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Review

Lymphatic filariasis and onchocerciasis prevention, treatment, and control costs across diverse settings: A systematic review

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ABSTRACT

The control and eventual elimination of neglected tropical disease (NTD) requires the expansion of interventions such as mass drug administration (MDA), vector control, diagnostic testing, and effective treatment. The purpose of this paper is to present the evidence base for decision-makers on the cost and cost-effectiveness of lymphatic filariasis (LF) and onchocerciasis prevention, treatment, and control. A systematic review of the published literature was conducted. All studies that contained primary or secondary data on costs or cost-effectiveness of prevention and control were considered. A total of 52 papers were included for LF and 24 papers were included for onchocerciasis. Large research gaps exist on the synergies and cost of integrating NTD prevention and control programs, as well as research on the role of health information systems, human resource systems, service delivery, and essential medicines and technology for elimination. The literature available on costs and cost-effectiveness of interventions is also generally older, extremely focal geographically and of limited usefulness for developing estimates of the global economic burden of these diseases and prioritizing among various intervention options. Up to date information on the costs and cost-effectiveness of interventions for LF and onchocerciasis prevention are needed given the vastly expanded funding base for the control and elimination of these diseases.

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1. Introduction

Despite renewed interest in the prevention and control of neglected tropical disease (NTD), lymphatic filariasis (LF) and onchocerciasis continue to cause widespread disease and disability in many parts of the world. LF is a leading cause of permanent and long-term disability, with approximately 40 million people either disabled or incapacitated by the disease; the risk of infection spans 73 countries, with the largest burden in Africa and South Asia (WHO, 2013; Simonsen, 2009). Onchocerciasis is endemic in 31 countries in Africa, 6 countries in Latin America and in Yemen; 38 million people are estimated to be currently infected, with 99% of cases found in Africa (WHO, 2013).

Financing and support for NTDs in general is on the rise (Zhang et al., 2010; London Declaration to Combat NTDs, 2013). The United States of America (USA) committed US$350 million to provide LF treatment in 2008; in 2012 the U.S. government committed an additional US$89 million to prevent and control NTDs, including LF and onchocerciasis. The United Kingdom committed £50 million over 5 years toward NTD control and elimination (Zhang et al., 2010), and recently the Bill and Melinda Gates Foundation awarded a US$34 million grant to leverage or develop new mechanisms to generate funding for NTD control and elimination (Zhang et al., 2010). In 2012, the London Declaration on NTDs was held to accelerate progress toward achieving the WHO 2020 targets toward eliminating several NTDs, including LF and onchocerciasis. Since 2012, partners and donors have contributed over US$785 million to support NTD programs, strengthen research and development mechanisms and bolster drug availability and distribution (London Declaration to Combat NTDs, 2013).

Financing for the control and elimination of LF through the Global Program for the Elimination of LF (GPELF) mostly comes from private organizations such as the Bill and Melinda Gates Foundation, as well as corporations such as Merck, Eisai, and GlaxoSmithKline. All three drugs used during mass drug administration (MDA) are donated: albendazole by GlaxoSmithKline, diethylcarbamazine (DEC) by Eisai Co. Ltd., and Mectizan (ivermectin) by Merck and Co. Inc. Additional funding for the elimination of LF comes from bilateral and multilateral organizations, NGOs, and national health budgets (London Declaration to Combat NTDs, 2013).

The majority of support for onchocerciasis treatment is currently provided in kind by Merck and Co. Inc.; Merck has donated more than 1.5 billion doses of ivermectin since the inception of the Mectizan donation program (MDP) (Ogoussan and Hopkins, 2011; Thylefors, 2008). Financial management for the African Program for Onchocerciasis Control (APOC) is carried out through the World Bank; the World Bank manages the APOC trust fund and the coordination with national onchocerciasis elimination committees, who determine local planning and financial needs. While direct cost recovery from the community has largely been abandoned as an approach to financing the Community Directed Treatment (CDTi) program, current discussion revolves around integration of the CDTi program into existing health structures and developing financing through the national health system of each country involved. The APOC program is proceeding toward curtailing activities and transitioning to local ownership by 2015. A major challenge during any transition is potential funding gaps as programs scale up (Rakers et al., 2009; London Declaration to Combat NTDs, 2013). Previously, it was suggested that key to a successful transition would be the development of private–public partnerships to finance and coordinate strategies (Benton et al., 2002; Blanks et al., 1998; Dadzie, 1998; Miri, 1998; Mutabazi and Duke, 1998; Okwero, 1998), although this may no longer be relevant as health systems strengthen, and partners and pharmaceutical companies renew their pledge to eliminate many NTDs (London Declaration to Combat NTDs, 2013).

The purpose of this paper is to review the existing literature on the costs, economic impact, and health systems implications of LF and onchocerciasis. The paper begins with a brief description of the treatment, prevention and control strategies for the two diseases to provide context. It then presents a systematic review of literature that included primary data on costs or cost-effectiveness related to LF and onchocerciasis programs.

1.1. Prevention, treatment and control of LF

The main strategy for interrupting LF transmission is annual MDA in endemic areas. Secondary activities focus on vector control (*Culex* genus in urban settings, and species within the *Anopheles*, *Mansonia*, or *Aedes* genus in rural settings). The main strategy for alleviating the disability resulting from LF infection focuses on preventing or reducing the severity of secondary fungal and bacterial infection.

