Scientific Working Group

Report on

Lymphatic filariasis

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Executive summary

WHA resolution 50.29 catalysed the development of the Global Programme to Eliminate Lymphatic Filariasis (GPELF). Implementation of the GPELF over the past five years has been extraordinarily successful. Exponential growth has occurred both in the number of participating countries and in the number of persons receiving combination therapy through mass drug administration (MDA). Data are accumulating that document the impact of the programme, both on the filarial parasite and on intestinal parasites that are also targeted by the drugs. At this early stage of the programme, it is important to critically evaluate the strategies upon which the global programme is based. Is GPELF achieving its objectives? Specifically:

- Is there evidence that transmission of lymphatic filariasis (LF) is eliminated by five years of MDA?
- Are disability prevention efforts alleviating the suffering of those with disease?

The Lymphatic Filariasis Scientific Working Group (SWG) was convened by WHO/TDR to review the current state of knowledge regarding the GPELF and to recommend research priorities that could best address the questions facing this global programme. More than 30 experts from around the world participated in the discussions, 10–12 May 2005, in Geneva. Working papers prepared in advance of the meeting summarized the available evidence with respect to the effectiveness of MDA in different epidemiologic settings, the status of the disability prevention programme, and the state of art of diagnostic and modelling tools to support the global programme (see annexes 3–8). These working papers represented the starting point for in-depth discussions at the SWG meeting. In addition, the SWG was able to capitalize on recent meetings at which LF research had been reviewed in detail. At the LF Research Forum held in December 2003, scientists were asked to summarize research needs and opportunities for research on LF. The products of these deliberations were published as a journal supplement.1 Furthermore, in November 2004, WHO sponsored an informal consultation to discuss issues arising out of five years of programme implementation.

Review of the latest evidence for impact of MDA, largely from TDR-funded studies, showed that MDA has resulted in dramatic declines in microfilaraemia everywhere the programme has been implemented. However, the impact on transmission (i.e. on infection in mosquitoes) is variable, ranging from complete interruption of transmission, as in one site in Papua New Guinea where four rounds of treatment were applied,2,3 through a significant reduction in transmission by *A. funestus* in Ghana and Mali after three rounds of MDA, to an area in Pondicherry, India, where low-level residual transmission remains after nine rounds of treatment4,5 (but in this latter area there is comparatively low compliance by the population). The SWG concluded that in many settings, more than 4–6 years of MDA will be required to
achieve elimination of transmission. This conclusion has significant implications, both for GPELF operations and for the LF research agenda.

The SWG used all of the available information, including many unpublished studies, to discuss research priorities related to the effect of MDA on LF transmission and to prevention and treatment of LF-related disability. In plenary sessions, the SWG tried to synthesize the recommendations emanating from different working groups into a single list of overarching priorities. It was recognized that the research needs of GPELF at this early stage of programme implementation are great and that a strong research effort will increase the likelihood of GPELF success. At the same time, limitations in human and financial resources must be considered, so the research agenda must be prioritized to focus on issues of greatest importance to GPELF. After a great deal of deliberation, priority research needs were defined by the SWG. These include:

- Fundamental socio-behavioural research on reasons for compliance and noncompliance, as well as studies on how to augment compliance.
- Development of the evidence base and tools for stopping MDA for major vector/parasite complexes.
- Establishment of the evidence base for implementing and scaling up disability prevention programmes.
- Research to improve implementation of MDA in urban settings and where opportunities exist for integration.
Background

Research support from TDR and other funding agencies played a critical role in developing the tools that spawned the Global Programme to Eliminate Lymphatic Filariasis (GPELF). Key studies sponsored by TDR in the late 1980s and early 1990s established the safety and efficacy of single-dose treatment with diethylcarbamazine (DEC) and ivermectin and led to field trials that demonstrated the utility of annual treatment for filariasis control at the community level. With the advent of sensitive and specific antigen tests for *Wuchereria bancrofti*, mapping the distribution of bancroftian filariasis became operationally feasible. It was these two advances that gave rise to the idea that elimination of lymphatic filariasis was attainable as a public health goal. Following on the heels of the World Health Assembly resolution (50.29) that called for elimination of LF as a public health programme, three additional events catalysed an exponential increase in the number of persons treated for LF: 1) the donation of albendazole by SmithKlineBeecham (now GlaxoSmithKline); 2) the donation of ivermectin by Merck; and 3) a US$ 20 million grant from the Bill & Melinda Gates Foundation for LF elimination.

