

Vulnerabilities to and the Socioeconomic and Psychosocial Impacts of the Leishmaniasis: A Review

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Abstract: The leishmaniasis are a group of four vector-borne neglected tropical diseases (NTDs) with 1.6 billion people in some 100 countries at risk. They occur in certain eco-epidemiological foci that reflect manipulation by human activities, such as migration, urbanization and deforestation, of which poverty, conflict and climate change are key drivers. Given their synergistic impacts, risk factors and the vulnerabilities of poor populations and the launch of a new 2030 roadmap for NTDs in the context of the global sustainability agenda, it is warranted to update the state of knowledge of the leishmaniasis and their effects. Using existing literature, we review socioeconomic and psychosocial impacts of leishmaniasis within a framework of risk factors and vulnerabilities to help inform policy interventions. Studies show that poverty is an overarching primary risk factor. Low-income status fosters inadequate housing, malnutrition and lack of sanitation, which create and exacerbate complexities in access to care and treatment outcomes as well as education and awareness. The co-occurrence of the leishmaniasis with malnutrition and HIV infection further complicate diagnosis and treatment, leading to poor diagnostic outcomes and therapeutic response. Even with free treatment, households may suffer catastrophic health expenditure from direct and indirect medical costs, which compounds existing financial strain in low-income communities for households and healthcare systems. The dermatological presentations of the leishmaniasis may result in long-term severe disfigurement, leading to stigmatization, reduced quality of life, discrimination and mental health issues. A substantial amount of recent literature points to the vulnerability pathways and burden of leishmaniasis on women, in particular, who disproportionately suffer from these impacts. These emerging foci demonstrate a need for continued international efforts to address key risk factors and population vulnerabilities if leishmaniasis control, and ultimately elimination, is to be achieved by 2030.

Keywords: leishmaniasis, risk factors, economic-psychosocial impacts, neglected tropical diseases, kala-azar

Introduction

Ancient, debilitating and stigmatizing, the leishmaniasis are among the neglected tropical diseases (NTDs) globally impacting nearly two billion people.¹⁻⁵ Representing parasitic, bacterial, viral, helminths and protozoan infections,^{4,5} NTDs are aptly called “diseases of the poor” because they are all strongly connected to poverty and impoverished environments even in high-income countries.^{6,7} The human health effects of NTDs are disproportionately distributed by disease

type, gender and age. In particular, the leishmaniasis stand out for their socioeconomic impacts, where various economic variables act as proxies for a range of important global risk factors, such as type of housing, malnutrition, livelihood patterns, labor migration and resource conflicts.^{8–16} The most severe form of leishmaniasis has been shown to cause significant financial and economic loss to as much as 75% of households affected by the disease in Asia and Africa.^{17–21} Annualized loss in productive economic input has been estimated to be 6–30% among affected households in a global assessment.²² Several recent systematic reviews have further highlighted significant economic impacts.^{23,24}

The leishmaniasis manifest in four severely neglected forms, namely visceral leishmaniasis (VL) (also known as Kala-azar), cutaneous leishmaniasis (CL), post-kala-azar dermal leishmaniasis (PKDL) and mucocutaneous leishmaniasis (MCL).^{25,26} Endemic in some 100 countries, the leishmaniasis are vector-borne diseases caused by about 20 species of protozoan parasites of the genus *Leishmania* and transmitted through a bite of infected female phlebotomine sandflies of over 90 species.^{25,27,28} Due to poor programming and reporting, the true level of disease prevalence is unknown. It is estimated that 1.6 billion of the world's population lives in areas of potential risk of leishmaniasis transmission.²⁹ With climate change, population growth and migration, this figure could increase in the years ahead. The World Health Organization (WHO) estimates that 50,000 to 90,000 and 600,000 to 1 million annual cases of VL and CL occur worldwide, respectively.³⁰ However, the latest data reported to the WHO from 98 countries in 2018 identified 17,223 cases of VL and 253,435 cases of CL,³¹ a vast underrepresentation that speaks to the neglected nature of these diseases. Cases are distributed almost equally across sub-Saharan Africa, Southeast Asia, the Middle East and Latin America³² with just ten countries (Brazil, China, Ethiopia, India, Iraq, Kenya, Nepal, Somalia, South Sudan and Sudan) reporting 95% of VL cases and ten (Afghanistan, Algeria, Bolivia, Brazil, Colombia, Iran (Islamic Republic of), Iraq, Pakistan, the Syrian Arab Republic and Tunisia) reporting 85% of CL cases.³⁰ Table 1 captures important characteristics for the leishmaniasis in each of these countries.

When left untreated, VL has been reported to result in 95% fatality and can result in PKDL.^{27,33,34} CL is a disfiguring and stigmatizing disease characterized by skin lesions, mainly ulcers, on exposed parts of the body

that leave life-long scars, cause disability and severe psychosocial and mental health outcomes.^{25,27,35–39} The contribution of VL to the disability-adjusted life years (DALYs) for all NTDs is among the highest⁴⁰ at 97% of the 774,000 DALYs from the leishmaniasis.^{41,42}

