Review Article

Social and Economic Burden of Human Leishmaniasis

Ifeoma Okwor and Jude Uzonna*

*Department of Medical Microbiology, Faculty of Health Sciences, University of Manitoba, Manitoba, Canada;
Department of Immunology, Faculty of Health Sciences, University of Manitoba, Manitoba, Canada*

Abstract. Leishmaniasis continues to pose a major public health problem worldwide. With new epidemics occurring in endemic areas and the spread of the disease to previously free areas because of migration, tourism, and military activities, there is a great need for the development of an effective vaccine. Leishmaniasis is a disease of the poor, occurring mostly in remote rural villages with poor housing and little or no access to modern health-care facilities. In endemic areas, diagnosis of any form of leishmaniasis puts a huge financial strain on an already meagre financial resource at both the individual and community levels. Most often families need to sell their assets (land and livestock) or take loans from informal financial outfits with heavy interest rates to pay for the diagnosis and treatment of leishmaniasis. Here, we discuss the disease with special emphasis on its socioeconomic impact on the affected individual and community. In addition, we highlight the reasons why continued research aimed at developing an effective *Leishmania* vaccine is necessary.

INTRODUCTION

Leishmaniasis is one of the neglected tropical diseases caused by different species of the protozoan parasite *Leishmania*, which are obligate intracellular protozoan parasites that are transmitted by the bites of infected female sandflies. Over 20 species of the parasite cause disease in both humans and animals.¹ Current estimates show an annual global incidence of 0.2–0.4 million cases of visceral leishmaniasis (VL) and 0.7–1.2 million cases of cutaneous leishmaniasis (CL). The disease currently affects 12 million people with 350 million people at risk of infection.² Over 90% of VL occur in poor rural and suburban areas in six countries: Bangladesh, Ethiopia, Brazil, India, Sudan, and South Sudan.² Unlike VL, CL is more widespread and occurs in the Americas, the Mediterranean, and western Asia. Globally, 70–75% of CL cases occur in 10 countries: Afghanistan, Algeria, Brazil, Iran, Peru, Ethiopia, North Sudan, Costa Rica, Colombia, and Syria.² The fact that leishmaniasis occurs as syndromes¹ coupled with lack of surveillance and reporting in the countries most affected by the disease² significantly limits the determination of actual burden of the disease. This poor reporting record leads to overall underreporting that affects intervention strategies. In one study, underreporting of VL was shown to be as high as eight times the actual disease prevalence in Muzzaffarpur District of Bihar, India.³ This was attributed to the fact that the official disease estimates are based on public health-care records that exclude good number of individuals that patronize the private health-care system.³ A similar and more recent study put underreporting of VL at 4.74 and 3.51 times in males and females, respectively, in Lalganj and Goraul villages in Bihar, India.⁴ Thus, it is generally believed that the current estimates of disease burden may not reflect the true impact of the diseases.^{1,2} The case fatality rate for leishmaniasis was estimated to be around 20,000–40,000 deaths.² Leishmaniasis is often related to poverty as well as, illiteracy, weak immune system, malnutrition, gender inequality, lack of resources, and poor housing.⁵ Generally,

high morbidity and low mortality of infectious diseases are well-recognized determinants of poverty.⁶ Leishmaniasis is classified as one of the most neglected tropical diseases and has strong links with poverty⁷ and together they create a mutual vicious cycle.⁶ Compared with other diseases, treatment of leishmaniasis is very expensive ranging from 30 to 1,500 U.S. dollars (USD) for the drugs alone, and this is considered a major contributor to poverty of affected individuals.⁸ Here, we review the literature on the socioeconomic impact of leishmaniasis and highlight potential benefits for continued research aimed at developing an effective vaccine to prevent the disease.

