A Review of Leishmaniasis in Eastern Africa

P Ngure, A Kimutai, W Tonui, Z Ng'ang'a

Citation

P Ngure, A Kimutai, W Tonui, Z Ng'ang'a. *A Review of Leishmaniasis in Eastern Africa*. The Internet Journal of Parasitic Diseases. 2008 Volume 4 Number 1.

Abstract

ObjectiveThe review presents the epidemiology of leishmaniases in the Eastern Africa region.
MethodsWe 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.
ResultsPoverty, wars, conflicts and migration have significantly aggravated leishmaniases 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.

ConclusionIn 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[1]. 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[2]. In these countries, it is estimated that 80% of the population earn less than $2 a day[3].

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[4]. There are two million new cases of leishmaniasis annually and 14 million infected people worldwide[5].

The leishmaniases 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)[4]. The outcome of infection depends on the species of Leishmania parasites and the host's specific immune response[6].

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[7]. In Africa, particularly Ethiopia and Sudan, it is estimated that 70% of adults with VL also have HIV infection[8].

Leishmaniasis is endemic to countries mostly in the north, central, east, west and the Horn of Africa[910]. 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[1112]. Visceral leishmaniasis in this part of Africa causes at least 4 000 deaths annually, a loss of approximately 385 000 DALYs[13].

Sudan is one of the five countries that constitute 90% of VL cases in the World [2]. The highest incidence of post-kala-azar dermal leishmaniasis in the world is also found in Sudan[14]. 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[5]. 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[15].

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[16]. 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[17].

LEISHMANIASIS IN SUDAN

In Sudan, visceral, mucocutaneous and cutaneous leishmaniases 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)[214]. 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[18]. 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 Frontiéres (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[18].

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[19]. 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[20]. 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%[21]. Although not yet documented in Africa, resistance to pentavalent antimonials is common in India[22].

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[23]. 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[2425] . Anthroponotic transmission is probably the main transmission cycle, especially during epidemics, because no animal species has yet been definitively identified as a reservoir[26]. Throughout the 20th century, VL has been reported in southern Sudan, and major outbreaks have followed population movement, flooding, food shortages, and conflict[27]. 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[2829]. Médecins Sans Frontiéres–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[26].

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[3031]. 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 [30]. 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]. PDKL 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[4041]. 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 Arvicanthis 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 leishmaniases 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[4650]. 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[4651]. Baringo and the neighbouring districts such as West Pokot were first identified as leishmaniases 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 Word 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[48]. Further outbreaks have since been reported in 1966 in Meru with 1,500 cases54 Machakos in the 1970s and Kitui again in the 1980s[505556], Kajiado district in the early 1990s and Baringo district in 1999[57]. 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[58].

CUTANEOUS LEISHMANIASIS IN KENYA

In Kenya, CL is caused by Leishmania major, L. aethiopica and L. tropica[59]. In this country CL due to L. major which is transmitted by P. duboscqi is rare in humans, but underreporting is likely. Phlebotomous duboscqi is mainly found in animal burrows where it feeds on rodents which are frequently infected[60]. 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[616263]. The proven vector for L. aethiopica 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[6465].

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

Although various aspects of the transmission and control of leishmaniases 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[46].

POST KALA-AZAR DERMAL LEISHMANIASIS IN KENYA

In Kenya, PKDL was first described by Manson-Bahr in 1959[68]. Reported PKDL rates in Kenya after VL show considerable variability in four studies of 0.05%[69], 1%[68], 6%[47] and 30%[49]. 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[47].

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[37]. 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[707172].

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[74]. The definitive reservoir of L. donovani remains unknown, although anthroponotic transmission has been implicated[70].

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[75].

CUTANEOUS LEISHMANIASIS IN ETHIOPIA

In Ethiopia, CL is primarily caused by L. aethiopica and less often by L. tropica and L. major[76]. Leishmania aethiopica causes both diffuse cutaneous leishmaniasis (DCL) and localized cutaneous leishmaniasis (LCL), which are found in the highlands of Ethiopia[7778]. Leishmania aethiopica occurs only in the Ethiopian and Kenyan highlands and its reservoir is the rock hyrax while the vector is P. larroussius[79]. 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[80].

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-) when stimulated with L. aethiopica 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[818283]. 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[84]. Both differences in the immune response of the infected patient81 and differences of the infecting parasites[82] 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[85].

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[33]. 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[86].

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[87]. The vector for VL in Uganda is the phlebotomine sandfly P. martini and the transmission is thought to be anthroponotic[88].

