Chapter

Visceral Leishmaniasis: An Overview and Integrated Analysis of the Current Status, Geographical Distribution and Its Transmission

Kaushal Kumar Mahto, Pooja Prasad, Mohan Kumar, Intzar Ali, Vikram Vohra and Deepak Kumar Arya

Abstract

Visceral leishmaniasis (VL) is a vector–borne disease transmitted by Phlebotomine sandflies, with up to 350 million people are at risk of developing infection globally. VL has a severe influence on the impoverished and undeveloped populations among several subcontinents. Early and accurate diagnosis and treatment remain crucial to the management of VL, which still depends on vector control. The present chapter objectives are to provide an overview of visceral leishmaniasis and to raise knowledge of the most recent progress in this condition's management, treatment, and prevention. Additionally, this chapter could be helpful for comprehending the difficulties and knowledge gaps in eliminating this protozoan disease as well as for learning the planning lessons from the global management of diseases like malaria and tuberculosis.

Keywords: visceral leishmania, endemicity, surveillance, strategy, transmission control, treatment

1. Introduction

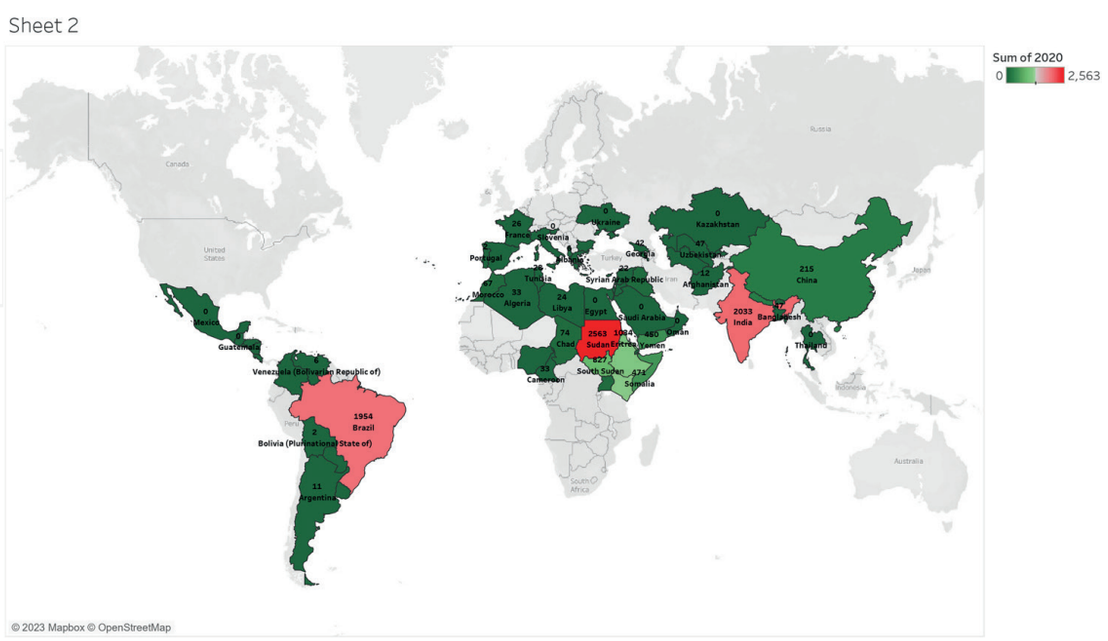
Visceral leishmaniasis (VL), also referred to as kala–azar in the Hindu vernacular, is caused by an obligate intracellular protozoon species of the genus *Leishmania* (Trypanosomatida: Trypanosomatidae) [1]. VL is transmitted by the bite of female sandfly's (Diptera, Psychodidae) [2]. VL is usually transmitted by the two species i.e. *Labrus donovani* and *L. infantum* (*L. chagasi infantum*) depending on the geographical area and generally affects internal organs such as spleen, liver, and bone marrow. It is one among the three leishmaniasis where it is life threatening, if untreated. It is mainly distributed throughout in tropical and subtropical areas and can range from asymptomatic to severe however; other forms such as cutaneous and mucosal leishmaniasis can cause substantial morbidity. VL caused by *L. infantum* mainly affects children under the age of 5 years whereas *L. donovani* infects all age groups and this may be due to malnutrition and other conditions of immunosuppression [3]. The

spatial distribution and the burden of VL is up surging year after year and it is now became a growing health concern worldwide. VL is thought to be an anthroponotic disease and is prevalent in several foci across Africa and the Indian subcontinent [4]. Most VL infections occur in the least developed countries and the most underdeveloped areas of middle–income countries. More than 90% of new cases reported to WHO in 2020 took place in ten countries: South Sudan, Sudan, Somalia,Yemen, Kenya, Ethiopia, Eritrea, India, Brazil, China respectively [5]. It should be possible to eradicate it with rapid case detection, treatment, and local vector control. Insecticide–impregnated materials, active case detection, and treatment are indeed the cornerstones of the current control techniques for VL.

