Perspective

Leishmaniases and schistosomiasis comorbidity potential in Kenya: the need for follow up studies

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Abstract

There are potential overlapping distributions of the protozoan parasite *Leishmania* and the parasitic helminth *Schistosoma mansoni* in eastern Africa most notably in endemic regions in the Sudan and Kenya. In murine model studies, the Th_1-Th_2 model of CD4+ T helper cell differentiation is a well-established paradigm for understanding the basis of protective versus pathogenic immune responses in the concomitance state that result in enhanced pathological changes and impaired parasite resolution. In complementation to the experimental studies, the concern for presages of human leishmaniases and schistosomiasis co-infections occurring is increased by their chronicity, displacement of people between endemic areas owing to conflict, climatic changes due to human activities, the spread through irrigation, pisciculture, water conservation schemes and human mobility in pursuit of economic dynamics and resources. Based on diseases prevalence, epidemiology and analyzing the associated risk factors undercurrents, several portents of comorbidity in Kenya are pinpointed. Taking into consideration the limited local resources and diminished surveillance of the areas affected by the two neglected tropical diseases, the discourse concludes that elimination of the diseases is still a challenge. There is need for pilot studies and/or elaborate field surveillance of concomitance and development strategies to mitigate the impending defy in Kenya and beyond.

Key words: Concomitance; Schistosomiasis; Comorbidity; Leishmaniases; Th_1 and Th_2

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Introduction

In the developing world, leishmaniases, caused by obligate intracellular kinetoplastid protozoa of the genus *Leishmania*, are endemic [1, 2] and schistosomiasis, caused by parasitic trematodes (schistosomes) have widely been reported [3-5]. Infection by *Leishmania* can result to visceral leishmaniasis (VL) or kala-azar, mucocutaneous leishmaniasis (MCL) and cutaneous leishmaniasis (CL) depending on the infecting species [6]. Statistical reports indicate that more than 12 million people are estimated to have leishmaniases worldwide. There are 2 million new cases every year, a number that is growing, and 350 million people are considered to be at risk [7]. The disease affects the poorest populations in 88 countries, majority being in the developing nations [7]. Schistosomiasis is the collective name for infection by one or more of five *Schistosoma* species adapted to humans namely *S. mansoni, S. japonicum, S. haematobium, S. mekongi* and *S. intercalatum* or by species adapted to other mammals which can occasionally infect humans which include *S. matheei* and *S. magrobowei* [8, 9]. Majority of schistosomiasis cases worldwide are attributed to three species: *S. mansoni* and *S. japonicum* (which cause the intestinal disease) or *S. haematobium* (responsible for the urinary form of the disease), named according to the site preferred by the adult worms [8]. It is estimated that over 600 million people worldwide are at risk of schistosomiasis whereas close to 200 million are actually infected continuously or intermittently mainly in rural agricultural and periurban areas [8]. The need for frequent re-treatment limits success of control efforts with core concern in Sub-Saharan Africa, which harbours about 85% of all schistosomiasis in the world [9].

Leishmania and *Schistosoma* overlap in their epidemiological distributions and indications of co-infecting the same individuals have been reported extensively [10-17]. How these two parasites might interact within co-infected hosts and the associated epidemiology continues to be debated. One line of argument indicates that the interactions between the helminth and protozoan parasites could affect both entities [18], while others argue that the helminth/protozoan co-infection prompts leishmaniases development without any effect on the helminth parasite [19-

21]. This bias may reflect the greater human disease burden imposed by leishmaniases compared to helminths [22], and the ongoing need to understand and evaluate what causes variability in leishmaniases infection outcomes.

Interactions among parasitic agents commonly alter disease severity and transmission dynamics [23-25]. Co-infecting parasites may interact either positively (facilitation) or negatively (competition) via a range of mechanisms including resource competition, immune-mediated interactions and direct interference [16, 22, 23]. To date, studies of helminth-protozoa concomitance have focused largely on immune-mediated mechanisms, no doubt largely due to the known immunomodulatory effects of helminths. Using the immune response mechanism, two major pathways have been proposed by which helminths might release parasites from immune pressure and thereby facilitate their replication, both of which involve the dampening of pro-inflammatory immune responses [26-31]. Thus it has been suggested that by polarizing immune responses towards Th2-type effector mechanisms, helminths will diminish the pro-inflammatory Th1-type mechanisms needed to down modulate *Leishmania* in concomitance. These suggest that helminth co-infection might thus impair the mechanisms necessary to control and/or modulate leishmaniasis. The current immunomodulatory account is in concurrence with observation in murine models, where comorbidity of *L. major* and *S. mansoni* exacerbated lesions development compared to mice infected with *L. major* alone [18-20, 32]. The action of helminth infection affecting the immune response of the host, may increase protozoa multiplication significantly thus enhancing leishmaniasis severity [19, 20, 22].

