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REVIEW

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Economic evaluations addressing diagnosis and treatment strategies for neglected tropical diseases: an overview

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ABSTRACT

Neglected tropical diseases (NTDs) are those affecting vulnerable people and causing additional social and economic burden. The aim of this study was to carry out a general overview of the health economic assessments involving the diagnosis and treatment of six NTDs: cutaneous leishmaniasis (CL), Chagas disease, cysticercosis, filariasis, schistosomiasis and visceral leishmaniasis (VL). The literature search was based on two of the main medical literature databases (Medline and SciELO) and identified 46 studies. Twenty-six studies (57%) addressed therapeutic strategies, while other 20 (43%) assessed diagnostic or both diagnostic and therapeutic approaches. The studies were published between 1994 and 2021, and 57% of them (26/46) were carried out in four countries. Cost-effectiveness analyses were conducted in 59% (27/46) of the studies. Economic studies of NTDs have timidly increased in recent years. Despite the improvement of analytical methods, completeness and accuracy of information, there are few new technologies applied to NTDs and public health systems. In addition, economic studies for NTDs are concentrated in a few countries. Thus, this review points out the need for investment in research, development and training of human resources dedicated to the economic analysis in health, especially on NTDs, as a strategy to reduce inequalities by optimizing the use of health resources.

KEYWORDS: Diagnosis. Economic evaluations. Neglected tropical diseases. Treatment.

INTRODUCTION

Neglected tropical diseases (NTDs) are diseases of poor, vulnerable, and voiceless people, living in remote, rural areas, urban slums or conflict zones in the developing world. These diseases include leishmaniasis, Chagas disease, cysticercosis/taeniasis, lymphatic filariasis, schistosomiasis, Buruli ulcers, dengue fever, dracunculiasis, echinococcosis, food-borne trematodiasis, human African trypanosomiasis, leprosy, onchocerciasis, rabies, soil-transmitted helminthiasis, trachoma, and yaws[1].

This diverse group of diseases prevails in tropical and subtropical regions of 149 countries, affecting more than one billion people and costing billions of dollars every year. Predominantly in Africa, Asia and the Americas, these NTDs affect some of the world's poorest and most marginalized communities[1]. These diseases cause death and disability and present growing challenges to health security and human progress. The social and economic burden of NTDs are explained by physical disabilities, including blindness and disfigurement, social stigma, discrimination, loss of social status, growth failure, malnutrition and impaired cognitive development[2].

Considering the socioeconomic complexity involved, an approach to reduce the burden of NTDs should necessarily include multilevel interventions. Control

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programs including transmission interruption, access to diagnosis, mass drug administration and surveillance systems are some of them[3]. The lack of diagnostic tests and drugs that are affordable and cost effective are key contributing factors that cause high mortality and disability, thereby imposing a huge burden with severe social and economic consequences[4].

Economic evaluations are still scarce for NTDs, and this is an alarming fact, considering that the most prevalent regions for these diseases are those that can least afford them. In general, a full health economic evaluation is defined as the comparative analysis of alternative courses of action in terms of costs and consequences[5].

Partial evaluations only address one aspect of a single intervention, such as cost. Cost minimization analysis refers to the simple comparison of cost between two interventions with equivalent clinical consequences. Cost-effectiveness analysis refers to the evaluation of the costs and consequences of interventions using clinical outcomes in natural units, such as complications avoided or cases diagnosed. These outcomes should be expressed as the "incremental cost-effectiveness ratio" (ICER), calculated by dividing the incremental cost of the new intervention by the incremental change in effectiveness[6,7].

Cost-utility analysis is a subtype of cost-effectiveness analysis that focuses on measuring the patient's preference for being in a particular health-state. The outcome is most commonly reported as the cost per quality-adjusted life year (QALY) or disability adjusted life year (DALY). Cost-benefit analysis measures consequences in monetary terms. Budget impact analysis complements the analyses mentioned above. It assesses the affordability of a new intervention with the resource constraints of a specific healthcare setting[6,8].

Supporting an efficient resource allocation process with health economic evidence is urgent, as poor populations are vulnerable to a wide spectrum of diseases and are assisted by budget-scarce health systems[8]. Health economic evaluations can potentially provide valuable information to clinicians and policy makers regarding the financial implications of decisions about the care of patients. New needs and technological solutions applied to health fields increase in proportion to the population growth, as the result of science progress and improvement of general expectations about healthcare and quality of life. At the same time, budgetary and human resource constraints impose complex decisions for health managers. In this context, economic assessments emerge as useful tools to strengthen decision-making and support public policies. This manuscript reviews health economic assessments for the diagnosis and treatment of six NTDs.

MATERIALS AND METHODS

Six NTDs are selected as of interest in this study, namely: cutaneous leishmaniasis (CL), Chagas diseases, cysticercosis, filariasis, schistosomiasis and visceral leishmaniasis (VL). A search was carried out in two of the largest databases in the health field: Medline by US National Library Medicine and the Brazilian SciELO (Scientific Electronic Library Online). As a strategy for a comprehensive and, at the same time, focused search on the topic of interest, MeSH (Medical Subject Headings) terms combinations using the name of each one of the six neglected diseases and the terms "cost" or "cost effectiveness" combined by Boolean operators was used. Partial or complete economic assessments, published in the English, Spain and Portuguese languages were included, with no restriction on data of publication. Studies addressing animals and vectors were excluded. The title, abstract and keywords of every retrieved study were revised independently by two researchers and discrepancies have been resolved by discussion and consensus. Studies retrieved in duplicate by the two databases were removed. A Flow diagram of the study selection process is available in Supplementary Material (Figure S1). The quality of the studies included in the present narrative review was analyzed according to the Consolidated Health Economic

Table 1 - Literature search strategies in Medline and SciELO.

