

Translating Research into Reality: Elimination of Lymphatic Filariasis from Haiti

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Abstract. Research provides the essential foundation of disease elimination programs, including the global program to eliminate lymphatic filariasis (GPELF). The development and validation of new diagnostic tools and intervention strategies, critical steps in the evolution of GPELF, required a global effort. Lymphatic filariasis research in Haiti involved many partners and was directly linked to the development of the national elimination program and to the success achieved to date. Ongoing research efforts involving many partners will continue to be important in resolving the challenges faced by the program today in its final efforts to achieve elimination.

INTRODUCTION

Lymphatic filariasis (LF) is the target of a global elimination program, aimed at preventing transmission of a disease which in its chronic phases, causes incapacitating lymphedema, elephantiasis, and hydrocele. After more than 15 years of concerted effort, Haiti is poised to eliminate LF. The country has successfully scaled up mass drug administration (MDA) to achieve 100% geographic coverage and is now carrying out World Health Organization (WHO)-recommended transmission assessment survey (TAS) to stop MDA across many areas of the country.^{1,2} This success reflects not only the strong commitment over many years by resilient partners, but also the robust foundation of a program built on decades of investment in field and laboratory research. Research is at the core of all successful disease elimination programs, including the Global Program to Eliminate LF (GPELF) through the development and validation of effective intervention tools and strategies. For GPELF, key advances including the development of new treatment strategies based on single-dose treatment and rapid diagnostic tools, were made with Haiti serving as a key partner.³ Furthermore, research done in Haiti provided the genesis of the public health effort to eliminate LF in the country. Engagement by the U.S. Centers for Disease Control and Prevention (CDC) on LF in Haiti, with the support of the University of Notre Dame and Ministry of Health, provides an excellent case study of how research activities can support the development and evolution of disease elimination programs. This review will describe how the research, carried out in the context of a global research initiative, contributed to the development of Haiti's program to eliminate LF.

INITIAL RESEARCH EFFORTS

The genesis of CDC's research effort in Haiti was National Institutes of Health (NIH) funding to Tulane University for an International Center for Medical Research (ICMR), which included funding for research activities in Colombia and Haiti in the 1980s. CDC staff members were involved in this research and on the closure of the ICMR, sustained the research with funding from CDC, NIH, WHO's Special Program for Research and Training in Tropical Diseases (TDR), and other donors.

Early work focused on studies of the epidemiology of LF and led to key observations, including demonstration that 1) individuals with microfilaremia as low as 1/mL could still infect mosquitoes, 2) a small proportion of individuals continued to be microfilaremic even after repeated 12-day courses of diethylcarbamazine (DEC), and 3) children born to microfilaremic mothers were more likely to acquire infection than children born to amicrofilaremic mothers.^{4–9} These studies established a field presence and framework to investigate public health strategies to control LF.

TREATMENT STRATEGY

Historically, treatment of LF was based on a 12-day course of DEC (6 mg/kg). Although a number of highly successful mass treatment campaigns were carried out with DEC, these were typically based on modified dosing strategies and were relatively limited in scope.¹⁰ Where community residents were provided with the full 12-day complement of tablets, treatment compliance was generally low and where treatment was directly observed, the number of persons who could be followed up effectively by a single team was quite limited. Alternative treatment strategies, including spaced weekly doses were tested in Haiti and found to be superior to daily dosing, but this approach afforded no advantages in terms of the logistics of treating on a large scale.¹¹ The inability to practically deliver 12 days of therapy based on directly observed treatment as well as the demonstration of the effectiveness of single-dose ivermectin for the treatment of onchocerciasis, another filarial infection, stimulated a series of multicountry studies to investigate the safety and efficacy of single-dose treatments, compared with a standard 12-day course of DEC. WHO-TDR and Merck and Co. were major supporters of these studies and different dosing strategies were used to determine if ivermectin had an adulticidal effect and to define the optimal microfilaricidal dose.^{12–15} An unexpected outcome of these studies was the demonstration that a single dose of DEC was as effective as a 12-day course. These studies provided the critical evidence to support the concept that annual mass treatment based on single-dose therapy represented a practical intervention strategy for the control of LF and raised new questions about the potential for coadministered combinations of drugs. CDC provided funding for studies in Haiti to investigate the potential contribution of albendazole (ALB) to antifilarial drug combinations based on evidence from

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pilot studies that multiple doses had a pronounced adulticidal effect.¹⁶

Recognizing the broad spectrum deworming benefits of ALB, randomized controlled trials of ivermectin plus ALB as well as DEC plus ALB combinations in Haiti were carried out in school-aged children to monitor the nutritional impact of treatment as well as the effect on soil transmitted helminths (STH). These studies documented the effectiveness of regimens including ALB for the treatment of both LF and STH, and in conjunction with studies carried out in other settings, established the framework of the MDA strategy for GPELF.¹⁷⁻¹⁹ In this context, it is also important to identify GPELF as the first global program to represent an integrated neglected tropical disease (NTD) program, through its impact on both LF and STH, a step that anticipated the later emphasis on NTDs as diseases of poverty that could be addressed by preventive chemotherapy.²⁰⁻²²

