Eliminating Lymphatic Filariasis

A View from the Field

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Among infections closely associated with poverty, lymphatic filariasis (LF) is a study in contrasts. It is both a consequence of and a contributor to poverty. Although rarely fatal, it is recognized as a leading global cause of lifelong disability as well as significant personal, social, and economic burdens coincident with disease. Infection is often considerably more prevalent in communities than the number of cases of overt pathology for which LF is best known (lymphedema, elephantiasis, and hydrocele). With an estimated 120 million to 130 million affected persons in 83 countries and 1.25 billion persons living in areas at risk, in some countries LF may be expanding its range, whereas in others, with economic development, it has disappeared with little if any targeted intervention. The transmission cycle is relatively inefficient, yet an association with pockets of deepest poverty remains tenacious. Thanks to scientific advances in diagnostic tools, and particularly in control strategies focused on large-scale drug donation and mass drug distribution programs, scientists and policy makers now consider LF eliminable. Together with new approaches for morbidity control, a hopeful tone surrounds a disease problem that as recently as two decades ago could easily have been categorized as among the most neglected of neglected diseases. Continued progress toward global LF elimination will require solutions to potential obstacles in the most challenging—that is, the poorest—endemic settings. This chapter reviews progress toward LF elimination and some of the remaining challenges from a perspective in Haiti, the only least developed country of the Americas.

Key words: **lymphatic filariasis; hydrocele; lymphedema; elephantiasis; poverty; disease elimination; mass chemotherapy; rapid diagnostics; drug donation; Haiti**

Introduction

Lymphatic filariasis (LF) is a vector-borne infection whereby human hosts are parasitized primarily by three species of filarial nematodes: *Brugia malayi*; *Brugia timori*; and for more than 90% of the total cases worldwide, *Wuchereria bancrofti*. An estimated 130 million people[1] are affected in 83 countries, including those infected and those with overt disease but no longer infected. Several genera of mosquitoes serve as obligatory hosts, supporting development and transmission of the parasites in a variety of settings. For *Brugia* spp. in Southeast Asia, the main vectors are of *Mansonia*. For bancroftian filariasis, *Culex* predominates in urban and semiurban zones, *Ochlerotatus* for subperiodic forms, *Anopheles* in more rural settings of Africa and Asia, and *Aedes*, also for subperiodic parasites across many Pacific islands.[2] Once in the human host, the parasite undergoes further development to adulthood, nesting in the lymphatic system. Typically these will mate, with females producing many microfilariae (MF; first-stage larvae) that are shed in the lymphatic system and eventually into the bloodstream. From there, MF are transferred to vectors during blood feeding by female mosquitoes. For microfilaremic individuals, usually there is at least asymptomatic disease.[3] The infection is often acquired during childhood, and damage to the lymphatic system and the kidneys may begin at this time.[4] For those persons who progress to more serious clinical manifestations, these are most

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Ann. N.Y. Acad. Sci. 1136: 53–63 (2008). © 2008 New York Academy of Sciences.
doi: 10.1196/annals.1425.036

commonly caused by pathology related to adult parasite secretions; inflammatory reactions associated with the death of adult worms; secondary infections; or for those who live long enough, simple failure of collateral lymphatic vessels. The consequences can be profound and debilitating, with the most serious of these being disabling localized febrile episodes or acute attacks (once known as filarial fevers), chronic lymphedema/elephantiasis, chyluria, and urogenital manifestations in men, such as hydrocele, lymph scrotum, and elephantiasis of the penis or scrotum.[2]