DEC is the drug of choice for patients with active LF, given that it is both micro- and macro-filariacidal. Ivermectin is also efficacious against microfilariae of LF but not adult worms, but is only used where onchocerciasis is also present and loaiasis (infection caused by *Loa loa*, the African eye worm) is absent. Albendazole has also been used in combination with DEC and ivermectin; given its generalized anti-helminthic properties the addition may increase compliance of MDA against LF (Remme et al., 2006). However, trials are still underway to quantify any added benefit of using albendazole in combination with DEC. A study in south India suggests that this combination therapy has an added benefit in reducing the prevalence of angioedema (Rajendran et al., 2002) and a study in Nigeria showed that the use of albendazole in combination reduced mosquito infection rates (Richards et al., 2005). A second line of defense is the use of doxycycline against *Wolbachia* bacteria; this drug stops embryogenesis and results in increased death rates of adult worms over a 12 month period (Eddleston et al., 2011).

Studies have suggested that prolonged vector control can contribute to LF elimination (Ramaiah et al., 1994), although it is now widely accepted that vector control should complement

chemotherapy (Reimer et al., 2013). One study in Tanzania reported that the use of polystyrene beads in larval habitats reduced annual biting rates of LF vectors by almost 100% (Maxwell et al., 1990); while this is important, there were likely other factors interacting to reduce biting rates. Studies in India have shown that vector control in combination with DEC reduced transmission potential by nearly 96% compared with chemotherapy alone (60% reductions) (Reuben et al., 2001). Studies in Kenya, Nigeria, Uganda and Papua New Guinea have also documented reductions in LF prevalence using insecticide treated bed nets (ITN) or long-lasting insecticide treated bed nets (LLIN) as well as untreated nets in combination with chemotherapy (Ashton et al., 2011; Bockarie et al., 2002; Emukah et al., 2009; Pedersen and Mukoko, 2002).

1.2. Prevention, treatment and control of onchocerciasis

Onchocerciasis, or river blindness, control in the modern era has largely been conducted by three programs: one in Africa (APOC), one in the Americas [Onchocerciasis Elimination Program for the Americas (OEPA)] and one in West Africa [WHO Onchocerciasis Control Program (OCP)]. Onchocercal disease control consists of three compartments: vector control [black flies from the genus *Simulium* (John et al., 2006), with the *S. damnosum* complex being the most important in Africa; in Latin America *S. ochraceum*, *S. metallicum*, *S. exiguum*, *S. guyanese*, and *S. oyapockense* are important vectors], treatment of patients, and community control of parasites through MDA. Given that *Simulium* flies lay eggs in flowing water, vector control consists of treating oviposition areas with temephos or other biological agents such as *Bacillus thuringiensis israeliensis* (*Bti*).

Patient treatment historically has consisted of symptomatic treatment to reduce pruritus and to prevent damage to eye tissue. In some cases surgical excision of nodules is recommended (when located on head or near the eyes), but otherwise treatment consists of annual or semi-annual administration of ivermectin. Recently, it was observed that a six-week regimen of doxycycline can lead to sterilization or reduced reproduction of adult female worms. This regime may also be administered in areas co-endemic with loaiasis where ivermectin is contraindicated due to adverse inflammatory events among persons with severe *Loa loa* infections. Ivermectin is also contraindicated among pregnant women or nursing mothers and small children.

The availability of microfilariacides and macrofilariastatic drugs has led to the widespread application of MDA in endemic communities to interrupt transmission. Annual or semi-annual distribution of ivermectin is currently the main strategy for onchocerciasis control. Transmission is relatively easy to interrupt with high community coverage of drug therapy, but because the adult filarial worms are long lived, continued MDA must be conducted until enough adult cases have resolved to ensure that transmission will not resume. While the use of concomitant doxycycline treatment might expedite the process, the length of the required treatment course (six-weeks) makes its large scale implementation difficult. Currently MDA is mainly delivered through a strategy known as CDTi, which focuses on the use of local agents and community directed distributors (CDDs) to identify and deliver medications.

2. Methods

A systematic electronic search of literature published in the English language between 1996 and 2010 was conducted using PubMed (MEDLINE), EMBASE, and JSTOR databases (Fig. 1). The following search terms were used for LF: lymphatic filariasis and (econ, economics, cost, cost-effectiveness, cost–benefit, economic, internal rate of return, eradication, elimination, health systems, vertical, integration). For onchocerciasis we searched for literature published in the English or French language between 1990 and 2010 using the following search terms: onchocerciasis and (econ, economics, cost, cost-effectiveness, cost–benefit, economic, internal rate of return, eradication, elimination, health systems, vertical, integration). All results were initially reviewed for relevance based on their abstracts; the selected publications were then collected and further reviewed for relevance using the full text. The bibliographies of identified references were also searched, as well as the gray literature using Google and Open Content search engines.