Historically, epic campaigns to end NTDs represent what the WHO has called a 'rags-to-riches story'⁴³ because these are some of the best pro-poor health policies and interventions to break the cycles of poverty caused by these diseases, thus presenting a strong case for accelerated investments.²² NTDs are the reason why the World Bank started working in the health sector decades ago in the 1970s.⁴⁴ Expanding our understanding of the scale and scope of the socioeconomic impacts of NTDs, such as the leishmaniasis, is timely for several important reasons. First, at the start of 2021, the WHO launched the 2030 NTDs Roadmap.⁴⁵ This Roadmap follows the 2020 Roadmap launched in 2012, where global organizations began an unprecedented and intensified focus on NTDs in what emerged as the London Declaration on NTDs.^{46,47} While the 2020 Roadmap accelerated efforts with various accomplishments, most targets related to the leishmaniasis were missed.⁴⁸ Secondly, the new 2030 Roadmap is aligned with the global United Nations Sustainable Development Goals (SDGs), in which "the end of NTDs" by 2030 is called for with eradication of chronic poverty as the top goal.⁴⁹ Third, understanding the impoverishing conditions in the cycle of leishmaniasis transmission is critical for the elimination of disease, with the current goal being <1 case per 10,000 inhabitants.⁵⁰ Of the 736 million people living in poverty in 2015,⁵¹ most reside in leishmaniasis-endemic regions (Table 1).²⁹ Although the global population living in poverty over the past two decades in low- and middle-income countries has been declining, it is necessary to assess persistence in vulnerability for regions where leishmaniasis is still largely prevalent. Fourth, the disruption of interventions caused by the raging COVID-19 pandemic threatens to set back years of progress on NTDs and related SDGs poverty targets because of synergistic exacerbating effects^{52–55} and further threatens the attainment of the 2030 NTDs Roadmap. Fifth, 17% of the global burden of infectious diseases is from vector-borne diseases including the leishmaniasis and the effect of climate change on these diseases is likely to get worse.⁵⁶ Using existing literature, here we examine the socioeconomic and psychosocial impacts of leishmaniasis, as well as exacerbating factors that can help inform policy

Table 1 Overview of Socioeconomic Factors and Populations at Risk in Countries with Highest VL or CL Prevalence

Country	Top 10 Countries for VL or CL ³⁰ (>95% of VL and >85% of CL Cases Reported in 2018) [# of Cases in 2018] ³¹	World Bank Income Classification ¹⁷⁸ (GNI ^a per Capita) ^b	2019 United Nations Population Estimates ¹⁷⁹	Estimated Population at Risk of CL and/or VL ⁸⁰ [% of Total Pop at Risk]	% of Population Living in Poverty Headcount Ratio at \$1.90 a Day in 2011 PPP ^{c,181} (Most Recent Year Data Available)
African Region (AFR)					
Ethiopia	VL [1828]	Low-income	112,079,000	VL - 36,732,612 [32.8%]	32.6 (2015)
Somalia	VL [411]	Low-income	15,443,000	VL - 2,363,005 [15.3%]	No data
South Sudan	VL [1867]	Low-income	11,062,000	VL - 3,749,817 [33.9%]	44.7 (2009)
Sudan	VL [2584]	Low-income	42,813,000	VL - 16,259,580 [38.0%]	12.2 (2014)
Algeria	CL [10847]	Lower-middle income	43,053,000	CL - 30,969,660 [71.9%]	0.4 (2011)
Kenya	VL [891]	Lower-middle income	52,574,000	VL - 14,151,164 [26.9%]	37.1 (2015)
American Region (AMR)					
Bolivia	CL [3127]	Lower-middle income	11,513,000	CL - 5,727,962 [49.8%]	4.5 (2018)
Colombia	CL [6362]	Upper-middle income	50,339,000	CL - 44,869,432 [89.1%]	4.2 (2018)
Brazil	VL [3466]	Upper-middle income	211,050,000	VL - 103,739,410 [49.2%]	4.4 (2018)
	CL [16,432]			CL - 148,786,750 [70.5%]	
South-East Asian Region (SEAR)					
India	VL [4360]	Lower-middle income	1,366,418,000	VL - 495,733,890 [36.3%]	22.5 (2011)
Nepal	VL [208]	Lower-middle income	28,609,000	VL - 13,864,455 [48.5%]	15.0 (2010)
Eastern Mediterranean Region (EMR)					
Afghanistan	CL [38,407]	Low-income	38,042,000	CL - 15,616,552 [41.1%]	No data
Syrian Arab Republic	CL [80,215]	Low-income	17,070,000	CL - 20,784,102 [121.8%] ^d	1.7 (2004)
Pakistan	CL [19,361]	Lower-middle income	216,565,000	CL - 156,427,700 [72.2%]	4.0 (2015)
Tunisia	CL [7467]	Lower-middle income	11,695,000	CL - 9,711,311 [83.0%]	0.2 (2015)
Iran, Islamic Rep.	CL [15,485]	Upper-middle income	82,914,000	CL - 60,143,656 [72.5%]	0.3 (2017)
Iraq	VL [259]	Upper-middle income	39,310,000	VL - 16,618,775 [42.3%]	1.7 (2012)
	CL [11,426]			CL - 29,738,302 [75.7%]	
Western Pacific Region (WPR)					
China	VL [180]	Upper-middle income	1,433,784,000	VL - 205,894,780 [14.4%]	0.5 (2016)

Notes: ^aGross National Income per capita. ^bLow-income economies (\$1035 or less); low-middle income economies (\$1036 and \$4045); upper-middle income economies (\$4046 and \$12,535); high-income economies (\$12,536 or more). ^cPurchasing Power Parity. ^dPopulation at risk calculated in 2014 when Syrian Arab Republic had a larger population (>20 million from 2008–2012).

interventions in the decade to 2030 that are likely to have an intense focus on NTDs in general, thereby ending their “neglect.”

