Mini-Review

Leishmaniasis in Sri Lanka

The need for effective targeting of island-specific issues through strategic implementation of global management plans for disease detection and control

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Abstract

Leishmaniasis, a vector-borne parasitic disease caused by *Leishmania sp*., has become a considerable global public health burden in recent decades, such that it is recognized by the World Health Organization as one of eight major neglected tropical parasitic diseases worldwide. The causative protozoan parasite is detected on every continent except Antarctica. There are three clinically distinct forms of leishmaniasis: cutaneous, mucocutaneous and visceral, the latter being the most serious manifestation.

In Sri Lanka, at the turn of this century, leishmaniasis was limited initially to a few imported cases but it is now a growing healthcare concern that is endemic to almost all districts. In particular, Hambantota, Matara, Kurunegala and Anuradhapura are seriously affected. Socioeconomic conditions, population mobility, environmental and climate changes are each considered important influences on the prevalence of leishmaniasis throughout the island nation. However, significant knowledge gaps remain regarding the precise epidemiology and severity of the disease, in large part due to the asymptomatic nature of the infection. Development of effective diagnostic tools, mapping disease distribution in unexplored locations and implementation of strategic management plans are all needed to meet the formidable challenge of eliminating leishmaniasis from Sri Lanka.

Keywords*: Leishmaniasis, Sri Lanka, diagnosis, prevalence, management, prevention*

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Introduction

Leishmaniasis is a zoonotic vector-borne disease that is caused by protozoan parasites of the genus *Leishmania* (Kinetoplastida: Trypanosomatidae).[1]The infective stage is the promastigote,[2] transmission of which occurs via the bite of an infected female phlebotomine sand fly whose vertebrate hosts include rodents, dogs, marsupials and humans.[1-3] Of the three distinct clinical presentations of infection, cutaneous leishmaniasis (CL) is the most common, producing ulcerated skin lesions on exposed body parts. Mucocutaneous leishmaniasis (MCL) damages the mucous membranes of the nose, mouth and throat. Visceral leishmaniasis (VL), also known as kala-azar, affects internal body organs, such as the spleen, liver and bone marrow, and is considered as the most severe form of the disease.[4,5] *Leishmania* promastigotes are transmitted to the skin, causing CL, while certain strains are able to disseminate to mucous membranes, initiating MCL even after CL healing. Particular protozoan strains disperse from the skin to lymphatic and vascular systems, leading to VL.[6]

Clinical signs and symptoms that serve as diagnostic indicators are not pathognomonic to either VL or CL. VL is frequently confused with similarly presenting conditions like malaria, tropical splenomegaly, schistosomiasis and typhoid fever. CL is often misdiagnosed as one or more of several medical conditions including tropical ulcers, impetigo, infected insect bites, leprosy, lupus vulgaris, tertiary syphilis, yaws, blastomycosis and skin cancer.[7,8,9] Several diagnostic methods are followed including parasitological, immunological and molecular biological techniques. Experimental infection of animals provides a robust biological means to confirm or refute suspected but unsubstantiated cases of leishmaniasis.[10] Serological methods of diagnosis are sensitive, specific and cost-effective, while molecular tools are extremely sensitive and applicable to molecular epidemiological studies beyond the scope of routine clinical diagnosis.[10] In many situations leishmaniasis is both treatable and curable.[11] Yet, several side-effects of treatment are emerging due to a combination of complexities of the host immune response to available drugs, variation in pharmacokinetics and differences in drug sensitivity of parasite strains.[12] Moreover, the current lack of both vector and parasite surveillance, together with poor public awareness of the serious health impact of infection, has led to high vulnerability to the disease in many tropical developing countries including Sri Lanka.[13]

In this mini-review, we discuss the several inter-related factors that have each contributed to the rapid progression of leishmaniasis in Sri Lanka from the first reported autochthonous case in the early 1990s to today being endemic to the whole island and with recorded cases rising annually. In light of the growing public health problem that this presents, appropriate measures to improve vector mapping and control, epidemiological surveillance and disease diagnosis are highlighted.

