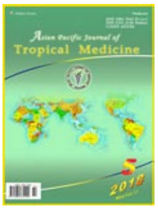

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Zoonotic leishmaniasis and control in Ethiopia

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ABSTRACT

Visceral leishmaniasis and cutaneous leishmaniasis are important public health problems in Ethiopian lowland and highland areas respectively. Failure of antimonial drugs to respond in some diffused cutaneous leishmaniasis and HIV/AIDS-leishmaniasis co-infected patients, side effects of these drugs, highly mutilating diagnostic procedures and high health care expense are among the problems associated with leishmaniasis. Control of leishmaniasis requires proper understanding of human parasites transmissions (anthroponotic or zoonotic or both). The aim of this review was to elaborate different ecologies of leishmaniasis based on evidences from previous researches and information from literatures obtained from different sources including PubMed to describe zoonotic leishmaniasis in Ethiopia with possible control methods. Although vectors of leishmaniasis in Ethiopia are not endophelic, night indoor visits of *Phlebotomus* vectors for possible blood meal on human have been indicated. Thus, application of indoor and domestic residual insecticides spraying, use of insecticide impregnated fine mashed bed net for visceral leishmaniasis, community based manipulation (destruction) and residual insecticide fogging of hyrax-sand fly habitats for cutaneous leishmaniasis are the visible vector and reservoir control methods that can be used for control of these diseases in Ethiopia. Use of repellants during night outdoor activities of people in the endemic areas requires further investigations.

1. Introduction

Visceral leishmaniasis (VL, also known as kala-azar), post-kala-azar dermal leishmaniasis, cutaneous leishmaniasis (CL), and mucocutaneous leishmaniasis are the four clinical forms of leishmaniasis that are caused by more than 20 *Leishmania* species (Kinetoplastida: Trypanosomatidae) and transmitted by the bite of 98 proven or suspected sandflies vectors in the Old and New Worlds[1,2]. The classical VL or kala-azar is characterized by fever, malaise, weight loss, hyperpigmentation and hepatomegaly. Post-kala-azar dermal leishmaniasis is caused due to complication of VL which is characterized by occurrence of skin lesions, or nodules, mainly on the face, after 2–7 years of unsuccessful treatment of VL. In India, patients with post-kala-azar dermal leishmaniasis are considered to be the most important reservoirs of the parasites and responsible for man to man (anthroponotic) VL transmission[3]. CL can be divided into localized CL, diffused CL and recidivate. Localized CL is a type of manifestation with sores or ulcers on exposed part of the body such as arms, legs and faces, which remain localized and may heal spontaneously. *Leishmania aethiopica (L. aethiopica)*, *Leishmania major (L. major)*, *Leishmania tropica (L. tropica)* and *Leishmania infantum (L. infantum)* are the four parasites in the Old World that cause localized CL[1]. Diffused CL due to *L. aethiopica*, however, consist of painless nodular lesions over wide area of the body which is non-self-healing and sometime unresponsive to standard sodium stibogluconate treatment[4].

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Globally, 0.2–0.4 million VL, 0.7–1.2 CL cases and about 20 000–30 000 VL related deaths occur annually from 350 million leishmaniasis risk population in 98 endemic countries[5]. Of the entire current VL incidence reported, about 90% cases are from seven countries (Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan). Similarly, the majority of CL cases occur in only nine countries (Afghanistan, Algeria, Brazil, Colombia, Iran, Pakistan, Peru, Saudi Arabia and Syria)[5,6]. In Ethiopia, 3 700–7 400 VL and 20 000–50 000 CL cases are reported annually[7,8] with almost similar trend in incidence of VL at present[2]. It could be due to zoonotic nature of leishmaniasis in Ethiopia where drug case management could not decrease incidences of leishmaniases as humans are incidental (dead end) hosts. The highest HIV prevalence (35%) among all leishmaniasis patients in Ethiopia is reported from northwest Ethiopia[9] where VL incidence is around 60%[8].