Figure 1 represents the number of VL cases across 83 countries. In which 28 countries data are not available for the year 2020. Maximum number of VL cases were found from Sudan (2563) and most of the countries had very smaller number of cases which indicate endemicity of VL. Country like Sudan, Brazil, and India were reported maximum number of cases of VL.

2. VL and India

In India, it is estimated that 165.4 million population are at risk in 4 states viz., Bihar (33 districts, 458 blocks), Jharkhand (4 districts, 33 blocks), West Bengal (11 districts, 120 blocks), and Uttar Pradesh where kala–azar is endemic (6 districts, 22 blocks) [6] (**Table 1**). India reported 810 cases and 39 deaths in the year 2022. In order to overcome remaining obstacles in eradication of visceral leishmaniasis, India is stepping up its efforts. India has made strengthening a widely spread network of comprehensive primary health care facilities, backed by health education and social mobilization, a top priority in its national health strategy in order to attain universal



Map based on Longitude (generated) and Latitude (generated). Colour shows sum of 2020. The marks are labelled by 2020andCountry. Details are shown for Country.The view is filtered on Latitude (generated),Longitude (generated)andsum of 2020.The Latitude (generated) filter keeps non-Null values only.The Longitude (generated) filter keeps non-Null values only.The sum of 2020 filter includes everything.

Figure 1.
Endimicity status of Visceral Leishmaniasis worldwide in the year 2020 (source: https://apps.who.int/gho/data/node.main.NTDLEISHVEND?lang=en).

Affected States/UTs	2014		2015		2016		2017		2018		2019		2020		2021(P)		2022(P)	
	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
Assam	1	0	1	0	0	0	0	0	0	0	—	—	—	—	—	—	—	—
Bihar	7615	10	6517	5	4773	0	4127	0	3423	0	2416	0	1427	0	893	20	547	26
Delhi*	0	0	0	0	0	0	0	0	0	0	—	—	—	—	—	—	—	—
Jharkhand	937	0	1262	0	1185	0	1358	0	752	0	541	0	424	0	275	5	187	8
Kerala	0	0	4	0	2	0	0	0	6	0	4	0	1	0	—	—	3	0
Punjab*	0	0	1	0	0	0	0	0	0	0	—	—	—	—	—	—	—	—
Sikkim	5	0	5	0	1	0	0	0	0	0	—	—	3	0	1	0	1	0
Uttarakhand	4	0	3	0	2	0	2	0	0	0	—	—	—	—	—	—	—	—
Uttar Pradesh	11	0	131	0	107	0	115	0	110	0	97	0	55	3	49	1	22	1
West Bengal	668	1	576	0	179	0	156	1	95	3	87	6	57	3	58	2	49	4
Total	9241	11	8500	5	6249	0	5758	1	4386	3	3145	6	1967	6	1276	28	810	39

** Imported.*
C = Cases, D = Deaths, P = Provisional, — = Data not available.

Table 1.
VL cases and deaths in India since 2014 [7].

health coverage. For instance, there is one community health volunteer, or certified social health activist (ASHA), for every 1000 residents of a village. India now uses a 5% wettable powder formulation of alpha–cypermethrin for indoor residual spraying. Sandflies that settle on surfaces of sprayed walls are killed by it.

3. VL and suspected countries

There are 53 *Leishmania* species found worldwide in five genera (*Leishmania, Viannia, Sauroleishmania, L. enrietti complex, and Paraleishmaia*) and 31 species are known to be mammalian parasite and out of which approximately 20 different species of *Leishmania* infect animals, reservoir host includes domestic dogs and cats, wild canids and many of them can contribute to leishmaniasis in humans [8] (**Table 2**).

