

# A Review of Leishmaniasis in Eastern Africa

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## Citation

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## Abstract

**Objective** The review presents the epidemiology of leishmaniasis in the Eastern Africa region.

**Methods** We searched Pub Med and MEDLINE with several key words—namely, “leishmaniasis”; “cutaneous”, “diffuse cutaneous”, “mucosal”, and “visceral leishmaniasis”; “kala azar” and “post kala azar dermal leishmaniasis”—for recent clinical and basic science articles related to leishmaniasis in countries in the Eastern Africa region.

**Results** Poverty, wars, conflicts and migration have significantly aggravated leishmaniasis in Eastern Africa. Of particular concern is the increasing incidence of Leishmania-HIV co-infection in Ethiopia where 20–40% of the persons affected by visceral leishmaniasis are HIV-co-infected. Sudan has the highest prevalence rate of post kala-azar dermal leishmaniasis (PKDL) in the world, a skin complication of visceral leishmaniasis (VL) that mainly afflicts children below age ten.

**Conclusion** In view of its spread to previously non-endemic areas and an increase in imported cases, leishmaniasis in Eastern Africa should be considered a health emergency.

## LEISHMANIASIS: THE NEGLECTED DISEASE

Leishmaniasis, a disease caused by obligate intracellular and kinetoplastid protozoa of the genus *Leishmania*, is an old but largely unknown disease that afflicts the World's poorest populations. The disease is transmitted by the bites of infected sandflies that belong to the *Phlebotomus* and *Lutzomyia* genera in the Old and the New World respectively<sup>[1]</sup>. Neglected by researchers and funding agencies, leishmaniasis is endemic in 88 countries of the World in which 350 million people who are considered at risk of infection live<sup>[2]</sup>. In these countries, it is estimated that 80% of the population earn less than \$2 a day<sup>[3]</sup>.

The global burden of leishmaniasis has remained stable for some years, causing a morbidity and mortality loss of 2.4 million disability adjusted life-years (DALYs) and approximately 70,000 deaths, a significantly high rank among communicable diseases<sup>[4]</sup>. There are two million new cases of leishmaniasis annually and 14 million infected people worldwide<sup>[5]</sup>.

The leishmaniasis are characterized by a spectrum of clinical manifestations: ulcerative skin lesions developing at the site of the sandfly bite (localized cutaneous leishmaniasis [LCL]); multiple non-ulcerative nodules (diffuse cutaneous leishmaniasis [DCL]); destructive mucosal inflammation

(mucosal leishmaniasis, MCL); and disseminated visceral infection (visceral leishmaniasis, VL)<sup>[4]</sup>. The outcome of infection depends on the species of *Leishmania* parasites and the host's specific immune response<sup>[6]</sup>.

Leishmania-Human Immunodeficiency Virus (HIV) co-infection has surged as a major complication of leishmaniasis and has ignited calls for the recognition of leishmaniasis as an Acquired Immunodeficiency Syndrome (AIDS) defining illness<sup>[7]</sup>. In Africa, particularly Ethiopia and Sudan, it is estimated that 70% of adults with VL also have HIV infection<sup>[8]</sup>.

Leishmaniasis is endemic to countries mostly in the north, central, east, west and the Horn of Africa<sup>[9,10]</sup>. However, much of the disease is concentrated in the eastern African region. In this region, VL is caused by *Leishmania donovani* and is endemic in remote parts of Sudan, Somalia, Ethiopia, Kenya and Uganda<sup>[11,12]</sup>. Visceral leishmaniasis in this part of Africa causes at least 4 000 deaths annually, a loss of approximately 385 000 DALYs<sup>[13]</sup>.

Sudan is one of the five countries that constitute 90% of VL cases in the World <sup>[2]</sup>. The highest incidence of post-kala-azar dermal leishmaniasis in the world is also found in Sudan<sup>[14]</sup>. The disease contributes significantly to the

propagation of poverty, because treatment is expensive and hence either unaffordable or it imposes a substantial economic burden, including loss of wages<sup>[5]</sup>. Current control measures against leishmaniasis rely on chemotherapy to alleviate disease and on vector control to reduce transmission. To date, there is no effective vaccine in routine use against leishmaniasis<sup>[15]</sup>.