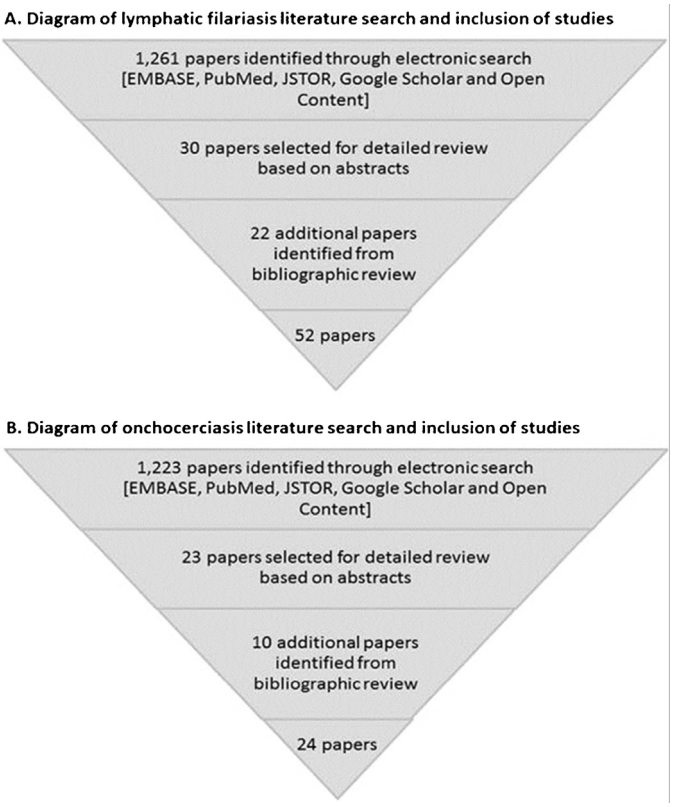

Fig. 1. Incremental results of the literature search for (A) lymphatic filariasis and (B) onchocerciasis.

All papers with primary data on economic burden, costs of interventions, or health system implications of control and elimination programs were selected for more detailed review. All papers with primary data on costs of any topic related to treatment, prevention or control were included. Fig. 1a and b illustrates the incremental results; a total of 52 papers were identified for LF; a total of 24 papers met the criteria for onchocerciasis. All cost data were adjusted to USD in the year of the initial study (if the researchers had not already done so) using historical exchange rate data from Oanda.com. All costs were then adjusted to 2012 USD using the U.S. Gross Domestic Product Deflator series from the U.S. Bureau of Economic Analysis. It is recognized that the search methods described above may have resulted in the introduction of bias, as some studies may not have been identified with a search of PubMed, EMBSE, JSTOR, Google Scholar, OpenContent or bibliographic references, published in English or French, or may have selectively presented cost data. Data on the financial costs of MDA was extracted from all available sources and compiled for more in-depth analysis.

3. Results

3.1. Economic burden of LF

The long-term disability and subsequent inability to carry out daily domestic and economic activity is the direct result of the painful swelling of the extremities and hydrocele commonly associated with advanced infection status. While treatment costs comprise the bulk of realized costs related to LF infection, much of the economic burden is the result of indirect costs related to lost economic productivity and educational opportunity. A meta-analysis found that approximately 94% of the total economic benefits of the GPELF were due to the prevention of indirect costs in the form of lost working time, resulting in a total of US$21.6 billion over an 8 year period (Chu et al., 2010). While the authors acknowledge that measuring the value of lost time is difficult given that many at-risk persons are located in countries where the informal labor market is large they estimate that average annual work days lost due to LF have been reduced by the GPELF.

Other studies corroborate the suggestion that the largest economic burden of LF comes in the form of indirect costs (Chandrasena et al., 2004; Gasarasi et al., 2000; Gyapong et al., 1996; Kessel, 1957; Rao et al., 1982), although these studies are somewhat narrowly focused geographically. A series of case–control studies have shown that on average, individuals with acute dermatolymphangioadenitis (ADLA) spent 2.7–3.6 h less per day on income generating activities than healthy individuals (Babu and Nayak, 2003; Gasarasi et al., 2000; Ramaiah et al., 1998, 2000). Studies in India and Ghana have also documented reduced labor force participation by individuals with ADLA (Babu and Nayak, 2003; Gyapong et al., 1996). A quasi-experimental study in 9 epidemiologically matched villages in India suggested that approximately US$79–111 billion may be lost nation-wide each year (Krishnamoorthy, 1999). In the Philippines, it was estimated that US$49 billion is lost each year due to ADLA (Kron et al., 2000).

Lymphoedema and hydrocele are also responsible for considerable indirect costs related to LF, although a lack of standardized case definitions hinders comparisons. Indeed, early studies failed to reach similar conclusions regarding the impact on productivity, and reductions were often not quantified (Evans et al., 1993; Giglioli and Beadness, 1960; Kessel, 1957; Wijers and Kinyanjui, 1977). More recently, longitudinal case–control studies in India found that a significant number of work hours per day are lost due to chronic LF, although higher for males than females (Ramaiah et al., 1999, 2000). This finding is similar to other case–control studies in India: one estimated that 0.81 work hours were lost per work day, and that 88% of patients reported absenteeism from work; 55.1% of female patients reported an inability to perform domestic activities (Babu and Nayak, 2003). A second study estimated that 1.13 h were lost per work day, representing 19% of annual workdays (Babu et al., 2002). Studies from Ghana suggest that female labor input lost due to lymphoedema approached 1.5% of all female labor input annually (Gyapong et al., 1996). A case–control cohort study among Indian weavers found similar results, with a 27% decrease in output among affected individuals (Ramu et al., 1996). In terms of chronic disease indirect costs, Chu et al. (2010) estimate that 10% of individual annual income among affected individuals might have been gained as a result of the first eight years of the GPELF. Similarly, the average wage was estimated to have increased from US$1.11 to US$1.48 as a result of control programs.