Vulnerability to and Risk Factors for Leishmaniases

Poverty, a Primary Risk Factor for the Leishmaniases

Poverty is a central risk factor for the leishmaniases that is related to a complex network of exacerbating factors as outlined in Figure 1. Research shows that the leishmaniases primarily affect the poorest people on Earth and infections are associated with a lack of financial resources.³⁰ Several studies have found low income to be a significant risk factor for VL.^{8,36,57,58} Low-economic household status adds multiple complexities to VL programming, such as: awareness, availability, access and adherence.¹⁵ For example, in India, those of the lowest caste disproportionately suffer from VL and have difficulty accessing care.^{11,59} Specifically, 83% of affected households belonged to the poorest 40% of the population.¹¹ In

Kenya, Uganda, Ethiopia, Sudan and South Sudan, more VL cases are found among the poorest households.^{13,36,60} In Nepal, low economic status was found to be a significant risk factor for CL.²⁰ Poverty led to a two-fold increase in risk for CL in Iran and a 28-fold increase in risk in Sri Lanka.⁵⁷

A systematic review of the socioeconomic risk factors of VL and CL in 2020 found that poverty is associated with inadequate housing and lack of sanitation, which foster continued incidence of leishmaniasis.⁵⁷ Specifically, certain types of household construction materials create the optimal survival conditions for sandflies, which rest and breed in cracks or holes in walls and floors. Lack of adequate sanitation attracts wild or domestic animals and may be breeding sites for the sandflies. Examples include: Posadas, Argentina, where most individuals with VL also lived in low-quality homes composed of sand floors, wooden walls, partially or totally open roofs and without window screens;⁶¹ Bihar, India, where mud-plastered walls increased the risk of VL two-fold compared to cement walls;⁶² and Fulbaria, Bangladesh, where the prevalence of VL was 59% in homes made with mud

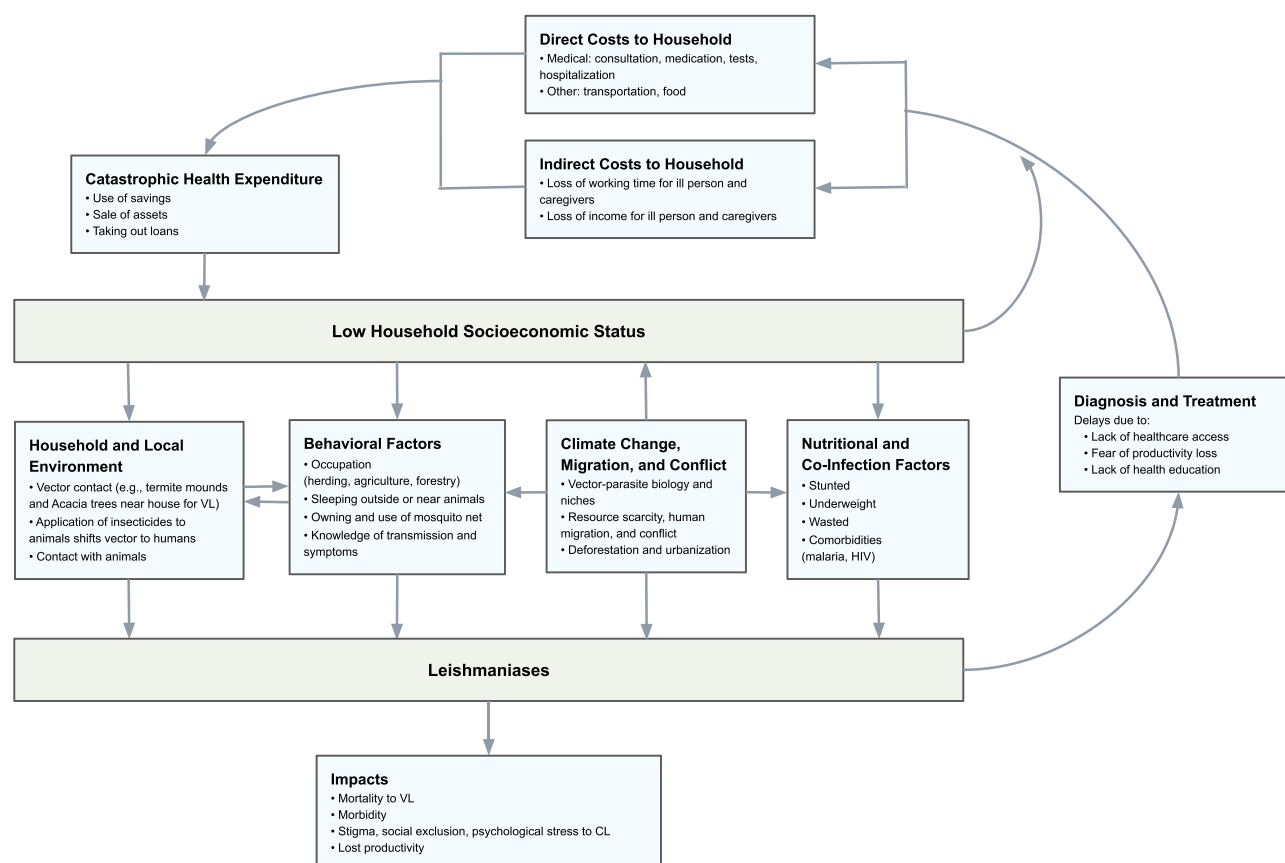


Figure 1 Framework of risk factors and impacts of the leishmaniases.

floors and tin walls.⁶³ Two studies in Brazil showed that a high incidence of VL was associated with a lack of appropriate sanitation and that low-income individuals resided in high-risk VL areas.^{7,8} Household characteristics were also found to be significant risk factors for CL: in Salta, Argentina, lack of locking windows increased the risk of CL almost three-fold;⁶⁴ homes built with nondurable materials in Alagoas State, Brazil experienced a two-fold increase in the risk of acquiring CL;⁶⁵ and brick walls increased risk two-fold in Kabul, Afghanistan.⁶⁶

Poor socioeconomic status exacerbates access to leishmaniasis services in other ways. With the onset of symptoms of VL, many patients avoid or delay seeking healthcare due to confusing symptoms with those of other diseases, gaps in VL awareness, disbelief in the severity of the condition,^{67,68} fear of loss of productivity,⁶⁹ particularly if the afflicted family member is male,^{67,68} and cultural barriers where the decision to seek care for women and children has to be granted by the male head.⁷⁰ Poor diet and low levels of education, all associated with poverty, are compounding risk factors for leishmaniasis.¹³ Lack of public health education on VL contributes to the morbidity of the disease.^{69,71} Many patients who are aware of VL and related symptoms may not seek care due to other factors, such as the absence of health facilities in remote areas, inability to afford transportation to health facilities and inability to afford appropriate diagnostics.^{15,67,72–74}