As yet, the concern for portents of leishmaniases and schistosomiasis co-infections occurring is prompted by their chronicity, displacement of people between endemic areas due to conflict, climatic changes due to human activity, the spread through irrigation, pisciculture, water conservation schemes and human mobility in pursuit of economic dynamics and resources [11, 14, 23, 24]. Based on the diseases pathognomonic implications in concomitance, prevalence, epidemiology and analyzing the associated risk factors undercurrents, portents of comorbidity in Kenya are pinpointed.

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Epidemiology and distribution of leishmaniases in Kenya

In Kenya the leishmaniases have been known to be endemic in some parts as far back as early in the 20th century where both CL and VL have been identified [6, 33-35]. The visceral form is present in 70 countries, with East Africa having approximately 30,000 cases per year, while new foci are appearing at an alarming rate and incidences are on the increase within the region [7]. A lack of surveillance systems and the frequency of misdiagnosis especially confusion with malaria mean that true incidence is underestimated [2, 5]. The expected annual cases in Kenya average 600 annually though in epidemic years caseloads can rise to over 1,000 [33, 36]. The sandfly vectors *Phlebotomus martini* and *P. orientalis* have been identified in endemic areas [6, 33]. The endemic areas for VL which is caused by *L. donovani* include Turkana and Baringo counties that neighbours South Sudan; West Pokot county that neighbours Nakapiriprit district in North Eastern Uganda; Kitui, Machakos, Meru, and Elgeyo Marakwet counties [6, 33, 37, 38]. Recent outbreaks of VL have been reported in the previously non-endemic North Eastern counties of Garissa, Wajir and Mandera between the year 2000 and 2001 where the counties neighbour with Somalia and Ethiopia [6, 33, 37, 38]. The majority of patients in these foci were nomads who grazed their cattle over the border area however Somali refugees in Kenyan refugee camps were also affected [39, 40].

There are reports of post kala-azar dermal leishmaniasis (PKDL) that can occur in patients who have been successfully treated and recovered from kala-azar [9, 10]. Increased cases of PKDL were reported at Kacheliba health centre in West Pokot county between 2007 and 2009 [33, 38].

Cutaneous leishmaniasis is present in at least 88 countries, with an estimated annual incidence of 1.5 million cases worldwide [7]. It was first described in Kenya in 1969 and its distribution is diverse ranging from semi-arid lowlands, river valleys and highland plateaus. The aetiological agents for CL include *L. major* which has been reported in Baringo; *L. tropica* in Laikipia, Samburu, Isiolo, Nakuru and Nyandarua counties while *L. aethiopica* has been reported in the Mt Elgon area [6, 37, 38, 41-43]. In Kenya, *P. duboscqi* and *P. guggisbergi* have been identified to be the vectors of *L. major* and *L. tropica* respectively while *P. pediffer*, *P. longipes* and *P.*

elgonensis have been implicated as vectors of *L. aethiopica* [6, 33]. CL has been described to be more endemic in Naivasha, Nakuru county and in Laikipia county, and an outbreak of at least 50 cases of CL was reported from Gilgil (Nakuru county) in April 2009 [36, 38]. Baringo county is a unique foci as both VL and CL are known to occur in the area [6, 38, 42].

Epidemiology and distribution of schistosomiasis in Kenya

In Sub-Saharan Africa, human schistosomiasis (bilharziasis) is caused mainly by *S. mansoni* and *S. haematobium* whose intermediate hosts are freshwater snails in the genera *Biomphalaria* and *Bulinus,* respectively [8, 9]. In humans, these blood flukes reside in the mesenteric and vesical venules and have a life span of many years and daily produce large numbers of eggs, which must traverse the gut and bladder tissues on their way to the lumens of the excretory organs [8, 9]. Many of the eggs remain in the host tissues, inducing immunologically mediated granulomatous inflammation and fibrosis while heavy worm burdens may produce hepatosplenic disease in *S. mansoni* (and *S. japonicum* in China and southeast Asia), and urinary tract disease in *S. haematobium* [8, 9].