SOCIOECONOMIC IMPACT OF LEISHMANIASIS

Leishmaniasis affects mostly people living in the most impoverished parts of developing countries and places further economic stress on already strained meagre financial resources. A 2006 study that looked at the economic impact of VL in Nepal found that the average VL treatment cost incurred by patients was greater than the annual household per capita income.⁹ Furthermore, the median cost per household diagnosed with more than one case of VL was USD 425, which is more than the median annual household income of USD 405. It was further found that direct costs, that is, costs that are directly related to treatment (such as consultation fees, payment for laboratory tests and drugs) accounted for 53% of the total costs while indirect costs were mainly as a result of loss of earnings because of illness.⁹ It is important to note that 75% of the mean direct total health-care cost occurred even before the patient received treatment of VL.⁹ All affected household in the study depleted their savings to get treatment. Some other families in addition to using up their saving took high-interest loans or sold some of their livestock to pay for treatment.⁹ Although health-care services are generally provided free in developing countries, affected household still incur a substantial amount of financial burden due to treatment of episodes of leishmaniasis.¹⁰ A recent study in Nepal showed that indirect cost increased from 47% in 2006⁹ to 53% in 2010.¹¹ This may be because most affected individuals live in remote villages that are far away from the free government health-care facilities, which are usually located in the cities and urban centers. Because leishmaniasis

*Address correspondence to Jude Uzonna, Parasite Vaccines Development Laboratory, Department of Immunology, Faculty of Health Sciences, University of Manitoba, 750 McDermot Avenue, Winnipeg, Manitoba, R3E 0T5, Canada. E-mail: jude.uzonna@med.manitoba.ca

is primarily more common in rural areas and villages, many of the affected individuals patronize the more expensive and often inadequate private health-care facilities located in these villages. The mechanism of financing out-of-pocket payments plays an important role in the economic impact on the households especially in developing countries where this is done through borrowing from informal sources of financing.¹⁰ The average cost of treatment of an episode of VL was shown to be 17.5% while the average total cost (for the entire duration of illness) was 44% of the average household income.¹⁰ In a similar study in India, the estimated annual overall household expenditure was USD 1,312, which is higher than the average household assets of USD 1,273. In this study, VL treatment represented 11% of the total household expenditure. Also, the economic impact of VL was equal to 13% of total household assets, and in the most vulnerable population, this was equivalent to 72%.¹² Similar findings were reported by a recent study in Nepal. Despite the provision of free medications by the government, the cost of treating one episode of VL was USD 165 and the economic burden, which includes direct and indirect cost, was estimated at 11% of annual household income or 57% of median per capita income.¹¹

Catastrophic payment is a measure of the cost of health-care services in excess of a given threshold (5–25%) that diverts consumption from basic needs or cause households to resort to using their savings. According to Adhikari and others,¹⁰ 93% and 31% of affected households spent at least 5% and 15%, respectively, of their income on VL treatment. In another study, 51% of households exceeded catastrophic threshold of 10% of the annual household income.¹¹ It is interesting to note that without the provision of free drugs, the catastrophic index would have increased from 51–74%.¹¹ The implication of catastrophic payments may be seen as changes in treatment-seeking behavior from the formal to informal health sector.¹⁰ Factors such as distance to facility, cost, staff, regularity of supplies, and cultural preferences can influence a person's choice of health-care provider, which may have significant impact on timeliness of diagnosis, treatment, and effectiveness.¹² The consequences of delay in seeking medical help include reduced quality of life and the development of chronic lesions.¹³