From the beginning of the GPELF, it has been clear that the success of this programme hinges on the ability of country programmes to adapt operations to local circumstances, i.e. on “learning by doing”. To accomplish this, it is critical to have an active and engaged research community, and TDR and partners have been responsible for stimulating operational research and disseminating the results of this research to LF programme managers. As a prelude to the current meeting of the SWG, two earlier meetings established a framework for relating filariasis research to the needs of GPELF. The first meeting addressed the research needs of the global programme and focused on four research areas: 1) tools and measurements of programme success; 2) efforts to enhance programme effectiveness; 3) improving clinical management for persons with LF disease; and 4) protecting the LF programme by monitoring the development of drug resistance and developing new drugs. Specific recommendations from this meeting were published as a journal supplement.

The second meeting, in November 2004, considered issues arising out of five years of programme implementation, and recommended that TDR convene a scientific meeting of “tool-makers”, modellers, epidemiologists, entomologists, and sampling statisticians, to define and develop strategies and protocols for assessing whether the “transmission threshold” has been reached in different settings, to assess transmission using different “tools”, and to carry out prospective studies of tool performance. These recommendations set the stage for the current meeting of the SWG.
GOALS, OBJECTIVES AND EXPECTED OUTCOMES

The goal of the SWG was to:
• Recommend research priorities for addressing the questions facing GPELF in the next five years.

The objectives of the SWG were to:
• Review the current state of knowledge regarding the global programme (GPELF).
• Identify the major research priorities for lymphatic filariasis.
• Develop a strategic plan for lymphatic filariasis research.
Experience with mass treatment to interrupt LF is building rapidly as the programme grows. In reviewing the available evidence, both published and unpublished, the SWG focused on multiyear (three years or more of MDA) studies that documented changes in infection in both humans and vectors (see Table 1 for key studies). In most settings, MDA has led to significant reductions in key measures of LF infection (as determined by microfilaraemia and antigenaemia) and transmission (as assessed by antifilarial antibody and vector infection); however, interruption of transmission has only been observed in settings with favourable combinations of programmatic and epidemiologic factors. For example, despite high levels of initial microfilaria prevalence, four years of MDA in Papua New Guinea appears to have eliminated transmission based on the absence of microfilaraemia recrudescence and of new infections in children several years after MDA ceased. The ease with which transmission has been interrupted in these villages may reflect facilitation – the process by which transmission by *Anopheles* mosquitoes becomes less efficient as parasite numbers decline. Success has also been observed in Egypt, where *Culex* is the vector. Five years of high MDA coverage with DEC and albendazole has decreased microfilaraemia and antigenaemia and, in addition, dramatic declines in antibody responses to Bm14, a marker of filarial exposure, have been observed among sentinel populations. These data suggest that new infections are not being observed following MDA.

In other settings, there is evidence of ongoing transmission even after five or more years of MDA. In one of the best studied examples, after 8–10 annual cycles of MDA with ivermectin or DEC alone in Pondicherry, India, microfilaraemia prevalence remained above the threshold (1%) established by the global programme for initiating MDA. Similarly, five years of DEC and albendazole in Leogane, Haiti, failed to interrupt transmission of LF or reduce microfilaria prevalence below 1% in two of four sentinel sites. In both programmes, compliance issues were considered to represent potential explanations for continued transmission. Vector-specific issues may also play a role in the persistence of LF. In the South Pacific where LF is transmitted by *Aedes* mosquitoes, historical evidence indicates that a microfilaria prevalence of less than 1% was reached in Samoa, only to see a rebound in microfilaria prevalence several years later.

Based on this work, the ease with which transmission can be interrupted is related to: 1) MDA coverage; 2) initial microfilaria prevalence; and 3) the parasite vector. In some settings with high treatment compliance and other favourable conditions (e.g. low baseline infection rates, inefficient vectors), 4–5 rounds of MDA can reduce microfilaria prevalence to near zero. However, in other areas, MDA alone may not be sufficient to eliminate LF due to poor compliance and other factors. This raises many research questions about how to improve the impact of MDA. Potential options include: improving treatment coverage through appropriate social mobilization; increasing the frequency of MDA; and supplementing MDA with adjunct measures such as vector control, insecticide-treated bed nets (ITN), and/or DEC-salt.

