Leishmania* spp., antimonials (sodium stibogluconate [SSG]), miltefosin (MIL), amfoterisin B (AmB) veparomomisin (PMM)) are being used [30]. Children and people with immune suppression, HIV infection or malignant diseases cause rapid spread of leishmaniasis. Apart from these, undiagnosed or untreated infected people create an important risk factor. Especially drug resistance and high expense of the medication cause insufficient treatment [27–29]. The first drug resistance was reported in VL treatment against SSG and against MIL, in India and Nepal, respectively [31–33]. Later, resistance against MIL was also reported in one patient with HIV and another two patients with Indian origin [34, 35].

Verma et al. showed that the effectiveness of PMM was decreased by 6 times for the promastigote forms of *L. donavani* [36]. Invasion of macrophages by PMM-R parasites led to increased nitric oxide (NO), whereas the levels of reactive oxygen species (ROS) remained unchanged. This finding shows resistance of *Leishmania* spp. against PMM [36]. Similarly, Deep et al., reported high recurrence rates in patients with VL and PKDL when treated with MIL [37].

In conclusion, due to immune problems of the patient, co-existence of other diseases, inappropriate use of the drugs during the medical treatment of leishmaniasis, "drug resistance" may occur via gene over-expression, deletion, single nucleotide

*Leishmania*species	Disease	Countries (suspected)	Landscapes	Reservoir hosts	Vector
Old World					
L. donovani	AVL, DCL, CL	Northeast India, Nepal, Bangladesh, (Bhutan), Sri Lanka, Republic of China, Sudan, Ethiopia, (Chad), (Yemen), Kenya	Rural, peri-domestic	Human anthroponosis	*P. (Eu.) argentipes, P. (La.) orientalis*, *P. (Sy.) martini*
L. donovani	AVL	People's Republic of China	Rural, peri-domestic	Unknown	*P. (Pa.) alexandri*, *P. (Ad.)* species
L. donovanib (*L. archibaldi*)	AVL, ZVL, ML	Sudan, Ethiopia, (Chad), (Yemen)	Rural, *Acacia—Balanites* forest	Human anthroponosis	*P.* (*Larroussius*) *orientalis*
L. donovanib (*L. archibaldi*)	AVL, DCL	Sudan, Ethiopia, Kenya, (Uganda)	Rural, savannatermite mounds	Human anthroponosis	*P. (Sy.) martini*
L. infantum	ZVL, ZCL	Med Europe, North Africa, Southwest Asia, People's Republic of China	Rural, peri-domestic	Domestic dog, wild canids, domestic cat	*P. (La.) ariasi*, *perniciosus*
L. infantumc (*L. chagasi*)	VL, CL	Latin America: not Peru or Guianas	Rural, peri-domestic	Domestic dog, wild canids	*Lu. (L.) longipalpis*
L. major	ZCL	North Africa, Ethiopia, Kenya, Sudan, Meadle Asia India	Peri-domestic	Human anthroponosis	*P. papatasi*, *P. duboscqi*
Le. (*Le.*) *tropica*	ACL	North Africa, Middle East, Iran, Afghanistan	Urban	Peridomestic, including suburbs; human	*P.* (*Paraphlebotomus*) *sergenti*
Le. (*Le.*) *tropicac (Le.* (*Le.*) *killicki*)	ZCL	North Africa, MiddleEast, Sub-Saharan Africa	Rural	Rockyarid; hyraxes, Rodents	*P.* (*Adlerius*) *arabicus P.* (*La.*) *guggisbergi*
Le. (*Le.*) *aethiopica*;	ZCL,DCL, ML	Ethiopia, Kenya	Rural, Rocky highlands	Hyraxes	*P.* (*La.*) *longipes P.* (*La.*) *pedifer*
New World					
Leishmania (*Leishmania*) *infantum*	ZVL, ZCL	Latin America: not Peru, Guianas	Peridomestic, including suburbs	Domestic dog	*Lutzomyia* (*Lutzomyia*) *longipalpis*s.l.
Leishmania(*Viannia*) *braziliensis*	ZCL, ML	East of Andes: not Guyana, Suriname	Peridomestic, silvatic	Rodents, marsupials, dog	*L.* (*Psychodopygus*) *wellcomei L.* (*Nyssomyia*) *neivai L.* (*Ny.*) *whitmani*