In Kenya schistosomiasis is endemic along the coastal belt, Lake Victoria regions of western, Machakos and Kitui counties [44, 45]. It has been estimated that over 3.5 million people are infected with *S. mansoni* in endemic areas of Taita-Taveta, Kitui, Machakos, Homa Bay, Siaya and Kisumu counties particularly along the shore of Lake Victoria (lake Victoria basin) for the later three [38, 46-49]. In Taveta (Taita-Taveta county), the localities mostly affected are Jipe, Eldoro and Kivalwa, and both *S. mansoni* and *S. haematobium* are present, while in Kitui county *S. mansoni* is mainly found in Mwingi on the eastern fringes of the central plateau [46, 48]. Around Lake Victoria, endemic areas include the North Nyakach, Mfagano and Rusinga islands while in the northern part of Nyanza the towns most affected are Bunyala, Samia and Nduru. Other regions where *S. mansoni* infections are found are the upper valley of the Tana River in the vicinity of Mwea and in the Rift valley around Lake Naivasha [46,5 0]. In Nyanza (lake Victoria basin), studies have indicated that schistosomiasis predominantly caused by *S. mansoni* has a direct relationship between the prevalence of *S. mansoni* and distance to Lake Victoria, such that

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schools within 5 km from the lakeshore can confidently be provided with mass treatment [47]. The mean prevalence for *S. mansoni* in school going children in Nyanza is 16.3 % [49].

In Baringo county, Lake Baringo has been shown to harbour the intermediate snail host of *S. mansoni* that is *Biomphalaria pfeiffei* (Krauss) and *B. sudanica* (Martens) with similar vector reported in Lake Naivasha in Nakuru County [50-52]. Pointing to the fact that swamps and small rivers in these areas may not be greatly different from the lakes cited due to similar geological area and eco-system, the intermediate vector may be available. Preview to the presence of intermediate host snails in the regions, case reports of patients presenting with schistosomiasis caused by *S. mansoni* have been noted in Baringo county [38, 52]. No transmission has yet been documented on the north of the equator although hospital reports have recorded cases at Wajir and Mandera [46].

The paradigm of immunology in concomitance

The Th_1-Th_2 classic of CD4+ T helper cell differentiation is a well-established paradigm for understanding the basis of defensive versus pathogenic immune response in *L. major* and *S. mansoni* co-infections. In these studies *L. major* is considered as an amenable model for studying *Leishmania*/*S. mansoni* co-infections using murine models. In experimental mice models, *S. mansoni* infections are known to induce a strong Th_2 type of response, a situation demonstrated by the occurrence of elevated levels of immunoglobulin E and eosinophil [27, 53, 54]. At the time point of egg production which is approximately five weeks post *S. mansoni* infection, a Th_2 response is seen in the host characterized with increased production of Th_2 cytokines (interleukin-4 [IL-4], IL-5, IL-10 and IL-13) and a concomitant down regulation in the secretion of Th_1 cytokines (IL-2 and gamma interferon [IFN-γ]) [53-56]. The progressive shift towards Th_2 is believed to down modulate the inflammatory response induced by egg deposition mainly in the liver that causes granuloma formation and tissue damage [54]. In laboratory animal studies, mice co-infected with *S. mansoni/L. major* or *L. donovani* showed impaired ability to resolve *L. major* or *L. donovani* infections, respectively [53, 57, 58]. In the co-infected mice, Th_1 and Th_2 responses were counter-regulatory by focusing on disease progression and responses development [53, 58]. Thus concomitant infection of *S. mansoni/L. major* or *L. donovani*

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suggests that Th_2 immune response induced by *S. mansoni* is protective for *S. mansoni* infection while the same response is associated with disease exacerbation in *L. major* or *L. donovani* infection, as Th_1 immune response induced by *L. major* or *L. donovani* does not appear to alter Th_2 response to *S. mansoni* [6, 7, 53, 57, 58]. The resolution mechanism is majorly characterized by induction of specific IFN-γ releasing CD4+ T cells while the failure to cure is associated with elevated levels of IL-4, IL-10 and IL-13 with low IFN- γ responses from *Leishmania*-specific CD4+ T cells in complementation of other immunological dynamics [56, 59, 60, 61].