LEISHMANIASIS AND GENDER INEQUALITY

Although CL is associated with low morbidity and mortality, it causes very severe disfiguring scars in infected individuals, which most often leads to stigmatization in both men and women. It was generally believed that more men are affected with CL than women, but recent studies reveal similar rates of infection in both men and women.¹⁴ However, infected women have less access to health-care services and also less likely to report to a health center even when available.¹³ In addition, men are usually engaged in productive labor (i.e., income-generating labor performed outside the home), whereas women are often involved in unpaid reproductive labor (i.e., work done within the home such as cooking, care of children and livestock, and gardening/farming).^{15,16} As a result, many women lack the financial resources for travel, clinical care, and drugs and most times will not be willing to spend the limited cash resources on their health needs.¹⁶ Furthermore, gender differences affect how illness is experienced, treatment-seeking behaviors, nature of treatment, as

well as care and support received from family, health caregiver, and the community.¹⁷ For example, in a study conducted in Medellin, Columbia, 80% of the 66 patients that attended a CL clinic had tried other therapies. Interestingly, only men had tried self-medication with an appropriate drug (glucantime) whereas all the women tried caustic agents and plants.¹⁴

LEISHMANIASIS AND POVERTY

The connection between poverty and the risk of developing leishmaniasis is very strong and mediated through many factors⁸: ecological factors such as poor housing conditions, including cracked walls that provide resting places for sandflies, damp earthen floors that enhance vector survival, and improper doors that allow sandfly entry.^{18–20} Also, some other socioeconomic factors such as housing, literacy, and the type of work done have been shown to influence the incidence of leishmaniasis.²¹ Poor sanitation and irregular garbage collection provide sandfly breeding grounds and are associated with increased risk for contracting leishmaniasis in Latin America.^{22,23} Although insecticide bed nets have been shown to be effective in the control of leishmaniasis, most families living in endemic areas cannot afford bed nets.²⁴ For example, in a study conducted in Afghanistan, 78% of respondents reported that they could not afford bed nets.²⁵ A concrete evidence for the impact of socioeconomic status on leishmaniasis is from the studies in India that investigated the prevalence of leishmaniasis among the different castes. The caste system is a very rigid hierarchical social structure that categorizes people into different groups based on economic status.²⁶ A study in Bihar, India, showed that people in the lower caste with VL had significantly delayed access to health care compared with those in the higher caste.²⁶

PSYCHOSOCIAL EFFECTS OF LEISHMANIASIS

Leishmaniasis also negatively impacts on the psychological and social status of women. The disfiguring scars lead to social stigmatization, exclusion from community activities, and may precipitate psychological problems. Young women who have disfiguring scars as a result of CL infection suffer social stigmatization and are usually unable to marry.¹³ Older married women suffer rejection from their husbands/partners who are afraid of contracting the diseases from them.¹⁴ CL lesion also affects a woman's ability to take care of her children and carry out daily house hold chores, which has profound consequences on their mental well-being.¹⁴ Other than outward stigma, there is also the issue of perceived stigma. Testimonies from infected women show they display shame, embarrassment, and have low self-esteem. Also in some societies, CL lesions are seen as marks of low social status and reflect underlying poverty, further enhancing stigma.²⁷ In some societies, leishmaniasis is believed to be contagious, and as such infected individuals are prevented from attending school and can be isolated from their families and communities.²⁷

OPINION: BENEFITS OF CONTINUED RESEARCH

A search of the literature show that very few studies have looked at the socioeconomic impact of leishmaniasis and almost all have focused on small disease-endemic communities

in Nepal and India. Thus, studies looking at national and global economic impact of leishmaniasis are lacking, and this may be due in part to lack of accurate data on both the incidence and prevalence of the disease in endemic regions.²⁸ Such studies are vital because they would inform strategies and plans for regional and/or global control and treatment programs against the disease. In addition, they would also greatly impact regional programs for disease eradication and management of disease-associated comorbidities.