Disease	Search strategy	
	Medline	SciELO
Cutaneous leishmaniasis	("Leishmaniasis"[Mesh]) AND "Cost-Benefit Analysis"[Mesh]	Leishmaniasis AND Costs
Chagas disease	("Chagas Disease"[Mesh]) AND "Cost-Benefit Analysis"[Mesh])	Chagas Disease AND Cost
Cysticercosis	("Cysticercosis"[Mesh]) AND "Cost-Benefit Analysis"[Mesh])	Cysticercosis AND Cost
Filariasis	("Filariasis"[Mesh]) AND "Cost-Benefit Analysis"[Mesh]	Filariasis AND Cost
Schistosomiasis	("Schistosomiasis mansoni"[Mesh]) AND "Cost-Benefit Analysis"[Mesh])	Schistosomiasis mansoni AND Cost
Visceral leishmaniasis	("Leishmaniasis"[Mesh]) AND "Cost-Benefit Analysis"[Mesh]	Leishmaniasis AND Cost

Evaluation Reporting Standards (CHEERS) statement[9], a checklist with recommendations on the minimum amount of information to be included when reporting economic evaluations.

RESULTS

The search strategy identified 316 publications and after screening, 46 of them were included in this review: 10 for CL, nine for Chagas disease, two for cysticercosis, five for filariasis, five for schistosomiasis and 15 for VL. Twenty-six studies (57%) addressed therapeutic strategies, and 20 (43%) studies addressed diagnostic or both diagnostic and therapeutic strategies (Table 2).

The studies were published between 1994 and 2021 (Figure 1); 57% of them (26/46) were performed in four countries: Brazil, India, Colombia and Mexico (Figure 2). Cost-effectiveness analyses were conducted in 59% (27/46) of the studies, cost estimates in 37% (17/46), cost-benefit analyses in 2% (1/46) and budget impact analyses in 2% (1/46) (Figure 3).

Below are the details of the main results presented in the 46 studies included in this narrative review.

Cutaneous leishmaniasis

Economic analysis of treatment

In Afghanistan, Reithinger and Coleman[10] calculated the cost effectiveness of intralesional and intramuscular administration of sodium stibogluconate for the treatment of CL patients attending clinics in a complex emergency setting. The cost per DALY averted was estimated to be US$1,200 per patient treated and cured, showing that the treatment of CL in that country is not a cost-effective health intervention according to the WHO-CHOICE criteria. Stahl *et al.*[11] estimated the cost effectiveness of two wound care regimens for CL in three groups: I - intralesional infiltration of sodium stibogluconate; II - wound debridement with high-frequency

Table 2 - Economic studies addressing diagnostic, diagnostic and therapeutic or therapeutic strategies for neglected tropical diseases.

Disease	Retrieved studies	Included studies	Included studies addressing diagnosis or diagnostic andtherapeutic strategies	Included studies addressing therapeutic strategies
Cutaneous leishmaniasis	70	10	0	10
Chagas disease	80	9	8	1
Cysticercosis	21	2	1	1
Filariasis	52	5	1	4
Schistosomiasis	20	5	3	2
Visceral leishmaniasis	70	15	7	8
Total	313	46	20	26

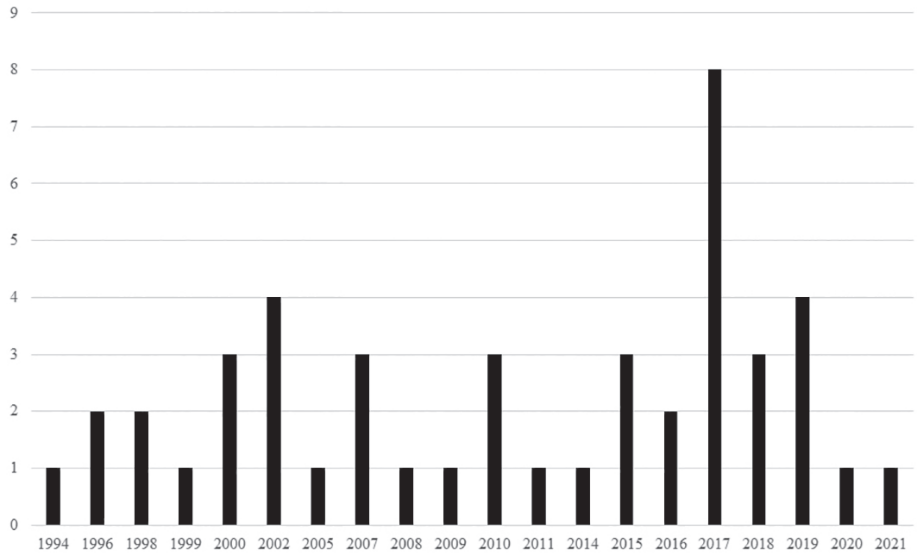

Figure 1 - Number of economic analyses for the diagnosis and treatment of neglected tropical diseases published per year.

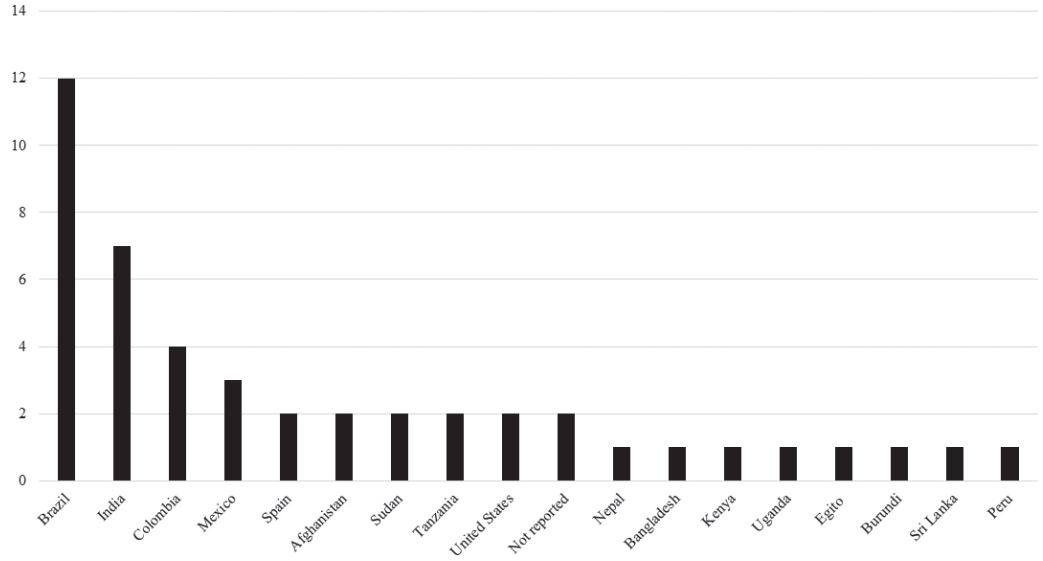

Figure 2 - Number of economic analyses for the diagnosis and treatment of neglected tropical diseases per country.