It has been postulated that there is an African origin for Old World species of *Leishmania* complex consisting of *L. donovani*, *L. infantum*, *L. tropica*, *L. major* and *L. aethiopica*, probably from an ancestral origin in East Africa<sup>[16]</sup>. Further evidence is derived from the fact that *L. aethiopica* occurs only in the Ethiopian and Kenyan highlands, its reservoir is the rock hyrax and its vector is *P. larroussius*. Due to its restricted geographical range, it seems reasonable to assume an African origin for this species as well as for other *L. (Leishmania) – hyrax* systems that occur in Africa such as that found in Namibia<sup>[17]</sup>.

### LEISHMANIASIS IN SUDAN

In Sudan, visceral, mucocutaneous and cutaneous leishmaniasis are prevalent. It is one of the five countries in the World that constitute 90% of VL cases and the highest incidence of post-Kalazar dermal leishmaniasis (PKDL)<sup>[214]</sup>. The civil wars in the north and the south of the country have aggravated the situation for the last two decades.

Since its resumption in 1983, the civil war in Sudan has resulted in estimates of over 2 million dead, 4 million internally displaced, and over 400 000 refugees<sup>[18]</sup>. The war has seriously affected health care systems and resources throughout the country, but especially in the south where many of the existing health structures have been destroyed. There has also been wide-scale displacement of qualified health staff, and drugs and medical equipment are insufficient in most areas. Médecins Sans Frontières (MSF) has been active in Sudan since 1985, where it has been providing medical humanitarian assistance to populations affected by war and/or epidemics, in various parts of the country, both in government- and rebel-controlled areas<sup>[18]</sup>.

From 1989 to 2002, MSF treated 51 000 cases of primary VL, relapsed VL, and post-kala-azar dermal leishmaniasis (PKDL) in Sudan. Almost 43 000 primary VL patients were cured (cure rate 90.8%), and 3900 patients died during treatment (death rate 8.2%). Despite the relatively high cost of treatment, the cost-effectiveness of this humanitarian intervention is very favourable due to the high effectiveness

of the treatment<sup>[19]</sup>. Especially in southern Sudan, where even basically trained local staff is scarce, good treatment outcomes can be achieved only when diagnostic, treatment, and patient management procedures are governed by strict protocols and strictly supervised<sup>[20]</sup>. Improvement of care systems and protocols are still contributing to progress in quality of care provided, and over the past 6 years cure rates in primary VL are still increasing, and have now reached almost 95%<sup>[21]</sup>. Although not yet documented in Africa, resistance to pentavalent antimonials is common in India<sup>[22]</sup>.

### VISCERAL LEISHMANIASIS IN SUDAN

Sudanese VL has been known since 1904 to be endemic along the Blue Nile where it enters Ethiopia and its tributaries<sup>[23]</sup>. The causative agent of VL in Sudan as in other regions of the Old World is *L. donovani*, and the main sandfly vector is *Phlebotomus orientalis* whose habitat is Acacia-Balanites woodland and black cotton soils<sup>[2425]</sup>. Anthroponotic transmission is probably the main transmission cycle, especially during epidemics, because no animal species has yet been definitively identified as a reservoir<sup>[26]</sup>. Throughout the 20th century, VL has been reported in southern Sudan, and major outbreaks have followed population movement, flooding, food shortages, and conflict<sup>[27]</sup>. The worst recorded epidemic probably killed 100,000 people in the western Upper Nile area of southern Sudan from 1984–1994, a loss of one-third of the population of that area<sup>[2829]</sup>. Médecins Sans Frontières–Holland has been running VL treatment centers since 1989, and 120,000 patients were treated by MSFH in southern Sudan between 1989 and February 2002<sup>[26]</sup>.

### MUCOCUTANEOUS LEISHMANIASIS IN SUDAN

Sudanese mucosal leishmaniasis is a chronic infection of the upper respiratory tract and/or oral mucosa caused mainly by *Leishmania donovani*<sup>[3031]</sup>. The disease occurs in areas of the country endemic for visceral leishmaniasis, particularly among Masalit and other closely related tribes in western Sudan. The condition usually develops during or after an attack of visceral leishmaniasis, but in most cases it is a primary mucosal disease. Unlike South American mucocutaneous leishmaniasis, mucosal leishmaniasis in Sudan is not preceded or accompanied by a cutaneous lesion<sup>[30]</sup>. Pathologically, the lesions show a mixture of macrophages, plasma cells and lymphocytes. An epitheloid granuloma may also be found. Parasites are scanty. Diagnosis is established by demonstration of parasites in smears or biopsies, by culture or positive results in the direct

agglutination test and leishmanin skin test. Patients respond well to treatment with pentavalent antimony compounds [31].