***Leishmanias*pecies**	**Disease**	**Countries (suspected)**	**Landscapes**	**Reservoir hosts**	**Vector**
Le. (*V.*) *braziliensis*	ZCL, ML	West of Andes, northern Venezuela: not El Salvador	Peridomestic, silvatic	Rodents, marsupials, dog	*L.* (*Pifanomyia*) *ovallesi*
Le. (*V.*) *peruviana*	ZCL, ML	Peru	Peridomestic, silvatic	Rodents, marsupials, dog	*L.* (*He.*) *peruensis*s.l. *L.* (*Pf.*) *verrucarum*s.l.
Le. (*V.*) *guyanensis*	ZCL, ML	East of Andes: not Paraguay	Silvatic	Arboreal edentates, others	*L.* (*Ny.*) *umbratilis*
Le. (*V.*) *panamensis*	ZCL, ML	West of Andes, northern Venezuela: not Mexico, Belize, El Salvador	Silvatic	Arboreal edentates, others	*L.* (*Ny.*) *trapidoi L.* (*Ny.*) *ylephiletor L.* (*Ny.*) *edentula L.* (*Tricholateralis*) *gomezi*
Le. (*V.*) *shawi*	ZCL	Brazil	Silvatic	Arboreal	*L.* (*Trichophoromyia*) *ubiquitalis L.* (*Pf.*) *nuneztovari*
Le. (*V.*) *lainsoni*	ZCL	Bolivia, Peru, Brazil, French Guiana, Suriname	Silvatic	Rodent *Agouti paca*	*L.* (*Trichophoromyia*) *ubiquitalis L.* (*Pf.*) *nuneztovari*
Le. (*V.*) *colombiensis*	ZCL	Panama, Colombia, Venezuela	Silvatic	*Choloepushoffmanni*	*L.* (*He.*) *hartmanni*
Le. (*V.*) *naiffi*	ZCL	Brazil, French Guiana, Panama	Silvatic	*Dasypusnovemcinctus*	*L.* (*Ps.*) *ayrozai* and other species *L.* (*Ny.*) *trapidoi*c
Le. (*Le.*) *amazonensis*	ZCL, DCL	East of Andes: not Guyana, Paraguay	Silvatic, non-climax forest	Terrestrial rodents, Marsupials	*L.* (*Ny.*) *flaviscutellata*
Le. (*Le.*) *mexicana*	ZCL, DCL, ML	West of Andes, southern United States: not Peru	Silvatic, non-climax forest	Terrestrial rodents, Marsupials	*L.* (*Ny.*) *olmecaolmeca*
Le. (*Le.*) *venezuelensis*	ZCL, DCL	Northern Venezuela	Silvatic	Unknown	*L.* (*Ny.*) *olmecabicolor*

Abbreviations: TC, transmission cycle; A, anthroponotic; Z, zoonotic; V, visceral; C, cutaneous; M, mucosal; D, diffuse; L, leishmaniasis. P., Phlebotomus; Pa., Paraphlebotomus; Pf., Pifanomyia; Sy., Synphlebotomus La., Larroussius; Lu., Lutzomyia.

Table 2.
Disease types and transmission cycles of leishmaniasis worldwide [6, 20, 21].

polymorphisms generating stop codons or amplification of sets of genes [38–40]. This very important for epidemiological standpoint and thus proper use of drugs when needed should be stressed, and also new drug formulations and/or vaccine should be investigated.

Technological advances let the people travel all over the world. This may cause vectored spread or spread directly by infected people [41].