Major risk factors associated with VL are socioeconomic conditions, malnutrition, population mobility, environmental changes, and climate changes.

4. Growth and development of sandfly

Sandflies are tiny holometabolous insects, completes their development in four stages i.e. egg, larva, pupa and adult (**Figure 2**). Female sandflies usually lay 30–70 eggs during a single gonotrophic cycle, which are deposited in cracks and holes in the ground or in building, animal burrows and among tree roots [15]. Eggs are elongated, oval–shaped and pale at first and darkening on exposure to air. Larvae feed on dead organic material. Larvae are mainly scavengers, feeding on organic matters such as dead and decaying leaves, decomposing insets etc. The pupal stage lasts 6–13 days before the adult sandflies emerge.

Visceral leishmaniasis			
Causative parasites	**Countries (suspected)**	**Reservoir hosts**	**Reference**
L. donovani	Northeast India, Nepal, Bangladesh, Bhutan, Sri Lanka	Human	[9]
L. donovani	People's Republic of China	Unknown	[10]
L. donovani	Sudan, Ethiopia, Chad, Yemen	Human	[11]
L. donovani	Sudan, Ethiopia, Kenya, Uganda	Human	[12]
L. infantum	Med Europe, North Africa, Southwest Asia, People's Republic of China	Domestic dog, wild canids, Domestic cat	[4]
L. infantum	Latin America: not Peru or Guianas	Domestic dog, wild canids	[11]
L. tropica	Central and North Africa, Middle East, Central Asia, India	Humans, Mammals	[13]
L. martiniquensis	Martinique, Thailand	Humans, Mammals	[14]

Table 2.
Suspected countries with reservoir hosts of visceral leishmaniasis worldwide.

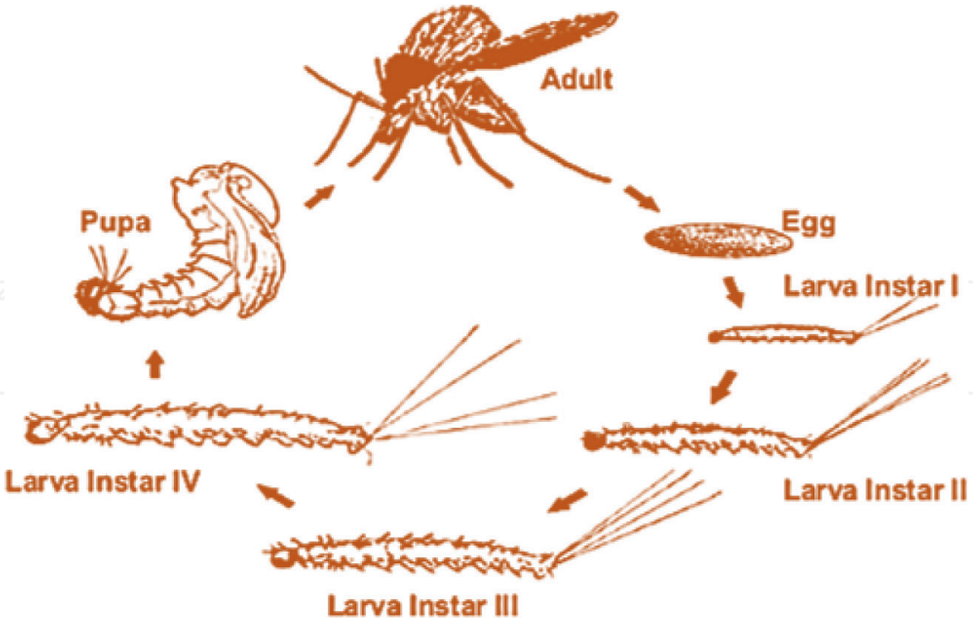


Figure 2.
A complete life cycle of sandfly.

4.1 Life cycle of *Leishmania* parasite in sandfly and host

The life cycle often involves two hosts: a phalebotomine sandfly and a vertebrate host (such as a dog or human).

According to Dawit [16], there are two evolutive forms: promastigotes for invertebrate hosts and amastigotes for vertebrate hosts.

The Following steps are involved to complete the life cycle of visceral leishmaniasis vector sandfly.