## **POST KALA-AZAR DERMAL LEISHMANIASIS IN SUDAN**

The first case of PKDL in Sudan was reported in 1938 by Kirk and Drew [32]. PKDL, a complication of visceral leishmaniasis, is mainly seen in Sudan as in India where it follows treated VL in 50% and 5-10% of cases respectively[33]. In Sudan, the disease may begin almost simultaneously with kala-azar but the interval between kala-azar and PKDL in eastern Sudan is 0.5-13 months[34]. Like VL, PKDL patients in Sudan are mostly children, with a mean age of 6 years and an equal number of boys and girls are affected[34]. In the 1990s, a severe VL outbreak occurred in the endemic area in eastern Sudan with incidence rates in one village of 20.4-38.4/1000 person-years, out of which 56% of the cases developed PKDL[35].

A study on the natural history of PKDL in the same endemic area indicated that the mean duration of PKDL was 9.7 months (range 2-28 months) before clearing[34]. Unlike in India, the disease in Sudan may occur while a patient is undergoing treatment for VL[33]. The disease is characterized by rashes which may range from papular or nodular in 51% of the patients, maculopapular in 23%, micropapular in 17% and macular rashes in 9% of the patients[36]. The rash usually begins around the mouth from where it spreads to other parts of the body depending on severity[33]. Further studies show a correlation between the interval between VL and PKDL, the more severe the cutaneous symptoms[37]. Spontaneous healing frequently occurs in most patients afflicted by PKDL in Sudan. However, patients with severe PKDL are treated with sodium stibogluconate and liposomal amphotericin B[38]. PKDL patients harbour parasites in their skin and are believed to be an important reservoir of infection and possibly epidemics in endemic foci[33].

## **CUTANEOUS LEISHMANIASIS IN SUDAN**

In Sudan, CL was first reported in 1910[39] and then the disease was reported in different parts of the country[40]. The first outbreak of CL in the Shendi Atbra area of Sudan was reported by Abdalla & Sharief in 1978[42]. The two studied 21 CL cases and classified the lesions into three main types: (a) nodule-ulcerative and nodular, (b) ulcerative and (c) diffuse infiltrative types[42]. Another severe outbreak of CL was reported by El Safi in 1988 [43].

Cutaneous leishmaniasis caused by *Leishmania major*

*zymodeme LON-1* is endemic in many parts of Sudan. The vector is *P. papatasi* and the animal reservoir is probably the Nile rat *Arvicanthus niloticus*[44]. Self-healing CL, usually occurs within 1 year but occasionally its duration is prolonged and treatment is required. The clinical forms of CL in Sudan are ulcers, nodules and noduloulcerative lesions, mainly on the exposed parts of the skin[45]. However, uncommon lesions that were difficult to recognize as *Leishmania* infections including mycetoma-like lesions, lesions that resembled *L. tropica* infection and Kaposi lesions in one HIV/AIDS patient with Kaposi's sarcoma and *Leishmania* parasites have been reported. Most of these uncommon clinical forms were difficult to treat[45].

## **LEISHMANIASIS IN KENYA**

In Kenya, both CL and VL are endemic[46]. In addition, PKDL has also been reported[47]. The leishmaniasis have been known to be endemic in parts of Kenya from as far back as early in the 20th century[48].

## **VISCERAL LEISHMANIASIS IN KENYA**

Visceral leishmaniasis was first reported in Kenya following an outbreak in the King's African Rifles troops encamped north of Lake Turkana in southwest Ethiopia in the 1940s[49]. The disease in Kenya is caused by *L. donovani* and transmitted by *P. martini* though other vectors including *P. orientalis* have been reported[46]. Man is the only known reservoir[46,50]. Since then Turkana, Baringo, Kitui, West Pokot, Machakos, Mwingi, Meru, Wajir, Mandera, Keiyo and Marakwet districts have been considered to be endemic for kala-azar[46,51]. Baringo and the neighbouring districts such as West Pokot were first identified as leishmaniasis foci in 1955[52]. Baringo district is the only foci reported where both VL and CL are known to occur in Kenya[46].