Many infectious diseases that originally threatened the existence of humankind such as smallpox and polio have been effectively controlled or even wiped out by the development of effective vaccines and vaccination strategies. Vaccines work by generating long-lived memory cells in vaccinated individuals that are able to rapidly recognize, respond, and eliminate the invading organism on subsequent encounters. There is currently no clinically effective vaccine against human leishmaniasis because we still do not fully understand the factors that regulate the development of *Leishmania* specific memory cells and protective immunity. Although both central and effector memory cells do develop after recovery from primary *Leishmania major* infection in experimental mice, central memory cells may be more important in protection after secondary challenge.²⁹ Interestingly, a study by Peters and others,³⁰ which used the vector (sandfly) challenge system, suggests that memory cells may only be relevant in artificial systems and that protection after infection initiated by sandflies is due to rapid recruitment of effector cells to areas of inflammation. The discrepancy between the two studies may be due to differences in the study plan and the fluidity in characterizing effector memory, central memory, and effector cells. Peters and others did not specifically characterize memory cells after challenge with infected or uninfected sandflies. The fact that the number of cells recalled by saliva from *Leishmania*-infected sandflies increased over time, whereas that recruited by uninfected saliva remained unchanged suggests that the observation may not be solely due to inflammation.

Currently, it is not known how memory cells are generated, maintained, and lost after *Leishmania* infection. However, it is generally accepted that maintenance of long-lasting immunity is dependent on persistence of live parasites at the primary site of infection.³¹ The inability to completely eliminate parasites after disease resolution may have huge implications in the maintenance of the disease in endemic areas as well as in cases of immunosuppression such as may be seen during human immunodeficiency virus (HIV) coinfection. Recently, we showed that it is possible to generate a relatively long-lasting immunity in the absence of live, replicating parasites.³² However, studies are needed to determine ways to maintain *Leishmania* memory cells generated in vivo by such repeated immunization with killed parasites.

An important aspect of vaccine development is formulation and delivery. Studies have shown that encapsulation of antigens in liposomes, nanoparticles, or inclusion of adjuvants greatly enhances their immunogenicity and protective ability,^{33–35} thus underscoring the need for continued studies in improving vaccine delivery. The development of a vaccine will benefit an estimated 350 million people who are at risk of developing the disease worldwide. In addition, market opportunities continue to emerge because of military conflicts and increased tourism to endemic places. For example,

leishmaniasis has been diagnosed in American, Canadian, Dutch, and British soldiers returning from active duty in *Leishmania*-endemic region including Afghanistan and Iraq.^{36,37} Furthermore, several cases of leishmaniasis have been reported in people who traveled to endemic areas for business or pleasure.³⁸ A recent study showed that 6% and 3% of people who traveled to industrialized nations in Europe (including Italy, Spain, and Turkey) and Latin America, respectively, were diagnosed with CL.³⁹ Also, several cases of leishmaniasis have been diagnosed in European travelers most of whom were tourists to other countries.⁴⁰ Thus, an effective *Leishmania* vaccine could be added to the list of travel vaccines for people living in non-endemic areas and wishing to travel to *Leishmania*-endemic regions of the world. Furthermore, in the absence of vaccines, prophylactic treatments as is done for malaria, could help prevent infection during short-term trips to endemic regions.

It has been recognized that development of new and effective drugs is the first step toward the control of neglected tropical diseases including leishmaniasis.⁸ With the high toxicity, development of resistance, relapse, and poor compliance associated with the current treatment of leishmaniasis, the need for the development of new drugs against the disease cannot be over emphasized. A new drug with mild or no toxicity will increase patient compliance and may reduce the chances of developing drug resistance.

In a recent study, Boer and others⁴¹ suggested that the issue of drug availability could be enhanced through proper forecasting of the disease to ensure that adequate numbers of drugs are produced and distributed in a timely manner. There has been an instance where hundreds of patients were treated with fake drugs in Bangladesh.⁴² This emphasizes the need for the establishment of centralized quality assurance/control laboratory, thus ensuring that all drugs meet the minimum established standard.⁴¹ The current drugs for treatment of leishmaniasis are expensive. There is also an urgent need for the development of generic drugs as well as drugs with mild or highly reduced side effects. Because generic drugs are generally cheaper than their branded counterparts, lowering the cost of effective drugs would make treatment more affordable and could improve patient compliance. Although there are several prophylactic treatments for malaria (another parasitic disease caused by a protozoa), none is available for leishmaniasis. Prophylactic treatment of leishmaniasis, if available, could be used in people living in non-endemic areas before or during their trip to endemic areas. This will reduce the chances of importation of the disease to *Leishmania*-free areas. More studies are required to establish a prophylactic drug regimen for leishmaniasis. Toxicity problems associated with the current treatments⁴³ clearly underscore the need for a randomized placebo-controlled clinical trial to improve the available pharmacokinetic information.⁴⁴ In the wake of increased resistance to current drugs, there is also a need for the establishment of policy and structure for the monitoring of drug resistance.⁴⁵