Although many VL treatment programs are funded by government and donors, or some means of health-insurance is provided,^{15,17,75} direct and indirect medical costs push patients and their families further into poverty as a result of catastrophic health expenditure,⁷⁶ promoting the cycle of poverty and disease.⁷⁷ In many cases, VL treatment may require multiple days at health facilities,^{75,78} with financial burden falling on patients for each night spent in a hospital bed if these are not otherwise covered by a program. Prohibitive hospitalization costs could lead to an incomplete treatment regimen due to premature patient discharge.⁷⁸ If treatment is administered at home, this accrues the direct overhead cost of a caregiver.⁶⁹ On the other hand, costs may be indirect when a family member must relinquish labor responsibilities to care for the ill person.⁷² To pay for the devastating costs of treatment, studies show that households leverage four methods of coping: use of savings, sale or rental of property, taking private loans at high-interest rates and asking for financial help from their

community.^{15,17,67,69,76} Due to this, the already impoverished, high-risk population falls into “iatrogenic poverty”.⁶⁹

Additionally, poor populations often reside in remote areas far from health facilities, limiting timely access to treatment. Studies on travel time to healthcare facilities find that 8.9% of the global population cannot reach healthcare within one hour with access to motorized transport, while 43.3% cannot reach a healthcare facility within one hour by foot.⁷⁴ The delay in healthcare-seeking is further exacerbated by the hope for self-resolution, which reduces quality of life, increases the development of chronic CL lesions, increases chances of VL mortality and increases the transmission of VL.^{67,72,74,79} Even with the use of peripheral testing sites and mobile clinics to reach remote areas, field clinicians lack the necessary equipment for diagnostic procedures,^{78,80} such as collecting spleen aspirates or bone marrow,⁸¹ making it difficult to diagnose VL. The use of rapid diagnostic tests, particularly rK39, can bridge this gap.^{17,69,82,83} However, in some countries where a six month follow-up appointment is required to confirm successful treatment, patients are not able to attend the final appointments.^{78,84,85}

Differential Leishmaniasis Vulnerability and Impacts by Gender

Not only do women account for the majority of the poor in what has been called “the feminization of poverty,” but the financial impacts of the leishmaniasis are experienced more significantly by women.^{67,86,87} The distribution of leishmaniasis infections by gender is therefore helpful to understand the additional vulnerability women may face.³⁶ While global data reporting on gender is incomplete, the latest WHO update shows substantial improvement between 2014 and 2018.³¹ Globally, 63% of VL patients were male and 34% were female.³¹ The majority of high-burden countries had an over-representation of males, reaching up to 90% of cases in Ethiopia and 73% of cases in Nepal.³¹ Greater proportions of female VL cases were reported in two countries, namely Uganda (67%) and Bangladesh (52%).³¹ The distribution appears to be more balanced for CL, with 52% of cases male and 47% female. There is a slightly higher proportion of CL cases in males in the American region.³¹

A substantial amount of recent literature points to the vulnerability pathways and burden of leishmaniasis on women in particular.^{37,88–90} In some communities, women are at a higher risk for vector exposure if they

spend more time in a home with livestock nearby or if they are tasked with responsibilities of animal care or procuring water, activities which typically occur in the morning or at dusk, which are times of heightened sandfly activity.⁸⁸ The general deficiency of healthcare for women is also considered an important factor contributing to their vulnerability to leishmaniasis.⁸⁸ Compared to men, women are less likely to seek healthcare in a timely manner when they have sought permission from their husbands,⁷⁰ leading to more severe complications and, in the case of CL, a greater likelihood of life-long, disfiguring scarring.⁸⁹ Late clinical presentations of women primarily stem from financial limitations and inadequate knowledge about the disease.⁸⁹ Furthermore, a lack of female healthcare providers is a significant barrier in places like Afghanistan, where women are often not allowed to visit male providers for cultural reasons.⁸⁹ To afford treatment and avoid stigmatizing scars, women may sell their assets and suffer financially.⁸⁸ The greater burden of disease and stigma limits the mobility of women and their capacity to work, affecting future economic opportunities.^{8,9} These findings suggest a need for research into interventions that target and minimize the specific vulnerabilities that place women at greater risk for the leishmaniasis.

Comorbidities Synergistically Act with Poverty to Exacerbate the Leishmaniasis

The leishmaniasis co-occur with poverty in settings where populations also face immunocompromising conditions. Malnutrition and HIV infection are the most significant comorbidities because they increase host susceptibility, are determinants for severity and clinical manifestations of the leishmaniasis, and complicate accurate diagnosis and treatment.^{25,85,91–93} For instance, case-controlled research in Ethiopia has shown a three-fold increase in susceptibility to VL in malnourished individuals.^{94,95} Additional research is needed to understand the impact of nutritional deficits on vector competence.⁹³ Due to similar immunopathogenic processes, HIV significantly increases the risk of developing VL, while VL acts as a catalyst for HIV, thus accelerating the onset of AIDS.^{96,97} While undernutrition is an outcome of inadequate food compounded by poverty, the impoverished rural settings in which the leishmaniasis largely occur are often co-endemic with other diseases, such as malaria, typhoid or typhus, tuberculosis and schistosomiasis, which make the diagnosis of VL

complex due to the similarity in clinical manifestations.^{25,30,98}

Leishmania-HIV coinfection has been reported in at least 35 countries since first being reported in 1985.⁹⁹ The Mediterranean basin accounted for the majority of VL-HIV coinfections in the 1990s, but East Africa now carries the majority of VL-HIV coinfections.^{31,91} Although the overall prevalence of HIV has been decreasing in African countries since the 2000s,¹⁰⁰ prevalence of HIV amongst VL-infected individuals remains high.⁹¹ During 2014–2018, 2590 cases of new and relapsed VL-HIV coinfection were reported, with the prevalence of co-infection in VL patients increasing from 1.6% in 2014 to 3.8% in 2018 in four WHO regions (AFR, EMR, EUR, SEAR).³¹ Ethiopia holds the highest burden of cases with up to 40% of VL patients positive for HIV.⁹¹ A potential factor contributing to high VL-HIV coinfection in northwest Ethiopia is the seasonal movement of cash-crop farmworkers, who become infected when traveling to VL-endemic regions.¹³ High VL-HIV coinfection rates have also been reported in Brazil and the state of Bihar, India.³⁰ In the Americas, 8% of VL cases were co-infected with HIV in 2017. Brazil carries 95% of these.¹⁰² VL co-infection can impact labor productivity as established in HIV studies,¹⁰¹ adding to cyclical poverty effects in these communities.