Some scientists believe that nomadic Turkanas may have introduced the disease into the area from the north while others speculate that Kenyan soldiers returning from North Africa after World War II were responsible for introduction of the parasite[53]. The disease occurring in Baringo District has a focal distribution in the dry, hot areas below 1500 metres and the infections may be characterized as follows: 1) asymptomatic 2) subclinical and self-limiting (not medically identifiable), and 3) clinically manifest disease (that is medically identifiable)[46]. Half of the reported VL patients are between 5 and 14 years of age and 66% of them are males. A human case of a mixed *L. donovani* and *L. major* infection has been reported in this dual focus of VL and CL[46].

A serious outbreak of VL was reported in Kitui district in 1952 with 303 cases and peaked in 1953 with 2,142 cases<sup>[48]</sup>. Further outbreaks have since been reported in 1966 in Meru with 1,500 cases<sup>54</sup> Machakos in the 1970s and Kitui again in the 1980s<sup>[505556]</sup>, Kajiado district in the early 1990s and Baringo district in 1999<sup>[57]</sup>. In 2001, an outbreak of VL was reported in the previously non-endemic Wajir and Mandera districts of North Eastern Kenya where between May 2000 to August 2001, 904 patients were diagnosed with VL, with patients coming from as far as southern Somalia and southeast Ethiopia<sup>[58]</sup>.

### CUTANEOUS LEISHMANIASIS IN KENYA

In Kenya, CL is caused by *Leishmania major*, *L. aethiopia* and *L. tropica*<sup>[59]</sup>. In this country CL due to *L. major* which is transmitted by *P. duboscqi* is rare in humans, but underreporting is likely. *Phlebotomus duboscqi* is mainly found in animal burrows where it feeds on rodents which are frequently infected<sup>[60]</sup>. In Africa south of the Sahara, the presence of *L. tropica* (*sensu stricto*) was not suspected until a new focus was discovered in the Rift Valley in Kenya<sup>[616263]</sup>. The proven vector for *L. aethiopia* in Kenya has been shown to be *P. guggisbergi*. In the Laikipia focus in Kenya, *P. guggisbergi* was collected from indigenous large animals such as goats, sheep and dogs, cats, rabbits and hyraxes (*Procavia capensis*); smaller rodents, giant rat (*Cricetomys gambianus*), crested rat (*Lophiomys imhausi*) and the exogenous hamster<sup>[6465]</sup>.

Diffuse cutaneous leishmaniasis (DCL) was first reported in Kenya in 1969 in Bungoma district and the Mount Elgon area<sup>[66]</sup>. *Leishmania aethiopia* has been identified as the aetiological agent, rodents as the animal reservoirs and *P. pedifer* Lewis<sup>[52]</sup> Mutinga et Ashford, and 1972 to be the vector of DCL in the Mt. Elgon region <sup>[5267]</sup>.

Although various aspects of the transmission and control of leishmaniasis have been studied in Kenya, the impact of the disease and particularly VL is still enormous. Drug development, vaccine-related and vector control studies have been and continue to be pursued by the Kenya Medical Research Institute (KEMRI) and the Institute of Primate Research (IPR) of the National Museums of Kenya<sup>[46]</sup>.

### POST KALA-AZAR DERMAL LEISHMANIASIS IN KENYA

In Kenya, PKDL was first described by Manson-Bahr in 1959<sup>[68]</sup>. Reported PKDL rates in Kenya after VL show considerable variability in four studies of 0.05%<sup>[69]</sup>, 1%<sup>[68]</sup>,

6%<sup>[47]</sup> and 30%<sup>[49]</sup>. A study involving twelve patients with diagnosis consistent with PKDL who were seen at the Centre for Clinical Research (CCR) of KEMRI from 1981 to 1985 indicated a wide range of clinical manifestations from macular hypopigmented lesions to generalized nodular lesions. All lesions cleared either by self-cure or by treatment with sodium stibogluconate<sup>[47]</sup>.