4.2 Dogs

Dogs are very important in terms of the epidemiology of leishmaniasis. All forms of leishmaniasis namely cutaneous, mucocutaneous and visceral types may be found in dogs. Since the infected dogs are important reservoir of the disease, their controls and treatments are mandatory for the disease control. Dogs as pets are being controlled by vets however stray or wild dogs, fox species like *Lycalopex vetulus* [42], *Cerdocyonthous* [43] may cause outbreaks. Dogs are natural hosts for *L. infantum*, *L. chagasi*, *L. tropica* and *L. peruviana* as well as being infected by them. Especially they are endemic in dogs in Mediterranean region, Asia and Latin America. *Leishmania infantum* is the causative agent of visceral leishmaniasis and it is prevalent especially in Mediterranean region. Vectors for this type are *Phlebotomus ariasi*, *P. major*, *P. perniciosus*, *P. longicuspis*, *P. chiensis*, *P. mongolensis*, *P. papatasi* [44, 45]. In the same region, the causative agent of zoonotic cutaneous leishmaniasis is *L. tropica* and the vectors are *P. perfilievi*, *P. papatasi* and *P. sergenti* [1, 46]. In South America, the causative agent of canine cutaneous leishmaniasis is *L. chagasi* and the vectors are *Lu. longipalpalis*, *Lu. evansi*, *Lu. gomezi* [1].

4.3 Rodents

Comparing to dogs, eradication of the infectious agent of leishmaniasis from the rodents is more difficult and even sometimes impossible.

Different rodents such as *Didelphis albiventris* (opossum), *Mus musculus* (domestic mouse), *Microtus socialis*, *Rattusrattus* (black rat), *Cercomys cunicularius* (wild rat), *Mesocricetus auratus* (Syrian hamsters) in America, Africa and Asia lead to spread of leishmaniasis [47–51].

Phlebotomus papatasi, vector of *L. tropica*, transmitted cutaneous leishmaniasis to small rodents such as *Psammomys obesus* (Israel), *Meriones crassus* (Israel), *Meriones libycus* (Iran), *Rhombomys opimus* (Iran), *Rhombomys opimus* (Iran), *Meriones sacramenti* (Egypt) [9].

Rattus rattus and *Rattus norvegicus* have been found naturally infected with *L. infantum* in the Mediterranean and in Next Orient endemic areas (**Table 2**) [49, 52, 53].

5. Transmission cycle

There are two different types of transmission;

1. In many geographic areas, infected people are not needed to sustain the transmission cycle of the parasite in nature; transmission cycle continue via the infected animals (rodents or dogs, felines). *Leishmania* infection in reservoir animals are specifically named; if it is in dogs, it is named as canine leishmaniasis whereas in cats, it is called feline leishmaniasis dogs species of *Leishmania* species in the reservoir in animals, canine leishmaniasis, which is in feline called leishmaniasis. *L. infantum* is the most common and important cause of canine leishmaniasis worldwide. The **zoonotic transmission** of *L.*

infantum, from canine to humans, is not only in the Mediterranean region where it may have originated, but also it may be found in many of the drier regions of Latin America. *Leishmania* species reported from dogs include *L. mexicana*, *L. donovani*, and *L. braziliensis*. These *Leishmania* species are occasionally reported from the cats. Cats are at risk of infection especially in areas where these parasites are endemic [6, 54, 55].

2. In some parts of the world, infected people are needed to sustain the cycle; this kind of transmission (human—*Phlebotomus*—human) is called **anthroponotic transmission**.

Full knowledge on these two transmission cycles is very important in effective prevention of leishmaniasis [54, 55].

6. Effect of deteriorated eco-system on spread of leishmaniasis

Unlike other parasites, it is extremely difficult to eradicate whole kinds of species of *Leishmania* in nature. This is contrary to some other parasites. As example *Plasmodium vivax* is specific to human, thus it can be eradicated by vector control. However, this is not the case for *Leishmania* spp. [54, 55].

There are many check points to establish the control of the disease. Firstly, all patients with leishmaniasis should be properly treated. *Leishmania* transmission is dependent on the togetherness of contaminated sandflies with the reservoir hosts, and humans. Additionally, climatic and environment factors are important, too.