3.2. Costs of treatment and control of lymphatic filariasis

3.2.1. Mass drug administration (MDA) costs

A study in Haiti reported a MDA per person delivery cost of US$0.44, although the albendazole was donated from the manufacturer (Goldman et al., 2011). Taking into consideration the donations and drug purchases, the average economic cost per person was US$0.68; the most substantial cost components included per diem (35% of total economic costs), supplies (14% of total economic costs) and personnel (7% of total economic costs) (Goldman et al., 2011). In a separate study of MDA in Haiti (with DEC and albendazole), approximately 24% of the treated individuals reported adverse reactions; the cost per person treated with adverse reactions was double the cost of the MDA (US$2.05 versus US$0.91: total cost for MDA plus management of adverse reactions = US$1.44 per person treated). Medications amounted to 43% of the adverse reaction costs (McLaughlin et al., 2003). A third study in Haiti estimated a MDA cost per person treated of US$2.75, US$2.42, and US$1.60 over three rounds, respectively (De Rochars et al., 2005).

A study in rural south India compared the costs of adding vector control to MDA with DEC plus ivermectin (Krishnamoorthy et al., 2002). The cost per treatment for two rounds of MDA was US$2.00 and US$2.29 for 2 years of larval habitat management (LHM) activities, and US$4.29 for both across two years; almost 80% of these costs were estimated to be drug delivery costs, mostly supplies and personnel time. In this study, the authors concluded that it was not cost-effective to integrate LHM with MDA, given that cost-effectiveness ratios (i.e. cost of preventing one case or reducing prevalence of microfilariae by 1%) for LHM and MDA together were almost double when compared to MDA alone. A study in Nigeria investigated the cost of integrating MDA (with donated drugs) programs for other vector-borne diseases, in essence producing a triple drug administration (TDA) strategy (Evans et al., 2011). These authors found that the total cost per treatment using the TDA approach was US$0.08 with single administration but only US$0.05 with TDA. The total cost to deliver a treatment of ivermectin + albendazole was US$0.05 and of praziquantel was US$0.28 (in 2008). Assuming a child was treated three times (two rounds of praziquantel + one round of albendazole + ivermectin) during 2009 yielded a cost estimate per person treated of US$0.11; US$0.17 less than the two rounds of praziquantel plus one of ivermectin + albendazole delivered in 2008. In Egypt, retrospective cost data were analyzed and showed per person treated cost using DEC plus albendazole to be between US$2.27 (total) and US$1.72 (Government costs); these estimates excluded the cost of donated drugs (Ramzy et al., 2005).

A cross-country comparative study used a prospective study design to collect data from 7 countries to estimate both the financial and economic cost per person treated with MDA (Goldman et al., 2007). This study reported financial cost ranging from US$0.07 to US$2.75 and an economic cost per person treated ranging from US$0.049 to US$7.20. This study also reports that countries with data from multiple MDA rounds showed considerable reductions in financial cost per person treated during subsequent MDA rounds, and that those countries where volunteers for delivery were used reported the lowest financial costs per person treated (Goldman et al., 2007).

Fig. 2 illustrates the financial cost per person treated using MDA from all available data sources for both LF and onchocerciasis control. Several features are apparent for a global view of this data. One is that most cost estimates come from the period 2000 to 2003 and almost half are from sub-Saharan Africa. Estimates of costs per person treated from sub-Saharan Africa are largely lower than other regions (mean = US$0.36 per person treated (not including drug costs)) and those from other regions are higher (mean = US$1.72 per person treated (not including drug costs)). Most cost estimates were of LF MDA (n = 24 of 29 total MDA cost point estimates). The mean cost of LF estimates was higher than that of onchocerciasis (LF MDA mean = US$1.46, onchocerciasis MDA mean = US$0.46).

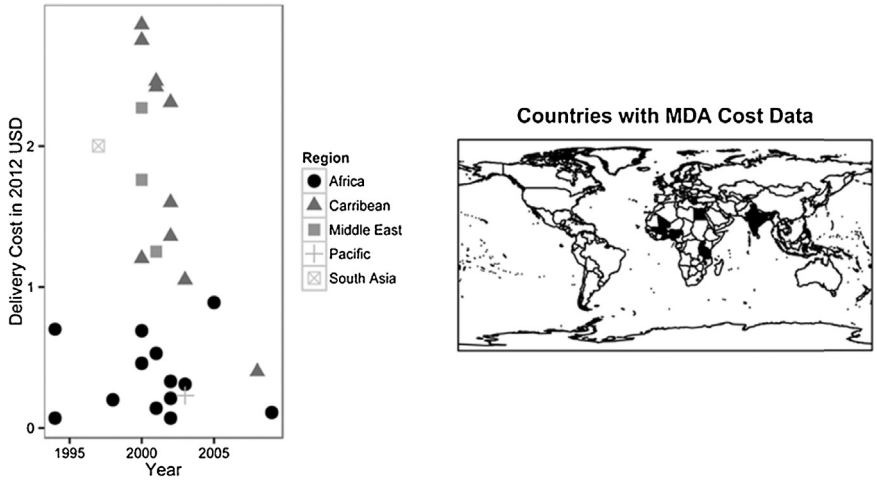

Fig. 2. Mass Drug Administration costs per person treated (not including drugs) for onchocerciasis and lymphatic filariasis.

3.2.2. Treatment costs

Capturing data on representative treatment costs is difficult due to the use of traditional healers, the frequency of in-kind payments for treatment, and frequent lack of appropriate microfilarial drugs. Below is information from the literature on costs associated with the treatment of different clinical conditions associated with LF.