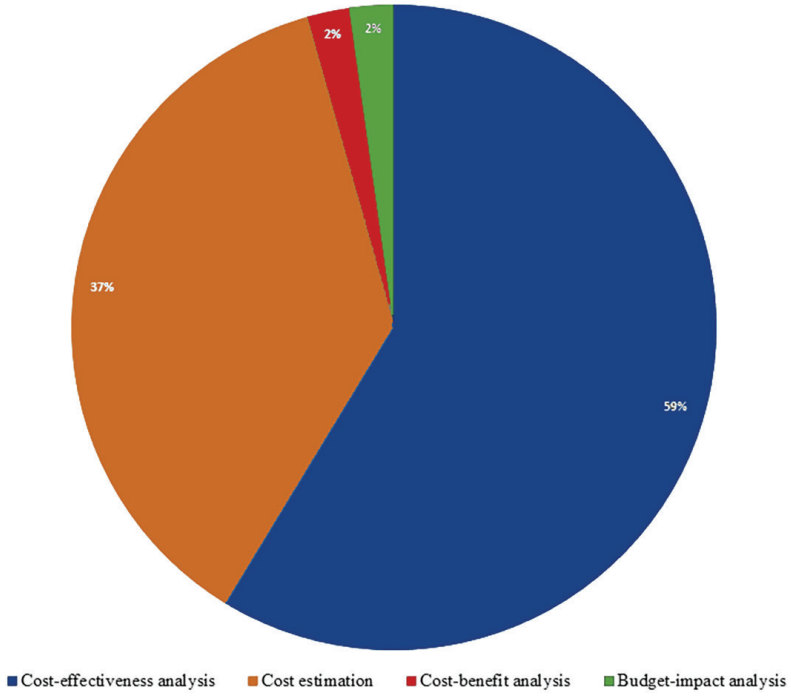

Figure 3 - Type of economic analysis performed.

electrothermo-debridement with subsequent moist wound treatment with DAC N-055; or III - moist wound treatment in patients with a single chronic CL ulcer with DAC N-055. The mean costs per patient and the effectiveness in wound-free days in groups I, II and III were US$11.43 and 129; US$15.91 and 177; US$24.97 and 147, respectively. The ICER of group II × I was US$0.09, and of group III × I was US$0.77, which is very cost effective. The authors concluded that wound debridement with high-frequency electrothermo-debridement with subsequent moist wound treatment with DAC N-055 was the most cost-effective treatment.

In Colombia, Vega *et al.*[12] estimated the cost per DALY averted in the treatment of CL in Chaparral. The costs of treatment with pentavalent antimony (Glucantime) per patient treated and cured and per DALY averted were estimated to be US$345 and US$15.000, respectively. The authors highlighted that according to the WHO-CHOICE criteria, treatment in Chaparral is not a cost-effective health intervention and may not even be justifiable from an economic point of view. Cardona-Arias *et al.*[13] compared the cost effectiveness of thermotherapy and pentavalent antimonial for the treatment of CL. The thermotherapy

showed average cost-effectiveness ratios ranging between $187 and $390, and Glucantime between $721 and $1,275. The authors pointed out that the excellent cost-effectiveness ratio observed for thermotherapy is a key feature for guiding decisions in the CL management in Colombia. In another study, the same authors estimated that the cost of thermotherapy would be US$2062 per DALY averted and US$69 per patient cured, and with pentavalent antimony (Glucantime), the cost would be US$4241 per DALY averted and US$85 per patient cured. The authors concluded that thermotherapy was a cost-effective strategy for the management of CL in Colombia, and this evidence adds to previous findings that have demonstrated the multiple benefits of this alternative treatment, such as better patient compliance, the simplicity of application, safety, and low costs[14]. Berger *et al*.[15] performed a cost-effectiveness analysis comparing meglumine antimoniate and miltefosine administered by caregivers' directly observed therapy (cDOT) for CL among children. The mean cost-per-cure by patient, government and social perspective for meglumine antimoniate and miltefosine were as follows: $442 and $30; $89 and $158; $531 and $188, respectively. The treatment of CL with miltefosine via cDOT showed cost savings from patients and social perspectives and was moderately more expensive from the government payer perspective. The authors highlighted that the development of such treatment programs represents an important opportunity to improve treatment and outcomes of pediatric CL patients.

In Brazil, Mistro *et al*.[16] compared the cost effectiveness of liposomal amphotericin B, pentavalent antimony and amphotericin B deoxycholate for the treatment of mucocutaneous leishmaniasis from the perspectives of the hospital and public health managers. After 12 months of treatment, pentavalent antimony showed mean costs of US$3,782.38, amphotericin B deoxycholate of US$5,211.27 and liposomal amphotericin B of US$11,337.44. The cure rate of patients with liposomal amphotericin B was 100%, with amphotericin B deoxycholate was 77.4%, and with pentavalent antimony was 72.2%. Regarding the outcome of therapeutic success, liposomal amphotericin B had an ICER of US$18,816.23 compared with pentavalent antimony amphotericin B deoxycholate (US$24.504,65). In this study, liposomal amphotericin B was cost effective when used as the first-line therapy for the treatment of mucocutaneous leishmaniasis. The authors suggest that this result encourages the negotiation of costs to aquire the drug and the mean price that the health system will be willing to pay for each patient treated.

