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

Khayeka−Wandabwa Christopher1,2*, Anjili O. Christopher2 (canjili@kemri.org), Nyambati C.S. Venny3 (n.venny@yahoo.com), Kutima H. Lydiah3 (hkutima@yahoo.com), Choge K. Joseph4,5 (jchoge@kabianga.ac.ke), Karani W. Lucy1 (lucynyauma@gmail.com) and Kemei W. Kipchirchir6 (wilkimei09@gmail.com)

1Institute of Tropical Medicine and Infectious Diseases (ITROMID), Jomo Kenyatta University of Agriculture and Technology (JKUAT), P.O. Box 62000 – 00200, Nairobi, Kenya; 2Centre for Biotechnology Research and Development (CBRD), Kenya Medical Research Institute (KEMRI), P.O. Box 54840 – 00200, Nairobi, Kenya; 3Biochemistry and Zoology Departments, Jomo Kenyatta University of Agriculture and Technology (JKUAT), P.O. Box 62000 – 00200 Nairobi, Kenya; 4School of Health Sciences, University of Eastern Africa, Baraton, P.O Box 2500-30100 Eldoret, Kenya; 5University of Kabianga, P.O. Box 2030, Kericho, 20200, Kenya; 6School of Public Health, College of Health Sciences Moi University, P.O Box 4606 -30100, Eldoret, Kenya

*Corresponding author: P.O Box 20617-00100 Nairobi., Email address; khayekachris@yahoo.com., Tel No +254 733 948 218

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 Th1-Th2 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; Th1 and Th2
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. mattheei* 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 [19-20].
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.
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.
Perspective

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, 50]. 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
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 Th1-Th2 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 Th2 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 Th2 response is seen in the host characterized with increased production of Th2 cytokines (interleukin-4 [IL-4], IL-5, IL-10 and IL-13) and a concomitant down regulation in the secretion of Th1 cytokines (IL-2 and gamma interferon [IFN-γ]) [53-56]. The progressive shift towards Th2 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, Th1 and Th2 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*
suggests that Th2 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 Th1 immune response induced by *L. major* or *L. donovani* does not appear to alter Th2 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 (Th1) response which is characterized by IFN-γ secretion, whereas in susceptible mice the dominant response is a CD4+ T helper 2 (Th2) 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 Th1 to Th2 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.
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.
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 below 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.
References
1. Singh N, Kumar M and Singh RK. Leishmaniasis: current status of available drugs and new potential drug targets. *Asian-Pacific Journal of Tropical Medicine*. 2012; 5:485–497.

2. Alvar J, Vélez ID, Bern C, Herrero M, Desjeux P, Cano J and den Boer JM. The WHO Leishmaniasis Control Team: Leishmaniasis worldwide and global estimates of its incidence. *PLoS One*. 2012; 7:e35671.

3. Hotez PJ and Kamath A. Neglected tropical diseases in sub-Saharan Africa: review of their prevalence, distribution, and disease burden. *PLoS Neglected Tropical Diseases*. 2009; 3:e412.

4. Gryseels B. Schistosomiasis. *Infectious Disease Clinics of North America*. 2012; 26:383–397.

5. Odiere MR, Rawago F, Ombok M, Secor WE, Karanja DMS, Mwinzi PNM, Lammie PJ and Won K. High prevalence of schistosomiasis in Mbita and its adjacent islands of Lake Victoria, Western Kenya. *Parasit Vectors*. 2012; 5:278. doi: 10.1186/1756-3305-5-278.

6. Tonui WK. Situational Analysis of Leishmaniases Research in Kenya. *African Journal of Health Sciences*. 2006; 13:1-8.

7. World Health Organization. Sixtieth world health assembly on Control of Leishmaniasis. GENEVA 2007 May 14-23.

8. Wu GY and Halim MH. Schistosomiasis: progress and problems. *World Journal of Gastroenterology*. 2000; 6(1):12-19.

9. World Health Organization. Report of the Scientific Working Group meeting on Schistosomiasis. GENEVA 2005.

10. el Gaddal, AA. The Blue Health Project: A comprehensive approach to prevention and control of water-associated diseases in irrigated schemes of Sudan. *Journal of Tropical Medicine and Hygiene*. 1985; 88:47–56.
11. Muigai RK, Wasunna K, Gachihi G, Kirigi G, Mbugua J and Were JBO. Schistosomiasis caused by *Schistosoma mansoni* in Baringo district, Kenya-case-report. *East African Medical Journal*. 1989; 66:700−702.

12. Zijstra EE, Ali AM, el-Tourn IA, Saitti M, Ghalib HW, Sondorp E and Winkler A. Kala-azar in displaced people from Southern Sudan: epidemiological, clinical and therapeutic findings. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1991; 85:365−369.