3.2.2.1. Hydrocele. In general, actual expenditure on treatment for hydrocele tends to be relatively low due to limitations in the types of treatment available and the infrequency of surgical reduction of hydrocele. In practice, most patients do not seek surgery due to its relatively high cost or lack of availability, although in many instances, hydrocele treatment in public facilities is performed at no cost to the patient. A study in urban areas of southern India found that hydrocele patients seeking treatment (other than surgery) paid on average between US$1.81 and US$5.63 per treatment seeking episode; this was estimated to be 1.5–4 times higher than the daily wage (Nanda and Krishnamoorthy, 2003). A 2002 study among rural Indians reported non-surgical treatment costs between US$0.14 and US$25.39 (Babu et al., 2002).

The average hospital stay for hydrocele surgery is between 4 and 12 days; surgical costs incurred thus vary as a function of duration of stay and procedure required. Surgical costs have been estimated between US$5.40 and US$64.73, depending on the setting (Addiss and Brady, 2007). A study by Ramaiah et al. (1999) in India reported costs between US$6.60 and US$18.36 for surgery in public hospitals and between US$19.67 and US$61.63 in private hospitals. Studies in Ghana report US$41.00–48.00 in costs (Gyapong et al., 1996, 2000), with costs ranging between US$41.00 and US$82.00 when performed by non-governmental organizations. This same study found that other costs associated with surgery were also important, including transportation costs (US$27.00–41.00) and food (Gyapong et al., 1996). In general, costs for treatment of hydrocele associated with acute filarial lymphangitis (AFL) are relatively low, given the limited supportive treatment measures available (Ahorlu et al., 2001).

3.2.2.2. Lymphoedema. In general, estimates of cost related to lymphoedema treatment vary widely. Chu et al. (2010) estimated US$1.11 per treatment globally, with a range of US$0.32–5.93. A study among weavers in India reported treatment costs between US$1.53 and US$182.13, with an average annual treatment cost of US$11.41 (Babu et al., 2002). A second study in India reported US$0.73 per visit on average, representing more than half of the daily wage for the study population (Nanda and Krishnamoorthy, 2003). While acute dermatolymphangioadenitis (ADLA) infection treatment related to either lymphoedema or hydrocele does occur, most of the costs are indirect in the form of lost productivity. Cost related to antibiotic soap, antibiotics and support groups are the main direct costs (Addiss and Brady, 2007), although specific price data were not found.

3.2.2.3. Adenolymphangitis (acute) ADL. A longitudinal case–control study in India reported treatment costs related to ADL (secondary infections) included medicine (69% of total), consultation costs (9% of total), travel (5.1% of total), self-medication costs (11%), food and stay costs (4% of total) and costs incurred by individuals traveling with the patient (3% of total) (Babu and Nayak, 2003). This same study found that the overall expenditure was US$0.22 per episode, with treatment at public health centers approaching US$0.51 and US$2.67 at private facilities. Local healer costs were reported to be US$0.12, while self-medication was estimated to cost US$0.01. Ramaiah et al. (1998) reported costs of US$0.10–1.34 per treatment; medicine and physician consultation comprised 83% of the costs. A similar year-long case–control study reported an average cost of US$2.75 per year for those with chronic ADL (Ramaiah et al., 1999).

3.2.3. Vector control costs

In rural and urban communities in a district of Orissa, India, the mean monthly expenditures on personal-protection measures such as coils, sprays and bed nets were US$2.51 in urban households and US$1.83 in rural households (Babu et al., 2007). Other studies in rural India found that integrating vector control with MDA was much more expensive per person than providing MDA alone, as measured by both per capita cost of implementation and cost to reduce the prevalence and intensity of microfilaremia (Krishnamoorthy et al., 2002).

Most of the costing literature on vector control for mosquito borne disease has historically focused on malaria prevention. Given that indoor residual spray (IRS), LLIN use, and to some extent larvicidal interventions may be operationally very similar whether LF prevention or malaria prevention is the goal, additional information on the cost of vector control can be found in a systematic review of the costs of malaria prevention interventions (White et al., 2011). Only one study was identified that quantified a community's willingness to pay for LF transmission prevention or treatment (Rheingans et al., 2004), although the results are not presented here. No studies were found on the cost of polystyrene beads for larval control.

3.2.4. Cost of diagnostic methods

Two studies were identified quantifying the cost of diagnostics. One study estimated the cost of examining 20 μl of blood to be US$0.06 per slide in rural areas of India (Das et al., 1995). A second study in Sri Lanka quantified the recurrent cost of immunochromatographic test cards (ICT) to be US$3.66 (Chandrasena et al., 2002). Additional information relevant to malaria may be useful for exploring the relative costs of diagnostics for LF. Microfilariae can be identified using similar staining and film preparation procedures as those used for malaria microscopy.

3.3. Economic burden of disease and indirect costs for onchocerciasis

Onchocerciasis produces socioeconomic costs through several pathways. The direct costs of treatment or prevention of the disease reduced labor productivity due to severe pruritus, reduced visual acuity, blindness, reduced productivity of caretakers of those blinded by the disease, and reduced physical capital productivity when land is not used due to disease. There is limited quantitative evidence on the actual amount of lost productivity resulting from blindness due to onchocerciasis; one case–control study in Burkina Faso found that visual impairment and blindness were associated with reduced mobility, reduced odds of being married, increased household food insecurity, and reduced likelihood of active occupational status (Evans, 1995). A cross sectional study undertaken in Cameroon, Nigeria and the Democratic Republic of the Congo (DRC) found that individuals believed that ivermectin treatment increased participants ability to work, and improved school attendance (Okeibunor et al., 2011). Kim et al. at the World Bank (1997) studied productivity of workers on a coffee plantation in Ethiopia and demonstrated reduced earnings among workers with severe onchocercal disease when compared to workers without onchocercal disease, despite the fact that the diseased workers had an average of two more work days per month.