2. Zoonotic VL and reservoir hosts

Generally, incrimination of reservoir hosts to show zoonotic leishmaniasis requires intensive ecological investigations including the demonstration for their gregarious abundance, survival at least during non-transmission season of the parasites, ability to remain infected without any sign and symptom and capacity to present the human *Leishmania* parasites in their skin or circulation for sand fly vectors bites[10,11]. All VL cases are due to intrusion of human into sylvatic zoonotic *Leishmania donovani* (*L. donovani*) parasite cycle which might circulate among the most probably rodent reservoir hosts by the vectors[12]. The only probable man-*Phlebotomus orientalis* (*P. orientalis*) vector-man *L. donovani* transmission cycle happened in Libo-kemkem district during 2004/5 epidemic, following the possible introduction of the diseases from Metema–Humera VL endemic lowlands by seasonal migrant laborers to non-immunized highland population[13]. The epidemic was controlled soon by drug case management of Medecins Sans Frontieres Greece working team. Of 7 161 suspected VL patients screened serologically (direct agglutination test) during 2005–2011, the direct agglutination test positivity rates were around 14% for 2005–2006 epidemic period and suddenly collapsed to about 2.8% during 2007–2008 with further decline to around 2% during 2009– 2011[14]. The sero-prevalence rate in suspected individuals after epidemic period was lower than the sero-prevalence rate of around 5% in general population in southern and northwestern VL endemic foci[15,16]. At present, there is no active local transmission in the previous epidemic villages except VL cases in men with travel history to Metema–Humera lowlands[14]. Dogs which were found infected with *Leishmania* parasites during epidemic time[13] might not been true reservoirs as the parasite cycle could not be sustained in the villages of Libo-Kemkem districts. Further research using molecular techniques on identification of animal reservoir hosts of VL in Libo-kemkem areas is needed to rule out the role of animals in maintaining zoonotic VL in the areas. Conclusive evidences could not been found during previous attempts of reservoir hosts investigation[17]. Probably, co-evolution of *L. donovani* parasites and rodent species occurred only in the endemic lowlands below 1 500 m[12]. In VL endemic lowland areas, the suspected rodent reservoir hosts which were also found infected with *Leishmana* parasites[12,18], exist abundantly in pre-domestic and extra-domestic habitats[12]. Rodents, most probably, have maintained the zoonotic *L. donovani* parasites cycle in all VL endemic foci. Further studies, however, are required to show frequent bites of the sand fly vectors on rodents, so that the human *Leishmania* parasites circulate among different rodent populations. In order to see infectiousness of rodents to the sand fly vectors, laboratory experimental infections are also needed by allowing the vectors to feed on infected rodents for subsequent re-isolation of human *Leishmania* parasites from the vectors. Population dynamics of rodents is also needed for demonstration of their survival during rainy *Leishmania* non-transmission season[12].

Generally, VL in Ethiopia is associated with settlement, agricultural involvements and guarding animals by rural farmers, seasonal migrant and non-migrant laborers in extra-domestic lowland areas[12]. Although VL in Ethiopia has been reported as zoonotic[12,19], the status of man-sand fly-man anthroponotic and animal-sand fly-animal-sand fly-man zoonotic transmissions require a proper description before design and use of any VL control tools[20,21]. Considering leishmaniasis in Ethiopia as anthroponotic as a whole[21,22] without evidence can mislead the control options. This review paper aimed to elaborate the different ecologies and evolutionary relationships of *Leishmania* parasites with vectors and reservoir hosts to describe zoonotic leishmaniasis before suggesting possible control methods in Ethiopia.

3. Zoonotic CL and reservoir hosts

Hyraxes in Ethiopia and Kenya highlands are the only perfect reservoir hosts of CL in Old World as they are long-lived, form gregarious colonies, share a habitat with *Phelobotomus* species and create ideal breeding sites for sand fly in their latrine[23-25]. Hyraxes and sand flies are infected at least seasonally[23,25]. In Ethiopian highlands, intense outbreaks of CL are usually associated with the existence of hyraxes[23]. There is no doubt about zoonotic transmission of CL in Ethiopian highlands.