With the increasing application of single-dose, nontoxic drugs that often clear MF and suppress parasite ovoviviparity for up to a year, thereby interrupting transmission of the infection, momentum grew during the 1990s for the concept of LF as an eradicable disease. Today, LF is among only six infections considered potentially eradicable or eliminable.[5] In 1997, when the 50th World Health Assembly passed a resolution calling for the elimination of LF as a public health problem, it rightly noted with concern the “widening spread and increased distribution” of the disease, as well as its “impact on all ages, both sexes, and people living in urban and rural settings alike.”[6,7] What was not mentioned explicitly was a tenacious link with poverty that this disease exhibits as much as any other. Although LF and its devastating sequelae do cross sex, geographic, and population density categories, the broad epidemiological indicators and local distribution of clinical disease suggest that it does not occur outside the lower socioeconomic categories. Relatively few exceptions to this observation typically involve infection and disease caused by circumstances of long-term travel to endemic areas, previous long-term exposure in endemic zones, and/or military duty.[8–10] Linkage of infection to an economic cline is strong; for those unusual endemic zones where there exists both poor and upper-class housing adjacent to one another, rare are reports of LF among the people of means. If a resident from the upper socioeconomic levels did become LF infected, such a scenario would leave that person an accidental, dead-end host; such an individual would be unlikely to contribute to further transmission because of access to microfilaricidal drugs, insecticide-treated bednets (ITNs), window screens, or air conditioning.

There are relatively few reports in the literature about the relationship between economic status and LF infection at the local level. In Leogane, Haiti, a study failed to show an association between lower tuition and *W. bancrofti* infection among schoolchildren,[11] but limited socioeconomic differentials within that community may have made the tuition indicator insensitive across a relatively homogeneous population in a least-developed country (LDC). In a community in the Philippines, a link was seen between markers of wealth (when compared to the overall population) and freedom from LF infection as detected by MF prevalence and disease.[12] Another study in Sri Lanka indicated differentials between low- and high-income persons with respect to health-seeking behavior of diseased persons, protection from stigma, and effect on the economic fortunes of affected families. For this study, the high-income category included individuals earning US$25/month, so such descriptors in LF-endemic areas are relative.[13] For a look at broader economic associations with LF within one country, turn again to the Philippines (a country with 79 provinces): 30 (77%) of the 39 provinces with a poverty rate higher than the national average were LF endemic.[14] At the global level as well, evidence for association of LF with poverty is available. For example, across all those countries classified as LDCs in 2002 by the United Nations, 32 (84%) of 38, possessing 86% of the population total for all LDCs, were endemic for LF.[15] If anything, these national and international assessments are perhaps biased to underestimate the effect of communicable diseases such as LF.[16]

Perusing the known infections of humans,[17] it is difficult to identify many other single, widespread etiologic agents of chronic disease so nearly exclusively associated with deepest poverty. The relationship between LF and poverty is strong, bidirectional, and complex, and the links between LF and poverty are evident if not yet thoroughly documented. Our discussion covers some of the aspects and reasons for this association, as well as how science contributes both to an understanding of these dynamics and helps point the way for permanent remediation through the elimination effort.

Lymphatic Filariasis as Consequent to Poverty

Culex mosquitoes exhibit a strong preference for larval habitats rich in organic content. Often such breeding sites are polluted by excreta from animals and humans or by waste from breweries, food processing, or textile processing. Although latrines can represent a significant source of *Culex* LF vectors, sanitation deficits experienced by billions of people include poorly designed or poorly managed (and often undesirable and therefore underused) latrines or no latrine access whatsoever. Poverty and governmental inadequacies lead to such waste management failures; indeed, 40% of the world’s population (~2.6 billion) does not have access to latrines or any decent sanitation, and

FIGURE 1. In the tropics the most degraded environments are often linked with poverty, and with lymphatic filariasis. (In color in *Annals* online.)

in our Latin American/Caribbean Region as an example, only 14% of all wastewater is treated.[18] Such circumstances of poverty contribute to open defecation and additional multiplication of vector breeding sites, when for instance, rainwater collects in untold numbers of depressions behind buildings or between rows of banana trees or sugar cane stands that have become informal, semiprivate latrines. This state of affairs can be compounded by the rapid, unplanned urbanization increasingly seen in poor countries. Although some progress in waste management has been made, population increases and migration patterns exacerbate problems faster than solutions can be implemented. This context of poor sanitation gives the peculiar landscape epidemiology of *Culex*-transmitted LF a role as driver for the most important causal connection between poverty and LF. Indeed, about 57% of the global LF disability burden[19] occurs where LF is transmitted by *Culex* mosquitoes, and although human densities in urban settings also probably play a role in enhancing transmission in these places,[20] vector breeding preferences are undoubtedly a key factor. For these areas, LF disability can be regarded as sanitation-related disease. Other linkages of poverty with the tropical house mosquitoes (so called because of their anthropophilicity and ubiquity) and their transmission of LF include lowered land and rental values of housing and work sites near degraded environments (where *Culex* breed); these economic factors tend to concentrate the poor. Comorbidities with poverty and degraded settings, such as water-borne illnesses, may leave people who are ill less likely to exhibit antimosquito defensive behaviors and strategies, and there are in these zones reduced levels of government services and access to health and education, each of which in many ways hinders avoidance of LF. Risk factors for overt LF disease manifestations consistently linked with poverty include illiteracy and poor hygiene.[21]