As the development of chemical insecticides use such as dichlorodiphenyltrichloroethane (DDT) against mosquito was a key component of the eradication, similarly they were proposed to have an effect on the sandflies, vectors of visceral leishmaniasis [56–58]. Since DDT use is found to be harmful to the environment and people, its use is prohibited by the World Health Organization [59]. At the moment there isn't any strategy to control *Phlebotomine* by using insecticides by governments [60, 61]. Preliminary experiments for developing a vaccine against *Leishmania* spp. was reported [62]. However, the vaccine did not appear to protect against visceral leishmaniasis [63]. fucose-mannose ligand from an extract of *L. donovani* has been used in conjunction with a saponin adjuvant in attempts to vaccine [64]. Further studies are needed to develop an effective vaccine against leishmaniasis.

7. Summary

Leishmaniasis is still an important parasite disease in all over the world. The reasons are presence of many different species of *Leishmania*, and their ability to survive in many different organisms, such as vectors, dogs, rodents, humans. *Leishmania* spp. may cause different clinical scenarios by affecting different tissues and organs. As eukaryotic cells, *Leishmania* spp. can survive in the immune system of the most advanced organism, human. Presence of amastigote forms even in the hosts' defensive cells shows the strength of the parasite.

Leishmaniasis is an important public health problem. Thus, relevant public health policies such as education of the people especially in endemic areas, multidisciplinary approach, diagnosis, treatment will be helpful in the elimination of the disease. Additionally, further epidemiological studies as well as vaccination studies will continue to strive for eradication.

Author details

Tonay Inceboz
Department of Parasitology, Medical Faculty, Dokuz Eylul University, Izmir, Turkey

*Address all correspondence to: tonay.inceboz@gmail.com

References

[1] WHO Expert Committee. Control of the leishmaniasis: Report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 2010; 22-26 March. WHO Technical Report Series; 949:1-186. Available from: http://apps.who.int/iris/bitstream/10665/44412/1/WHO_TRS_949_eng.pdf

[2] Ghaffar A. Microbiology and Immunology Online, Parasıtology—Chapter Two Blood and Tıssue Protozoa Part 1 Trypanosomiasıs and Leishmaniasis. 2013. Available from: http://www.microbiologybook.org/parasitology/blood-proto.htm

[3] Okwor I, Uzonna J. Social and economic burden of human leishmaniasis. The American Journal of Tropical Medicine and Hygiene. 2016;**94**(3):489-493. DOI: 10.4269/ajtmh.15-0408

[4] Zijlstra EE. Visceral leishmaniasis: A forgotten epidemic. Archives of Disease in Childhood. 2016;**101**(6):561-567

[5] Gouzelou E, Haralambous C, Antoniou M, Christodoulou V, Martinković F, Živičnjak T, et al. Genetic diversity and structure in *Leishmania infantum* populations from southeastern Europe revealed by microsatellite analysis. Parasites & Vectors. 2013;**6**:342. DOI: 10.1186/1756-3305-6-342

[6] Ready PD. Biology of phlebotomine sand flies as vectors of disease agents. Annual Review of Entomology. 2013;**58**:227-250. DOI: 10.1146/annurev-ento-120811-153557

[7] de Vries HJ, Reedijk SH, Schallig HD. Cutaneous leishmaniasis: Recent developments in diagnosis and management. American Journal of Clinical Dermatology. 2015;**16**:99-109. DOI: 10.1007/s40257-015-0114-z

[8] Krotoski MJ. Medical Parasitology. 8th ed. London: W.B. Saunders Company; 1999. pp. 147-154

[9] Klaus SN, Frankenburg H, Ingber A. Epidemiology of cutaneous leishmaniosis. Clinical Dermatology. 1999;**17**:257-260. DOI: 10.1016/S0738-081X(99)00043-7

[10] Bensaid M, Guerbouj S, Saghrouni F, Fathallah-Mili A, Guizani I. Occurrence of *Leishmania infantum* cutaneous leishmaniasis in Central Tunisia. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2006;**100**:521-526. DOI: 10.1016/j.trstmh.2005.08.012

[11] Özbel Y, Töz ÖS. Leishmaniosis. In: Özcel MA, editor. Tıbbi Parazit Hastalıkları. 1.Baskı ed. İzmir: Meta Basım Matbacılık Hizmetleri; 2007. pp. 198-230