Epidemics of leishmaniasis have led to delays in the implementation of economic programs especially in the Amazon basin, Morocco, and Saudi Arabia with major implications for the socioeconomic development of these regions.⁴⁶ Urbanization and migration from rural areas to peri-urban cities with inadequate housing and sanitary conditions have led to increased epidemics of leishmaniasis in different parts of the

world.⁴⁶ Cost-benefit analysis studies have shown that treatment of leishmaniasis could be quite profitable and would also provide other benefits such as poverty reduction, improvement in economic welfare of the local community, and improvement in disability-adjusted life years.⁴⁷ To our knowledge, no studies have estimated the potential target market for a *Leishmania* vaccine or determined if such a vaccine would yield a good return on investment. However, given the disease epidemiology (particularly, the population at risk), it is fair to speculate that such a venture would yield high returns. These kinds of studies are crucial to attract potential investors and encourage pharmaceutical companies to intensify efforts in research aimed at vaccine development. Leishmaniasis is often described as the disease of the poor, which is true for the most part and may be the reason why there is very little interest in developing new therapies. However, with increased travel, war, immigration, environmental changes, and HIV pandemic, the disease is spreading to non-endemic areas, thereby expanding the potential target market for a *Leishmania* vaccine or drug beyond the poor rural communities in endemic areas. In the future, leishmaniasis could be seen not only as a disease of the impoverished rural dwellers, but also as a global public health problem that can affect people in developed rich nations.

There is a definite need for improvement of health-care delivery in areas mostly affected with leishmaniasis. In a study conducted in Bangladesh, most participants expressed anger and resentment toward the health-care system because of high cost of medication, fees paid to facilitate access to diagnosis and treatment, unnecessary medications, diagnostic tests and procedures, as well as lack of respect at hospitals.⁴⁸ Anthropological research with gender orientation will be valuable in showing how the consequences of infectious diseases may be different for men and women and may help in the development of gender-tailored preventive, coping, and intervention strategies.¹⁶

Education, increase in the awareness of the disease, and control measures using health education materials that specifically target communities as well as increase in community participation have been identified by the World Health Organization as ways to enhance leishmaniasis control measures in marginalized endemic regions.⁴⁹ A study carried out in a CL-endemic region of Iran revealed that the total knowledge score of participants was 17.47 of possible 30. Their knowledge about CL symptoms, carriers, and reservoirs was higher than their knowledge about preventive measures.⁵⁰ In another study, health education gave the community important insights on the vectors, their habits, habitats, and disease transmission, which resulted in environmental management actions/changes. These changes led to observable decrease in the sandfly frequencies in the study area.⁵¹ Education of endemic communities in disease etiology, transmission, and control measures has an essential role to play in the management, prevention, and control of leishmaniasis. More studies are needed to access the impact of community education in the control and prevention of leishmaniasis.

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Authors' addresses: Ifeoma Okwor, Department of Medical Microbiology, Faculty of Health Sciences, University of Manitoba,

Manitoba, Canada, E-mail: umokwor@myumanitoba.ca. Jude Uzonna, Department of Immunology, Faculty of Health Sciences, University of Manitoba, Manitoba, Canada, E-mail: jude.uzonna@med.umanitoba.ca.

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