Atypical clinical manifestations of VL in people living with HIV complicate the deleterious relationship between these diseases, leading to delayed diagnosis and treatment.⁹¹ Although generally presenting as immunocompetent hosts, atypical signs and symptoms of VL (ie, splenomegaly, fever) may be confused for other opportunistic infections in the immunocompromised host.¹⁰³ *Leishmania* parasites are also generally grouped by disease presentation of either CL or VL, but in patients with HIV, this tropism can be lost.¹⁰⁴ For example, parasites that classically cause CL may cause visceralization and patients with VL may have skin lesions.¹⁰⁴ Additionally, atypical cases may be missed and underreported in resource-poor settings using disease detection guidelines strictly based on clinical case definitions.⁹¹ VL-HIV coinfecting patients may also present with amastigotes at unusual sites, such as the gastrointestinal tract.⁹⁶ Misdiagnosis leads to an increased case fatality rate.⁹⁹

Comorbid HIV also leads to poor diagnostics outcomes and therapeutic response. Parasitological methods remain the gold standard for diagnosis due to the low sensitivity of serological tests in detecting VL in HIV-infected individuals.⁹⁶ Given the prevalence of relapse in this population, the use of polymerase chain reaction (PCR) testing

to identify circulating *Leishmania* DNA can indicate imminent VL relapse.¹⁰⁵ Initiation of antiretroviral therapy (ART) can delay VL relapses and reduce mortality, in combination with secondary prophylaxis.^{85,96} However, the lack of access and suboptimal adherence to ART, drug toxicity from combined treatment and expense remain as barriers to care.^{97,106} Recommended drug combinations for VL-HIV treatment also vary based on location, which complicates access and monitoring treatment outcomes.^{97,106} Research on CL-HIV coinfection remains scarce and current treatment guidelines are based on immunocompetent individuals.¹⁰⁶ Like PKDL patients, coinfecting patients can act as human reservoirs for the *Leishmania* parasites, perpetuating sandfly infection rates in communities.^{97,107,108} A comprehensive survey of the variable presentations of the leishmaniasis in co-infected patients would provide useful diagnostic information for clinicians who may see a growing number of these complex medical cases.

Environment, Migration, Conflict and Climate Change Exacerbate Vulnerability to the Leishmaniasis

Aside from being associated with impoverished environments, the leishmaniasis occur in certain eco-epidemiological foci that reflect manipulation by human activities, such as migration, urbanization and deforestation.²⁵ Poverty and conflict are key drivers of population displacement and forced migration among the poor.¹⁰⁹ These drivers have led to the catastrophic expansion of CL, especially in North Africa and the Middle East.^{110,111} In the Indian sub-continent, elimination is hindered by cross-border movements;¹¹² in Eastern Africa, control is complicated by both migration, conflict and a changing climate (Figure 1).^{14,60,113} The intersection of climate change and the leishmaniasis adds other complexities, as it is a multi-faceted process entangled with other socioeconomic drivers and impacts of the disease. As both a lever for exacerbating the existing inequalities that drive leishmaniasis risk and as a risk factor in and of itself, climate change will likely introduce new disease foci and further impoverish at-risk communities.¹¹⁴ While climate change will affect everyone, the most vulnerable – poor communities without the capacity to develop resilient infrastructure – are most at risk of the compounding economic disaster driven by climate change and disease.¹¹⁵ Discussed here are several mechanisms through which

climate change is thought to drive leishmaniasis risk, including: interactions between vector-parasite biology and temperature, human migration, and conflict.

There is evidence that the pace of human migration for economic reasons or because of conflict is exacerbated by climate change.^{116–118} The accelerating international movement of people and goods has increased the likelihood that *Leishmania* parasites may gain a foothold in unaffected countries where a stable vector and reservoir population is already present.¹¹⁹ During 2017–2018, estimated 1882 cases of CL and 141 cases of VL globally were caused by transnational migration and importation, creating opportunities for parasites to establish footholds in non-endemic regions with competent vectors.³¹ Urbanization also provides opportunities for the introduction of the leishmaniasis to previously unaffected niches. In Brazil, an increasing number of cases are seen in urban centers, rather than in the traditionally endemic rural regions, due in part to urbanization and internal migration of peoples from rural communities into peri-urban centers with poor sanitation.¹²⁰ Driven by migration and climate change, recent case reports from Eritrea, Kenya, and Tanzania have demonstrated that the territories in which autochthonous leishmaniasis occur are expanding.^{121–123} Additionally, deforestation and changing patterns of land use for agriculture provide new ecological niches for sandflies.^{124,125} Local agriculture, an important source of calories and nutrients for poor communities, is additionally threatened by climate change as rising CO₂ levels contribute to nutrient leaching.^{126,127} Thus, as farmers are put at greater risk of infection through agricultural practices that provide opportunities for sandflies to spread, the risk is exacerbated through the loss of nutritional value within the food produced.