4. Evolution and zoonotic leishmaniasis in Ethiopia (East Africa)

The first hematophagous winged insect appeared on earth during the Cretaceous [140 million years ago (MYA)][26]. Fossile evidence indicated the existence of 100 million-year-old amastigotes and promastigotes of *Leishmania* like *Paleoleishmania proterus* in the extinct sand fly (*Palaeomyia burmitis*) with non-human vertebrate (reptiles) blood (dixenous life cycle) in Burmese amber in the supper content (Gondwana)[27]. The evolution of dixenous *Euleishmania* (*Leishmania*, *Viannia* and *Sauroleishmania* subgenera) and *Paraleishmania* from monoxenous trypanosomatid in the supper continents (Gondwana) were also reported between 90 and 140 MYA[28]. Gondwanan origin of *Leishmania* (dixenous parasitism) were also reported recently[29]. After the split of Gondwana, the Second 20–30 million-year-old fossilized extinct sand fly *Lutzomyia adiketis* with *Paleoleishmania neotropicum* trypanosomatid parasite preserved in amber was found from the Dominican Republic (New World)[30]. These results supported the Neotropical/African Origin of *Leishmania* theory which states the separation of Gondwana in the Mesozoic era resulted in the evolution of the genus *Leishmania* into subgenera *Leishmania* and *Sauroleishmania* in Africa, and *Viannia* and *Paraleishmania* in South America[31]. Evolution of human blood-feeding in insects (anthropophagy) started from about 10 million years ago[32]. That means *Leishmania* parasite cycle was maintained in non-human vertebrates and sand fly vectors for million years in sylvatic system both in New and Old worlds before the evolution of human on earth and beginning of anthropophagy[31]. The Old World *Leishmania* (*Leishmania*) parasites originated approximately 30 MYA[28,29] with the earlier separation of the ancestral *L. donovai* form from those of *L. aethiopica*, *L. tropica* and *L. major*[29]. Evidence for African origin of Old World leishmaniasis derived from the fact that all Old World *Leishmania* species (*L. aethiopica*, *L. donovani*, *L. infantum*, *L. major* and *L. tropica*) are found in Africa with their intimate relationships with certain rodent species and hyraxes[31] in addition to the restriction of *L. aethiopica* in Ethiopian and Kenyan Highlands[31,33].

Due to restricted geographic range of *L. aethiopica* parasite, vectors in Ethiopian and Kenya highlands[23,34,35] and hyraxes in Africa and middle east[36,37], African origin of *L. aethiopica/L. tropica*-hyrax system has been indicated[38-40]. Isoenzyme characterization of the four different *Leishmania* promastigotes cultures of the isolates obtained from wild cought *Phlebotomus saevus* (*P. saevus*) and *Phlebotomus sergenti* in Ethiopia rift valley in the Istituto Superiore di Sanita Rome (Italy) has also identified the existence of *L. tropica* and *L. aethiopica* in Ethiopian lowlands[41]. In Ethiopia, outside the previously reported *L. tropica* case in Afar region, in the rift valley[40], other seven cutaneous *Leishmania* patients presenting the typical *L. tropica* features (recidivate) were reported from Italian Dermatological Center in Mekelle, Ethiopia[42]. Based on evidences from reservoir hosts, sand fly vectors distribution and cases, it is possible to suggest that the ancestral *L. tropica* and *L. aethiopica* in Ethiopia or East Africa could give rise to the following: *L. aethiopica-Phlebotomus longipes* (*P. longipes*) and *Phlebotomus pedifer* (*P. pedifer*)-hyrax system in Ethiopian/Kenyan highlands, *L. tropica* (*L. killicki*)-sand fly-hyrax system in Namibia and *L. tropica* (*L. killicki*)-sand fly-rodent system in north Africa and *L. tropica*-sand fly (*P. sergenti* and *P. saevus*)-hyrax system in Africa and Mediterranean region. BLAST genome databases searches of sequences of internal transcribed spacer 1 regions of *L. aethiopica* isolates from CL patients in Ethiopia and a *L. aethiopica* reference strain (MHOM/ET/1972/L102) showed 99% homology among themselves compared to 90% homology to *L. tropica* and 83% to *L. major* isolates[43]. The ancestoral *L. major* form separated earlier before ancestoral *L. tropica* and *L. aethiopica* radiated into the present time *L. aethiopica* in hyrax system and zoonotic and anthroponothic *L. tropica* system in different part of Old World[29]. *L. major* has the most primitive *Leishmania-Arvicanthis* system in sub-Saharan Africa which assumed to give rise the *L. major-Psammomys*, *Meriones*, and *Rhombomys* systems[44]. An African origin of *L. major* and reservoir systems are also possible. In Ethiopia or elsewhere, *L. major* infection has not been reported in hyraxes; however, *L. major* was identified from an *Arvicanthis* species and sandflies (*Phlebotomus duboscqi*) in the lowlands of Southern Ethiopia[45,46]. Probably, Zoonotic *L. major* and *L. donovani* transmissions evolved from a common ancestor in Africa[29] in non-human reservoir hosts before evolution of anthroponotic transmission in India and radiation of *L. donovani* into *L. infantum* in Mediterranean region[31,33]. Monophyletic origin of *L. donovani* and *L. infantum* complexes[47] has been indicated with most probable East African origin of all the strains of *L. donovani* complexes[47,48]. Movement of people and their domestic animals to the New World during historical time most probably brought *L. infantum* strains into the New World which later evolved to *Leishmania chagasi*[49,50].