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[88]. 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[12].

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[89].

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[9091], the area along the Shebelle river in the south of Somalia[92], Lower Juba region90 and Baidoa in Bay region[94]. 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[88]. A study in Kenya revealed that transmission occurs in and around houses[95], 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[9697].

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[93].

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[11]. 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. vansomerenae 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[93].

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[98]. In Eritrea as in Ethiopia, cases of Leishmania/ HIV co-infection have been reported[99]. 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[100].

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 leishmaniases go unreported.

ACKNOWLEDGEMENT

We wish to acknowledge Miss Milkah Mwangi and Mr. Geoffrey Kinuthia for critiquing the review.

References

1. Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's principles

and practice of infectious diseases, 6th edition. Elsevier, 2005:2428–2442.

2. Desjeux P. Leishmaniasis: current situation and new perspectives. Comp Imunnol Microbiol Infect Dis 2004;27:305–318.
3. Davies CR, Kaye P, Croft SL, Sundar S. Leishmaniasis: new approaches to disease
control. BMJ 2003;326:377–382.
4. Reithinger R, Dujardin J-C, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous
leishmaniasis. Lancet 2007;7:581–596.
5. World Health Organization. Control of leishmaniasis. Report of the secretariat. 2006
www.who.int/gb/ebwha/pdf_files/EB118/B118_4-en.pdf. Accessed on 19th December
2008.
6. Roberts MTM. Current understandings on the immunology of leishmaniasis and recent
developments in prevention and treatment. Br Med Bull 2006;75 and 76:115–130.
7. Singh S. New developments in diagnosis of leishmaniasis. Indian J Med Res 2006;123:311-330.
8. Desjeux P. The increase in risk factors for leishmaniasis worldwide. Trans R Soc Trop
Med Hyg 2001;95:239-243.
9. Sheik-Mohamed A, Velema JP. Where health care has no access: the nomadic populations of sub-Saharan Africa. Trop Med Int Hlth 1999;4:695-707.
10. Boakye DA, Wilson MD, Kweku M. A review of leishmaniasis in West Africa. GMJ 2006;39:94-97.
11. Marlet MV, Wuillaume F, Jacquet D, Quispe KW, Dujardin JC, Boelaert M. A. Neglected disease of humans: a new focus of visceral leishmaniasis in Bakool, Somalia. Trans R Soc Trop Med Hyg 2003;97:667-671.
12. Kolaczinski JH, Reithinger R, Worku DT, Ocheng A, Kasimiro J, Kabatereine N Brooker S. Risk factors of visceral leishmaniasis in East Africa: a case-control study in Pokot territory of Kenya and Uganda. Int J Epidemiol 2008;1-9.
13. Reithinger R, Brooker S, Kolaczinski JH. Visceral leishmaniasis in eastern Africa—current status. Trans R Soc Trop Med Hyg 2007; 101:1169-1170.
14. Ghalib H, Modabber F. Consultation meeting on the development of therapeutic vaccines for post kala azar dermal leishmaniasis. Kinetoplastid Biol Dis 2007;6:7.
15. Handman E. Leishmaniasis: current status of vaccine development. Clin Microbiol
Rev 2001;14:229-243.
16. Momen H. and Cupolillo E. Speculations on the origin and evolution of the genus Leishmania. Mem Inst Oswaldo Cruz 2000;95:583-588.
17. Lanotte G, Rioux JA, Serres E. Approche cladistique du genre Leishmania, Ross, 1903. A propos de 192 souche originaires de l´Ancien Monde. Analyse numerique de 50 zymodèmes identifiés par 15 enzymes et 96 isoenzymes. In JA Rioux Leishmania,
Taxonomie et Phylogenèse. Application Écoepidemiologiques (Colloque International du CNRS/INSERM, 1984), IMEE, Montpellier, 1986; 269-288.
18. Ritmeijer K and Davidson RN. Médecins Sans Frontiéres interventions against kala-azar in the Sudan, 1989–2003. Trans R Soc Trop Med Hyg 2003;97:609-613.
19. Griekspoor A, Sondorp E, Vos T. Cost-effectiveness analysis of humanitarian relief interventions: visceral leishmaniasis treatment in the Sudan. Health Policy and Planning 1999;14:70-76.
20. MSF. Manual for the Diagnosis and Treatment of Visceral Leishmaniasis (Kala-Azar) Under Field Conditions. Amsterdam: MSF-Holland 2003.
21. MSF. Violence, Health, and Access to Aid in Unity