### LEISHMANIASIS IN ETHIOPIA

One unique feature of leishmaniasis in Ethiopia is the presence of a significant number of patients co-infected with HIV and VL<sup>[37]</sup>. Since 1970, the number of leishmaniasis cases in Ethiopia has increased, which appears to correspond to an extensive programme of agricultural development with an annual influx of migrant workers in the Tigray region<sup>[707172]</sup>.

### VISCERAL LEISHMANIASIS IN ETHIOPIA

In Ethiopia, VL caused by *L. donovani* is endemic in the lowlands around Humera and Metema in northern Ethiopia, with an incidence of 1000–2000 cases annually; 20% – 40% of the persons affected are HIV co-infected<sup>[74]</sup>. The definitive reservoir of *L. donovani* remains unknown, although anthroponotic transmission has been implicated<sup>[70]</sup>.

Like in Uganda and Somalia, Médecins sans Frontières (MSF) opened a VL treatment centre which offers free treatment to patients afflicted by kala azar in the Tigray region of Ethiopia in 1997<sup>[75]</sup>.

### CUTANEOUS LEISHMANIASIS IN ETHIOPIA

In Ethiopia, CL is primarily caused by *L. aethiopia* and less often by *L. tropica* and *L. major*<sup>[76]</sup>. *Leishmania aethiopia* causes both diffuse cutaneous leishmaniasis (DCL) and localized cutaneous leishmaniasis (LCL), which are found in the highlands of Ethiopia<sup>[7778]</sup>. *Leishmania aethiopia* occurs only in the Ethiopian and Kenyan highlands and its reservoir is the rock hyrax while the vector is *P. larroussius*<sup>[79]</sup>.

Diffuse cutaneous leishmaniasis shows multiple skin lesions on the face, trunk, and extremities and is usually not self healing, whereas LCL is mostly seen as single lesions which are self-healing over time<sup>[80]</sup>.

Studies performed in Ethiopia on the stimulation of peripheral blood mononuclear cells (PBMC) from CL and DCL, a disease clinically and pathologically distinct from disseminated leishmaniasis (DL), have shown that PBMC from CL produce more gamma interferon (IFN- $\gamma$ ) when stimulated with *L. aethiopia* antigen from CL than by

antigen from DCL. Interestingly, lymphocyte proliferation among control individuals of that endemic area was higher in response to LCL antigen than diffuse cutaneous leishmaniasis antigen, supporting the idea that differences in the parasites may contribute to the clinical outcome of infection with *L. aethiopica*<sup>[81,82,83]</sup>. Also, the humoral responses in DCL patients are manifested by the presence of antibodies with specificities against antigens of different size, whereas antibodies in sera from LCL patients showed a limited recognition of the low-molecular-weight antigens<sup>[84]</sup>. Both differences in the immune response of the infected patient<sup>81</sup> and differences of the infecting parasites<sup>[82]</sup> have been proposed as an explanation for the difference in clinical manifestations between DCL and LCL. Studies in the country have also shown that genetic variability within the species *L. aethiopica* does not correlate with clinical variations of cutaneous leishmaniasis<sup>[85]</sup>.

### POST KALA-AZAR DERMAL LEISHMANIASIS IN ETHIOPIA

In Ethiopia, PKDL is endemic in the Metema-Humera focus which is an extension of the endemic area of eastern Sudan<sup>[33]</sup>. A recent study showed a PKDL rate of 14% in patients who were seen only once at 6 months after treatment. By contrast with the Sudanese focus, HIV infection is spreading in this area. The prevalence rates were 27.3% and 13.3% in HIV-positive and HIV-negative patients respectively<sup>[86]</sup>.

### LEISHMANIASIS IN UGANDA

Although VL was reported in East Africa early in the last century, it was not described in Uganda until the 1950s and remained largely unnoticed until 1997, when MSF (Swiss Section) began to provide assistance to Amudat Health Centre in Pokot County. The disease in this country appears to be restricted to the Pokot County, a semi-arid lowland area in Nakapiripirit District and an extension of the larger focus of West Pokot District in Kenya<sup>[87]</sup>. The vector for VL in Uganda is the phlebotomine sandfly *P. martini* and the transmission is thought to be anthroponotic<sup>[88]</sup>.