5. Ecologies of zoonotic VL

The two known ecological settings of VL in East Africa are black cotton soil usually with trees (*P. orientalis*-VL Ecology), redish soil with termite mounds [*Phlebotomus martini* (*P. martini*) and *Phlebotomus celiae* (*P. celiae*)-VL ecology] where the *P. orientalis*, *P. martini* and *P. celiae* vectors and possible rodent reservoirs co-exist[12]. The termite mounds of redish soil of *P. martini* and *P. celiae*-VL ecologies of southern Ethiopia are located on wide areas bordering Kenya similar to black cracking *P. orientalis*-VL ecologies among boarder areas of Ethiopia, Eastern Sudan, South Sudan and Eritrea. Cracks of black cotton soil in extra-domestic and pre-domestic open agriculture fields were reported as resting and breeding sites of *P. orientalis* in northwest and northern Ethiopia[16,51-53]. Probably, only the presence of black soil with deeper cracks to support decomposition of organic matter for larval development and existence blood meal sources for female *P. orientalis* in the lowland areas (<1 800 m) are the most important determinants for the distribution of this vector. The endemicity of VL in the lowlands may be related with the existence of the reservoir hosts. Dense mixed forests on black cotton soil in lowlands are not breeding sites of *P. orientalis* due to non-cracking or shallow cracking of the soil with wet underneath[51]. Human agricultural practice of transforming dense forest to agricultural fields, therefore, favors the expansion of VL ecologies or VL prevalence. VL incidences and vectors distributions in Ethiopia or other east African countries are, therefore, greatly influenced by presence of reservoir hosts, altitude, presence of black cracking soil or redish soil with termite mounds, temperature and rainfall. Temperature is known to affect survival of the parasite and the speed of development of the different stages in the life cycle. Tropical species like *P. orientalis* require 20–30 ℃ constant temperature for their survival and development[54]. During the study of environmental determinants affecting the distribution of *P. orientalis* and VL cases in Sudan, the positive sites for *P. orientalis* were characterized by higher maximum and minimum daily temperature than the negative site[55]. Rise in temperature accelerates the insect's metabolic rates, increases egg production, makes blood feeding more frequent and shortens pathogens development within insects[56,57]. Rainfall is one of the most important climatic factors affecting the existence of *P. orientalis* and incidence of VL[51-53]. Peak *P. orientalis* was reported in March and April dry season and gradually decreases until decline to almost zero in August and September during rainy season[51,53]. Similarly, the presences of rain affect the presence of *P. martini* and *P. caelae* in southern and southwestern Ethiopia[58]. The effect of altitude might be related with its effect on temperature and rainfall. Vectors of VL are rarely found at altitude more than 1 800 m above sea level. In Ethiopia, people contract VL when they either seasonally visit VL endemic areas during agriculture rainy seasons or when they shepherd animals or permanently settle on/near black cracking or redish soil with numerous micro and macro-termite mounds[12]. An epidemiological study using leishmanin skin test[59] and sero-prevalence studies[16] in Northwest Ethiopia have also shown most infections were acquired in extra-domestic habitats. After 7% (629/127 457) *P. orientalis* collected from both indoor and outdoor using 175 Center of Disease Control traps during 1997–2000 entomological investigations in eastern Gedarif states, *P. orientalis*-dog-*P. orientalis*-man or *P. orientalis*-man-*P. orientalis* (anthroponotic) VL transmissions were also been suspected[60]. That means *P. orientalis* has also a habit of visiting indoor at night for searching for blood meal like *P. longipes* in highlands of Ethiopia[23,25].