DIAGNOSTICS STUDIES

A key requirement for conducting mass treatment is defining the populations in need of treatment. Diagnosis of LF, traditionally, required the demonstration of microfilariae. In Haiti, and in much of the world where *Wuchereria bancrofti* is transmitted, microfilaremia is nocturnal, necessitating night blood surveys to diagnose infection. These surveys represent an inconvenience to both the survey teams and the populations being surveyed and were not well accepted by many communities. The discovery that monoclonal antibodies developed against nonhuman filarial parasites recognized a circulating *W. bancrofti* antigen that could be detected in blood collected at any time of the day led to important insights in the epidemiology of filarial infection.^{23,24} In Haiti, antigen assays were incorporated into field work and clinical trials as soon as tests became available. These studies documented that 1) infection prevalence as measured by antigenemia was much higher than microfilaremia; 2) children as young as 2 years of age were acquiring infection; 3) chemotherapy led to slow and partial reductions in antigenemia; and 4) most lymphedema and elephantiasis patients were antigen-negative and thus, would not be expected to benefit from antifilarial chemotherapy.²⁵⁻³⁰ A revolutionary advance for LF programs was the introduction of a rapid diagnostic test, the immunochromatographic card test (ICT), which opened the door to daytime surveys to map the distribution of LF across all countries where LF was known or suspected.³¹ In Haiti, antigen surveys were conducted in schools across the country and documented that LF was more widespread than anticipated and follow-up studies documented transmission in several of these low prevalence settings.^{32,33} The widespread distribution of LF and LF transmission in Haiti led the Ministry of Health and Population (MSPP) to conclude that a program to eliminate LF would have to be national in scope.

MASS DRUG ADMINISTRATION

The recognition that single-dose treatment was efficacious opened the door to the development and testing of community-based mass treatment campaigns. CDC supported operational research to evaluate MDA approaches, initially based on house-to-house distribution of ivermectin in the community of Belloc near Leogane. The house-to-house

strategy proved challenging due to the number of household visits required to achieve acceptable coverage. As a result, MDA strategies employing active social mobilization campaigns and the use of centrally located distribution posts were tested and adopted as the foundation of the CDC-funded Leogane Demonstration Project, a comprehensive study designed to determine if five annual rounds of MDA would be sufficient to eliminate LF transmission in the commune.

When research studies demonstrated the effectiveness of drug combinations that included ALB, WHO asked that countries generate safety data from carefully monitored populations following administration of either ivermectin or DEC plus ALB. Combinations that included ivermectin were used in sub-Saharan Africa where onchocerciasis was endemic; in Haiti and the rest of the world where only LF was endemic, DEC was used. Safety studies in Leogane documented that the DEC + ALB combination had an acceptable safety profile.³⁴ Adverse events included fever, headache, and malaise associated with the killing of microfilariae as well as localized reactions associated with the killing of adult worms. Based on similar findings from other countries, WHO gave a "green light" to the use of MDA strategies based on the two drug combinations.³⁵ In Haiti, MSPP expressed concern about the treatment of women of child bearing age with ALB, since ALB is not recommended during the first trimester, when pregnancy may not be recognized. Consequently, only men and children received both drugs for the first 2 years of MDA in Leogane (MDAs in 2000 and 2001). Women were treated with DEC alone. As part of the monitoring and evaluation (M and E) strategy developed for the Leogane project, stool samples were collected to monitor the impact of MDA on STH infections. These data documented the differential benefit of MDA for men and children who received ALB, compared with women who did not and led MSPP to reverse their earlier decision and make women eligible to receive ALB, both in Leogane and other communes as the program scaled up.³⁶ When funds from the Bill & Melinda Gates Foundation to the University of Notre Dame made it possible to begin to expand MDA to other high-prevalence communes, women in these settings were eligible to receive the dual drug combination. As documented in other publications, scaling up MDA to reach all LF-endemic communes was hampered by limitations in funding, civil strife, and natural disasters.¹ Full national coverage was not achieved until after the catastrophic 2010 earthquake. Postearthquake funding from CDC and other donors supported the scale-up of MDA in Port au Prince, a major logistic effort and the last piece needed to achieve national coverage.³⁷

MONITORING AND EVALUATION

The Leogane Demonstration project included a rigorous M and E component to inform requirements for the scale-up of the national program. Adverse events, coverage, and cost were monitored for each round of MDA.³⁸⁻⁴¹ Surveys of microfilaremia, antigenemia, and STH burden were conducted in sentinel sites on an annual basis and filarial infection in mosquitoes was monitored periodically. These surveys documented the impact of MDA on STH as well as filarial infection in humans and mosquitoes.^{36,39,42} After five rounds of MDA, microfilaria prevalence was less than 1%⁴³; however, civil strife led to interruptions in funding and MDA, not only for

Leogane, but for other high prevalence or “zone rouge” communes as well. Follow-up surveys in 2007 demonstrated a significant recrudescence of microfilaremia and antigenemia in Leogane sentinel sites, leading to the conclusion that a single round of missed MDA set the program back by at least 2 years.⁴⁴