In addition to direct studies of the economic costs of onchocerciasis infection, multiple cost–benefit analyses (CBA) have also been conducted. These studies were largely carried out in the early to mid-1990s toward the end of the Onchocerciasis Control Program (OCP) and have been reviewed previously (Waters et al., 2004). These studies include increased labor productivity and earnings due to prevention of blindness as benefits, which in most cases was assessed by estimating averted cases of blindness and scaling by the average annual earnings for the relevant population assuming that in the case of blindness earnings would be reduced to zero (Benton, 1998; Benton and Skinner, 1990; Haddix, 1997; Kim and Benton, 1995; McFarland and Murray, 1994). Only two of these studies were published in peer-reviewed journals (Benton, 1998; Benton and Skinner, 1990). Other studies have included economic benefits of increased land use, however these studies have not been peer-reviewed and the methods for estimating the area of land and increases in productivity resulting are likely to be speculative. None of the CBAs included the costs of donated ivermectin in their base case analysis (Waters et al., 2004). While all CBA found favorable Internal Rates of Return (IRR) and positive Net Present Values (NPV) for the OCP and African Program for Onchocerciasis Control (APOC) programs, none included the valuation of donated drugs. A sensitivity analysis conducted by Waters et al. (2004) indicated that inclusion of the drugs donated by Merck in only one year, valued at market prices, would outweigh the economic benefits of the OCP and APOC programs over the entirety of their lifetimes.

In the America the consequences of the disease are similar to those that occur in Africa. No studies of the economic impact of the disease in the America were identified in the peer reviewed literature.

3.4. Costs of interventions used in control, treatment and elimination of onchocerciasis

3.4.1. MDA

MDA with ivermectin is the mainstay of all current onchocerciasis control and elimination programs. Treatment is one dose either once or twice per year administered to all non-pregnant adults and children >15 kg. Treatment with a four or six week course of doxycycline is also possible where loaiasis co-endemicity exists. Several studies have estimated the costs of MDA either as part of the APOC or OCP programs. MDA delivered by national mobile teams is likely more expensive than delivery by CDDs. A WHO report estimated the costs of MDA with mobile teams to be higher than with CDTi (Amazigo et al., 1998). Several studies have also examined willingness to pay for ivermectin administration and concluded that the delivery and administration could be affordable if financed on a cost recovery basis, as willingness to pay ranged from US$0.06 to US$1.25 (Onwujekwe et al., 1998, 1999, 2001). Fig. 2 illustrates the financial cost per person treated using MDA from all available data sources for both LF and onchocerciasis control. Onchocerciasis specific estimates constituted only a fraction of the available data points ($n = 5$ of 29 estimates for LF and onchocerciasis combined; mean = US$0.46).

3.4.2. CDTi

Several studies have estimated the costs of MDA using a CDTi approach. One study estimated the costs of CDTi in Nigeria as a financial cost of US$0.20 per person, with aggregate costs of US$0.29 (Onwujekwe et al., 2002). A second study estimated the costs of MDA with ivermectin distributed through CDTi in Uganda to be between US$0.40 and US$0.52, but ranging from US$0.13 to US$1.20 across districts (Katabarwa et al., 2002). The main driver of the variation was thought to be the size of the population, suggesting there may be economies of scale when CDTi is conducted in more heavily populated areas. WHO studies in the early 1990s estimated CDTi costs per person per year from US$0.07 to as high as US$6.96 in some situations; these costs were generally estimated to be lower using the CDTi approach as compared to mobile teams hired by the OCP program (Amazigo et al., 1998). Evans et al. (2011) estimated the costs of treatment to be lower when onchocerciasis treatment was integrated with LF, schistosomiasis and soil transmitted helminth infection treatment with TDA. Ndyomugyenyi et al. (2007) demonstrated that both economies of scope and scale exist with integration of multiple treatments and in more dense populations.

3.4.3. Treatment

Treatment for acute onchocerciasis infection is largely through the administration of ivermectin in areas with no loaiasis endemicity. Ivermectin is currently donated by Merck® pharmaceuticals at no cost to the APOC program. However, the unit cost of a dose of ivermectin is currently estimated at US$1.77 (Coyne and Berk, 2001; Waters et al., 2004). Additional treatment options include the treatment of symptoms, such as pruritus, and surgical excision of nodules. No peer reviewed studies examined the costs of symptomatic treatment directly or the costs of the surgical excision of nodules. In areas with low onchocercal infection rates and relatively high loaiais infection rates the administration of a six week course of doxycycline targeting the sterilization of adult female worms is indicated for treatment instead. Only one peer reviewed study estimated the cost of this regimen. However, mechanisms to deliver such therapy are likely to resemble those used for ivermectin treatment, except with more extensive follow up. Evidence indicates that such a delivery mechanism could be effective for the administration of a six-week doxycycline course (Wanji et al., 2009). While no specific studies of costs for the treatment of *Wolbachia* were

identified, one study in Cameroon (2006–2008) estimated the cost of a 6 week doxycycline treatment for onchocercal infection to be US$2.77 (Wanji et al., 2009).

3.4.4. Diagnosis

Diagnostics can be used to target treatment to only infected individuals in the context of medical approach to symptomatic disease, and additionally diagnostics are used during prevalence surveys to determine levels of endemicity of the disease for the purpose of targeting control programs and MDA campaigns.