In studies on mammalian immunology to leishmaniases the role for IFN-γ as evidence in the control of *Leishmania* infection emanates from research demonstrating that IFN-γ knockout (KO) mice fail to cure infection [62]. In experimental studies it has been revealed that *L. major* infections genetically resistant mice develop a dominant CD4+ T helper 1 (Th_1) response which is characterized by IFN-γ secretion, whereas in susceptible mice the dominant response is a CD4+ T helper 2 (Th_2) as described by levels of interleukin (IL)-4, IL-5 and IL-13 secretion [55, 56]. In studies between coinfection of leishmaniases and schistosomiasis the immune response and infection consequence led to the conception that the balance of Th_1 to Th_2 responses determines the outcome of the disease progression [55, 63]. The peril modeled by the concept provided the basis for studies of co-infections between leishmaniases and schistosomiasis [53, 54, 57, 58].

Kenya situational analysis on concomitance

Water resources expansion takes place in most parts of the world inclusive of Kenya, at different scales and at a rapid pace [10, 11, 14, 50]. Over 33,000 dams are listed in the latest edition of the World Register of Dams of which, about 3000 were built in the 1990s while the total area under irrigation was 277 million hectares in 2002, an upsurge of nearly 10% over the past 10 years [14]. So far, one way to meet the increasing food and energy demands of the growing world population is through the construction of dams and irrigation schemes. As such, irrigated agriculture usually results in increased crop outputs and hydropower, reducing dependency on domestic and/or imported fossil fuels. In addition, reservoirs are one way to gapping for water scarcity through increased storage capacity [14]. Even so, key facts by WHO indicate that people

are at risk of infection with schistosomiasis due to agricultural, domestic and recreational activities which expose them to infested water [64]. Schistosomiasis particularly affects agricultural and fishing populations. It significantly puts women doing domestic chores in infested water, such as washing clothes at risk while hygiene and play habits make children vulnerable to infection. The rise in eco-tourism and travel has seen an increased number of tourists contract schistosomiasis [64]. Subsequently, the development and management of water resources in tropical and subtropical climate zones has often resulted in transmission intensification and/or the introduction of diseases into previously non-endemic areas [11, 14, 22, 50]. Against the varied fortunes and odds, it is well documented that schistosomiasis is considered a sensitive pointer disease for monitoring ecological transformations, as it is extensively distributed and infection rates can be transformed promptly [11, 14].

Surveillance study done around Lake Naivasha and its environs in Nakuru county, for a period of seven years (between 1967 and 1973) had a series of revelations in periodical determination of schistosomiasis prevalence rates. The highest prevalence rate of 2.9% and the lowest of 0.75% were recorded in 1971 and 1968 respectively out of 3185 and 3758 total people examined in the order [50]. The study concluded that the prevalence rates of *S. mansoni* were low although conditions seem ideal for transmission [50]. High rates of schistosomiasis due *S. mansoni* were noted in farm workers, students, fishermen and their families from endemic areas majorly in Kenya and a few from as far as Uganda [50]. The vast agroindustry employment opportunities within Naivasha coupled by eco-tourism and the need to exploit abundant tilapia fish in Lake Naivasha impelled by the establishment of fisheries department, contributed immensely to the incursion of the region by migrants in pursuit of socio-economic gains [50, 65, 66]. As a consequence, an influx of fishermen from Nyanza, especially Nyakach location, where schistosomiasis due to *S. mansoni* is known to be endemic was observed where majority of the positive housewives were wives of fishermen [65, 66]. Despite the ecological transformations that have taken place with regard to the lake and therefore possible diminished fishing activities, the unlimited agroindustry potential and eco-tourism in Naivasha continues to attract migrants from far and wide terrains as farm workers and eco-tourism entrepreneurs and personnel.