[12] Achtman JC, Ellis DL, Saylors B, Boh EE. Cutaneous leishmaniasis caused by *Leishmania* (Viannia) panamensis in 2 travelers. JAAD Case Reports. 2016;**2**:95-97. DOI: 10.1016/j.jdcr.2015.11.018

[13] Marsden PD. Mucosal leishmaniasis ("espundia" Escomel, 1911). Transactions of the Royal Society of Tropical Medicine and Hygiene. 1986;**80**:859-876. DOI: 10.1016/0035-9203(86)90243-9

[14] Calvopiña M, Martinez L, Hashiguchi Y. Cutaneous leishmaniasis "chiclero's ulcer" in subtropical Ecuador. The American Journal of Tropical Medicine and Hygiene. 2013;**89**:195-196. DOI: 10.4269/ajtmh.12-0690

[15] Lainson R, Shaw JJ, Ready PD, Miles MA, Póvoa M. Leishmaniasis in Brazil: XVI. Isolation and identification of *Leishmania* species from sandflies, wild mammals and man in north Para

state, with particular reference to *L. braziliensis guyanensis* causative agent of "pian-bois". Transactions of the Royal Society of Tropical Medicine and Hygiene. 1981;**75**:530-536. DOI: 10.1016/0035-9203(81)90192-9

[16] Llanos-Cuentas EA, Roncal N, Villaseca P, Paz L, Ogusuku E, Pérez JE, et al. Natural infections of *Leishmania* peruviana in animals in the Peruvian Andes. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1999;**93**:15-20. DOI: 10.1016/S0035-9203(99)90163-3

[17] Ovallos FG, Silva YR, Fernandez N, Gutierrez R, Galati EA, Sandoval CM. The sandfly fauna, anthropophily and the seasonal activities of Pintomyia spinicrassa (*Diptera*: *Psychodidae*: *Phlebotominae*) in a focus of cutaneous leishmaniasis in northeastern Colombia. Memórias do Instituto Oswaldo Cruz. 2013;**108**:297-302. DOI: 10.1590/S0074-02762013000300007

[18] WHO. Neglected Tropical Diseases, Hidden Successes, Emerging Opportunities. Geneva: World Health Organization; 2009. p. 59

[19] Aversi-Ferreira RAGMF, Galvão JD, da Silva SF, Cavalcante GF, da Silva EV, Bhatia-Dey N, et al. Geographical and environmental variables of leishmaniasis transmission. In: Claborn DM, editor. Leishmaniasis—Trends in Epidemiology, Diagnosis and Treatment. InTech; 2014. DOI: 10.5772/57546

[20] Pigott DM, Bhatt S, Golding N, Duda KA, Battle KE, Brady OJ, et al. Global distribution maps of the leishmaniases. eLife. 2014;**3**. DOI: 10.7554/eLife.02851

[21] Ready PD. Epidemiology of visceral leishmaniasis. Clinical Epidemiology. 2014;**6**:147-154. DOI: 10.2147/CLEP.S44267

[22] Amro A, Hamdi S, Lemrani M, Idrissi M, Hida M, Rhajaoui M, et al. Moroccan *Leishmania infantum*: Genetic diversity and population structure as revealed by multi-locus microsatellite typing. PLoS ONE. 2013;**8**:e77778. DOI: 10.1371/journal.pone.0077778

[23] Kavur H, Eroglu F, Evyapan G, Demirkazik M, Alptekin D, Koltas IS. Entomological survey for sand fly fauna in imamoglu province (cutaneous leishmaniasis endemic region) of Adana, Turkey. Journal of Medical Entomology. 2015;**52**:813-818. DOI: 10.1093/jme/tjv064

[24] Kasap OE, Belen A, Kaynas S, Simsek FM, Biler L, Ata N, et al. Activity patterns of sand fly (*Diptera*: *Psychodidae*) species and comparative performance of different traps in an endemic cutaneous leishmaniasis focus in cukurova plain, Southern Anatolia, Turkey. Acta Veterinaria. 2008;**78**:327-335. DOI: 10.2754/avb200978020327