State/ Western Upper Nile, Sudan. Amsterdam: Médecins Sans Frontiéres 2002.
22. Sundar S, More DK, Singh M.K. et al. Failure of pentavalent antimony in visceral leishmaniasis in India: report from the center of the Indian epidemic. Clin Infect Dis 2000;31:1104-1107.
23. De Beer P, el Harith A, Deng LL, Semiao-Santos SJ, Chantal B, van Grootheest MA. Killing disease epidemic among displaced Sudanese population identified as visceral leishmaniasis. Am J Trop Med Hyg 1991;44:283-289.
24. Schorscher JA, Goris M. Incrimination of Phlebotomus (Larroussius) orientalis as a vector of visceral leishmaniasis in western Upper Nile province, southern Sudan. Trans R Soc Trop Med Hyg 1992;86:622–623.
25. Seaman J, Mercer AJ, and Sondorp E. The epidemic of visceral leishmaniasis in western Upper Nile, southern Sudan: course and impact from 1984 to 1994. Int J Epidemiol 1996;25:862–871.
26. Collin S, Davidson R, Ritmeijer K, Keus K, Melaku Y, Kipngetich S, Davies C. Conflict and Kala Azar: Determinants of Adverse Outcomes of Kala-Azar among Patients in Southern Sudan. Clin Infect Dis 2004;38:612–619.
27. Zijlstra EE, El-Hassan AM. Leishmaniasis in Sudan. Trans R Soc Trop Med hyg 2001;95(Suppl 1):S1–76.
28. Seaman J, Ashford RW, Schorscher J, Dereure J. Visceral leishmaniasis in southern Sudan: status of healthy villagers in epidemic conditions. Ann Trop Med Parasitol 1992;86:481–486.
29. Seaman J, Mercer AJ, Sondorp HE and Herwaldt BL. Epidemic visceral leishmaniasis in Southern Sudan: Treatment of severely debilitated patients under wartime conditions and with limited resources. Ann Intern Med 1996;664-772.
30. El-Hassan AM, Meredith SE, Yagi H et al. Sudanese mucosal leishmaniasis: epidemiology, clinical features, diagnosis, immune responses and treatment. Trans R Soc Trop Med Hyg 95;89:647-652.
31. El-Hassan AM, Zijlstra EE. Leishmaniasis in Sudan. Mucosal leishmaniasis. Trans R Soc Trop Med Hyg 2001; 95(Suppl)1:S19-26.
32. Kirk R and Drew C.B. Preliminary notes on dermal leishmaniasis in the Anglo-Egyptian Sudan. Trans R Soc Trop Med Hyg 38;32:265–270.
33. Zijlstra EE, Musa AM, Khalil EAG, El Hassan IM and El-Hassan AM. Post-Kala-azar dermal leishmaniasis. Lancet 2003;3:87-98.
34. Musa AM, Khalil EA, Raheem MA, Zijlstra EE, Ibrahim ME, Elhassan IM, et al. The natural history of Sudanese post-kala-azar dermal leishmaniasis: clinical, immunological and prognostic features. Ann Trop Med Parasitol 2002;96:765-72.
35. Khalil EAG, Zijlstra E, Kager PA, El-Hassan AM. Epidemiology and clinical manifestations of L. donovani infection in two villages in an endemic area in eastern Sudan. Trop Med Int Health 2002;7:35–44.
36. Zijlstra EE, Khalil EAG, Kager PA, El-Hassan AM. Post-kala-azar dermal leishmaniasis in the Sudan: clinical presentation and differential diagnosis. Br J Dermatol 2000;142:136–143.
37. Berman J. Visceral leishmaniasis in the New World & Africa. Indian J Med Res 2006;123:289-294.
38. Musa AM, Khalil EAG, Mahgoub FA, Elkadaru AMY, El-Hassan AM. Efficacy of liposomal amphotericin B (AmBisome) in the treatment of persistent Post kala-azar dermal leishmaniasis (PKDL). Ann trop Med Parasitol 2005;99:563-569.
39. Thomson DS, Balfour A. Two cases of non ulcerating oriental sore better termed leishman nodules. Trans R Soc Trop Med Hyg 1910;3:107-128.
40. Archibaldi R.G. A case of parasitic granuloma in which development forms of Leishmania tropica were present. 4th report of Wellcome Tropical Research Laboratory of Gordon Memorial college Khartoum 1911;A: 207-211.
41. Kirk R, Drew CB. Preliminary notes on dermal leishmaniasis in the Anglo-Egyptian Sudan. Trans R Soc Trop Med Hyg 1938;32:265–270.
42. Abdalla RE, Sharief HS. Epidemic of cutaneous leishmaniasis in northern Sudan. Ann Trop Med Parasitol 1978;72:349- 352.
43. El-Safi SH, Peters W, Evans DA. Current situation with regard to leishmaniasis in the Sudan, with particular reference to the recent outbreak of cutaneous leishmaniasis in Khartoum pp 60-77 in research on control strategies for leishmaniasis. Proc Int Ottow 1988; IDRC.Mr.184e.
44. El-Hassan AM, Zijlstra EE. Leishmaniasis in Sudan. Cutaneous leishmaniasis. Trans R Soc Trop Med Hyg 2001;95 (Suppl) 1:S1-17.
45. Elamin EM, Guerbouj S, Musa AM, Guizani I, Khalil, EAG, Mukhtar MM, et al. Uncommon clinical presentations of cutaneous leishmaniasis in Sudan. Trans R Soc Trop Med Hyg 2005;99:803-808.
46. Tonui WK. Situational analysis of Leishmaniases research in Kenya. Afr J Health Sci 2006;13:7-21.
47. Muigai R, Gachihi GS, Oste CN, Were JBO, Nyakundi PM, Chunge CN, Kirigi G, Rashid J.R. Post kala-azar dermal leishmaniasis: the Kenyan experience. East Afr med J 1991;68:801–806.
48. Fendall NR. The spread of kala-azar in Kenya. East Afr med J 1961;38:417-419.
49. Cole ACE, Cosgrove PC, Robinson G. A preliminary report of an outbreak of kala-azar in a battalion of King's African Rifles. Trans R Soc Trop Med Hyg 1942;36:25-34.
50. Wijers DJ, Kiilu G. Studies on the vector of kala-azar in Kenya, VIII. The outbreak in Machakos District: epidemiological features and a possible way of control. Ann Trop Med Parasitol 1984;78:597-604.
51. Wasunna MK, Rashid JR, Mbui J, Kirigi G, Kinoti D, Lodenyo H, Felton JM, Sabin AJ, Horton J. A phase II dose-increasing study of sitamaquine for the treatment of visceral leishmaniasis in Kenya. Am J Trop Med Hyg 2005;73:871–876.
52. Mutinga MJ. Phlebotomus fauna in the cutaneous leishmaniasis focus of Mt. Elgon, Kenya. East Afr med J 1975;52:307-307.
53. Ryan JR, Mbui J, Rashid JR et al. Spatial clustering and epidemiological aspects of visceral leishmaniasis in two endemic villages, Baringo district, Kenya. Am J Trop Med Hyg 2006;74:308-317.
54. Wijers DJB, Mwangi S. Studies on the vector of kala-azar in Kenya. VI. Environmental epidemiology in Meru district. Ann Trop Med Parasitol 1966;60:373-391.
55. Ngoka J M, Mutinga M J. Visceral leishmaniasis in Kenya: The onset of an epidemic outbreak in the Machakos district of Kenya. East Afr med J 1978;55:328-331.
56. Ho M, Siongok TK, Lyerly WH, Smith DH. Prevalence and disease spectrum in a new focus of visceral leishmaniasis in Kenya. Trans R Soc Trop Med Hyg 1982;76:741-746.
57. Mbati PA, Githure JI, Kagai JM, Kirigi G, Kibati F, Wasunna K, et al. Evaluation of a standardized direct agglutination test (DAT) for the diagnosis of visceral leishmaniasis in Kenya. Ann Trop Med Parasitol 1999;93:703-10.
58. Marlet MV, Sang DK, Ritmeijer K, Muga RO, Onsongo