13. Hotez PJ, Molyneux DH, Fenwick A, Ottesen E, Ehrlich Sachs S and Sachs JD. Incorporating a rapid-impact package for neglected tropical diseases with programs for HIV/AIDS, tuberculosis, and malaria. *PLoS Medicine*. 2006; 3:e102.

14. Steinmann P, Keiser J, Bos R, Tanner M and Utzinger J. Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. *Lancet Infectious Diseases*. 2006; 6:411−425.

15. Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Ehrlich Sachs S, Sachs JD and Savioli L. Control of neglected tropical diseases. *New England Journal of Medicine*. 2007; 357:1018−1027.

16. O’Neal SE, Guimaraes LH, Machado PR, Alcantara L, Morgan DJ and Passos S. Influence of helminth infections on the clinical course of and immune response to *Leishmania braziliensis* cutaneous leishmaniasis. *Journal of Infectious Diseases*. 2007; 195:142−148.

17. Galán-Puchades MT and Osuna A. Chagas Disease in a Wormy World. *Rev Ibero-Latinoam Parasitology*. 2012; 71(1): 5−13.

18. Yole DS, Shamala KT, Kithome K and Gicheru MM. Studies on the interaction of *Schistosoma mansoni* and *Leishmania major* in experimentally infected BALB/c mice. *African Journal of Health Sciences*. 2007; 14:80−85.

19. Yoshida, A, Maruyama, H, Yabu Y, Amano T, Kobayakawa T and Ohta N. Immune responses against protozoal and nematodal infection in mice with underlying *Schistosoma mansoni* infection. *Parasitology International*. 1999; 48:73−79.

20. La Flamme AC, Scott P and Pearce E. Schistosomiasis delays lesion resolution during *Leishmania major* infection by impairing parasite killing by macrophages. *Parasite Immunology*. 2002; 24:339−345.
21. Hassan MF, Zhang Y, Engwerda CR, Kaye MP, Sharp H and Bickle QD. The Schistosoma mansoni Hepatic Egg Granuloma Provides a Favorable Microenvironment for Sustained Growth of Leishmania donovani. American Journal of Pathology. 2006; 169(3): 943–953.

22. Abruzzi A and Fried B. Co-infection of Schistosoma (Trematoda) with Bacteria, Protozoa and Helminths. Advances in Parasitology. 2011; 77: 1–85.

23. Petney TN and Andrews RH. Multiparasite communities in animals and humans: frequency, structure and pathogenic significance. International Journal of Parasitology. 1998; 28: 377–393.

24. Buck AA, Anderson RI and MacRae AA. Epidemiology of poly-parasitism. IV. Combined effects on the state of health. Tropenmedizin Und Parasitologie. 1978; 29: 253–268.

25. King CH, Dickman K and Tisch DJ. Reassessment of the cost of chronic helminthic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. Lancet. 2005; 365: 1561–1569.

26. Mosmann TR and Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. Immunology Today. 1996; 17: 138–146.

27. Jankovic D and Sher A. Th1/Th2 effector choice in the immune system: a developmental program influenced by cytokine signals. In: Segel LA, Cohen IR, eds. Design principles for the immune system and other distributed autonomous systems. New York: Oxford University Press; 2001: 79–93.

28. Maizels RM and Yazdanbakhsh M. Immune regulation by helminth parasites: cellular and molecular mechanisms. Nature Reviews Immunology. 2003; 3: 733–744.

29. Hartgers FC and Yazdanbakhsh M. Co-infection of helminths and malaria: modulation of the immune responses to malaria. Parasite Immunology. 2006; 28: 497–506.

30. Specht S and Hoerauf A. Does helminth elimination promote or prevent malaria? Lancet 2007; 369: 446–447.

31. McManus DP and Loukas A. Current status of vaccines for schistosomiasis. Clinical Microbiology Reviews. 2008; 21: 225–242.
32. Osada Y and Kanazawa T. Schistosome: Its Benefit and Harm in Patients Suffering from Concomitant Diseases. *Journal of Biomedicine and Biotechnology* 2011, ID 264173.

33. Malaria Consortium. Leishmaniasis control in Eastern Africa: Past and present efforts and future needs. Situation and gap analysis 2010.

34. Muigai R, Gachihi GS, Oster CN, Were JBO, Nyakundi PM and Chunge CN. Post kala-azar dermal leishmaniasis: the Kenyan experience. *East African medical Journal*. 1991; 68:801–806.

35. Manson-Bahr PEC. East African kala-azar with special reference to the pathology, prophylaxis and treatment. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1959; 53:123–136.

36. Njau J. Leishmaniasis Control in Kenya: Current Challenges and Future Strategies. Geneva Health Forum, April 19-21, 2010.