- The vector insect regurgitates the parasites when taking its blood meal.
- The host's macrophages and other mononuclear phagocytic cells phagocytose the promastigotes.
- Promastigotes transform in amastigotes and it infects other phagocytic cells.
- When sandfly ingest blood meal from another host the amastigotes are also ingested along with the blood meal.
- In the sandfly, the amastigotes develop into promastigotes in the gut, and migrate to the proboscis and the cycle continues.

The life cycle of the *Leishmania* parasite is indicated in below in **Figure 3**.

4.2 Source of infection

In both urban and rural environments, the domestic dog (*Canis familiaris*) is the primary reservoir. Foxes (*Cerdocyon thous* and *Lycalopex vetulus*) and other marsupials are among the identified reservoirs in the wild (*Didelphis spp.)* [17]. In a study

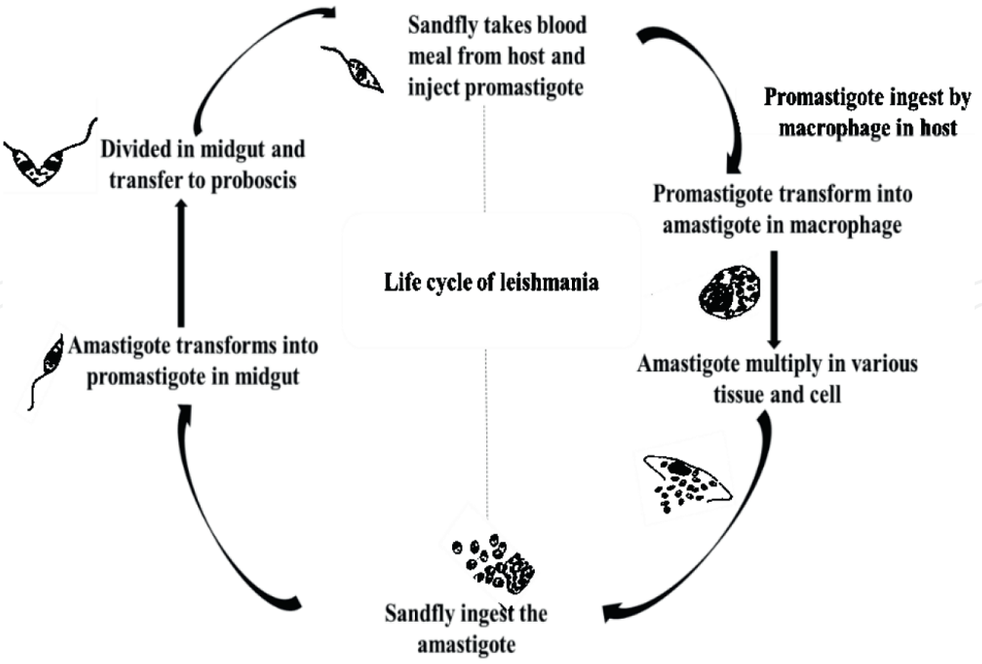


Figure 3.
Life cycle of Leishmania parasite in host and sandfly.

conducted in Iran, Gavgani *et al.* [18], the use of collars medicated with deltamethrin decreased the incidence of infection in dogs (by 54%) and children (by 43%). If a successful vaccine could be devised, vaccination of dogs would be the best approach.

4.3 Mode of transmission of VL

Leishmaniasis is caused the bite of infected female phlebotomine sand flies. The infected sand flies regurgitates the parasites infective stage (i.e., promastigotes) during blood meals According to some research studies the use of needles also contributes to parenteral and congenital transmission. No direct transfer occurs from one person to another [17]. The kind of transmission where (human—sandfly—human) involved is known as anthroponotic transmission because it occurs in some areas of the world where infected individuals are needed to keep the cycle going. For instance, the spread of *L. donovani* is anthroponotic in the Indian subcontinent (South Asia). Early diagnosis and appropriate treatment of those who are infected in these areas can act as a control strategy, whereas insufficient care can result in the development and spread of drug resistance. Spraying with residual–action pesticides and using bed nets sprayed with long–lasting insecticides may offer protection since the spread is intra– and peridomiciliary (rather than sylvatic).

4.4 Signs and symptoms

A wide spectrum of clinical manifestations, from mild to moderate to severe clinical symptoms, are present in the infection. Although it can be as long as 24 months, the incubation phase usually lasts between 2 and 6 months.

Clinical symptoms visceral infection has the following stereotypical symptoms [3, 19].