Brito *et al*.[17] estimated the cost effectiveness of meglumine antimoniate intralesional infiltration (IL) compared to endovenous (IV) meglumine antimoniate therapy for the treatment of CL; the strategies had a total cost per patient cured of US$330.81 (IL) and US$494.16 (IV), respectively. The ICER showed that the intralesional meglumine antimoniate approach could result in savings of US$864.37 for each additional patient cured, confirming that the IL meglumine antimoniate strategy is cost effective in the context of the Brazilian public health scenario.

Galvão *et al*.[18] evaluated direct medical and non-medical costs related to CL treatment in a Brazilian referral center. One hundred patients were included; 50% had a monthly per capita income of up to USD 259.60 and spent on average USD 187.32 with the disease, representing an average monthly impact of 22.5% (USD 133.80). The disease imposed direct medical costs and although the Brazilian public health system guarantees access to health care, CL still represents a substantial economic impact.

Carvalho *et al*.[19] estimated the direct medical costs of the treatment for mucosal leishmaniasis using three therapeutic approaches in the Brazilian context: meglumine antimoniate, liposomal amphotericin B, and miltefosine. Treatment with meglumine antimoniate had the lowest average cost per patient (US$ 167.66), followed by miltefosine (US$ 259.92) in the outpatient treatment regimen. On the other hand, the average cost of treatment with liposomal amphotericin B was US$ 715.35. These results showed marked differences in costs between the therapeutic alternatives for mucosal leishmaniasis.

Chagas disease

Economic analysis on diagnosis, diagnosis and treatment or treatment

In the United States, Wilson *et al*.[20] evaluated the cost effectiveness of the implementation of three testing strategies in blood banks: A) *Trypanosoma cruzi* serology for the screening of all blood donations - enzyme-linked immunosorbent assay (ELISA); B) verbal screening initiating with three questions and then continuing with serological testing only for those positive on the verbal screening; and C) no verbal screening or serology testing for Chagas disease at all. The authors concluded that the A and B strategies are highly cost-effective compared with the C strategy across a wide range of risk levels to Chagas disease.

In Mexico, Agapova *et al*.[21] estimated the cost effectiveness of seven testing strategies against no testing: 1) risk question; 2) donations only; 3) donors for the first time and donors with repeated risks; 4) test everyone once and those with repeated risks; 5) test everyone twice and those with repeated risks; 6) test whole blood and PLT donations; and 7) universal testing. Compared with no testing, the cost effectiveness of testing all blood donors

once was $757,000 per QALY, testing all donors twice was $970,000 per QALY, and universal testing was $1.36 million per QALY. The authors highlighted that the selective screening provides approximately the same effectiveness as the universal screening, but with reduced costs.

Ramsey *et al.*[22] analyzed costs and impacts of the early treatment of Chagas disease using Markov's decision model based on previous publications. The lifetime cost for a timely diagnosed and treated Chagas disease patient was estimated at US$ 10,160, while the cost for an undiagnosed individual was estimated at US$ 11,877. The authors concluded that it is cheaper to diagnose and treat chagasic patients early, instead of doing nothing.

Bartsch *et al.*[23] evaluated the impact, costs, cost effectiveness and cost-benefit of identifying and treating patients with acute and indeterminate Chagas disease. In the acute stage, identifying and treating patients averted 0.5-5.4 acute cases, 0.6-5.5 chronic cases, and 0.6-10.8 DALYs, saving $694-$7,419 from the third-party payer perspective and $6,976-$79,950 from a social perspective. In the indeterminate stage, treating patients averted 2.2-4.9 acute cases, 6.1-12.8 chronic cases, and 11.7-31.1 DALYs, saving $7,666-$21,938 and $90,530-$243,068 from the third-party payer and social perspectives, respectively. The authors concluded that treating Chagas cases in the acute and indeterminate stages result in cost savings.

Sánchez-Gonzalez *et al.*[24] calculated the ICER for total compliance of current guidelines from both, Mexican primary healthcare and regular salaried workers' health service institutions. ICER was US$ 383 life-years gained for the Secretary of Health, while the cost for an additional life-year gained was US$ 463 for the Social Security Institute. The authors highlighted that due to incomplete compliance of Mexico's national legislation during 2013 and 2014, 15,162 *T. cruzi* infections were not confirmed and 2,347 avoidable infections were not prevented.

In Peru, Moya-Salazar *et al.*[25] evaluated the impact of seroprevalence and indeterminate results on lost units and cost per donation. A total of 7,723 donations were evaluated and the total loss was of 49,750 US dollars. The authors concluded that the prevalence of indeterminate results was elevated, causing a great impact on economic losses to the Blood Bank and the Transfusion Therapy Department of the Hospital Central de la Policia Nacional del Peru in Lima.

In Spain, Sicuri *et al.*[26] performed an economic evaluation of screening Chagas disease in pregnant women from Latin America and their newborns, against the alternative hypothesis of no screening of mothers and newborns. In any scenario, the screening option showed to be cost effective compared with no screening. In the newborns, the cost-effectiveness ratio of the strategy "test" was US$22/QALYs gained versus US$125/QALYs gained using the strategy "no test". In the mothers, the cost-effectiveness ratio of the strategy "test" was US$96/QALYs gained, and US$1675/QALYs gained in the "no test" strategy. The authors showed that the screening option proved to be cost effective against no screening and provided useful information in the decision-making process. Imaz-Iglesia *et al.*[27] carried out a cost-utility analysis of several strategies for Chagas disease screening among Latin American residents living in Spain: 1) no screening; 2) screening of the Latin American pregnant women and their newborns; 3) screening extended to the relatives of positive pregnant women; 4) screening extended to the relatives of negative pregnant women. The authors concluded that no screening was the most expensive and least effective strategy evaluated, and among the evaluated screening strategies, the most efficient was to extend the antenatal screening of Latin American pregnant women and their newborns up to the relatives of positive women.

In Europe, Requena-Mendez *et al.*[28] performed an economic evaluation of systematic Chagas disease screening of Latin American populations attending primary care centers. The modeling compared the option of the test performed (screening of asymptomatic individuals, treatment, and follow-up of positive cases) versus the no test option (screening, treating, and follow-up of symptomatic individuals). The total costs for the test and no test option were €32 163 649 and €6 904 764, respectively, and the QALYs gained were 64 (634,35) and 59 (875,73) in the probabilistic analysis, respectively. For a treatment efficacy of 20%, ICER was €6840,75 per QALY gained and for a treatment efficacy of 50%, it was €4243 per QALY gained. The authors highlighted that screening for Chagas disease in asymptomatic Latin American adults living in Europe is a cost-effective strategy.