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Positive cases among the Kikuyu tribe had history of having visited or lived in an endemic area of *S. mansoni* in central Kenya. The positive Kamba tribesmen were also from schistosomiasis endemic zones of Machakos county. The positive Baluhya tribesmen were from the Bunyala irrigation scheme known to be endemic for *S. mansoni*. It is worth noting that, there was no any indication to demonstrate fishermen were limited from deciding to work and/or earn a living as farmworkers if they so wished. In consideration of the migrants transposition with their wives/children and moving on to enroll the school going children to the learning institutions within Naivasha and its environs is an indicator of their long term relocation arrangements. From the findings, the infection dynamics of the people around Lake Naivasha would suggest that the infections rate is still below a critical level which must be reached before the cycle can be established. The contention can be substantiated by the concept of critical value or break point as discussed in detail by MacDonald [67]. However, since the study was completed, about four decades ago, and the realization of the fact that majority of the schistosomiasis cases reported in an otherwise *Leishmania* endemic zone may have been imported from other schistosomiasis endemic areas even though there were also cases of indigenous population affected, there have been dismal if any or no known follow up studies to enable comprehend the current transmission dynamics either as imported cases and/or those within the indigenous population if any. The concern is further coupled by the fact that population trends have immensely changed where Nakuru county accounts for (1,603,325) 4.15% of the republic population thus being the fifth most populated county out of the 47 counties [68]. Naivasha and its environs is a well-known agribusiness zone and a popular tourist centre attributed to its bird life, beauty and water-sport activities [50]. Cutaneous leishmaniasis has been described to be more endemic in Naivasha constituency of Nakuru county with further reports in April 2009 indicating an outbreak with at least fifty CL cases from Gilgil constituency of Nakuru County [36, 38]. Based on agroindustry and tourism activities within and around Naivasha and the need for manpower either as fully employed or self-employed in a quest to promote tourism and other agricultural activities like floriculture with the aim of economic gains for life sustainance, portents for co-infections cannot be underestimated. Apparently no pilot/surveillance study has been considered to investigate possible mixed infections among the predominant groups of migrants who migrated and continue

to relocate from schistosomiasis endemic areas to Naivasha and its vicinities in Nakuru county, where they have since established their economic lifeline with visits back to their ancestral land.

Reports by [6, 42] have shown that Baringo county is a unique foci where both VL and CL are known to occur. Vogel et al have shown Lake Baringo to harbour the intermediate snail host of *S. mansoni* with further findings indicating that swamps and small rivers in the area may not be greatly different from the lake cited due to similar geological area and eco-system [50-52]. Preview to the presence of intermediate host snails in the region, Muigai et al [52] have identified schistosomiasis caused by *S. mansoni* in Baringo county. An area which in the past has not been documented as a foci of *S. mansoni* despite having Lake Baringo that harbours the intermediate snail host for *S. mansoni* [52]. Incidentally, further to the Vogel et al and Muigai et al findings and pointers, there exist limited and/or no idea of the possible trends and dynamics of schistosomiasis in the Baringo area and the surrounding. Attribution to the absence of the disease along the shores of Lake Baringo despite the presence of the vector snail has been argued to be due to the arid terrain, low population density and form of land usage [52]. The advent of land reclamation policy by the government, pisciculture and irrigated agricultural activities are certainly presenting a situation where schistosomiasis would gain much presence in an otherwise leishmaniases endemic county, risking co-infections unless measures are taken to prevent water contamination by viable schistosome ova [14, 52, 69]. This is in appreciation of the concern that water conservation and utilization projects have the capacity to influence human mobility and settlement patterns while providing ideal habitats for vector snails [14]. In an effort to stop desertification and make semi-arid areas more productive, small dam-building schemes are being encouraged [14, 69]. Baringo county being no exception such dams have been built where Chemoron dam is outstanding as one of the most valuable. As yet, development and management of water resources in tropical and subtropical climate zones has often resulted in transmission intensification and/or introduction of schistosomiasis into previously non-endemic areas [14, 22] while schistosomiasis is considered a sensitive pointer disease for monitoring ecological transformations, as it is extensively distributed and infection rates can be transformed promptly

[14]. Distribution patterns and location of the two parasitic diseases in Kenya are shown in Figures 1 and 2 respectively [70-73].