J, Davidson RN. Emergence or re-emergence of visceral leishmaniasis in areas of Somalia, northeastern Kenya, and south-eastern Ethiopia in 2000-01. Trans R Soc Trop Med Hyg 2003;97:515-518.
59. Mebrahtu YB; Lawyer PG; Pamba H, Koech D, Perkins PV, Roberts CR, et al. Biochemical characterization and zymodeme classification of Leishmania isolates from patients, vectors, and reservoir hosts in Kenya. Am J Trop Med Hyg 1992;47:852-892.
60. Schaefer KU, Kurtzhals JA, Sherwood JA, Githure JI, Kager PA. Muller AS. Epidemiology and clinical manifestations of visceral and cutaneous leishmaniasis in Baringo District, Rift Valley, Kenya. A literature review. Trop Geogr Med 1994;46:129-133.
61. Mebrahtu Y, Oster CN, Shatry AM, Hendricks LD, Githure JI, Rees PH, Perkins PV, Leeuwenburg J. Cutaneous leishmaniasis caused by Leishmania tropica in Kenya. Trans R Soc Trop Med Hyg, 1987;81:923–924.
62. Lawyer PG, Mebrahtu YB, Ngumbi PM, Mwanyumba P, Mbugua J, Kiilu G et al. Phlebotomus guggisbergi (Diptera: Psychodidae), a vector of Leishmania tropica in Kenya. Am J Trop Med Hyg 1991;44:290–298.
63. Sang DK. Transmission of cutaneous leishmaniasis due to Leishmania tropica in Kenya. East Afr Med J 1991;68:151–152.
64. Johnson RN, Ngumbi PM, Mwanyumba JP, Roberts CR. Host feeding preference of Phlebotomus guggisbergi, a vector of Leishmania tropica in Kenya. Med Vet Entomol 1993;7:216–218.
65. Jacobson RL. Leishmania tropica (Kinetoplastida: Trypanosomatidae) - a perplexing parasite. Folia Parasitologia 2003;50:241-250.
66. Kungu A, Mutinga MJ and Ngoka JM. Cutaneous leishmaniasis in Kenya. East Afr med J 1972;48:158-465.
67. Sang DK, Chance ML. Cutaneous leishmaniasis due to Leishmania aethiopica, on Mount Elgon, Kenya. Ann Trop Med Parasitol 1993;87:349-357.
68. Manson-Bahr PEC. East African kala-azar with special reference to the pathology, prophylaxis and treatment. Trans R Soc Trop Med Hyg 1959;53:123–136.
69. Southgate BA, Oriedo BVE. Studies in the epidemiology of East African leishmaniasis. J Trop Med Hyg 1967;70:1–4.
70. Mengesha B, Abuhoy M. Kala-azar among labour migrants in Metema-Humera region of Ethiopia. Trop Geog Med 1978;30:199–206.
71. Maru M. Clinical and laboratory features and treatment of visceral leishmaniasis in hospitalized patients in northwestern Ethiopia. Am J Trop Med Hyg 1979;28:15–18.
72. Berhe N, Hailu A, Abraham Y, Tadesse Y. Knut Breivik K. and Abebe Y. Inter-current and nosocomial infections among visceral leishmaniasis patients in Ethiopia: an observational study. Acta Trop 2001;80:87–95.
73. Ritmeijer K, Dejenie A, Assefa , Hundie TB, Mesure J, Boots G, Den Boer M, Davidson RN. A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. Clin Infect Dis 2006;43:357–364.
74. World Health Organization. Manual on Visceral Leishmania Control. 1996. WHO, Geneva.
75. Lyons S, Veeken H and Long J. Visceral leishmaniasis and HIV in Tigray, Ethiopia. Trop Med Int Health 2003;8:733–739.
76. Jirata D, Kuru T, Genetu A, Barr S, Hailu A, Aseffa A, Gedamu L. Identification, sequencing and expression of peroxidoxin genes from Leishmania aethiopica. Acta Trop 2006;99:88-96.
77. Mengistu, G, Humber DP, Mulugeta E, Tadesse M. High prevalence of elephantiasis and cutaneous leishmaniasis in Ocholo, south west Ethiopia. Ethiop. Med J 1987;25:203-207.