Cysticercosis

Economic analysis of diagnosis

In India, the total cost of imaging studies of the brain was 8,180 Indian rupees ($1 is approximately 28 rupees), respectively. The authors highlighted that magnetic resonance imaging is far more specific in detecting and evaluating lesions than computed tomography scanning and that the risk of anaphylactic reactions and overall patient morbidity using this technique is also reduced[29].

Economic analysis of treatment

In Mexico, Medina-Santillán *et al.*[30] compared the cost of two therapeutic schemes of praziquantel for the treatment of neurocysticercosis: 1) conventional treatment

with praziquantel 50 mg/kg/day for 15 days; and 2) three doses of praziquantel 25 mg/kg per dose administered on the same day in a two-hours intervals. The total direct cost of conventional treatment was 2,073.28 *peso*s compared with 212.04 *pesos* for the one-day treatment. The authors concluded that the second scheme had a direct impact on costs, with a 90% reduction with respect to the traditional scheme, and with this short-scheme, hospitalization was unnecessary, and the costs of hospital visits for patient and family were avoided.

Filariasis

Economic analysis of diagnosis

In Sri Lanka, Chandrasena *et al*.[31] estimated the cost effectiveness of an immunochromatographic card test (ICT) compared with two standard parasitological techniques: thick blood film (TBF) and nucleopore membrane filtration. In this study, ICT was more effective (sensitivity of 100% and specificity of 94%) than the parasitological techniques in diagnosing infection by lymphatic filariasis. The direct costs of the TBF and ICT were US$0.30 and US$2.75, respectively. The authors highlighted that although TBT is the standard survey tool in Sri Lanka, in a situation of lack of good laboratory facilities and trained staff, the ICT would be an alternative.

Economic analysis of treatment

In Tanzania, Michael *et al*.[32] examined the cost effectiveness of four different mass diethylcarbamazine (DEC) chemotherapy regimens in reducing the microfilarial (mf) prevalence at the community level: I) regimens-standard; II) semi-annual single dose; III) low monthly dose; and IV) DEC-medicated salt. The implementation cost of strategies I, II, III and IV was US$970,0; US$355,7; US$392,8 and US$1442,9, respectively, and the cost per case cured was US$25,5; US$5,2; US$5 and US$17,4, respectively. Strategy IV was the most effective in terms of reducing the prevalence of microfilaremia and has potential to be the predominant intervention. The authors reported that this strategy becomes significantly cost efficient only when the salt delivery mechanism is simplified.

In India, Krishnamoorthy *et al*.[33] compared the cost effectiveness of mass drug administration alone versus mass drug administration associated with vector control. The cost for stopping an infective mosquito from biting a villager using mass drug administration alone was US$1.80 compared with US$3.32 to achieve the same result using mass drug administration in addition to vector control.

In 2010, Chu *et al*.[34] analyzed the economic benefits of the Global Program to Eliminate Lymphatic Filariasis between 2000-2007. During the first eight years of the program, an estimated US$21.8 billion of direct economic benefits were gained over the lifetime of 31.4 million individuals treated with albendazole, ivermectin, diethylcarbamazine. More than 28 million individuals already infected were benefited by the program, resulting in an associated lifetime economic benefit of US$19.5 billion, and the reduced morbidity saved the health systems of endemic countries approximately US$2.2 billion. The authors highlighted that the economic rate of return of the program is high and proves itself an excellent investment at the level of public health.

In 2017, Turner *et al*.[35] evaluated the cost effectiveness and cost-benefit of the preventive chemotherapy provided under the Global Program to Eliminate Lymphatic Filariasis between 2000 and 2014 in addition to the potential cost effectiveness of hydrocele surgery. The authors concluded that the preventive chemotherapy and hydrocele surgeries were cost effective, defined as less than $246 per DALY averted, and represented a very good investment in public health.

Schistosomiasis

Economic analysis of diagnosis or diagnosis and treatment

In Kenya, Worrell *et al*.[36] compared the costs of a single stool Kato-Katz test, triplicate stool Kato-Katz tests, and point-of-contact circulating cathodic antigen assays (POC-CCA) for the detection of *Schistosoma mansoni*; the unit cost of the diagnostic tests was US$6.89, US$17.54, and US$7.26, respectively. The authors suggested that the slightly higher cost of POC-CCA may be justified for its greater sensitivity to detect schistosomiasis.

In Burundi, Carabin *et al*.[37] evaluated the cost effectiveness of three alternative screening strategies in delivering treatment to patients with symptoms suggestive of *S. mansoni*: A) screening all symptomatic individuals using a Kato-Katz test and treating only positives; B) treating all symptomatic individuals; or C) treating only those with symptoms of severe diarrhea. In this study, the A strategy was more cost effective than treating all symptomatic patients, with cost-effectiveness ratios estimated at US$4.2 and US$12.43 per infected person treated, respectively. The authors concluded that the sustainability of strategy B is closely related to the endemic level and the the price of the drug.

In Brazil, Nascimento *et al*.[38] estimated the cost of schistosomiasis in 2015 from the social perspective. The study included 26,499 infected people, 397 hepatosplenic cases, 284 hospitalizations, 48 cases with the neurological form. The total cost of schistosomiasis was estimated to be US$ 41,7 million, including spending on diagnosis,

adverse events of treatment, transportation, patients' care at home and premature death. The authors concluded that the economic burden of disease in Brazil is high.

Economic analysis of treatment

In Tanzania, Guyatt and Chan[39] investigated the cost effectiveness of school-targeted treatment for *S. mansoni*. In this study, drugs with low efficacy produced high and variable cost-effectiveness ratios. The authors highlighted that the interactions between drug price and drug efficacy are complex and suggested that given the current price range of praziquantel, a drug with less than 50% effectiveness in killing the worms is not to be recommended.