As shown in studies in the Middle East, North Africa and Eastern Africa,^{14,60,110,111,113} conflict drives the spread of the leishmaniasis in multiple ways, some of which intersect with patterns of human migration. While climate change is not the exclusive driver of violent conflict, climate change and resulting resource scarcity will likely contribute to many conflicts in the coming decades when additional destabilizing factors are in place.¹²⁸ The breakdown of health systems during conflicts, including drug delivery, clinician training, availability of diagnostics, and health systems financing and reporting, pose great risks to leishmaniasis control in endemic countries and perpetuate its status as a neglected disease. This process was exemplified by the conflict in Sudan which began in the 1980s

and the subsequent leishmaniasis outbreaks which resulted in approximately 100,000 deaths.^{14,129–131} Refugees from conflict zones in endemic regions of the Middle East can carry new species of *Leishmania* parasites into territories where transmission is possible due to the presence of appropriate vectors,^{132–134} and the breakdown of treatment and care for patients can result in more serious disease progressions with a greater likelihood for complications and stigmatizing disfigurement.¹³⁵

Several mechanisms through which climate change is thought to drive leishmaniasis risk include interactions between vector-parasite biology and temperature, human migration and conflicts intensified by climate change. Ostfeld and Keesing describe how arthropods, such as the vector for leishmaniasis, the *Phlebotomine* and *Lutzomyia* sandflies, increase the rate of metabolic activity under warmer conditions, increasing the risk of disease for those within endemic regions and introducing risk to warming climates where sandflies can newly thrive.¹³⁶ Studies of both vector and parasite biology have demonstrated a positive relationship between metabolic activity and temperature.¹³⁷ Climate models in Europe and the Americas have predicted the northward expansion of the sandfly's territory,^{138,139} and recent entomological surveys of sandfly distribution in Europe suggest the introduction of *Leishmania* competent vectors into new regions.^{140–142} The territorial expansion of these vectors heightens the need for clinician and public awareness, appropriate public health intervention and continued monitoring as the climate continues to change.

The complex relationship between climate change, conflicts, migration and the leishmaniasis requires nuanced models that account for more than the direct effects of warming surface temperatures. Consideration of the human response to climate change, the local and national socioeconomic contexts in which climate policy will be enacted and the relationship between the leishmaniasis and other disorders, such as malnutrition, are critical for understanding the changing geography and burden of disease.

Socioeconomic Impacts of the Leishmaniasis

To better understand the various economic impacts of the leishmaniasis, we disentangle them by types of costs (direct and indirect costs) incurred by households and healthcare systems.

Types of Costs Incurred

Visceral Leishmaniasis

Although treatment for VL varies by drug combination and by patient, the regimen requires several (up to 30) days of daily injections. In many cases, patients are hospitalized for the duration of treatment with significant cost implications.^{25,78} As such, significant direct and indirect costs can be incurred by the patient and program, as several studies show. A systematic review using 2016 US dollars found that the median total direct cost per treated patient was \$760 in Sudan, \$128 in Nepal, \$197 in India, and \$220 in Bangladesh.²³ Direct medical costs were most common in the care-seeking phase and direct non-medical costs, such as food and transportation, were higher during treatment.²³ Direct medical costs varied based on the type of provider visited (traditional healers, chemists or pharmacists, clinics, hospitals) and the type and source of administered VL treatment.²³ Other studies have identified food as a significant direct non-medical cost for patients and caretakers throughout the treatment period.^{21,77} Indirect costs have been reported as working days lost for patients and/or caretakers or as loss of wages:²³ Patients and household members lost 57 days of productivity in Nepal,^{20,69} 120 days were lost amongst the economically active in India¹⁴³ and 51 days of productivity were lost among patients in Sudan.¹⁴⁴

Cutaneous Leishmaniasis/Post-Kala-Azar Dermal Leishmaniasis

To the best of our knowledge, there has not been a comprehensive, multi-country review of the types of costs incurred during diagnosis and treatment of CL and PKDL. We identified singular studies in Iran, Sri Lanka, and Brazil. In the Iranian Province of Golestan in 2015, CL patients spent an average of \$129 (43% direct medical costs, 20% direct non-medical costs, and 37% indirect costs).¹⁴⁵ A 2017 cross-sectional study of all 31 provinces in Iran found that the out-of-pocket (OOP) payments per patient was \$7.¹⁴⁶ In Sri Lanka, the total median cost per patient (both direct and indirect) was \$67.¹⁴⁷ This study reported that 59% of patients traveled over 100 kilometers to receive treatment, which resulted in a loss of income for both the patient and the person traveling with them. A 2017 cross-sectional study in Brazil found the total medical costs to CL patients was \$125.¹⁴⁸ Top contributors to direct medical costs included medications (17%), medical appointments (15%), medical exams (9%) and health insurance costs (10%). Top contributors to direct non-

medical costs were transportation to health centers (26%) and food (8%).¹⁴⁸

Only one study of the economic impact of PKDL was found.¹⁹ In Bangladesh, the mean total direct cost per treated patient was \$179.¹⁹ The major contributors to this cost were food (largest), treatment and transportation costs. Indirect cost measured was the asset loss per patient (median of \$170) and lost days of work (median of 43 days).¹⁹

Catastrophic Health Expenditure

The impact of OOP payments is difficult to conceptualize, since costs of living and income vary drastically between studied populations. Thus, looking at this data in the context of catastrophic health expenditure (CHE) is necessary. CHE is defined as the cost of health services that divert money from supporting basic household needs or cause households to resort to using their savings.^{76,149} CHE ranges from 5% to 15% of total household income, with exact values depending on the study. Several studies have examined CHE for VL, CL and PKDL in multiple countries.