In Haiti and elsewhere, the degree to which the degraded ecology (Fig. 1) may support increased incidence of LF contrasts with a potential contribution to declines in other vector-borne diseases. Such deforested and polluted environments may no longer be able to support habitats for snail vectors of schistosomiasis (Haiti has none) or adequate habitat for anopheline vectors, leading to declines in the malaria parasites that they transmit.[22]

For other pairings of vectors and lymphatic-dwelling filaria, poverty-associated drivers of infection and transmission are less clear but do occur. Abundance and output of vector breeding sites tend to show an inverse relationship to the local level of economic development—even if not as dramatically as for *Culex*; discarded byproducts of agricultural work, proximity of arboreal vector habitats to workplaces for day laborers, and undesirable swampland are risk factors that place the poor at higher risk for LF.[20] The introduction of irrigation can increase particularly the number of *Anopheles* larval habitats, and although this is a positive indicator of land use and economic development that has been associated with an increase in LF, it may also involve increased human density and local introduction of new infections as influxes of the unemployed poor looking for work arrive in the vicinity. As for all vector-borne infections and especially those that (like LF) are more commonly transmitted at night, household and lifestyle features associated with development can minimize mosquito exposure and infection for people. Possibilities include access to environmental manipulation; physical and/or chemical barriers, such as ITNs and window screens; and other public and private vector-control measures, including reductions in mosquito breeding sites via everything from information/education/communication campaigns to modern water and effluent management or high-rise living, or even the ubiquity of televisions and air conditioners. Each of these mitigates vector–human contact as quality of life improves. Without these, LF may thrive in the community. With the current interest in climate change and changes in particularly tropical disease distributions that might accompany it, any discussion of LF would have to be prefaced by the observation that the principal worldwide vector of LF, *Culex quinquefasciatus*, has of late aided in the expansion of the range of the West Nile arbovirus by serving as vector across large portions of temperate North America. So this vector of LF is already present in temperate zones; the more critical ingredient for cycling of LF is abject poverty and the conditions that accompany it, such as those discussed.

There are, if you will, biological and structural reasons that poverty supports LF. First, the cycle of LF transmission is inefficient. With the required development in each host, adult pathogen numbers in the definitive human host are limited to the number of third-stage larvae that may establish an infection and the quantity of worms in the mosquito host limited to that number taken up during engorgement. Although many MF are produced in the human host, tremendous wastage marks each subsequent point in the cycle; few of the MF end up in a mosquito, still fewer survive to become infectious third-stage larvae (many mosquitoes do not live to support this transition), and few of the infectious larvae successfully penetrate a human host to migrate, develop, and nest with a mate to continue the cycle. These inefficiencies require that there be a substantial number of possible contact points between humans and vectors for maintenance of the cycle.[2] These contact points between the human and vector occur with great frequency only in the ecosystems of human poverty. The population and migration dynamics of our rapidly changing world may be increasing the prevalence of these sorts of contexts and the number of persons living in them.[23] Second, there are a variety of inequities and challenges for the poorest countries and communities that adversely affect public health overall and help specifically to maintain LF as a threat. The "brain drain" phenomenon, the failure to decentralize and other critical impediments to functioning health systems that plague many governments, or market and trade barriers for drugs and diagnostics are among several such systemic and structural issues that deprive the poor of their right to health. The very poverty associated with victims of LF and other diseases of poverty typically leaves those affected relatively voiceless in priority-setting and budgeting processes for health policy, and even in the philanthropic/charitable communities, exacerbating inequalities of access to preventive public health measures.