In Egypt, Carabin *et al.*[40] estimated the cost and effectiveness of reaching non-enrolled children through school-based programs: school-based (coverage of 85%) and school-aged targeted (coverage of 25, 50 and 85%) programs. Programs in which only 85% of children were treated would prevent 77% of the early disease cases. However, the authors pointed out that to use school-aged targeted strategy, raised from US$0.06 to US$1.03 the extraunitcosts and that the strategy could be designed to reach non-enrolled children and be even more cost effective.

Visceral leishmaniasis

Economic analysis of diagnosis or diagnosis and treatment

In Sudan, Boelaert *et al.*[41] compared four strategies for treatment of VL suspects cases: 1) treatment of all suspects; 2) parasitological tests followed by treatment of positives; 3) two-step testing using the direct agglutination test (DAT) followed by treatment of patients with high titers as well as those with parasitological confirmed infections after a borderline DATresult ; or 4) DAT followed by treatment of positives with high titres. The strategy B was the most cost-effective estimating US$448 per death averted. The authors suggested that the introduction of DAT in diagnostic-therapeutic algorithms contributed to decision making and favored the effective use of resources allocated to control the disease. Boelaert *et al.*[42] have also evaluated whether the potential improvements in chemotherapy would affect the choice of the 'optimal' test-treatment algorithm: Strategy A: treats all clinically suspect patients without testing, leading to either a correctly treated VL case or an erroneously treated non-VL case; Strategy B: relies on parasitological diagnosis in which only persons with positive parasitology are treated, leading either to a correctly treated VL case or an erroneously treated non-VL case; and Strategy C: serology (DAT) differs only from the former to the extent that a serological test is used instead of a parasitological one. The authors highlighted that strategy C is the best option and constituted the optimal choice.

Vanlerberghe *et al.*[43] compared the cost effectiveness of four drug regimens for VL associated with a serological rapid test: 1) amphotericin B deoxycholate (Amb-D); 2) pentavalent antimonial; 3) miltefosine; and 4) liposomal amphotericin B. Treatment with AmB-D was the most effective (349 deaths averted per 1000 clinical suspects) approach, and miltefosine was the most cost-effective approach (US$ 327.9 per death averted). The authors highlighted that miltefosine has the advantage of oral administration, but there is a disadvantage of the potential teratogenicity of this drug. Therefore, one of the challenges is to reduce the price of the drugs, mainly of liposomal amphotericin B.

In Brazil, Machado de Assis *et al.*[44] reported the process and costs of implementing two tests to decentralize the diagnosis of VL in an endemic city: a rapid test (IT LEISH) and a direct agglutination test (DAT-LPC). Estimation of the training costs considered the proportional remuneration of all professionals involved and the direct costs of the tests used for training. During November 2011 and November 2013, 17 training sessions were held, and 175 professionals were trained. The training cost for each professional was US$ 7.13 for the IT LEISH and US$ 9.93 for the DAT-LPC. The direct costs of the IT LEISH and DAT-LPC were estimated to be US$ 6.62 and US$ 5.44, respectively. This evaluation on the implementation of these diagnostic tests indicated the feasibility of decentralizing both methods to extend the access to VL diagnosis in the country. Machado de Assis *et al.*[45] evaluated the cost effectiveness of six diagnostic options for VL: the rapid test IT LEISH, rapid test Kalazar Detect, DAT, indirect immunofluorescence antibody test (IFAT), polymerase chain reaction (PCR) and direct examination of bone marrow aspirate. In this study, DAT presented the lowest cost (US$4.92) and highest effectiveness (99%) per correctly diagnosed case. The authors suggested that these results highlight the need for a revision of the algorithm for VL diagnosis in Brazil. Replacements of IFAT with DAT-LPC are cost-effective public health measures. In an analysis of budgetary impact, Machado de Assis *et al.*[46] estimated the financial costs of the incorporation and/or replacement of the six diagnostic tests evaluated previously. The costs to diagnose VL cases over three years using IFAT and DAT were estimated at US$280,979.91 and US$121,371.48, respectively. The analysis indicated that, compared with the use of IFAT, the incorporation of DAT would result in savings of US$159,608.43. With regard to the budgetary impact of rapid tests, the use of IT LEISH resulted in savings of US$21.708,72 over three years. Compared with

the parasitological examination, the diagnosis by PCR resulted in savings of US$3,125,068.92 over three years. In addition, the cost effectiveness of six diagnostic-therapeutic alternatives was analyzed: 1) IT LEISH and pentavalent antimonial; 2) IT LEISH and liposomal amphotericin B; 3) IFAT and pentavalent antimonial; 4) IFAT and liposomal amphotericin B; 5) DAT and pentavalent antimonial; and 6) DAT and liposomal amphotericin B. Machado de Assis *et al*.[47] showed that IT LEISH and liposomal amphotericin B emerged as the best option, presenting lower costs (US$659.79) and higher effectiveness (62.95) per year of life gained. The authors showed that liposomal amphotericin B should be used as the first-line drug for VL in Brazil.

Economic analysis of treatment

In Bihar, India, Thakur *et al*.[48] compared a daily (group A) and an alternate-day regimen of amphotericin B (group B) for the treatment of VL. The cost of drugs and intravenous administration was the same in groups A and B; however, the expenses of board and lodging of two relatives per patient was higher in group B (US$225 versus US$92 in group A). The authors highlighted that a daily regimen of amphotericin B was as efficacious as the alternate day regimen, much more cost effective and should be adopted for the treatment of this condition.

Sundar *et al*.[49] evaluated if the costs of treatment with liposomal amphotericin B could be reduced by using ultrashort courses. The final cost per patient of treatment using amphotericin B lipid complex given daily ranged between US$561-1010 and given on alternate days ranged between US$490-715. The authors emphasized that treatment using liposomal amphotericin B is indicated for VL patients who fail to respond to the antimony therapy. Sundar *et al*.[50] tested standard amphotericin B deoxycholate mixed with a commercial fat emulsion as a short-course treatment. The cost of treatment per patient was estimated to be US$260, and the authors showed that the short-course treatment was cost effective for patients with VL. Olliaro *et al*.[51] assessed the cost effectiveness of current monotherapies and combinations (liposomal amphotericin B; paromomycin; miltefosine) for treating VL. The cost of monotherapies per averted years of life lost (YLL) ranged from US$2 for paromomycin to US$20-22 for liposomal amphotericin B and for combinations ranged from US$5-8 per YLL averted. The authors demonstrated that the combinations evaluated were more cost effective than most monotherapies and emphasized that cost equalization policies are important to encourage the use of certain treatments.