78. Gadisa E, Genetu A, Kuru T, Jirata D, Dagne K, Aseffa A, et al. Leishmania (Kinetoplastida): Species typing with isoenzyme and PCR–RFLP from cutaneous leishmaniasis patients in Ethiopia. Exp Parasitol 2007;115:339-343.
79. Momen H, Cupolillo E. Speculations on the Origin and Evolution of the Genus Leishmania. Mem Inst Oswaldo Cruz 2000;95:583-588.
80. Bray RS, Ashford MA, Bray MA. The parasite causing cutaneous leishmaniasis in Ethiopia. Trans R Soc Trop Med Hyg 1973;67:345-348.
81. Bryceson ADM. Diffuse cutaneous leishmaniasis in Ethiopia. IV. Pathogenesis of diffuse cutaneous leishmaniasis. Trans R Soc Trop Med Hyg 1970;64:387-393.
82. Akuffo, H, Schurr E, Anderson G, Yemaneberhan T, Britton S. Responsiveness in diffuse versus local cutaneous leishmaniasis is due to parasite differences. Scand J Immunol 1987;26:717-721.
83. Melby PC, Neva FA Sacks DL. Profile of human T cell response to Leishmanial antigens. Analysis by immunoblotting. J Clin Invest 1989;83:1868-1875.
84. Mengistu G, Akuffo HO, Yemane-Berhan T, Britton S and Fehniger TE. Serum antibody specificities to Leishmania aethiopica antigens in patients with localized and diffuse cutaneous leishmaniasis. Parasite Immunol 1990;12:495-507.
85. Schönian G, Akuffo H, Lewin S et al. Genetic variability within the species Leishmania aethiopica does not correlate with clinical variations of cutaneous leishmaniasis. Mol Biochem Parasitol 2000;106:239-248.
86. Ritmeijer K, Veeken H, Melaku Y, Leal G, Amsalu R, Seaman J, et al. Ethiopian visceral leishmaniasis: generic and proprietary sodium stibogluconate are equivalent; HIV coinfected patients have a poor outcome. Trans R Soc Trop Med Hyg 2001;95:668–672.
87. Mutero CM, Mutinga MJ, Ngindu AM, Kenya PR, Amimo FA. Visceral leishmaniasis and malaria prevalence in West Pokot District, Kenya. East Afr med J 1992;69:3-8.
88. Kolaczinski JH, Worku DT, Chappuis F, Reithinger R, Kabatereine N, Onapa A, Brooker S. Kala-azar control, Uganda. Emerg Infect Dis 2007;13:507-509.
89. Chappuis FH, Mueller Y, Nguimfack A et al. Diagnostic Accuracy of Two rK39 Antigen-Based Dipsticks and the formol gel test for rapid diagnosis of visceral leishmaniasis in northeastern Uganda. J Clin Microbiol 2005;43:5973–5977.
90. Penso G. II kala azar nella Somalia Italiana. Bolletini e Atti di Ricerca Accademia Medica Roma 1934;60:292–293.
91. Moise R. A proposito dei casi di kala azar finora segnalati. Annli di Medicina navale e Tropicale 1955;68:481–501.
92. Shiddo SA, Mohamed AA, Akuffo HO et al. Visceral leishmaniasis in Somalia: prevalence of markers of infection and disease manifestations in a village in an endemic area. Trans R Soc Trop Med Hyg 1995;89:361–365.
93. Raguenaud M-E, Jansson A, Vanlerberghe V et al. Epidemiology and clinical features of patients with visceral leishmaniasis treated by an MSF Clinic in Bakool region, Somalia, 2004–2006. Plos Negl Trop Dis 2007;1(1):e85. doi:10.1371.
94. Woodhead A. A recent case of visceral leishmaniasis in Somalia. Ann Trop Med and Parasitol 1995;89:687–688.
95. Schaefer KU, Kurtzhais JAL, Gachihi GS, Muller AS and Kager PA. A prospective sero-epidemiological study of visceral leishmaniasis in Baringo District, Rift Valley