[25] Silva Jde A, Araújo Ide M, Pavanetti LC, Okamoto LS, Dias M. Visceral leishmaniasis and pregnancy in renal transplanted patient: Case report. Jornal Brasileiro de Nefrologia. 2015;**37**:268-270. DOI: 10.5935/0101-2800.20150041

[26] de Silva AA, Silva Filho ÁPE, Sesso Rde C, Esmeraldo Rde M, de Oliveira CM, Fernandes PF, et al. Epidemiologic, clinical, diagnostic and therapeutic aspects of visceral leishmaniasis in renal transplant recipients: Experience from thirty cases. BMC Infectious Diseases. 2015;**25**(15):96. DOI: 10.1186/s12879-015-0852-9

[27] Fishman JA. Infections in immunocompromised hosts and organ transplant recipients: Essentials. Liver Transplantation. 2011;**17**(Suppl 3):S34-S37. DOI: 10.1002/lt.22378

[28] Alvar J, Aparicio P, Aseffa A, Den Boer M, Canavate C, et al. The relationship between leishmaniasis and

AIDS: The second 10 years. Clinical Microbiology Reviews. 2008;**21**:334-359. DOI: 10.1128/CMR.00061-07

[29] van Griensven J, Ritmeijer K, Lynen L, Diro E. Visceral leishmaniasis as an AIDS defining condition: Towards consistency across WHO guidelines. PLoS Neglected Tropical Diseases. 2014;**17**(8):e2916. DOI: 10.1371/journal.pntd.0002916

[30] Croft SL, Coombs GH. Leishmaniasis—Current chemotherapy and recent advances in the search for novel drugs. Trends in Parasitology. 2003;**19**:502-508

[31] Mittal MK, Rai S, Ashutosh, Ravinder, Gupta S, Sundar S, et al. Characterization of natural antimony resistance in *Leishmania donovani* isolates. The American Journal of Tropical Medicine and Hygiene. 2007;**76**(4):681-688

[32] Rijal S, Ostyn B, Uranw S, Rai K, Bhattarai NR, Dorlo TP, et al. Increasing failure of miltefosine in the treatment of Kala-azar in Nepal and the potential role of parasite drug resistance, reinfection, or noncompliance. Clinical Infectious Diseases. 2013;**56**(11):1530-1538. DOI: 10.1093/cid/cit102

[33] Mondelaers A, Sanchez-Cañete MP, Hendrickx S, Eberhardt E, Garcia-Hernandez R, Lachaud L, et al. Genomic and molecular characterization of miltefosine resistance in *Leishmania infantum* strains with either natural or acquired resistance through experimental selection of intracellular amastigotes. PLoS ONE. 2016;**11**(4):e0154101. DOI: 10.1371/journal.pone.0154101

[34] Srivastava S, Mishra J, Gupta AK, Singh A, Shankar P, Singh S. Laboratory confirmed miltefosine resistant cases of visceral leishmaniasis from India. Parasites & Vectors. 2017;**10**(1):49. DOI: 10.1186/s13071-017-1969-z

[35] Cojean S, Houze ÂS, Haouchine D, Huteau F, Lariven S, Hubert V, et al. *Leishmania* resistance to miltefosine associated with genetic marker. Emerging Infectious Diseases. 2012;**18**(4):704-706. DOI: 10.3201/eid1804.110841

[36] Verma A, Bhandari V, Deep DK, Sundar S, Dujardin JC, Singh R, et al. Transcriptome profiling identifies genes/pathways associated with experimental resistance to paromomycin in *Leishmania donovani*. International Journal for Parasitology: Drugs and Drug Resistance. 2017;**7**(3):370-377. DOI: 10.1016/j.ijpddr.2017.10.004

[37] Deep DK, Singh R, Bhandari V, Verma A, Sharma V, Wajid S, et al. Increased miltefosine tolerance in clinical isolates of *Leishmania donovani* is associated with reduced drug accumulation, increased infectivity and resistance to oxidative stress. PLoS Neglected Tropical Diseases. 2017;**11**(6):e0005641. DOI: 10.1371/journal.pntd.0005641