In 2000, MSF initiated a kala-azar control program, focusing on passive case detection and treatment. Information on local vector control behaviour and risk factors for infection or disease in Uganda is limited, but a pilot entomologic study demonstrated that termite mounds are important vector breeding and resting sites and that the practice of sitting on termite mounds while guarding livestock might increase the risk of infection<sup>[88]</sup>. A recent study has also identified low

socio-economic status and treating livestock with insecticide as risk factors for VL while sleeping near animals, owning a mosquito net and knowing about VL symptoms were associated with a reduced risk of VL<sup>[12]</sup>.

A study on the diagnostic accuracy of two serological tests based on the detection of antibodies against a recombinant antigen derived from a 39-amino-acid repeat in *Leishmania chagasi* (rK39) antigen-based dipsticks and the formol gel test (FGT) for rapid diagnosis of visceral leishmaniasis was conducted in northeastern Uganda. The study recommended the use of the DUAL-IT LM dipstick (a dipstick detecting both antibodies to rK39 antigen (for VL diagnosis) and specific plasmodial LDH (pLDH; for malaria diagnosis) based on the high sensitivity and specificity of the kit<sup>[89]</sup>.

### VISCERAL LEISHMANIASIS IN SOMALIA

To date there are no reports of cutaneous and mucocutaneous leishmaniasis in Somalia. However, visceral leishmaniasis is present. Areas of Somalia where VL has been reported include the coastal areas in the south of the country<sup>[90,91]</sup>, the area along the Shebelle river in the south of Somalia<sup>[92]</sup>, Lower Juba region<sup>90</sup> and Baidoa in Bay region<sup>[94]</sup>. Information on local vector behaviour and risk factors for infection or disease in Somalia are very limited. As in other endemic areas of the region such as Uganda, Southern Sudan and Kenya, transmission of VL in Somalia is thought to be anthroponotic<sup>[88]</sup>. A study in Kenya revealed that transmission occurs in and around houses<sup>[95]</sup>, but whether a similar scenario is replicated in Somalia is unknown. Termite hills are the favoured breeding and resting sites of *P. martini* and these mounds are very common in Bakool<sup>[96,97]</sup>.

The political turmoil and factional fighting that followed the overthrow of President Mohammed Siad Barre's regime in 1991 has left large parts of Somalia without any form of effective government. As a result, the majority of health care provided in South Central Somalia is carried out by non-governmental organizations but with very limited coverage of the Somali population<sup>[93]</sup>.

The consequences of the lack of a central government in Somalia are clearly observed in the spread of various diseases including leishmaniasis. A case in point is the discovery of VL in children in the Bakool region of Somalia, an area where VL had not been reported before<sup>[11]</sup>. Using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis of cysteine proteinase

B genes to identify the causative agent, it was found that the parasites in the Bakool region were most similar to Sudanese and Ethiopian reference strains of the *Leishmania donovani* complex. The sandfly captures showed *Phlebotomus martini* and *P. vansomeranae* as the possible vectors of VL in the area. Food insecurity might have contributed to the emergence and detection of VL in this area.

The international humanitarian organization MSF which has been running a primary health-care project in the Huddur area since the year 2000, has witnessed a dramatic increase in the number of patients with VL admitted to its treatment center. The upsurge of VL has mostly been reported in the Bakool region, where the average caseload that was previously stable at around 140 VL cases per year until September 2005, had increased seven-fold to a total of 1002 patients in year 2006 alone<sup>[93]</sup>.

Other countries in the east and the Horn of Africa region where cases of leishmaniasis have been reported include Djibouti and Eritrea. In Djibouti, an unusual observation of a chronic midface ulcerative and necrotizing lesion that resembled mucocutaneous leishmaniasis has been documented<sup>[98]</sup>. In Eritrea as in Ethiopia, cases of *Leishmania*/ HIV co-infection have been reported<sup>[99]</sup>. In general the number of *Leishmania*/HIV co-infections in Africa has been on the rise, affected by social phenomena such as mass migration and wars<sup>[100]</sup>.

## CONCLUSIONS

In view of its spread to previously non-endemic areas and an increase in imported cases, leishmaniasis in Eastern Africa should be considered a health emergency. Innovative and integrated control measures in war-torn countries such as Somalia and the Darfur region of Sudan should be instituted in order to prevent further spread of the disease. Although resistance to pentavalent antimonials has not been reported in the region, there is need to investigate this phenomenon in view of the fact that many cases of leishmaniasis go unreported.

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