Any historic index of the cause–effect relationship between poverty and LF needs to include this striking fact: For at least one subtropical (South Carolina, USA) and one tropical (Northeastern Australia) locale, when the most extreme communal poverty was alleviated with economic development (and improvements in sanitation), active LF transmission disappeared without any specific targeted public health measures.[2,24,25]

Lymphatic Filariasis as Contributor to Poverty

There are a variety of ways in which infection and disease represent burdens that deepen poverty at the individual, family, community, and national levels. Because the prevalence and incidence of disease manifestations of LF vary worldwide with differences in vector–parasite pairings and local transmission dynamics, so too does the effect profile of LF morbidity as a contributor to poverty in different settings.[20] Acute and chronic LF disease may both lead to loss of productivity both at the workplace and in the home; loss of employment and wages; and significant and recurrent treatment costs. Each of these contributes to financial burdens on patients. Of acute manifestations, febrile episodes may last from 1 day to more than 2 weeks,[21] and total workdays lost may exceed this period. Secondary bacterial infections are the most common cause of acute attacks, and these reduce community-wide workforce availability at critical times during agricultural cycles because of synchrony of acute dermatolymphangioadenitis. In Haiti, increased risk of infection and disease within individual families has been demonstrated for children of LF-infected mothers,[26] and by some clustering of overt disease in families,[27,28] suggesting the possibility of LF as a sort of inherited medical and economic burden, even though LF is not vertically transmitted in the strict sense. People disabled by LF over many years also have increased risk of exposure to other infections and diseases of environmental exposure precisely because limited mobility or embarrassment confines them to zones of high risk.[13] For example, the same polluted water sources that contribute to local LF transmission may limit access to potable water for the disabled living nearby, adding to disease burden and economic hardship. Chronic LF disease isolates individuals not just economically and not just from communities but even within families. The economic disability, lost productivity, reduced possibilities for successful marriage, and even the repulsive odor associated with poor hygiene, as well as perceptions that the patient is a burden and an embarrassment, all affect prospects for patients and their families intergenerationally and over many years, disrupting regular dynamics of interaction and support networks so important in disadvantaged communities. Disease progression and increasing disability burdens are themselves in turn exacerbated by the condition itself, when patients are physically unable or unwilling to seek appropriate medical care because of shame, even when the care is free, and the condition worsens as a result.[13]

Notwithstanding recognition that standardization in determining the global burden of individual diseases via calculation of disability-adjusted life-years has been an important work in progress since 1990,[29–31] LF was in 1995 designated as the leading infectious contributor to the total number of disabled persons worldwide, ranked at that time second after affective disorders.[32] Later evaluations have placed the burden of LF calculated in disability-adjusted life-years at second among tropical diseases after malaria,[33] or sixth among parasitic diseases.[34] So it is fairly evident that among the poor, cycles of acute and chronic LF disability and dependence to an important degree maintain pressure to reduce economic opportunities for victims and, by extension, for their families and communities as well. These burdens are currently underappreciated—particularly at the local and national levels—for a variety of reasons.

Although acute episodes cause the most distress for affected patients,[21] it is logical that the chronic, disabling manifestations of LF disease, such as lymphedema, elephantiasis, and male genital involvement, represent significantly greater contributions to the overall disease and economic burden for individuals, communities, and nations. Worldwide, 40 million suffer chronic manifestations of LF,[35] and many of these people are disabled. These numbers are impressive, but this global estimate of 40 million persons with overt disease represents less than one-third of the number of persons infected worldwide (120 million to 130 million), most of whom suffer at least some subclinical disease. Couple how the infection manifests obviously in only a minority of those infected with the idea that because of social stigma and shame, many of those with chronic disease hide it (particularly the 25 million men with genital disease),[36,37] and effectively then, at the global scale, the full extent, effect, and risk of LF has long been qualitatively underestimated in communities. Moreover, that people in endemic communities may not realize that lymphedema and hydrocele share a common etiology,[38] or that there is confusion of hydrocele and hernia, may further reduce a sense of the total LF threat and burden. Considering finally the strong association of LF with poverty and the aforementioned political invisibility of infected and diseased persons, the wider public health community has only in recent years come to appreciate the real scope of LF and its effects on people's lives.[2]