[38] Ponte-Sucre A, Gamarro F, Dujardin J-C, Barrett MP, LoÂpez-VeÂlez R, Garcõ Âa-HernaÂndez R, et al. Drug resistance and treatment failure in leishmaniasis: A 21st century challenge. PLoS Neglected Tropical Diseases. 2017;**11**(12):e0006052. DOI: 10.1371/journal.pntd.0006052

[39] Hefnawy A, Berg M, Dujardin JC, De Muylder G. Exploiting knowledge on *Leishmania* drug resistance to support the quest for new drugs. Trends in Parasitology. 2017;**33**(3):162-174. DOI: 10.1016/j.pt.2016.11.003

[40] Rastrojo A, García-Hernández R, Vargas P, Camacho E, Corvo L, Imamura H, et al. Genomic and transcriptomic alterations in *Leishmania donovani* lines experimentally resistant to antileishmanial drugs. International Journal for Parasitology: Drugs and

Drug Resistance. 2018;**8**(2):246-264. DOI: 10.1016/j.ijpddr.2018.04.002

[41] Kotton CN. Travel and transplantation: Travel-related diseases in transplant recipients. Current Opinion in Organ Transplantation. 2012;**17**:594-600. DOI: 10.1097/MOT.0b013e328359266b

[42] Lund PV. Fortsatte Bemaerkninger over Brasiliensuddö de Dyrskagning. Kongelige Danske Videnskabernes Selskabs Naturvidenskabeligeog Mathematiske Afhandlinger. 1842;**9**:1-136

[43] Lainson R, Elizabeth FR. *Lutzomyia* longipalpis and the eco-epidemiology of American visceral leishmaniasis, with particular reference to Brazil: A review. Memórias do Instituto Oswaldo Cruz. 2005;**100**:811-827. DOI: 10.1590/S0074-02762005000800001

[44] Capelli G. Asymptomatic and symptomatic dogs in endemic areas, their role in the epidemiology of canine leishmaniosis. In: The 2nd Canine Vector-Borne Disease (CVBD) Symposium; Mazara del Vallo, Sicily, Italy; 2007. pp. 58-63. Available from: http://www.cvbd.org/static/documents/digest/CVBD_Easy-to-digest_no_1_leishmaniosis.pdf [Accessed: 14 june 2016]

[45] Baneth G, Koutinas AF, Solano-Gallego L, Bourdeau P, Ferrer L. Canine leishmaniosis—New concepts and insights on an expanding zoonosis: Part one. Trends in Parasitology. 2008;**24**:324-330. DOI: 10.1016/j.pt.2008.04.001

[46] Banuls AL, Hide M, Prugnolle F. *Leishmania* and the leishmaniases: A parasite genetic update and advances in taxonomy, epidemiology and pathogenicity in humans. Advances in Parasitology. 2007;**64**:1-109-455-458. DOI: 10.1016/S0065-308X(06)64001-3

[47] Sherlock IA. Ecological interactions of visceral leishmaniasis in the state of Bahia, Brazil. Memórias do Instituto Oswaldo Cruz. 1996;**91**:671-683. DOI: 10.1590/S0074-02761996000600003

[48] Lainson R. The American leishmaniases: Some observations on their ecology and epidemiology. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1983;**77**:569-596. DOI: 10.1016/0035-9203(83)90185-2

[49] El-Adhami B. Isolation of *Leishmania* from a black rat in the Baghdad area, Iraq. The American Journal of Tropical Medicine and Hygiene. 1976;**25**:759-761

[50] Inceboz T, Lambrecht FY, Eren MŞ, Girginkardeşler N, Bekiş R, Yilmaz O, et al. Evaluation of ^{131}I-pentamidine for scintigraphy of experimentally *Leishmania tropica*-infected hamsters. Journal of Drug Targeting. 2014;**22**:416-420. DOI: 10.3109/1061186X.2013.878943

[51] Pourmohammadi B, Motazedian MH, Kalantari M. Rodent infection with *Leishmania* in a new focus of human cutaneous leishmaniasis, in northern Iran. Annals of Tropical Medicine and Parasitology. 2008;**102**:127-133. DOI: 10.1179/136485908X252223