- Fever

- Weight loss
- Hepatosplenomegaly
- Pancytopenia
- Hypergammaglobulinemia

Lymphadenopathy has been reported in a few locations, most significantly Sudan and South Sudan. Other signs and symptoms include jaundice, bleeding from the mouth or nose, abdominal fluid buildup, respiratory issues, gastrointestinal issues including vomiting and diarrhea, and in extreme instances, malnutrition and lower limb edoema. In these persons deaths are eventually brought on by bacterial infection or hemorrhage.

Despite the fact that the terms kala–azar and visceral leishmaniasis are occasionally used interchangeably, kala–azar—which in Hindi is described as "black fever"—is frequently used to refer to severe (advanced) cases of visceral leishmaniasis. If untreated, visceral leishmaniasis in its most severe forms typically causes mortality, either directly from the disease or indirectly through its side effects, such as secondary Mycobacterium infection or hemorrhage.

5. Post–kala–azar dermal leishmaniasis

The dermal leishmaniasis known as post–kala–azar dermal leishmaniasis (PKDL), which typically follows visceral leishmaniasis, manifests as a macular, papular, or nodular rash on the face, upper arms, trunks, and other areas of the body [20]. The infection is said to develop in 5–10% of kala–azar patients, and it mostly affects people in East Africa and the Indian subcontinent [21] (**Table 3**). India reported 613 cases in the year 2022 where state Bihar has the heighted number of cases reported (311) followed by Jharkhand (164), West Bengal (109), and Uttar Pradesh (29). Although it can develop earlier, it often manifests 6 months to a year or more after kala–azar has purportedly been treated [6]. The Kala-azar Elimination Program (KAEP) is built around five pillars: surveillance, vector management, societal mobilization, early case detection for rapid diagnosis, treatment, and operational research. *Leishmaniasis* is thought to be transmitted by people who have PKDL.

6. VL and HIV co–infection

Due to the vulnerability of HIV–infected patients to the disease, *leishmania* and HIV confections have been a challenge to the treatment and eradication of visceral leishmaniasis. HIV and *leishmania* reinforce one another, creating serious clinical and public health challenges. Both conditions induce immune system suppression, which leads to increased death rates, exposure to drugs with higher toxicity, and more severe morbidity with fewer available treatments and higher rates of relapse. The coinfection was first identified in southern Europe in the middle of the 1980s, but is now known to exist in as many as 45 countries [6]. Brazil, Ethiopia, and the Indian state of Bihar have all recorded increased incidence. In India the subsequent cases of VL + HIV has been decreased from 9241 in 2014 to 881 cases in 2022 (**Table 4**).

Affected States	2014	2015	2016	2017	2018	2019	2020	2021 (P)	2022 (P)
	C	C	C	C	C	C	C	C	C
Bihar	119	247	542	593	731	439	351	453	311
Jharkhand	81	153	873	1211	361	281	193	208	164
West Bengal	221	255	240	166	87	51	39	59	109
Uttar Pradesh	0	0	2	12	66	50	34	50	29
Total	421	655	1657	1982	1245	821	617	770	613

C = Cases, P = Provisional.

Table 3.
PKDL situation in India since 2014 [7].

Affected States	2014	2015	2016	2017	2018	2019	2020	2021 (P)	2022(P)
	C	C	C	C	C	C	C	C	C
Bihar	NR**	40	120	181	146	121	75	74	61
Jharkhand		2	3	8	6	3	7	4	6
West Bengal		3	5	3	1	0	3	1	4
Uttar Pradesh		0	0	0	0	0	0	2	0
Total		45	128	192	153	124	85	81	71
Grand Total VL + HIV (VL)	9241	8545	6377	5950	4539	3269	2052	1357	881

*NR** = Not Reported, C = Cases, P = Provisional.*

Table 4.
VL and HIV coinfection status and situation in India from 2014 onwards [7].

Liposomal amphotericin B injections are the current treatment standard for HIV/visceral leishmaniasis co–infection (LAmB). The new treatment regimen combines LAmB and miltefosine, an oral medication. Patients who are co–infected are at risk of developing a variety of forms of stigma and human rights issues in addition to other comorbid conditions including TB and cryptococcal meningitis. The co–infection of pulmonary TB with visceral leishmaniasis is a problem for public health in many countries. *Leishmania* infection can change the immune system's protective response to the BCG TB vaccine [22].