Insensitive blood sampling for circulating MF was long the standard for assessing LF infection and transmission and was the principal approach for studying the epidemiology of LF. For most of the world, blood collections for thick smears had to be conducted at night owing to the nocturnal periodicity of first-stage larval parasites in the peripheral circulation. The development of field-friendly rapid immunochromatographic filarial antigen detection tests (ICT for *W. bancrofti*),[39] which can be administered at any time for a fairly sensitive assessment of infection prevalence, has led to a significantly improved picture of the extent of infection in endemic countries. With dramatically more accurate assessments of LF epidemiology pointing to greater burdens of subclinical disease, starting in childhood, a more complete elucidation of some of the social and economic costs has been made possible, helping to raise the profile of LF as a public health concern and disease of poverty in recent years.[2,40,41] In Haiti, presentation of results from the initial nationwide mapping in 2000 for *W. bancrofti* antigenemia suggested that transmission was ongoing in 88% of 133 communes.[42] Because the survey protocol called for testing at most a modest 250 children for filarial antigen in each commune and the districts where no antigen positive children were identified were not clustered, these results suggested that health officials would need to consider the entire country as being at risk for transmission. Before the survey, LF disease was well known to be particularly associated with a few pockets across coastal plains but was thought limited to those locales. Although these nidi for LF had been documented since the 1920s,[43] because of the widespread infection (and transmission) that became apparent with the use of ICT cards, some health ministry officials were initially concerned about LF as an emerging problem throughout the country. Ultimately, a more sober reaction to the findings prevailed: that the infection had probably been widespread for a long time. Nonetheless, official recognition of the extent of LF in the country probably helped to hasten a welcome administrative reorganization to create an office for LF elimination and a dedicated position for a program manager in 2001. Moreover, initial budgetary allocations during fiscal year 2002–2003, at least, set spending for LF elimination ahead of the budgets for malaria at both the central administrative/technical level and for six unified community health service districts.[44] Even where health systems are relatively sophisticated and well organized, notice of infection and transmission of LF can still be missed, potentially relegating LF in economically marginalized areas to a continued neglected status. Other means for identifying areas of LF transmission, such as collecting clinical assessments and/or for screening groups, such as soldiers at military bases, can be considered when possible.[45] Doing so can help avoid underassessments of the LF burden, which occur precisely because of poverty-associated weaknesses in local health system abilities. The development of the ICT antigen tests and social science work to document burden of disease and costs of lost productivity represent the types of steps critical to recognizing and documenting the true effect of LF and eliciting the kind of political will and investments that elimination efforts will require.

Moving toward Elimination

As a public health problem, LF has moved from being a widespread disease for which there were serious gaps in diagnostic capabilities and appropriate drug regimens—and one with only limited effective treatments overall—to the point today where there is good reason to believe that during this generation (1) transmission can be interrupted and the number of new infections brought to zero and (2) assistance delivered to the millions who do or (lacking preventive measures) would suffer the associated debilitations.[40] These twin goals have provided impetus for a change that has been largely scientific and philanthropic, aided as a political mechanism by a transnational initiative known as the Global Program to Eliminate LF (GPELF). The GPELF was founded and is supported by traditional leaders in public health, policy, and research, including the World Health Organization (WHO). After establishment in 1998, the GPELF was quickly attended by a global alliance of partners to support it. These programs, engaged with governments worldwide, have already brought about a coordinated series of achievements in a short time. Control and treatment strategies, and systems for monitoring and evaluation, have been developed and disseminated to governments. Accompanying this effort has been a critically important ongoing effort to define, prioritize, and address research questions and issues that arise during execution and expansion of the program, or those that have long been outstanding and might help yet lead to additional solutions. By 2005, there were active LF programs in 42 countries, where more than 381 million persons received chemotherapy designed to interrupt transmission.[40] It is argued that this is the fastest-growing international health intervention.[13] With the status of LF as a neglected tropical disease (NTD) and its being coendemic with poverty in many localities, ongoing advocacy, continuing nurturing of resources, and political will in both donor and affected countries are particularly critical aspects for continued progress. On the basis of the experience of the past 10 years, if there are questions about the potential for continued success, they would seem to surround the issue so often germane to problems of the poor; are these efforts and the will that underpins them sustainable through to the goal? Over the next years, will the GPELF (and other networks that integrate the GPELF goals) be able to identify, define the extent of, and extinguish remaining links of transmission where they may hide among program-noncompliant populations in the deepest recesses of poverty, perhaps through the chaos of social and political upheaval in many settings? Efforts to eradicate smallpox, polio, and dracunculiasis have enjoyed as hallmarks of success an overall, indefatigable persistence, unmistakably coupled with an informed and data-driven flexibility to adjust strategies in light of new insights and in different settings. Much the same will be required for the success of the GPELF.