After analyzing several epidemics in Sudan, Hoogstraal and Heynemen[61] indicated exceptional wet years might have been related with those epidemics which resulted in man-fly-man anthroponotic transmissions in clustered villages[61,62]. In Ethiopia, the famous malaria epidemic in the whole country which affected 15 million people in 2003[63] and VL epidemic in the Libo-kemkem rural clustered villages during 2004 and 2005[13], might have been related with such exceptional wet year. It is not yet clear how wet year is associated with VL epidemic in East Africa as already reported[61]. But, a shift of habitats of *P. orientalis* from cracks of the black cotton soil to any shelters including tukuls (huts) during rain stress months (June–July)[52], can increase *P. orientalis*-human contact. The extent of habitat shift and rate of human bites could be grater in wet years.

Generally, *L. donovani* infection is a rural problem in Ethiopia, there is no active man-sand fly-man transmission in clustered villages, towns, urban and sub-urban areas except at the periphery of clustered villages (small towns) where cases occasionally reported mostly in children[19,64]. During two different parallel studies conducted in rural village of Tahtay Adiabo district and extra-domestic habitats of Kafta-Humera district in Tgray region during May, 2011–April, 2012, indoor, pre-domestic and dense mixed forests were not important breeding sites of *P. orientalis*[51,53]. Generally, VL in Ethiopia is zoonotic and VL incidence is associated with involvement of people to wild set up.

6. Control of zoonotic VL

Control of zoonotic VL based on reservoir hosts in Ethiopia requires further studies. The rodents, the probable reservoir hosts of VL in Ethiopia[12,18], are found in domestic, pre-domestic, agricultural fields, forests and other wild areas[12]. It is not cost effective to target rodents of different species in wild setup to control VL. Strategies to control zoonotic VL better depend on vector control methods than controls based on reservoir hosts. Effective use of insecticides to control VL in Ethiopia requires proper understanding of VL ecologies in different foci. In VL-malaria endemic insecticide sprayed areas, *P. orientalis* would not visit indoor[65] compared to non-sprayed VL endemic rural villages where both indoor pyrethrum spray and sticky traps collections indicated indoor visit habit of *P. orientalis*[53] as already reported in eastern Sudan using Center of Disease Control-light trap collections[60]. A possible habitat shift from black cotton soil to any shelter including hollows in tree trunks in dense mixed forest, huts in rural villages and camps during June–July rainy season[51] could be the most important factor which increases *P. orientalis*-human contact and affects VL transmission. The control measures in *P. orientalis* VL ecologies, thus, should target both indoors of rural villages and camps of agriculture fields for indoor residual insecticide spraying in addition to the use of insecticide impregnated fine mashed bed nets. Efficacies of the exito-repellency of different insecticides and including the use of fine mash in preventing VL in endemic lowlands of Ethiopia have to be evaluated. Shelter seeking behavior in *P. martini* and *P. celiea* during rainy season may not exist in southern Ethiopia where termite mounds can protect sand flies from the moderate rain fall in the area. But, there is no clear evidence for these sand flies not visiting indoor at night seeking for blood meals. In *P. martini* and *P. celiea* VL ecologies, communities participated in indoor insecticide spraying campaign by including domestic termite mounds in addition to the proper use of insecticide impregnated fine mesh, most probably help to protect human from sand fly vectors bites or VL transmission. For *P. orientalis*, *P. martini* and *P. celiae* VL ecologies, working or sleeping outdoor unprotected from sand fly bites at night during agriculture seasons or guarding cattle are the main reason for the VL incidence[12,16]. An application of repellents like diethyltoluamide on the skin or clothing to prevent bites of sand fly vectors is most probably useful. Further studies on the efficacy of different repellents in preventing sand fly vectors bites in outdoor setups are required.