Visceral Leishmaniasis

A systematic review found that if a 10% threshold is used to measure CHE, then VL imposes heavy financial burdens on households.²³ The percentage of household income diverted to VL treatment ranged from 11% to 44% in Nepal, 21–37% in India and was 21% in Bangladesh.²³ In Sudan, 40% of household income was diverted to VL treatment.²¹ One study in Nepal found that 51% of households made payments exceeding the 10% CHE threshold and that the cost of VL treatment was equal to 57% of the median per capita income.²⁰ Had the medications not been free of cost, 74% of households would have exceeded the 10% CHE mark.²⁰ Another study in Nepal found the median cost per household diagnosed with more than one case of VL was \$425, which is greater than the median annual household income of \$405.⁶⁹ In other studies, it was found that the cost associated with VL forced 20% of families in Nepal below the poverty line.^{150,151} In rural Bihar, India, VL treatment costs the equivalent of 7 months of daily wages.¹⁴³ In Bangladesh, India, Nepal and Sudan, 25–75% of affected households experienced some form of financial catastrophe throughout diagnosis and treatment, despite the free provision of tests and medication.^{17–21}

Cutaneous Leishmaniasis/Post-Kala-Azar Dermal Leishmaniasis

CHE data for CL and PKDL are more limited and no systematic analyses have been identified. We identified singular studies in Sri Lanka, Brazil and Bangladesh. In Sri Lanka, the \$67 total cost of CL treatment accounted for 5.4% of annual household income and 21% of the mean annual per capita income,¹⁴⁷ both of which could qualify as CHE depending on the threshold used. In this study, 57% of the patients identified as the only household member contributing to income.¹⁴⁷ In Brazil, 50% of study participants paid an average of 22% of their household income for CL-related costs.¹⁴⁸ In Bangladesh, the median total household cost per patient for PKDL treatment was \$367, which was more than twice the per capita annual income of the studied population.¹⁹

Costs from the Healthcare System Perspective

Visceral Leishmaniasis

Costs from the healthcare system perspective in diagnosis and treatment for VL have been analyzed in Morocco, Brazil, India, and Sudan. In a seven-hospital study in Morocco that analyzed 127 records of VL patients, it was found that the median cost to the health provider was \$520 per VL patient, which comprised: 50% came from hospitalization, 15% diagnosis and treatment and 33% drug costs or tests not related to VL.¹⁵² Indirect costs were not measured. When care was provided at an outpatient facility, costs were significantly reduced (\$307 vs \$636).¹⁵² A study in Brazil found direct costs varied based on which drugs were used for treatment and which route they were administered (intramuscular vs intravenous).¹⁵³ A 2014 study in Brazil measured direct medical costs and found that the total VL medical direct costs to the institution were \$1,873,682, which comprised: 41% hospital and ambulatory care, 22% treatment, 18% diagnostics and 18% from VL/HIV secondary prophylaxis.¹⁵⁴ A retrospective review of 250 medical records from 2008 from three public hospitals in Sudan showed that the medical cost per patient varied between \$117 and \$366, depending on the hospital.²¹

Cutaneous Leishmaniasis/Post-Kala-Azar Dermal Leishmaniasis

Individual studies for CL were identified in Iran, Afghanistan and Sri Lanka. A 2017 cross-sectional study of the economic burden of CL in 31 provinces in Iran found that costs to the government health systems associated with diagnosis and treatment of CL were high:

nearly \$6 million over the study period.¹⁴⁶ Elements of governmental costs included salaries to health-care providers (15% of total cost), medical materials and devices used (drug purchase, syringes, cotton, etc.) (37%), building depreciation and physical space costs (14%), administrative, health and treatment facilities cost (6%) and urban amenities (28%).¹⁴⁶ A 2010 study in Kabul, Afghanistan, found that costs varied based on drug used and route delivered.¹⁵⁵ In Sri Lanka, the total median cost per patient to the provider was \$23.¹⁴⁷ No studies were found on PKDL.

Overall, there is a need for new studies to be conducted to examine the economic impacts of the leishmaniasis in endemic regions since the majority of studies are dated. Most published studies have focused on VL and CL, so there is a serious need for studies examining the economic impacts of PKDL. Lastly, it is difficult to compare costing studies due to differences in definitions of costs and the methods used to measure and quantify those costs. A uniform approach to costing methodology is essential for future studies.

Psychosocial Impacts of the Leishmaniasis

Leishmaniasis may result in profound psychological and social burdens due to reduced quality of life (QoL), social exclusion and poor mental health.³ Physical impairments and disfigurements, primarily observed in the dermatological presentations of CL and PKDL, lead to stigmatization, discrimination and ultimately psychosocial impact (Figure 1).³⁸

The psychosocial burden of CL has been well documented in the literature, with an estimated 70% of all CL cases (active and inactive) experiencing some degree of psychological morbidity, generally depending on the severity and visibility of disfigurement.^{37,156} Individuals with CL are restricted from social participation, affecting their community interactions and personal relationships.¹⁵⁷ Misconceptions about disease transmission fuel stigma and discrimination, as many societies erroneously believe CL to be directly contagious through person-to-person physical contact.³⁷ For example, studies in Afghanistan reported that women with CL are often separated from their children and prevented from breastfeeding, leading to depression and anxiety.^{158,159} Social exclusion and resulting isolation induce internalized self-stigma and decreased self-esteem, which in turn contribute to psychological

manifestations of stress, anxiety and depression.³⁷ Studies in Iran and Turkey have revealed significantly decreased body satisfaction and QoL in CL patients.^{35,160,161} Severe self-isolation and self-contempt may sometimes even contribute to suicidal ideations.³⁷ Stigma further hinders treatment-seeking behavior due to the shame of being seen in public, which may exacerbate health outcomes.¹⁵⁷ These psychosocial impacts often influence educational and employment opportunities.¹⁵⁷

The greatest psychosocial burden of CL is experienced by young, single women, particularly those with visible facial scars.^{37,90,162} As shown in the 2018 global data, 47% of CL cases are women.³¹ CL lesions generally occur on visible parts of the body, such as the face or hands, due to opportunistic sandfly bites on exposed skin.¹⁵⁷ Women consistently report that such lesions alter the perception of beauty and cause negative body image, which has a significant impact on marriage opportunities.³⁷ Furthermore, women tend to be less likely than men to seek treatment promptly, often due to limited healthcare accessibility or cultural barriers.⁸⁸ Untimely treatment results in life-long scarring and women may suffer financially in attempts to afford basic treatments or permanent surgical solutions.^{37,88}