[52] Pozzio E, Gradoni L, Bettini S, Gramiccia M. Leishmaniasis in Tuscani (Italy) V. Further isolation of *leishmania* from Rattusrattusin the province of Grosseto. Annals of Tropical Medicine and Parasitology. 1981;**75**:393-395 doi.org/10.5169/seals-312840

[53] Papadogiannakis E, Spanakos G, Kontos V, Menounos PG, Tegos N, Vakalis N. Molecular detection of *Leishmania infantum* in wild rodents (*Rattus norvegicus*) in Greece. Zoonoses and Public Health. 2010;**57**:e23-e25. DOI: 10.1111/j.1863-2378.2009.01264.x

[54] Ashford RW. The leishmaniases as model zoonoses. Annals of Tropical Medicine and Parasitology. 1997;**91**: 693-701. DOI: 10.1080/00034989760428

[55] Lukes J, Mauricio IL, Schönian G, Dujardin JC, Soteriadou K, Dedet JP, et al. Evolutionary and geographical history of the *Leishmania donovani* complex with are vision of current taxonomy. Proceedings of the National Academy of Sciences of the United States of America. 2007;**104**:9375-9380. DOI: 10.1073/pnas.0703678104

[56] Deane LM. Leishmaniose visceral no Brasil. Serviço Nacional de Educação Sanitária. 1956:1-162. Available from: http://www.scielo.br/scielo.php?script=sci_nlinks&ref=000065&pid=S0102-311X2008001200024000008&lng=en

[57] Deane LM. Epidemiologia e profilaxia do calazaramericano. Revista Brasileira de Malariologia. 1958;**10**:431-450. Available from: http://www.scielo.br/scielo.php?script=sci_nlinks&ref=000022&pid=S0102-311X2008000700026000001&lng=en

[58] Alencar JE. Profilaxia do calazar no Ceará Brasil. Revista do Instituto de Medicina Tropical de São Paulo. 1961;**3**:175-180. Available from: http://www.scielosp.org/scieloOrg/php/reflinks.php?refpid=S0034-89101990000500003000003&lng=pt&pid=S0034-89101990000500003

[59] World Health Organization (WHO). Control of Leishmaniasis. Tech Rep Series. 793, Geneva; 1990. 158 pp

[60] Alencar JE. Kala-azar in Brazil. Scientific Reports of the Istituto Superiore di Sanità. 1962;**2**:116-123

[61] Apostila UFPE. Available from: http://www.ufpe.br/biolmol/Leishmanioses-Apostila_on_line/infogerais.htm. 2013;**16**:99-109

[62] Mayrink W, Genero O, Silva JCF, Costa RT, Tafuri WL, Toledo VPCP, et al. Phase I and II open clinical trials of a vaccine against *Leishmania* chagasi infection in dogs. Memórias do Instituto Oswaldo Cruz. 1996;**91**:695-697. DOI: 10.1590/S0074-02761996000600006

[63] Genaro O, Pinto JA, Costa CA, França-Silva JC, Costa RT, Silva JC, et al. Phase III randomized double blind clinical trial on the efficacy of a vaccine against canine visceral leishmaniasis in urban area of Montes Claros, MG, Brazil. Memórias do Instituto Oswaldo Cruz. 1996;**91**(Suppl):166. Available from: http://memorias.ioc.fiocruz.br/component/k2/item/5932-immunology-212-phase-iii-randomized-double-blind-clinical-trial-on-the-efficacy-of-a-vaccine-against-canine-visceral-leishmaniasis-in-urban-area-of-montes-claros-mg-brazil

[64] Silva VO, Borja-Cabrera GP, Correia Pontes NN, Souza EP, Luz KG, Palatinik M, et al. A Phase III trial of efficacy of the FML-vaccine against canine calazar in an endemic area of Brasil (São Gonçalo do Amarante, RN). Vaccine. 2000;**19**:1082-1092. DOI: 10.1016/S0264-410X(00)00339-X