In the Indian subcontinent (India, Nepal and Bangladesh), Meheus *et al*.[52] assessed the cost effectiveness of ten isolate and combined therapies for VL treatment. The combination miltefosine-paromomycin was the most cost-effective strategy (US$92 per death averted). The authors suggested that there are concerns about drug resistance and that, in this context, combination therapies should be considered.

In Brazil, Machado de Assis *et al*.[53] estimated the direct costs of therapies recommended by the Ministry of Health. The estimated direct costs of treatment for an adult patient using pentavalent antimonial administered by intramuscular and intravenous routes were US$418.52 and US$669.40, respectively. The estimated cost of treatment with amphotericin B deoxycholate was US$1,522.70, while the costs of liposomal amphotericin B were US$659.79 and US$11,559.15, considering the price subsidized by WHO and the market price, respectively. The authors emphasized that replacing N-methyl glucamine antimoniate by liposomal amphotericin B is economically feasible.

Carvalho *et al*.[54] estimated the Brazilian direct and indirect costs of VL in 2014. The total cost of disease was estimated US$ 14,190,701.50. The direct medical costs corresponded to US$ 1,873,681.96, and most of it was associated with hospitalization (40%). Productivity loss corresponded to US$ 11,421,683.37 for premature mortality and US$ 895,336.18 for work absence due to hospitalization. The authors concluded that VL represents an expensive problem for the public health system and the society.

In another study, also considering the Brazilin scenario, Carvalho *et al*.[55] estimated the cost effectiveness of three therapeutic options for the treatment of VL: 1) pentavalent antimonial, 2) liposomal amphotericin B and 3) a combination of liposomal amphotericin B and pentavalent antimonial. In this study, the second strategy proved to be cost effective for treating VL. The authors highlighted that the use of liposomal amphotericin B can improve the care offered to patients with VL in Brazil.

Quality of the articles included

Eighty percent (40/46) of the articles included in this narrative review presented at least 19 out 24 CHEERS items. The CHEERS item with the highest rate of missing data among those retrieved in studies refers to the choice of discount rate(s) used for costs and outcomes (item 9), presented in 20/46 (44%) studies (Supplementary Material, Figure S2).

DISCUSSION

The growth in health spending has become a major problem for developing countries. In this context, economic

health assessments represent a valuable tool to support decision making, optimizing the benefits of a technology according to the local health needs and cost possibilities. In developing countries, where resources are scarce and health needs are expensive, these assessments are particularly important[56].

In the present study, a small number of publications concentrated in a few countries addressing diagnosis and treatment strategies for NTDs were identified. This observation allowed some extrapolations related to the current scenario of evidence development: 1) there is little investment in research and development of new diagnostic tests and medicines for NTDs; 2) there is a lack of trained professionals to conduct economic assessments; and 3) there is a lack of political interest to carry out decision making based on economic evidence.

Marinho *et al*.[8] reviewed the economic evaluations for VL treatment and had already reached the same conclusions. On the other hand, the quality of analyses produced is generally adequate and is improving over time. Most of the selected studies carried out cost-effectiveness analyses, corresponding to complete economic assessments.

Some general notions can be extracted from the economic analyses available to date for NTDs. Regarding CL, two of the main findings are the confirmation of cost effectiveness of liposomal amphotericin B for hospitalized patients with mucocutaneous leishmaniasis and of the meglumine antimoniate intralesional approach, both in the context of the Brazilian National Health System. As a direct implication, these results should support the acquisition of liposomal amphotericin B for mucocutaneous leishmaniasis[16] and the implementation of an intralesional approach with meglumine antimoniate, as has already been done, for patients with localized CL in Brazil[17].

In the case of Chagas disease, the set of evidence consolidated by several studies advocates in favor of serological testing of donors in blood bank as well as in antenatal screening[20-28] as cost-effective public health strategies. These results corroborate the resolution of the World Health Assembly, which recommends Chagas disease screening for pregnant women in non-endemic areas if they were born in disease-endemic areas, if they have lived for a long time in disease-endemic areas, or if they were born to mothers who lived in disease-endemic areas[57].

Considering cysticercosis, studies addressing cost estimates for magnetic resonance imaging, computed tomography and different praziquantel therapeutic schemes were identified. For filariasis, an immunochromatographic card test[31] and mass drug administrations[32,33] were suggested as cost-effective strategies. In addition, a multicenter study assessing different diagnostic tools for bancroftian filariasis elimination showed that the immunochromatographic card test is relatively inexpensive, requires no laboratory equipment, has satisfactory sensitivity and specificity and can be processed in 10 minutes[58]. In this sense, a mass drug administration program to eliminate lymphatic filariasis was initiated in 2000 in 55 endemic countries. After 13 years, the program resulted in a significant reduction in the burden of disease[59] and Srividya *et al.*[60], reported disease elimination in 11 of the 72 endemic countries, with enormous efforts on systematic planning and implementation of the strategy.

In respect to schistosomiasis, the treatment of positive cases was shown to be more cost effective than treating all symptomatic patients[37]. However, preventive chemotherapy for schistosomiasis is still a subject of debate. Several authors emphasized the need for a better tailoring of preventive chemotherapy to the local environment in endemic areas and to emphasize the use of other measures in addition to chemotherapy[61].

Concerning VL diagnosis, based on data mainly from Brazil and Africa, DAT and immunochromatographic rapid tests were identified as cost-effective strategies for diagnosing the disease[44,46]. Corroborating these findings, a recent validation of DAT and rapid test in Spain has also shown an acceptable sensitivity and specificity of these methods[62]. Regarding treatment, liposomal amphotericin B was confirmed as a cost-effective option for VL[47,55].