7. Prevention and control

No vaccination exists to protect against VL disease, however; the following are some preventive care practices for the human population to prevent vector contact [3].

1. For the human population: Avoid outdoor activities from dusk to dawn, use mosquito nets, wear protective clothes, and use insect repellents are some of the recommended personal protection measures to prevent contact with vectors.

People with clinical symptoms of the disease should receive treatment as soon as possible.

2. For vector control: Preventive methods for vector control are similar to those for cutaneous leishmaniasis in that they focus on integrated management strategies in environmental sanitation. It is recommended as a control method to apply residual insecticides safely.

3. To control the urban reservoirs: In addition to using personal protective collars on dogs, recommended preventive measures have included the placement of mosquito–proof meshes in dog kennels to keep away sandflies. In the Americas, dogs are the primary host of visceral leishmaniasis, which helps to keep the parasite alive in populated areas. As a result, it is advised to undertake canine serological surveys in areas with endemic transmission, and when a dog tests positive for the parasite, compassionate euthanasia is urged.

Drugs that are already available in the market have significant limitations in terms of cost, stability, resistance, and safety. When administered alone, they have a poor tolerability, a prolonged course of treatment, and are challenging to deliver. Most often, pentavalent antimonials are used to treat visceral leishmaniasis. However, while choosing a medicine, it is important to take the patients' clinical circumstances, the existence of any co–infections, and pregnancy in to the consideration (**Table 5**).

8. Diagnosis

Clinical: People from endemic areas are considered a high clinical suspicion of disease if they have a chronic condition, an unexplained fever, and suggestive signs and symptoms [3].

Laboratory: Following immunological and parasitological tests are performed to treat VL condition. The rapid immunochromatographic test based on recombinant rK39 antigen and the alternative Direct Agglutination Test (DAT) to confirm infection are the only immunological tests currently available at the primary level. Other levels of care also use indirect immunofluorescence (IIF) and enzyme immunoassay (ELISA) [24, 25].

Drugs	Issues
Pentavalent antimonials (Sodium stibogluconate and meglumine antimoniate)	Resistance, toxicity in HIV coinfection higher costs
Amphotericin	Need for intravenous infusion dose–limiting toxicity
Lipid–associated liposomal	Cost and cost effectiveness reportedly more effective and less toxic, intolerance and HIV–*leishmania* co–infection.
Colloidal dispersion	Should be administered in hospital setting
Lipid complex Pentamidine	Increasing unresponsiveness (in India)

Table 5.
Anti–leishmanial drugs in current use and issues [23].

Figure 4.
Methods used for the diagnosis of Visceral leishmaniasis.

By conducting direct examinations or isolating parasites in culture, parasitological procedures can identify parasites in affected organs, primarily the bone marrow (in vitro). PCR could also be used to find out *Leishmania* infection (**Figure 4**).

9. Planning lessons from the global management of diseases like malaria and tuberculosis

- Monitoring disease trends, evaluating the effectiveness of control measures, and supporting national leishmaniasis control programmes financially and technically.

- Encouraging the development and use of leishmaniasis prevention measures, including as vaccinations, diagnostic tools, and safe, efficient, and affordable therapeutics.

- Creating norms and policies based on scientific evidence, ensuring their application, and preventing and controlling leishmaniasis Healthcare professionals should receive pre- and post-assessment training.

- Digital data reporting employing mobile application surveillance tools can be utilized for effective control and successful programme in the system.

- To decide whether to use alternative therapies, it is necessary to rigorously and continuously assess resistance. Insecticides and next-generation drugs should both be the subject of concurrent study.

10. Conclusion

In high–burden countries, early detection, management, and treatment results should be improved by good community knowledge of the condition, the availability of resources, the development of clinical and health professionals' capacities, and reliable surveillance data. In summary, there is a strong need for continuous investment in VL diagnostic, treatment, and prevention, even though much can be accomplished with the already available tools and techniques. All of the existing drugs have one or more limitations, thus further funding for drug development is still desperately necessary to fill the pipeline with novel drugs. The investigation of combination therapy using already available medicines continues to be a top goal in the meantime. In areas where *L. infantum* is prevalent, novel approaches to reduce the animal reservoir (such as dog collars) or minimize human infection are needed (such as insecticide impregnated bed nets or blankets).

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Conflict of interest

The authors declare that they have no known competing financial interests or personal ties that would seem to have influenced the work presented in this study.

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