Role of Science

Scientific understanding of the biology and dynamics of transmission, infection, and disease are the critical base upon which the concept of LF elimination has been built. Single-dose antifilarial mass drug administration (MDA) for 4–6 years with good population coverage is the most critical intervention of the GPELF. As in this example where drugs developed for the veterinary market were vetted for application in human medicine, science has rather recently given us an understanding to know both the challenges and possibilities surrounding a massive public health problem. The widespread global distribution of LF, diversity of vectors, unique features of the biology of the filarial parasites, the fact that it does not often kill, and particularly some of the points already highlighted regarding the lack of awareness about the effect of disease and the associations with marginalized populations have all been cited as possible challenges to elimination. In contrast, biological aspects of LF, such as that there are no reservoirs of infection, that the parasite must develop in both human and vector hosts (rendering both targets for transmission interruption), and the relative weakness of transmission are regarded as particularly favorable to the concept of elimination. Important scientific developments have provided the critical technical capacity needed for elimination, key among which include the tools to know where the infection is (ICT), and, as mentioned, the therapeutic drug regimens to eliminate MF and halt transmission through MDA (400 mg albendazole plus 6 mg of diethylcarbamazine (DEC) per kilogram of body weight, or albendazole plus 200 μg of ivermectin per kilogram of body weight in African countries where onchocerciasis is coendemic, for 4–6 years, or DEC-fortified salt for a shorter period).[2]

Definition of complementary measures to aid in control and the elimination of LF transmission, program monitoring, and evaluation are important parts of the scientific agenda for LF in the immediate future. Entomology provides opportunities for supplementing interruption of transmission via vector control (which may in fact be required in some endemic areas),[46,47] as well as for monitoring progress with tools, such as polymerase chain reaction–based xenomonitoring for parasite DNA in mosquitoes.[48] Further understanding must continue to be brought to bear on this program especially by social science—increasingly important for advancing past potential barriers to the success of MDA, such as systematic noncompliance, in maximizing the effect of training, education, and/or mobilization or via studies of program-associated costs–benefits and economic burdens on the diseased. Continued modeling studies of LF dynamics will also help with advocacy and with practical concerns, such as projecting or certifying endpoints for MDA.[49] The role of clinical research in defining the pathogenesis and really the first comprehensive approach toward reducing LF-associated morbidity has been absolutely critical for the inclusion of care for those disabled by LF as the second tenet of the GPELF mission.[2,3] Further research is needed into pipeline solutions, such as macrofilaricidal drugs or treatment that targets *Wolbachia* obligatory filarial endosymbionts; also, all widely used MDA drugs must be monitored for resistance.[50] These efforts may help provide for important adjuncts or backups for program strategies downstream. The recent release of the *Brugia malayi* genome will begin the process of providing multiple targets for exploiting weaknesses in LF parasites and their relationships with endosymbionts, humans, and mosquito hosts alike.[51]

Perhaps the most innovative role of science in the GPELF, and the subsequent integration of GPELF goals within integrated approaches to address multiple NTDs,[52] has been a key, successful role in advocacy. Beginning with the support and momentum provided by massive drug donations from GlaxoSmithKline (albendazole) and Merck and Company (ivermectin for African countries where LF and onchocerciasis are coendemic), scientists have been at the forefront of marshalling opinion and informing policy with hard data; one result is that the GPELF initiatives have been quickly embraced by governments and the donor community. Aware that because of the numbers of affected persons, large amounts of external support would be necessary even for relatively inexpensive interventions per person, the scientific community and particular institutions, such as WHO, have moved to fill roles often taken by governments in the poorest countries. The political silence of those affected by LF (previously discussed) has been replaced by scientists' serving as a proxy for millions of persons.