Several methods for the diagnosis of onchocerciasis are available. These are nodule palpation, skin snip examination, nodulectomy, DEC patch test, enzyme linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR). In practice however, survey and field control programs have relied heavily on nodule palpation and skin snips for diagnostics in prevalence surveys. Data on the costs of the various testing measures is lacking. No specific studies of the cost of diagnostics have been conducted. One study reported that integration of loaiasis mapping and surveys with onchocerciasis mapping and surveys could reduce the cost, compared to conducting either mapping and survey exercise alone through economies of scope, but provided no actual cost data or evidence of this (Tekle et al., 2011).

3.4.5. Vector control

Vector control is currently only important for onchocerciasis in very limited areas. Only a limited number of studies include any cost estimates for onchocerciasis larval control; as such, any attempt to estimate these costs will require review of OCP Program records, primary data collection, or theoretical budget estimation. Relatively little literature has focused on the direct costs of vector control; however, as these approaches were part of the original OCP, several of the cost–benefit and cost-effectiveness analysis of that program include examinations of vector control costs as a component of total program costs. However, the one peer reviewed analysis of the costs of the OCP Program fails to break out the cost component by any line item other than total expenditures and thus provides no information useful for the estimation of unit costs of vector control approaches (Prost and Prescott, 1984). Though vector control was a mainstay of the OCP program historically, today most control and disease prevention for onchocerciasis is conducted through MDA campaigns.

4. Integration of NTD control and health systems impact

4.1. Opportunities for integration of NTD prevention and control

Integration of NTD prevention and control programs with other public health programs or interventions has become a goal in many settings (Gyapong and Twum-Danso, 2006; Molyneux and Nantulya, 2004). That being said, integrating NTD programs into health care systems poses challenges, although natural synergy does exist between many NTD control programs. The rationale for integration is based on the following: ivermectin and albendazole are highly effective for treating LF, as well as onchocerciasis and intestinal worm infections (Gyapong and Twum-Danso, 2006); LF control via GPELF is already an integrated program, especially in areas where albendazole is being used in combination with ivermectin and DEC; there is already evidence that LF treatment has positive effects for reducing the prevalence of hookworm and ascaris infection under programmatic settings (De Rochars et al., 2004); and lastly, MDA programs are already popular and well received in many communities.

Other rationales include the potential efficiency gains of integrating MDA against LF, schistosomiasis, soil-transmitted helminthis (STH), and other NTDs (Lammie et al., 2006). Given that the programs use the same public health framework, target similar communities, and often target similar age groups, integration could potentially save donors and programs both time and money. In Nigeria, integration has already occurred, whereby ivermectin, albendazole and praziquantel are distributed by community health workers in areas where LF, STH and schistosomiasis are co-endemic (Hopkins et al., 2002). In Zanzibar, STH and schistosomiasis control activities have been implemented after an LF elimination campaign, effectively de-worming participants at a 6 month interval (Mohammed et al., 2006).

There are also promising synergies between LF elimination and integration with malaria and dengue programs; this integration could improve the sustainability of all programs via cost-sharing. There are very few papers documenting processes to integrate LF or onchocerciasis control with other vector born disease control strategies. Blackburn et al. (2006) used cross-sectional data to describe an integrated campaign (bed net distribution with ivermectin/albendazole treatment) in central Nigeria. These authors observed improvements in net ownership and use, with no adverse influences on the MDA campaign. Studies in the Pacific have already documented LF elimination in areas where vector control was used to combat malaria. In these areas, DDT and indoor residual spray strategies were highly successful at reducing vectorial capacity for both LF and malaria (Burkot et al., 2006). Given that many of the LF vectors also transmit other infectious agents (e.g. malaria parasites, dengue virus) the use of indoor residual spray and insecticide treated nets may also be viable synergistic approaches that could be explored further (Burkot and Ichimori, 2002).

4.2. Health system implications of NTD prevention and control

A number of identified publications contained discussions relevant to health systems (i.e. organizations, institutions, people and resources that deliver health services to target populations); however, very few of these publications contained primary quantitative or qualitative data on factors related to health systems or health systems strengthening. The evidence base included one survey of CDDs of ivermectin in Nigeria (Emukah et al., 2008); a large multi-country study commissioned and conducted by the Tropical Disease research Program (TDR) of the WHO to investigate the sustainability of existing CDTi programs (Brieger, 2000); a multi-country study also commissioned by TDR on the inclusion of other activities in the portfolio of CDD (TDR, 2003); and several specific case studies of the health system and management implications and interactions of onchocerciasis control.

No specific studies of health information systems were identified. While surveillance is likely to become increasingly important as countries approach elimination of onchocerciasis, strategies for the surveillance of onchocerciasis are likely to be geographically and technically focused on estimating transmission intensity and prevalence of parasite infection and will require specialized surveys which are implemented outside of routine health system activities. Integration of these activities could potentially be used to build capacity within the health system but are unlikely to be used to improve routine health statistics.