In the present study, the quality of information available in the primary studies was assessed considering the CHEERS checklist[9]. Most studies (40/46) presented clear and complete information about the economic assessment performed. In this evaluation, the item 9 of CHEERS was the least scored and this result can be related to the fact that most studies have estimated cost and effectiveness at the present time and in the same year, thus not requiring the application of discount rates.

Decimoni *et al*.[63] have also evaluated the number, characteristics, and quality of reporting of published economic studies in a Brazilian setting between January 1980 and December 2013. In total, 535 studies were included in the review, and overall, the quality of reporting was satisfactory and has increased progressively over time; however, some items were generally poorly reported. The authors pointed out that the following items need improvement: reporting of funding source, conflict of interest, methods for the estimation of resources quantities and unit costs, methods and source of evidence to estimate utility parameters. These deficiencies may be related to a lack of trained professionals to conduct the economic assessments mentioned above.

CONCLUSION

In summary, this review confirms the scarcity of new health technologies being economically evaluated for NTDs. Given the existence of many unresolved issues and scientific but mainly financial obstacles related to access the nature of the NTD approach task, this observation deserves not only reflection but also a coordinated action. Particularly for countries with insufficient health budgets, economic analyses should be seen as essential tools for the rational allocation of resources. As a final message, our observations must serve as a warning to managers and health organizations with global influence on the need to create investment convergence strategies for diseases related to poverty, without which this reality can hardly be overcome.

AUTHORS' CONTRIBUTIONS

Data collection for this research was carried out by TSMA. All authors contributed to data analysis and the writing of this article.

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CONFLICT OF INTERESTS

The authors have declared that no conflict of interests exist.

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SUPPLEMENTARY MATERIAL

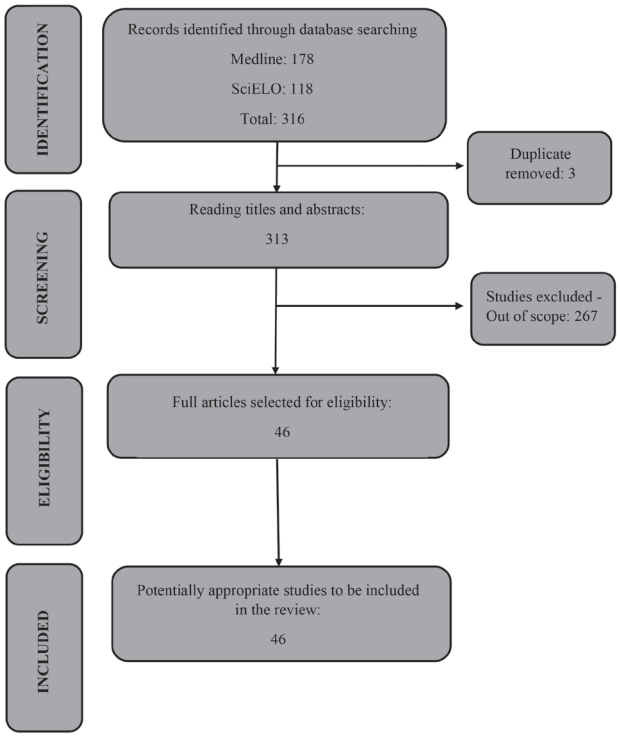

Figure S1 - Flow diagram of the study selection process.

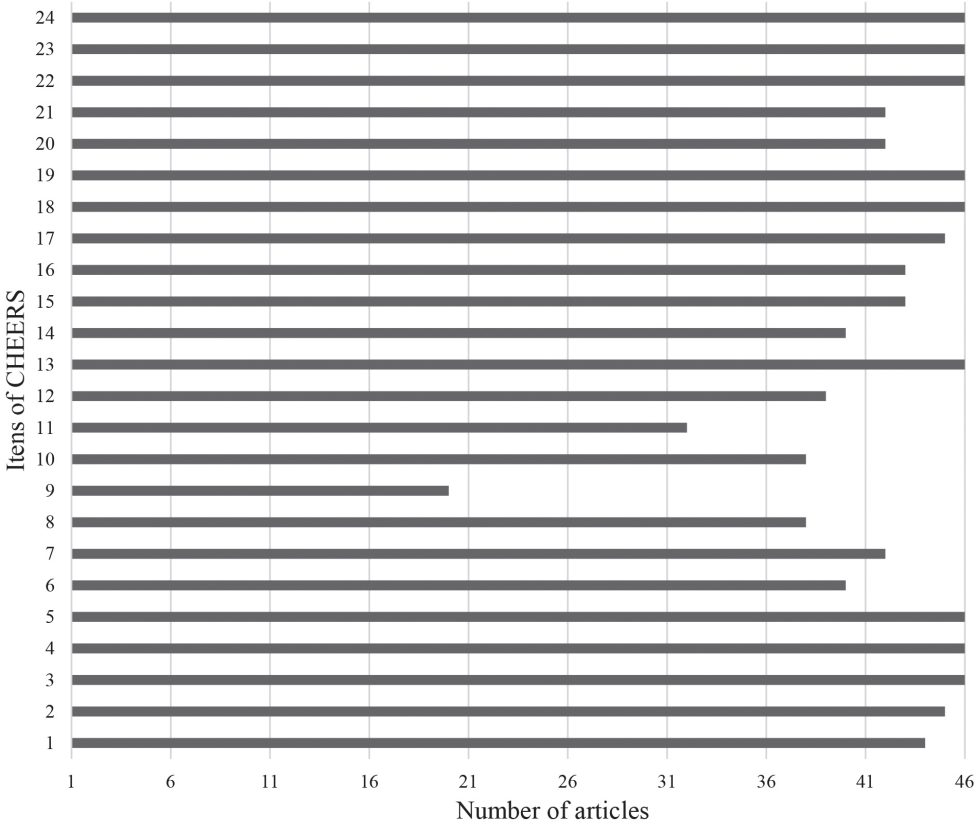

Figure S2 - Adequacy of the 46 articles included in the present narrative review to the 24 itens of Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.