7. Control of zoonotic CL

For highland zoonotic CL control in Ethiopia (where hyraxes live mostly in crevices of basalt rocks in the gorges and tree cavities in forests), trapping, diagnosis and culling or treating infected hyraxes is almost impossible as it was practiced in dogs during attempt to control VL in Brazil[66]. But, it is cost effective and ethically sound to mobilize local communities and manipulate (destruct) the habitats of hyraxes very close to densely populated highly CL endemic areas so that hyraxes find some other further habitats, at least more than the flight range of *P. longipes* or *P. pedifer* (> 1 km). Man-made environmental management such as construction of bridge in “Silti” town in Southern Ethiopia, in contrary, has resulted in CL epidemic due to the creation of an ideal habitat for sandflies and hyraxes to reproduce underneath[24]. In a situation like this, where human-made environmental change results in increased risks for leishmaniasis, contractions should be made by taking into account the possible epidemics of leishmaniasis. Probably, environmental management for control of CL due to *L. aethiopica* in Ethiopian highlands is a more visible and cost effective method than a possible control by shooting hyraxes close to a heavily infected villages or by encouraging specific predators such as the eagle, mongoose, genet cat, *etc*. (biological control) as it was suggested by Ashford[18]. Successes in use of insecticides to control sand flies vectors of leishmaniasis in China and South America were reported[10]. Mostly CL endemic highland areas of Ethiopia are malaria free zones and neither insecticide impregnated bed nets nor indoor residual sprayings are practiced. *P. longipes* and *P. pedifer* are not endophilic, although they visit human dwellings at night and return to their outdoor resting sites[16]. Use of bed nets and residual insecticide spraying, during malaria control in some endemic areas for both malaria and leishmaniasis, may have little use due to exophilic behavior of CL vectors - Humans are also bitten by these vectors during the day time when they visit hyrax, *P. longipes* and *P. pedifer* habitats during fetching of water, collecting woods, guarding animals and so on[14,16]. In CL endemic villages, the effectiveness of fogging of insecticides in habitats where the vectors and hyraxes co-exist, has not been evaluated. Probably, fogging pre-domestic areas (where vectors and reservoir hosts of CL co-exist)[10] can be the second alternative of CL control in Ethiopian highlands where the incidence of CL also increased by frequent day visit of hyrax-sand fly habitats.

8. Conclusions

The probability for anthroponotic transmission in scattered rural settlement and laborers working in agriculture fields is almost rare and it is better to consider leishmaniasis as zoonotic in Ethiopia with the vectors visiting indoor for blood meal. Thus, indoor insecticide residual spraying and use of fine mashed insecticide impregnated bed net are recommended for VL control. Domestic residual insecticide spraying in *P. martini* and *P. celaiea* ecologies are also been suggested. The use of repellents during outdoor night activities requires further validations. Community based habitats manipulation and destruction of hyrax-*P. longipes* / *P. pedifer* by chasing hyraxes away from human settlement areas or residual insecticide fogging of these habitats are the visible options to control CL in highlands. More researches on investigations of zoonotic leishmaniasis are recommended.

Conflict of interest statement

The author declares that he has no conflict of interest.

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