Even with the setbacks resulting from the interrupted MDA, there was a growing recognition that 5 years of MDA might not be sufficient to interrupt transmission in the “zone rouge” communes. Data from coverage surveys and the evidence of persistent transmission in Leogane also led to concerns that systematic noncompliance could be contributing to persistent transmission by maintaining a reservoir of infection.^{40,45,46} Additional surveys demonstrated that non-compliance rates differed across communities and were associated with greater prevalence of antigenemia.⁴⁷ Systematic noncompliance was driven by a complex array of factors, including fear of adverse reactions to drug treatment and mistrust of institutions. Although these challenges are unlikely to be unique to Leogane, it is possible that the initial restriction of ALB use to children and men in the first 2 years of the program exacerbated the problem in Leogane. These experiences highlighted the need for all programs to develop effective communication strategies and clear messages to support MDA programs.

After years of challenges with scaling up MDA, the LF program in Haiti achieved full geographic coverage in 2012. After multiple rounds of treatment of at risk populations, national LF elimination programs must be able to assess whether MDA has succeeded in lowering the prevalence of infection to a level where transmission is likely no longer sustainable. Determining whether MDA can be stopped requires the use of appropriate diagnostic tools and robust survey methodologies. Research activities conducted in *W. bancrofti* endemic countries, including Haiti, led to the selection of the ICT as the diagnostic tool to assess whether MDA can safely be stopped.⁴⁸ Subsequently, the TAS was designed and is currently the WHO recommended survey for making the programmatic decision to stop or continue MDA.⁴⁹ In Haiti many areas of the country are meeting the criteria for conducting TAS. In addition to providing important information for the LF program, the TAS platform provides excellent opportunities to collect additional public health data. Haiti is exploiting this opportunity by piloting an integrated TAS that includes malaria and STH assessments to guide public health decisions for these diseases.⁵⁰

LYMPHEDEMA MANAGEMENT

In early stages of the CDC research activities in Leogane, patients with lymphedema and elephantiasis were frequently included in house-to-house and clinic-based night blood surveys for microfilaremia. Though such patients were almost universally microfilaria-negative, they were typically offered a standard 12-day course of DEC in the hopes that they would derive some benefit from antifilarial treatment. That these patients never benefitted clinically was a puzzle until the introduction of antigen testing, as noted earlier, when it became clear that 95% of lymphedema patients in Haiti were antigen-negative and thus, had no evidence of active LF.^{26,28,51} This led to the realization that lymphedema patients would not benefit from MDA and raised questions about

how to provide appropriate care for these patients. At this same time, pioneering clinical work by Gerusa Dreyer in Brazil demonstrated that recurrent skin infections were responsible for acute attacks of adenolymphangitis (ADL) in lymphedema patients and for disease progression.^{52–55} This recognition led to the development of strategies to manage lymphedema based on prevention of ADL through improved skin hygiene.^{56–58} Collaboration with Dreyer introduced these principles of self-care to a newly developed lymphedema clinic in Leogane and follow-up of these patients also documented a reduced frequency of ADL as well as decreased skin pathology and inflammation.^{59–61} As a result of these and other studies, GPELF was based on two pillars—one focused on MDA and the second on providing access to appropriate care for patients already affected by filarial disease.⁶²

LOOKING FORWARD: OPERATIONAL RESEARCH NEEDS FOR THE LAST MILE

Though the LF program has matured, both in Haiti and in many countries around the world, the need for operational research has not ended. Persistent transmission, even after 10 years of MDA in several of the “zone rouge” communes, represents a particular challenge for Haiti. DEC-fortified salt, an exceptionally effective intervention in early pilot studies in Haiti,⁶³ is still being investigated as one potential solution. The recent demonstration of the increased efficacy of triple drug therapy (ivermectin plus ALB plus DEC) raises hopes that this drug combination may represent another option to solve the problem of persistent transmission.⁶⁴ Trials to demonstrate the safety, community acceptability, and efficacy of this combination are now planned for Haiti and other countries. Even if this strategy proves to be successful, stopping MDA does not represent the end of the LF program; post-MDA surveillance is needed to demonstrate that LF does not return. Current surveillance efforts are based on repeated TAS, but these surveys are not powered to detect changes in antigen prevalence. New diagnostic tools and surveillance platforms continue to be needed and Haiti is a logical place to test and validate these new approaches.^{65,66} The new focus on malaria elimination and the requirement for enhanced surveillance to achieve this target may provide Haiti with new opportunities to test options for integrated surveillance that will help to achieve both LF and malaria elimination. If focal MDA emerges as an effective strategy to eliminate malaria, the long-standing experience with LF MDA will also surely be advantageous. LF elimination, though not fully complete, is no longer a distant goal, but is approaching rapidly. The success of this program reflects the commitments of partners and communities over many years and through many challenges, but also represents the dividends from investments in research over this same period of time. Finally, it is important to note that the Haitian population is not alone realizing the benefits of the research that they have so patiently supported over the years; many LF-affected communities around the world are benefitting as well.

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