Factors affecting disease epidemiology

The widespread prevalence and rapid increase in cases of leishmaniasis in recent times in both endemic and non-endemic regions are attributed to several risk factors.[14] Socioeconomic conditions, population mobility, malnutrition,[15] saturation of sub-clinical infection in local areas,[16] immunogenic profiles and genetic predisposition are all major factors in the involvement of humans as a host to *Leishmania spp*.[17] In relation to housing, mud or thatched walls, damp earthen floors and peridomestic vegetation each act to promote vector resting and breeding sites.[18] Long-term changes in meteorological conditions, notably global warming, have facilitated the incremental northward expansion of mosquito-borne tropical diseases such as dengue and malaria from more equatorial latitudes.[19] Environmental conditions including altitude, precipitation and humidity also influence the abundance of sandflies,[3] and there is justified concern that the distribution of phlebotomine vectors of *Leishmania* transmission may increase with climate change. Recently, leishmaniasis has exhibited an ominous epidemiological trend in its potentially deadly co-existence with HIV.[4,10] *Leishmania spp.* have evolved several complex strategies to evade host immunity, such as altering chemokine expression profiles in infected cells to allow parasite dissemination, in order to survive within a host individual.[20]

Disease prevalence globally

According to the most recently available statistics, the World Health Organization estimates that 12 million people are infected with leishmaniasis worldwide.[4] This includes 1.5-2 million newly reported clinical cases each year, comprising 1.0-1.5 million cases of CL and 500,000 cases of VL. Between 26,000-65,000, leishmaniasis-related deaths occur annually.[4] More than 90% of global VL incidence occurs in just six countries; India, Bangladesh, Sudan, South Sudan, Ethiopia and Brazil. In contrast, CL is distributed widely across three epidemiological regions: the Americas, the Mediterranean basin, and Western Asia from the Middle East to Central Asia. Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica and Peru are the ten countries with highest number of cases, which together account for about 75% of global estimated CL incidence.[21]

Human leishmaniasis is caused by infection of more than 20 species of *Leishmania.* These include: the *L. donovani* complex with two species, *L. donovani* and *L. infantum* (also known as *L. chagasi* in the New World); the *L. mexicana* complex with three main species (*L. mexicana*, *L. amazonensis* and *L. venezuelensis*); *L. tropica*; *L. major*; *L. aethiopica*; and the subgenus *Viannia* with four main species (*L. [V.] braziliensis*, *L. [V.] guyanensis*, *L. [V.] panamensis* and *L. [V.] peruviana*). The amastigote stage of all these parasite species that is examined microscopically are morphologically indistinguishable, but they can be differentiated through isoenzyme analysis, molecular analysis and monoclonal antibody tests.[10]

Leishmania spp. parasites are transmitted by around 30 of over 500 known phlebotomine sandfly species.[4] The vector species come from three genera: *Phlebotomus*in the Old World, and *Lutzomyia* and *Psychodopygus* in the New World.[22] The increasing incidence of leishmaniasis is influenced largely by the expanding global distribution of sandflies. In general, *Phlebotomus* species occur frequently in desert or semi-arid ecosystems, breeding in close proximity to human habitation and often enter human housing. In contrast, *Lutzomyia* species dwell in forests and so bite humans living in or near dense vegetation.[23]

The changing global epidemiology of leishmaniasis is due to multiple factors associated with parasite, host and vector relationships. For instance, the unrecognized introduction of exotic parasitic species and strains via global passenger travel and the importation of domestic dogs each fosters the increased prevalence of infection within a local community.[23,24] Climate variability also may impose a considerable impact on disease epidemiology even in the absence of other biological and social factors.[25] Hence, while decades ago leishmaniasis was almost exclusively a substantial burden to the public health of tropical developing countries,[23] today it is spreading beyond low income nations into other more affluent parts of the world.