Strategic early benefactions from the Bill and Melinda Gates Foundation and others that supported initial implementation plus essential operational research proved to confirm the validity of certain aspects of the GPELF approach, thereby raising issues that must be addressed to ensure continued progress and ultimate success.[53] The transparency of documenting successes and failures, together with addressing challenging data in a straightforward fashion, has no doubt been constitutive to dramatic increases in support for GPELF implementation and overall momentum. Review articles, letters, and media-friendly "lay-speak" presentations and news articles have been many and well received; these have documented successes and challenges and served occasionally as a sort of public brainstorming forum—enhanced by the rapidity of publication afforded by new electronic journal options. There is no doubt that these fora and the strong tone of advocacy to some of these articles has not only increased awareness but also encouraged cross-national, public–private partnerships. More recently, such advocacy has helped movement toward integration of approaches and strategies for multiple NTDs that can be addressed via MDA (including LF) and that share certain characteristics and distribution, making them amenable to low-cost, highly effective, pro-poor programs. Again in the public forum, scientists have offered data that have served to contrast, compare, and discuss synergies of NTD work with the recent welcome, but more costly, initiatives to address human immunodeficiency virus, tuberculosis, and malaria.[13,15,30,52–70]

The Future

From our perspective in Haiti, it is essential that research underpinning the GPELF continue to answer challenges faced in reaching for the goal of LF elimination. We have seen significant progress in (1) scaling up MDA for LF and geohelminths to cover nearly all the zones of highest LF endemicity (and about one-half of all persons infected with LF), (2) offerings to address filarial morbidity at three referral centers, and (3) enhancement of health systems that has devolved from items 1 and 2. That an undertaking of this scale is a challenge that has been met and enjoys this degree of progress and support in a resource-poor LDC should not be underestimated. Moreover, political turmoil and insecurity, which have kept United Nations peacekeepers in Haiti since 2004, are obvious impediments to progress, although remarkably, these in no case halted the program even for a short time. Despite the earlier-mentioned prioritization of LF in the health ministry budget, the overall budget controlled by the Haitian government is so meager as to provide only partial support for ministry staff; there are no funds for any health programming *per se*. Ironically, recent infusions of large grants for human immunodeficiency virus, tuberculosis, and malaria have created dramatic inflation in the biomedical sector, particularly in the area of salaries for health professionals. Although this movement is welcome in that it will help to combat the brain drain, it is not clear what will be the more immediate effect on the overall health system (if these programs are not well integrated into the sector) and on the continued ability of more streamlined programs designed with sustainability as a priority.

Consequently, in this context and others like it, maximizing resources, overall efficiency, and achieving good coverage are basic requirements for any program, making essential the kind of monitoring and evaluation as well as careful operational research to understand problems and find solutions for problems as they arise. Such documentation can also help to ensure continued required donor support in settings where there may arise an almost automatic skepticism about the ability of any effort to reach 80% of the population amid an occasionally chaotic situation. For an example of a critical issue requiring further study in Haiti, we mention the importance of beginning to define endpoints for MDA with DEC and albendazole (the current primary strategy for the country's LF and geohelminth programs). These endpoints will vary for different settings around the world, with dynamics of different vectors, human host densities, and intensity and prevalence of infection, etc.; these variations may even be marked at the within-nation level. Because these dynamics change as transmission is reduced,[71] and because of differences in local force of infection, one approach to endpoints will probably not fit all settings, even when the vector, for example, is the same. Patterns to characterize these dynamics are not yet fully understood.

Some of these factors and others may be at work at one site in Haiti where despite only moderately suboptimal coverage (averaging more than 70%) through six annual cycles of MDA at lower elevations in the commune of Leogane, a recent 30-cluster survey found evidence of continued transmission, based on the detection of *W. bancrofti* exposure and infections in young (aged 2–4 years) children. Families of the positive children were queried as to residence since the child's birth, and all positive children were deemed autochthonous cases. Parsimonious explanations for this somewhat surprising finding include the following: systematic noncompliance, which was found among one-quarter of the population; human migration into the area after upheaval and insecurity across adjacent endemic zones; or that annual assessments of microfilaremia did not capture the degree to which higher infection rates contribute to either ongoing or recrudescent transmission. The full explanation is probably multifactorial. In any case, with transmission ongoing, some adjustment in strategy is called for at this local level and probably elsewhere in the country. Haiti is considering augmenting annual MDA in areas of intense transmission, namely, increased frequency of mass chemotherapy, increasing coverage through adding school-based distribution, enhanced vector control measures (through integration with malaria programming), and/or increased distribution of DEC-cofortified salt. Each option is attractive because of leveraged health effect on geohelminths, malaria, and dengue control or on iodine deficiency. The ultimate distribution of such packages will be tailored to some degree by ongoing operational research, something clearly critical for moving toward effective transmission interruption nationwide.