37. Independent Electoral and Boundaries Commission (IEBC) [homepage on the Internet]. County summaries. [Updated 2012 Jan; cited 2012 July 10]. Available from http://www.iebc.or.ke/index.php/371-boundaries.html.

38. Independent Electoral and Boundaries Commission (IEBC) [homepage on the Internet]. Delimitation of Constituencies and Recommendations on Local Authority Electoral Units and Administrative Boundaries for Districts and Other Units. [Updated 2012 Jan; cited 2012 July 10]. Available from http://www.iebc.or.ke/index.php/resource-centre/downloads.html.

39. Boussery G, Boelaert M, Van Peteghem J, Ejikon P and Henckaerts K. Visceral leishmaniasis (kala-azar) outbreak in Somali refugees and Kenyan shepherds, Kenya. *Emerging Infectious Diseases*. 2001; 7: 603-4.

40. Marlet MV, Sang DK, Ritmeijer K, Muga OJ and Davidson RN. Emergence or re-emergence of visceral leishmaniasis in areas of Somalia, north-eastern Kenya, and south-eastern Ethiopia in 2000-01.*Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2003; 97:515-8.

41. Sang DK, Njeru WK and Ashford RW. A zoonotic focus of cutaneous leishmaniasis due to Leishmania tropica at Utut, Rift Valley Province, Kenya. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1994; 88:35-7.
Perspective

42. Chan AST, Ryan JR, Mbiu J, Rashid JR, Wasunna MK and Kirigi G. Spatial clustering and epidemiological aspects of visceral Leishmaniasis in two endemic villages, Baringo District, Kenya. *American Journal of Tropical Medicine and Hygiene*. 2006; 74(2):308–317.

43. Beach R, Young DG and Mutinga MJ. *Phlebotomus (Phlebotomus) duboscqi* from Kenya: a new record. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1982; 76: 707-708.

44. Kahama AI, Odek A, Kihara RW, Vennervald BJ, Kombe Y and Nkulila T. Urine circulating soluble egg antigen in relation to egg counts, Hematuria, and urinary tract pathology before and after Treatment in children infected with *Schistosoma haematobium* in Kenya. *American Journal of Tropical Medicine and Hygiene*. 1999; 61 (2): 215–219.

45. Wanyoike PK and Qureshi MM. Schistosoma mansoni of the conus medularis: case report. *East African Medical Journal*. 2004; 81(5): 271-273.

46. World Health Organization. Atlas of global distribution of schistosomiasis. CEGET-CNRS/OMS 1987.

47. Brooker S, Miguel EA, Waswa P, Namunyu R, Moulin S and Guyatt H. The potential of rapid screening methods for *Schistosoma mansoni* in western Kenya. *Annals of Tropical Medicine and Parasitology*. 2001; 95: 343–351.

48. Brooker S, Kabatereine NB and Smith JL. An updated atlas of human helminth infections: the example of East Africa. *International Journal of Health Geographics*. 2009; 8(42):1-11.

49. Handzel T, Karanja DM and Addiss DG. Geographic distribution of schistosomiasis and soil-transmitted helminthes in western Kenya: implications for antihelminthic mass treatment. *American Journal of Tropical Medicine and Hygiene*. 2003; 693:18-23.

50. Pamba HO and Roberts JMD. Schistosomiasis in and around Lake Naivasha, Kenya: Seven years Surveillance. *East African Medical Journal*. 1979; 56(6): 255-262.

51. Vogel LC, Muller AS and Odingo RS. Schistosomiasis. In Health and Disease in Kenya. *E African Literature Bureau, Nairobi* 1974.
Perspective

52. Muigai RK, Wasunna K, Gachihi G, Kirigi G, Mbugua J and Were JBO. Schistosomiasis caused by *Schistosoma mansoni* in Baringo district Kenya: case report. *East African Medical Journal*. 1989; **66**(10): 700-702

53. La Flamme A, Scott P and Pearce E. Schistosomiasis delays lesion resolution during *Leishmania major* infection by impairing parasite killing by macrophages. *Parasite and Immunology*. 2002; **24**: 339-345.

54. Helena H, Marika K and Marita T. Altered immune responses in mice with concomitant *Schistosoma mansoni* and *Plasmodium Chabaudi* infections. *Infection and Immunity*. 1998; **66**: 5167-5174.

55. Mansueto P, Vitale G, Seidita A, Guarneri FP, Pepe I and Rinallo C. Advances in leishmaniasis immunopathogenesis. *Acta Medica Mediterranea*. 2011; **27**: 7-16.

56. Awasthi A, Mathur RK and Saha B. Immune response to *Leishmania* infection. *Indian Journal of Medical Research*. 2004; **119**: 238-258.

57. Yole DS, Shamala KT, Kithome K and Gicheru MM. Studies on the interaction of *Schistosoma mansoni* and *Leishmania major* in experimentally infected BALB/c mice. *African Journal of Health Sciences*. 2007; **14**: 80-85.