Disease emergence and prevalence in Sri Lanka

Sri Lanka is a tropical island of total square area 65,610 km^2 in the Indian Ocean (5º55"10' 9º50"6'N; 79º31"19' 81º52"36'E) where CL, caused by *L. donovani*, is the most frequently observed manifestation of leishmaniasis.[26,27,28] *Leishmania donovani* zymodeme MON-37, the strain responsible for CL in the country, differs only by a single isoenzyme (glucose-6-phosphate dehydrogenase) from *L. donovani* zymodeme MON-2,[29] the strain related most closely with the many cases of VL cases in India.[30] Given the proximity of southern India to Sri Lanka, just 18 nautical miles at the narrowest point of the Palk Strait, VL was recognized recently as an emerging health threat in Sri Lanka,[31]while at present MCL is rarely reported.[32,33]

Phlebotomus argentipes is the principal vector of leishmaniasis transmission in Sri Lanka, while the other two members of the *Phlebotomus* complex, *P. glaucus* and *P.annandalei*, are additionally found.[34,35] Sandflies of the genus *Sergentomyia* were recently also identified as potential vectors of leishmaniasis in CL-endemic areas of the island.[36] Eleven species from the genus *Sergentomyia* have been recorded to date,[37] which provided a challenge to identify accurately a number of sibling species and vector sibling counterparts. Subsequently, implementation of DNA barcoding using cytochrome C oxidase subunit 1 was able to delineate Sri Lankan sandfly species.[38] Nevertheless, the exact number of species that are capable of transmitting leishmaniasis in Sri Lanka is still not known, while the possibility of disease transmission by other potential vectors such as biting midges is yet to be established.[18]

In a detailed nationwide entomological trapping study, the highest number of sandflies collected was from the south-west coastal area of Kathaluwa, located in the Galle District.[39] This is part of the Southern Province, which experiences a hot and humid tropical rainforest climate. However, a clear picture of the population dynamics is not yet established due to a lack of survey data from the whole island.[18] On the other hand, the development of insecticide resistance in sandflies, predominantly to DDT and occasionally to Malathion and Pyrethroids,[40] will be associated directly with the epidemiology of leishmaniasis. Therefore, implementation of national vector control measures for malaria could explain the increasing rate of leishmaniasis over the last two decades.[41]

Humans are currently recognized as the only reservoir host for *L. donovani* in Sri Lanka. Nevertheless, *Leishmania sp.* parasites were reputedly detected by PCR in dogs from the Central Highlands in 2009, which supports the possibility of animal involvement as zoonotic foci.[42]

CL was initially only documented among immigrants and returnees from the Middle East.[6] Locally acquired CL was first reported in 1992 in Ambalangoda, a coastal town in the Hambantota District, in the Southern Province.[43] The first case of autochthonous VL followed in 2007 in Anuradhapura, the capital city of North Central Province.[44] In 2005, the first case of MCL was reported in Omanathai, in the Northern Province district of Vavuniya.[45] Since the early 2000s the country has experienced a significant escalation in the reported incidence of leishmaniasis[41] (shown for the last decade in Figure 1), with increasing invasion into forested regions and prevalence affected by frequently changing climatic conditions.[46] Of great public health concern, by far the highest annual numbers of leishmaniasis patients have been recorded in 2018 and 2019, each well over double the numbers reported for 2017, the next greatest incidence on record (Figure 1). It is therefore anticipated that the recent epidemiological trend for serious outbreaks will continue in future unless effective control and preventive measures are instigated. Although listed by the Sri Lankan

Ministry of Health as a notifiable disease since 2008 the detailed epidemiology of leishmaniasis remains largely unknown.[18]