Much of the genius of the GPELF lies in its simplicity. The approaches to chemotherapy are straightforward and inexpensive—particularly because some drugs are donated. Local health workers, and especially community leaders, may embrace the effort partly because of their opportunity for a prominent role. With a programmatic focus on MDA with target zones and referral clinics for those disabled by LF outside the capital city, the Haiti effort was one of few nationwide health campaigns that continued on track despite upheavals and the deposition of a president during 2003–2006. In 2007, the Haiti LF program was by default the primary driver of deworming and domestic salt iodization alike—further testimony to its integrative potential. Haiti was recently ranked by Transparency International (http://www.transparency.org) as the nation most plagued by corruption. Apropos this, the relative simplicity and ability to adjust strategy on the basis of data leave the low-cost, highly effective, decentralized chemotherapy or ITN interventions associated with LF elimination by their nature highly accountable; if part of the program is not delivering, this will be readily apparent. In welcome contrast to the corruption story, the percentage of Haitians living abroad who send remittances to friends and family in-country is the highest in the world. Development experts repeatedly stress the important role of the Haitian diaspora in addressing the country's ills. Again here, that the LF program comprises basic public health measures that are nationwide and data driven and in this sense adjustable and accountable makes these activities attractive to support from the educated diaspora who, in this case, represent increasing influence and an important source of economic inputs to the country. There is a risk, however, inherent in this situation. An argument can be made that the simpler the intervention strategy, if and where the strategy performs at a suboptimal level, the greater the negative effect. Slight adjustments in strategy and unmonitored local variables can have inordinate effect on outcomes. Again then, the importance of monitoring and evaluation, as well as operational research, is highlighted.

Recent, timely initiatives by advocacy organizations like Research!America (http://www.researchamerica.org/pgr_society) are welcome in that they have begun to highlight and deliberately link the recent growth in funding for global health program initiatives with a need to maintain support for and enhance the research that will guide the way forward. Today's global health initiatives, though examples of appropriate technology for developing countries, are nonetheless products of various levels of the research apparatus. The same open-minded approach to generation of concepts in this arena must be maintained as shifts to programmatic activities scale up. Everything in the GPELF from serologic assessments of parasite exposure to program cost analysis are essential to maintain momentum. Implementation of programs with adequate operational research—and the data it produces—helps to build sustainability not just of programs but also the political will of policy makers in-country and donors abroad.

Conclusion

As a disease coupled with poverty throughout its global distribution, there are unique but surmountable challenges to the proposed elimination of LF as a public health problem over the next decade-plus. Science has played a key role in outlining possibilities for this historic opportunity by beginning to shed light on a complicated and heretofore poorly understood but widespread affliction and through devising simple concepts for interruption of transmission and care for the diseased. Science and pharmaceutical firms have also played unprecedented, effective roles in joining with WHO and other traditional stakeholders to create and sustain the GPELF initiative. Relying heavily on data to promote the logic of this remarkable public health opportunity, scientists have convinced particularly donors and governments of rising, developing-country economies of the value of deliverables; the rapid program growth for the GPELF over the last decade at low cost per head and with high efficacy for populations is testimony of its popularity. To match this success in the more challenging settings of the LDCs, where policy makers are faced with a myriad of priorities and few resources, a continued emphasis on program adjustments and advocacy based on field data may help to ensure that the GPELF goal is reached at the global level. This would represent a significant achievement in itself but also present a strategic near-term stepping stone toward fulfilling United Nations Millennium Development Goals and maintaining momentum toward amelioration of global health and economic inequities.

Conflicts of Interest

The authors declare no conflicts of interest.

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