58. Hassan MF, Zhang Y, Engwerda CR, Kaye PM, Sharp H and Bickle QD. The *Schistosoma mansoni* Hepatic Egg Granuloma Provides a Favorable Microenvironment for Sustained Growth of *Leishmania donovani*. *American Journal of Pathology*. 2006; **169**(3): 943-953.

59. Kemp M, Hey AS, Kurtzhals JAL, Christensen CBV, Gaafar A and Mustafa MD. Dichotomy of the human T cell response to *Leishmania* antigens. I. Th1-like response to *Leishmania major* promastigote antigens in individuals recovered from cutaneous leishmaniasis. *Clinical Experimental Immunology*. 1994; **96**: 410-415.

60. Gaafar A, Kurtzhals JAL, Ismail A, Kemp M, Hey AS and Christensen CBV. Dichotomy of the T cells response to Leishmania antigens in patients suffering from absence of cutaneous leishmaniasis; absence or scarcity of Th1 activity is associated with severe infection. *Clinical Experimental Immunology*. 1995; **100**: 239-245
61. Ajdary S, Alimohammadian MH, Eslami MB, Kemp K and Kharazmi A. Comparison of the immune profile of nonhealing cutaneous Leishmaniasis patients with those with active lesions and those who have recovered from infection. *Infection and Immunity.* 2000; 68(4): 1760-1764.

62. Wang ZE, Reiner SL, Zheng S, Dalton DK and Locksley RM. CD4+ effector cells default to the Th2 pathway in interferon gamma-deficient mice infected with *Leishmania major.* *Journal of Experimental Medicine.* 1994; 179: 1367–71.

63. Scott P, Natovitz P, Coffman RL, Pearce E and Sher A. Immunoregulation of cutaneous leishmaniasis T cell lines that transfer protective immunity or exacerbation belong to different T helper subsets and respond to distinct parasite antigens. *Journal of Experimental Medicine.* 1988; 168: 1675–84.

64. World Health Organization [homepage on the Internet]. Schistosomiasis. [Updated 2012 Jan; cited 2012 July 11]. Available http://www.who.int/mediacentre/factsheets/fs115/en/index.html

65. Pamba HO. Distribution, prevalence and epidemiology of schistosomiasis in Nyakach Location Kenya. *East African Medical Journal.* 1977; 4: 99-109.

66. Kinoti, GK. Epidemiology of *S. mansoni* infection on the Kano Plains of Kenya. *Transactions of the Royal Society of Tropical Medicine and Hygiene.* 1971; 65: 646-656.

67. MacDonald, G. The dynamics of helminth infections, with special reference to schistosomes. *Transactions of the Royal Society of Tropical Medicine and Hygiene.* 1965; 59(5):489-506.

68. Kenya national Bureau of Statistics (KNBS). Kenya 2009 population and housing census highlights.

69. Ministry of Water and Irrigation (MWI) [homepage on the Internet]. National land reclamation policy. [Updated 2011 Dec 14; cited 2012 August 15]. Available from http://www.water.go.ke/index.php?option=com_docman&Itemid=125.

70. Marlet MVL, Sang DK, Ritmeijer K, Muga RO, Onsongo J and Davidson RN. Emergence or re-emergence of visceral leishmaniasis in areas of Somalia, north eastern Kenya, and south-eastern Ethiopia in 2000–2001. *Transactions of the Royal Society of Tropical Medicine and Hygiene.* 2003; 97(5): 515–518.
71. Boussery G, Boelaert M, Peteghem JV, Ejikoh P and Henckaerts. Visceral leishmaniasis (kala-azar) outbreak in Somali refugees and Kenyan shepherds, Kenya. *Emerging Infectious Diseases*. 2001; 7(3): 603-604.

72. Elnaiem DA, Hassan HK, Osman OF, Maingon RDC, Killick-Kendrick R and Ward RD. A possible role for *Phlebotomus (Anaphlebotomus) rodhaini* (Parrot, 1930) in transmission of *Leishmania donovani*. *Parasites & Vectors*. 2011; 4: 238. doi:10.1186/1756-3305-4-238

73. Global Atlas of Helminth Infections (GAHI) [homepage on the Internet]. [Updated 2013 June 27; cited 2013 October 13]. Available from http://www.thiswormyworld.org/
List of figures and legend

Figure 1: Distribution of Leishmaniases in Kenya

VL:
- Wajir
- Dadaab
- Sudan border
- Kekonyokie
Figure 2: Prevalence and location of *S. mansoni* in Kenya: Parasitological surveys update

In total, 1100 surveys were available between 1975 and 2012. Where multiple surveys exist for the same location, the average prevalence is shown.