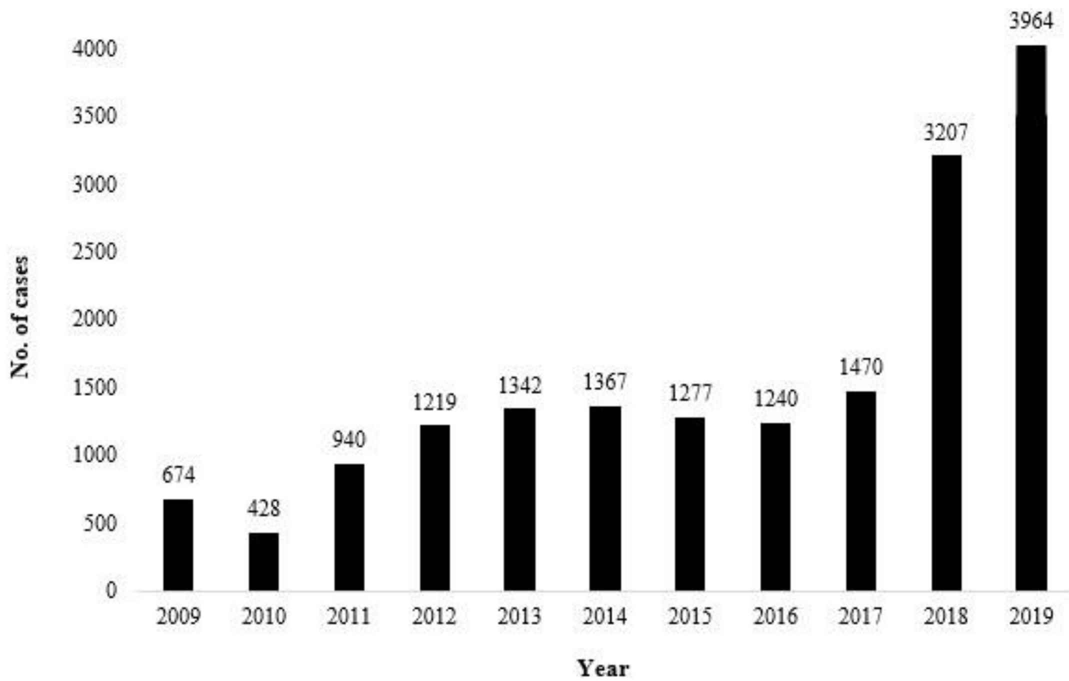

Figure 1. Annual number of recorded leishmaniasis cases in Sri Lanka from 2009 to 2019

Source: Weekly Epidemiology Report, Epidemiology Unit, Ministry of Health.

When leishmaniasis first became established in Sri Lanka it was limited to the districts of Anuradhapura and Polonnaruwa in the northern part of the island, later becoming evident in Hambanthota and Matara at its southern-most tip.[47] While these are still hotspots for the disease, it has now a far broader – almost island-wide – geographical distribution (Figure 2). Between 2005-2015, CL was reported most frequently (47.9%) from Kurunegala, located to the immediate south of Anuradhapura; of these cases 58.9% were males and 40-49 years was the most affected age group.[48] Among such populations of patients referred for hospital treatment men are more likely to be engaged in outdoor occupations, thereby placing them at greater risk of being infected.[49,50] In the three most recent years, 2017 to 2019, the highest number of patients has been recorded from the Hambanthota District (2,049total cases) followed in decreasing order by Matara, Kurunegala and Anuradhapura. A considerable burden of clinical cases was also reported in Polonnaruwa, Matale and Ratnapura. Evidently, the disease is now endemic to dry, wet and intermediate climate zones and it affects every district in Sri Lanka (Figure 2).