A systematic review examining psychosocial well-being for all forms of leishmaniasis revealed substantial gaps in the literature for VL and MCL in particular.³⁸ While VL has been shown to decrease the QoL of patients, this review calls for more research to explore how neurological manifestations of VL may potentially relate to psychological impacts.³⁸ Additionally, stigma has been reported among patients co-infected with VL and HIV, significantly affecting QoL.^{163,164} PKDL, a dermatological consequence of VL characterized by visible rash and disfigurement, has been associated with poor mental health and impaired QoL due to social stigma and exclusion.^{165,166} Stigmatization further impacts PKDL and VL-HIV outcomes by influencing treatment-seeking behavior and drug compliance.^{165,166}

Following these findings, leishmaniasis programs are encouraged to broaden in scope to include mental health support and community educational interventions to address the growing psychosocial burden.¹⁶⁷ This approach was endorsed by the WHO, which recently published its first guide on the mental health of people with NTDs, highlighting the negative impacts of NTD-related stigma on psychosocial well-being and treatment-seeking behavior.¹⁶⁸ Further studies of the psychosocial impact of leishmaniasis could focus on the bidirectional relationship

between stigma and poverty. Recognition of the complex network between poverty, health and social exclusion would provide a more complete picture of the psychosocial impacts of the leishmaniasis.

Discussion and Conclusion

The literature on the socioeconomic and psychosocial impacts of the leishmaniasis, vulnerability and risk factors are wide-ranging. In general, much research has been done on the disease relative to disease burden and other NTDs.¹⁶⁹ However, a full accounting of their various impacts is lacking. Here we have reviewed a large body of literature to try to fill in the gap. Overall, it is difficult to compare costing studies due to differences in definitions of costs and methods to measure and quantify those costs. There is a need for a uniform approach to costing methodology to ensure all appropriate variables are accounted for and collected in the same manner so comparisons can be made between countries where culture and disease factors differ. In addition, the majority of studies identified in our analysis are retrospective or cross-sectional with limited timeframes. Longitudinal studies could provide additional information on the impact of the leishmaniasis (both direct and indirect) on individuals and their households long term, the impact of various financial coping strategies and the impact on poverty and health systems.^{78,170} Such longitudinal studies should be developed in the context of national and international improvements to leishmaniasis data collection and reporting, a need emphasized by the discrepancies between predicted and observed leishmaniasis cases reported by the WHO.^{30,31}

As this review shows, financial barriers preventing diagnosis and treatment of leishmaniasis must be reduced in the pursuit of universal health coverage, a key target of the SDGs and the 2030 NTDs Roadmap.^{45,49} Mechanisms such as transporting patients early to treatment centers, the introduction of peripheral testing sites, community healthcare workers, telemedicine and use of mobile clinics can simplify access to care, eliminate costs and facilitate early detection of rural patients to drive elimination of VL.^{15,71,73,74,170} In addition, less expensive diagnostic and treatment measures must continue to be developed, as demonstrated by the introduction of rK39 leading to dramatic increases in the ability to diagnose rural populations.^{73,88,171}

An evaluation of the various socioeconomic costs of the leishmaniasis would not be complete without an understanding of the socioeconomic losses averted by improving leishmaniasis care. Using data collected in a systematic literature review, Lenk et al identified the economic benefit from averted OOP payments and

averted productivity loss by calculating the difference between a “counterfactual scenario,” which assumed the 1990 VL prevalence/incidence continued uninterrupted, and an “ideal scenario,” which assumed the 2020 targets described by the 2012 London Declaration and the WHO were achieved.¹⁷² In 2005 \$US, the total economic benefit from OOP payments averted was calculated to be \$100 million from 1990 to 2030. The total economic benefit from productivity loss averted was \$70 million from 2011 to 2030. When deaths are taken into account, the productivity loss averted rises to \$7.2 billion from 2011 to 2020.¹⁷² This study shows there is a clear long-term benefit to early detection and effective treatment of VL, and other researchers have determined these are cost-effective.¹⁷³ While we found no similar studies that have been conducted for CL and PKDL, we believe such would be needed for a full accounting of the costs of the leishmaniasis.

Understanding the economic consequences of leishmaniasis and the benefits of treatment on a global scale will encourage prevention, while also assuring policy-makers and donors that the monetary resources directed to leishmaniasis control and elimination are a good investment.^{22,23,58} This is especially important as most programming is financed by donors whose operations have been dramatically hindered by the COVID-19 pandemic that will impact present and future NTD work.^{52–55,174} Additionally, competing priorities in global health across diseases and programs accompanied by limited resources^{175,176} justifies a call to leverage opportunities to integrate efforts to combat the leishmaniasis with other diseases, such as HIV and malaria, that have more funding.^{176,177} In light of the long-term severe disfigurement from CL leading to stigmatization, social exclusion, discrimination and psychosocial impacts, especially on rural women, which negatively affect social and economic opportunities, integrating mental health support and community educational interventions as the WHO has championed is warranted.¹⁶⁸

The world faces worrying trends in human migration coupled with climate change and conflict that compound global and national phenomena that introduce new vulnerabilities within communities at risk for the leishmaniasis and produce new opportunities for the disease to spread.^{4,118,129} Without mitigation efforts on all of these aspects, the 1.7 billion at risk of the leishmaniasis could increase. Elimination of the leishmaniasis is possible. The NTDs Roadmap to 2030 and the 2030 SDG framework

offer unprecedented opportunities to mitigate the cyclical and synergistic socioeconomic and psychosocial impacts of the leishmaniasis shown in this review.

Disclosure

All authors report no conflicts of interest in this work.

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