Despite the geographical variability in distribution patterns of leishmaniases and schistosomiasis, the land reclamation dynamics pointed [69], would definitely lead to the presence of pockets of leishmaniases and schistosomiasis coexistence resulting impelled co-infections in and around Machakos county [14]. The concern is by the fact that leishmaniasis caused by *L. donovani* and schistosomiasis caused by *S. mansoni* are endemic in various localities of this county as previously described [32, 33, 36, 44-46]. Moreover, the imminent risk is with due regard to the geographical variability in the distribution of the two parasitic diseases where in Kenya leishmaniasis due to *L. donovani* is endemic in arid and semi-arid regions [36]. These are the areas known to be low lying at altitude bellow 800 metres above sea level and categorized as Agro-Ecological Zones five and six experiencing an annual precipitation that does not exceed 300mm. The areas thus stands out to be among the core zones targeted in land reclamation policy like pisciculture, irrigation schemes and construction of dams for water conservation [14, 23, 24, 52, 69]. It follows that migrants between leishmaniases and schistosomiasis endemic zones within the counties would prospectively be attracted to working and settling in these areas as a result of economic opportunities as attested by previous findings [14] hence prompting possible mixed infections. The fears for development of water utilization projects occasioning spread of schistosomiasis in an otherwise non-endemic area has been confirmed in Mwea Tebere Irrigation Schemes where *S. mansoni* has increased rapidly and the disease is well established.

Conclusion

The overlap in the distribution patterns of the two parasitic diseases with regard to human activities, economic factors, effects of co-infection based on mammalian immunology paradigm, parasitic burdens, pathological changes and the government projects to make arid and semi-arid land more productive, emphasizes on the portent for comorbidity. Pilot and/or surveillance studies to target and evaluate the magnitude of the impending defy in the affected regions and populations should be instituted and measures to alleviate the spread of either of the diseases be established and/or fast tracked.

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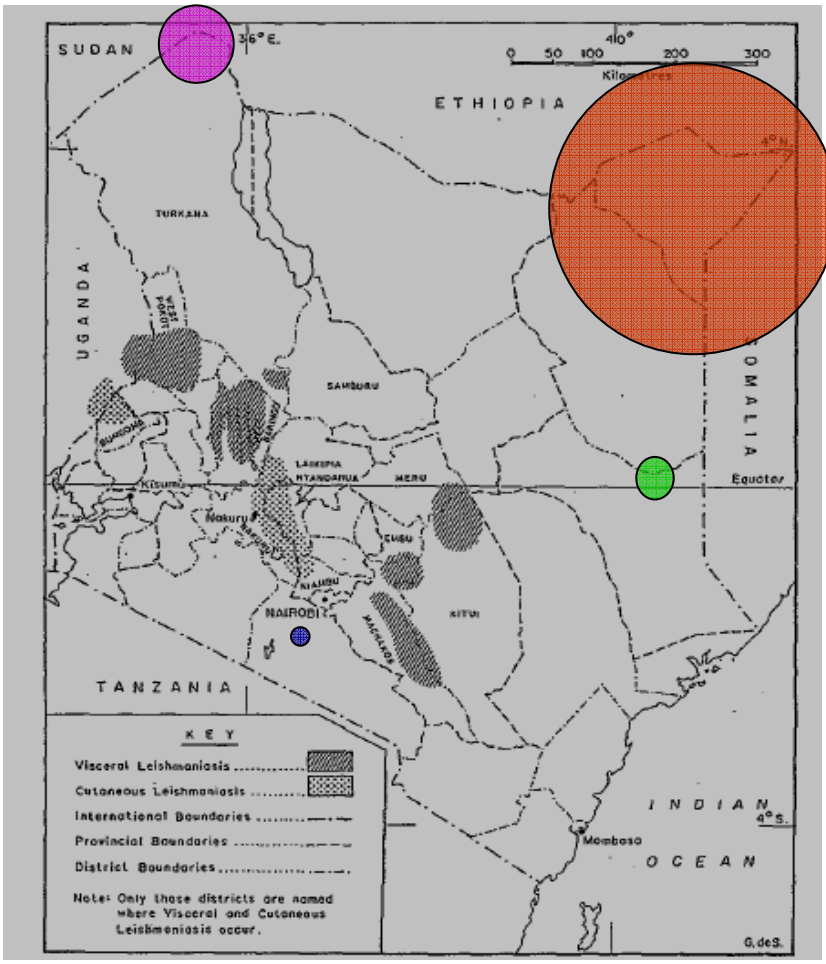
List of figures and legend

Figure 1: Distribution of Leishmaniases in Kenya



VL:

- Wajir
- Dadaab
- Sudan border
- Kekonyokie

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Figure 2: Prevalence and location of *S. mansoni* in Kenya: Parasitological surveys update