The relatively rapid spread of the disease nationwide is associated with the movement of people infected with leishmaniasis, often while infectious but still undiagnosed, and of reservoir hosts from endemic areas to hitherto non-endemic sites. In the north-eastern coast of the island the deployment of armed forces personnel to areas formerly uninhabited, due to the civil war (1983-2009) led to an epidemic outbreak of CL that was not detected by public health systems. Initially, soldiers who had become infected while stationed for six months or longer at military camps in Mullaitivu District were correctly diagnosed and treated only when posted to other areas of the country where testing was available.[51]

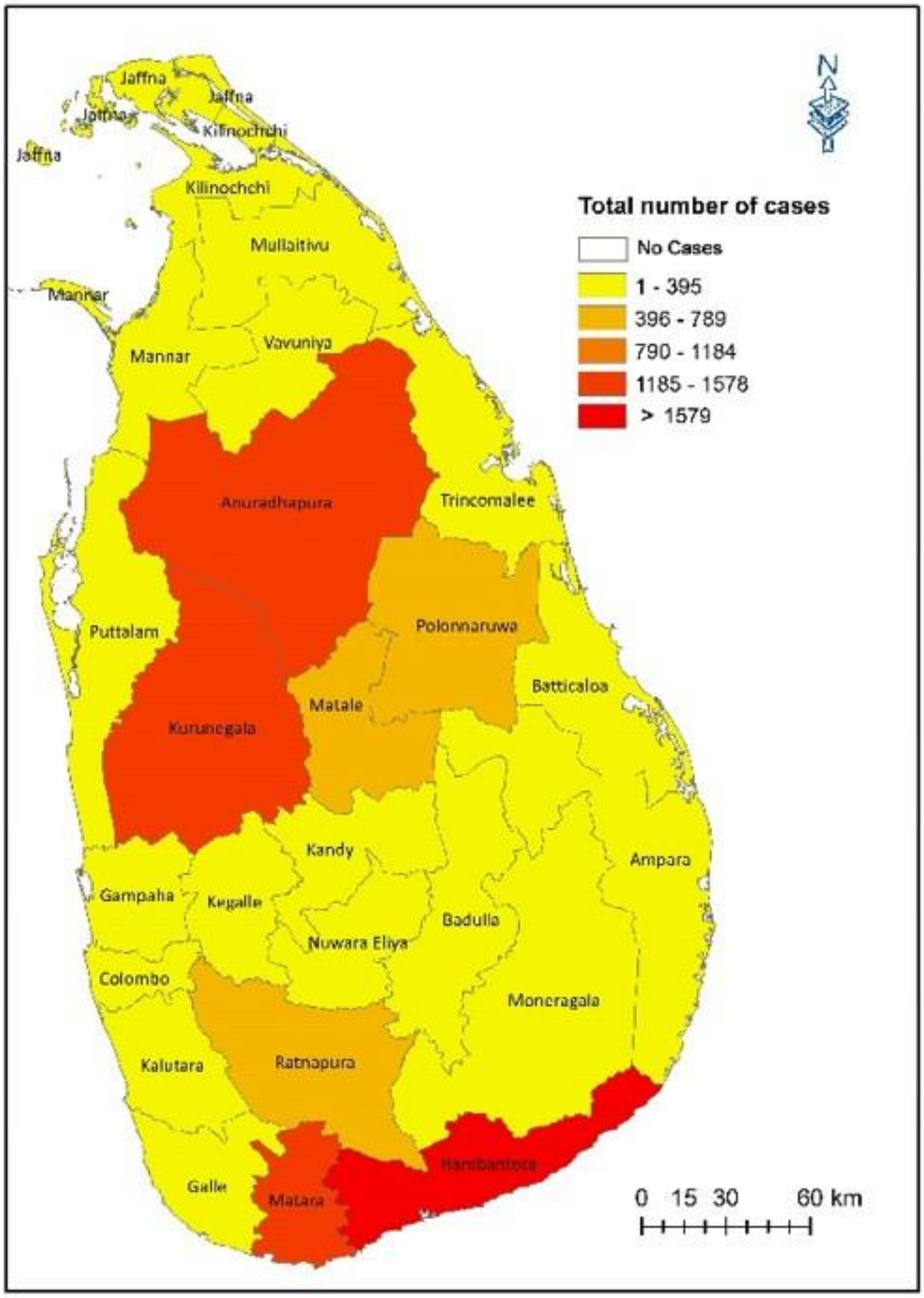

Figure 2. Total number of leishmaniasis patients by district of Sri Lanka for the three-year period 2017-2019. Source: Weekly Epidemiology Report, Epidemiology Unit, Ministry of Health.