Province, Kenya. Trans R Soc Trop Med Hyg 1995;89:471–475.
96. Robert LL, Schaefer KU and Johnson RN. Phlebotomine sand flies associated with households of human visceral leishmaniasis cases in Baringo District, Kenya. Ann Trop

Med Parasitol 1994;88:649–657.
97. Ngumbi PM, Irungu LW, Robert LL, Gordon DM and Githure JI. Abundances and
nocturnal activities of phlebotomine sandflies (Diptera: Psychodidae) in termite hills and
animal burrows in Baringo District, Kenya. Afr J Health Sci 1998;5:28–34.
98. Farge D, Frances C, Vouldoukis I, Wechsler B, Boisnic S, Monjour L et al.
Chronic destructive ulcerative lesion of the midface and nasal cavity due to leishmaniasis
contracted in Djibouti. Clin exp dermatol, 1987;12:211-213.
99. Meenken C, Agtmael MA van, Kate RW ten, Horn GJ van den. Fulminant ocular leishmaniasis in an HIV-1 positive patient. Aids 2004;18:1485-1486 .
100. Cruz I, Nieto J, Moreno J, Cañavate C, Desjeux P and Alvar J. Leishmania/HIV co-infections in the second decade. Indian J Med Res 123;2006:357-388.

Author Information

Peter Ngure, MSc (Phd Candidate)
Daystar University, Science Department

Albert Kimutai, MSc
Kenyatta University

Willy K. Tonui, PhD
Kenya Medical Research Institute.

Zipporah W. Ng'ang'a, PhD
Jomo Kenyatta University of Agriculture and Technology