No specific studies of the human resource implications of onchocerciasis elimination activities were identified. However, the integration of other health products and interventions into CDTi delivery and in the integration of CDTi activities into the routine health system both are likely to carry implications for human resource use and development. On the one hand, the use of CDDs for the delivery of other health interventions has been attempted in many onchocerciasis programs with considerable success reported. On the other, at higher levels human resources may be attracted from the public sector to non-governmental organizations (NGO) or other organizations which directly support vertical campaigns

and interventions and offer better pay or working conditions. While this may be limited to higher levels of the health system there is also evidence that the volunteer (unpaid) method for recruiting and retaining CDDs may lead to eventual attrition (Emukah et al., 2008). This finding raises concern that if additional interventions are added to the portfolio of the CDDs that higher attrition rates may result. However, there is some evidence that many CDDs are already involved in such additional health activities and that when these do not take up significant amounts of time that they may enhance CDTi programs, especially if, as is the case with EPI activities, they allow the CDDs to benefit financially from their role as agents of health promotion in the community (TDR, 2003). Either way, it will be important to consider several key components needed to ensure successful integration and health system strengthening, including adequate training of managerial and technical staff, regular supervision, support, acceptance of integration and re-orienting the role of health care personnel to accept an integrated program (Baker et al., 2007).

No specific studies of the effect of the onchocerciasis program on the delivery of other essential medicines or technologies were identified. However, access to ivermectin should be considered essential in the context of endemic communities; ample evidence exist that document the impact of the MDP, OPC and APOC programs on the access of rural impoverished populations to this essential medicine.

The provision of ivermectin though CDTi offers opportunities to extend service delivery though the incorporation of other interventions delivered by the existing network of CDDs, or by reaching populations with minimal interaction of access to the health system through the CDD network (Haddad et al., 2008; Hopkins, 2009; Mbanefo et al., 2010). Studies of sustainability and service delivery under the CDTi system have indicated that most CDDs are involved in health activities beyond those of the CDTi program (TDR, 2003). While high quality randomized community control trial evidence of the ability of CDDs to offer extended services and its impacts on service delivery of specific interventions is lacking, there is a high probability that the extensive systems already developed offer opportunities to extend services to populations with little previous access. Furthermore, integration of these systems into the routine health system may offer possibilities to improve service coordination and reporting at remote rural and underserved areas of many SSA counties (Homeida et al., 2002). While some risk of "brain drain" of health cadres into the direct vertical delivery systems is possible – as the majority of the delivery mechanism for ivermectin is community directed – this risk is most prominent at higher health system levels and likely of minimal general impact.

Although several studies have been conducted comparing the effectiveness of community directed treatment versus the traditional use of health systems to deliver drugs to the community, there is a paucity of generalizable studies to inform service delivery strategies. Cross-sectional data in India show that while community directed treatment was effective (reaching 68% of the population across 90% of the villages with 53% compliance), the health system approach was more effective; when the health system delivery strategy was used, DEC reached every village and covered 79% of the population with 59% compliance (Ramaiah et al., 2001). A second study in urban India found that the use of community health workers increased coverage and compliance of DEC by 30% (Ramaiah et al., 2006). In Ghana however, the results were reversed. Gyapong et al. (2001) showed that community directed treatment was much higher than the traditional health system approach (74.5% versus 43.5%). These authors also showed that health system coverage was extremely poor in villages further than 5 km from a health facility; these results suggest that in this context, community directed treatment could work where populations have poor access to health facilities. A prospective cross-sectional study in Kenya demonstrated that community directed treatment plus health system delivery was much more effective than health system delivery alone (Wamae et al., 2006). In this study, treatment coverage of individuals was significantly different between arms, whereby the health system delivery approach alone achieved 46.5% and the combined approach 88%.

5. Discussion

This paper reviews the evidence base on the costs, economic impact, and the health systems implications, of LF and onchocerciasis prevention and control. This information is important to inform donors and programs of the strategies that are available and their relative implementation costs across diverse settings. There is a wide range of unit costs presented, representing diverse study methodology and contextual factors interacting with the local landscape to influence cost. Importantly, this review lends insight into opportunities for possible synergies related to integration of programs and health system strengthening; both of which could reduce the relative cost of elimination of each disease. A major challenge however, is the paucity of literature available on integration and health system strengthening strategies.

Much of the literature on the costs of control and treatment for these diseases is dated, there is also a general lack of standardization in the presentation of cost estimates; the methods for presenting results and the criteria for including specific costs also lack standardization. Many studies do not adequately specify whether economic or financial costs were presented; nor do they adequately identify all of the inputs included in the study, define the year and currency in which results are presented, or identify the time period during which data were conducted. Due to these methodological variations direct comparison of many of the results is challenging.

Given the age of many of the studies identified, their usefulness for planning, cost estimation or for comparison of cost and cost-effectiveness among different interventions and studies is further limited by the need to make large adjustments to costs for inflation and for collection of data in different currencies, environments and time periods. While it appears that onchocerciasis and LF are a major source of disease burden in some areas of the world, the ability to use this literature to generate estimates of the global economic burden of onchocerciasis and LF and for prioritizing interventions for their prevention and control across different settings is highly limited. In the context of large expansions in funding, up to date information on the costs, burden and cost-effectiveness of different interventions and especially the cost and cost-effectiveness of integrated programs is urgently needed.

6. Conclusion

Onchocerciasis and LF are important sources of economic burden, disease and disability in affected areas and individuals. In some countries they may have large effects on general productivity. Unfortunately, the literature available on costs and cost-effectiveness of interventions is generally older, extremely focal geographically and of limited usefulness for developing estimates of the global economic burden of these diseases and prioritizing among various intervention options. Up to date information on the costs and cost-effectiveness of various interventions for LF and onchocerciasis primary and secondary prevention are urgently needed in the context of vastly expanded funding for the control and elimination of these diseases. This is especially the case for integrated programs which have been strongly promoted but little studied or implemented to date.

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