It is acknowledged that the true disease burden associated with leishmanial infection may be much higher than official statistics indicate, due to under reporting and misdiagnosis of clinical cases.[52] Moreover, the date when VL emerged may be less recent than previously thought due to its asymptomatic nature.[53] Historically, most epidemiological studies and case reports have relied on diagnostic methods that enable detection of active infections only, yet two recent studies reported zero prevalence of apparent asymptomatic VL.[31,53] This highlights that at present it is possible to acquire accurate and detailed information on asymptomatic carriers of leishmaniasis in some locations but that this capacity is still generally lacking throughout Sri Lanka.

Major challenges for disease control in Sri Lanka

By virtue of its geographical isolation as an island nation, Sri Lanka has in theory if not in practice the capability to prevent the introduction of non-native diseases. Indeed, prior to 1990 it was believed to be free of any kind of locally acquired leishmaniasis.[43] Thirty years on however, Sri Lanka is now a leading endemic focus of the disease in South Asia.[48] Despite this, the country is still not a part of a leishmaniasis elimination program in the Indian subcontinent.[31] There is a significant knowledge deficit regarding the disease, how it is transmitted and its diagnosis among at-risk communities.[54]

Currently there is poor scientific understanding of the association between parasite, host dynamics and distinct clinical features.[55] The use of diagnostic markers of infection and an adequate disease management action plan are also yet to be implemented in the country, particularly highlighting the threat of VL.[31] Another major issue is the shortage of suitably trained technical personnel across a range of impacted disciplines including early detection of infection, health worker education, community awareness and disease notification.[56,57] Most importantly, in Sri Lanka, diagnosis of leishmaniasis relies heavily upon traditional light microscopic identification of amastigote stage parasitized phagocytes in Giemsa-stained tissue specimens from skin lesions for CL, or from bone marrow for VL. More sophisticated molecular or immunological techniques like PCR, ELISA and indirect fluorescent antibody tests are cost-limited to very few laboratories.[18] Highly sensitive diagnostic methods that enable detection of non-disturbing early stages of CL and asymptomatic conditions of VL are not yet available in the country.[18]

Since very few detailed studies have been undertaken on phlebotomine sandfly biology, ecology and control in Sri Lanka, the knowledge is lacking to instigate effective vector control programs.[18] In addition, detailed entomological surveys are required to gain an in-depth understanding of potential reservoir hosts and local disease transmission patterns.[48,58,59]

Conclusions

Leishmaniasis is considered second only to malaria in importance as a protozoan disease causing human mortality and morbidity worldwide.[60] Despite the sizeable public health burden to Sri Lanka, the severity of the disease and the extent of its spread have been underestimated since its introduction three decades ago. Hence, the clinical case count has increased year on year and the entire island is now recognized as a disease-emerging region. Consequently, there is a pressing need to implement a nationwide standard disease management plan to target epidemic areas. In addition, to achieve the ultimate goal of achieving zero prevalence of leishmaniasis in the whole country, highly sensitive diagnostic tools are required that are able to identify asymptomatic carriers of infection. Investment in strategic research that focuses on the key areas of epidemiological surveying of infection, early and effective diagnosis of disease and entomological mapping of vector species will help to plug existing knowledge gaps, thereby supporting Sri Lanka in its bid to regain leishmaniasis-free status.

Author contribution statement

JMNJJ: Data acquisition, analysis & interpretation, Writing – original draft & editing. AWT-R: Study conception and design, Supervision, Data analysis & interpretation, Writing – review & editing. Both authors read and approved submission of the final version of the manuscript. Both authors are accountable for all aspects of the work.

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