In sub-Saharan Africa, GPELF is faced with another critical issue. Serious adverse events (SAE), including neurologic changes and coma, have been linked temporally with mass treatment with ivermectin for onchocerciasis in *Loa*-endemic areas. As a result, mass treatment for lymphatic filariasis (LF) in *Loa*-endemic areas has been halted. This has prevented implementation of LF elimination programmes in several African countries. New approaches to treat LF in
Table 1. Summary table of results of mass drug administration and its impact on lymphatic filariasis transmission

<table>
<thead>
<tr>
<th>Study site</th>
<th>Vector species</th>
<th>Study type, population size</th>
<th>MDA, duration, coverage</th>
<th>Pre-treatment Mf+ rate</th>
<th>Pre-treatment Ag+ rate</th>
<th>Pre-treatment vector infection data</th>
<th>Time of data collection</th>
<th>Post-MDA Mf+ rate</th>
<th>Post-MDA Ag+ rate</th>
<th>Post-MDA vector infection data</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td><em>Culex</em></td>
<td>Research, 30 000: 7% of total population</td>
<td>DEC, 10 years, 54–75%, eligible</td>
<td>7–17%</td>
<td>ND</td>
<td>1.1% L3 dissection</td>
<td>1 year after 9th MDA</td>
<td>0–3.8%</td>
<td>ND</td>
<td>0.06% L3 dissection</td>
<td>Control, low level transmission</td>
</tr>
<tr>
<td>Egypt</td>
<td><em>Culex</em></td>
<td>Research, national, total population 17 000</td>
<td>DEC/Alb, 5 years, 80–90% eligible</td>
<td>0.75–13%</td>
<td>16.9%</td>
<td>2.3–4% by PCR (0 by dissection)</td>
<td>1 year after 4th MDA</td>
<td>0–0.6%</td>
<td>2.3%</td>
<td>0–0.26% (PCR)</td>
<td>Elimination promising</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td><em>Anopheles</em></td>
<td>Research, 3000</td>
<td>DEC, 4 years, 78–87%, eligible</td>
<td>33–50%</td>
<td>~80%</td>
<td>1.1% L3 dissection</td>
<td>6 years after 4th MDA</td>
<td>0%</td>
<td>23%</td>
<td>0% L3 dissection</td>
<td>Probably elimination in moderate transmission area</td>
</tr>
<tr>
<td>Ghana</td>
<td><em>Anopheles</em></td>
<td>Research, 921</td>
<td>IVR/Alb, 3 years, 67% eligible</td>
<td>4.6%</td>
<td>8.7%</td>
<td>0.42% L3 dissection</td>
<td>1 year after 3rd MDA</td>
<td>0.9%</td>
<td>8.7%</td>
<td>?</td>
<td>0.47% L3 dissection</td>
</tr>
<tr>
<td>Mali</td>
<td><em>Anopheles</em></td>
<td>Research, 3185</td>
<td>IVR/Alb, 2 years, 80% eligible</td>
<td>21.4%</td>
<td>46.5%</td>
<td>2.3% L3</td>
<td>1 year after 2nd MDA</td>
<td>12.3%</td>
<td>46.5–50%</td>
<td>0.12% L3</td>
<td>Ongoing study, transmission decreasing</td>
</tr>
<tr>
<td>Pacific Islands</td>
<td><em>Aedes</em></td>
<td>National</td>
<td>DEC/Alb</td>
<td>ND</td>
<td>&gt;10 years</td>
<td>&gt;1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td><em>Anopheles</em></td>
<td>Research, 758</td>
<td>DEC every 6 months x 4, 68–87% total population</td>
<td>29.4%</td>
<td>0.63% L3 dissection</td>
<td>6 months after 4th MDA</td>
<td>4.8%</td>
<td>43.3–52.9%</td>
<td>1.1% L3 vector abundance diminished</td>
<td>No evidence of decreased transmission</td>
<td></td>
</tr>
<tr>
<td>Haiti</td>
<td><em>Culex</em></td>
<td>Research, 150 000</td>
<td>DEC/Alb, 5 years, 55–86% total population</td>
<td>0.8–15.1%</td>
<td>10.8–50.1%</td>
<td>1.1% L3 dissection</td>
<td>9 months after 5th MDA</td>
<td>0–3%</td>
<td>8.3–22%</td>
<td>0.09% L3 dissection</td>
<td>Ongoing study, transmission decreasing</td>
</tr>
</tbody>
</table>

MDA: mass drug administration, ND: not done, DEC: diethylcarbamazine, Alb: albendazole, IVR: ivermectin, PCR: polymerase chain reaction, Mf+: microfilaria positive, Ag+: antigen positive, L3: larval stage 3
communities with *Loa loa* infection are urgently needed.

**Priority research needs identified by the Scientific Working Group:**

- Field studies and cost-efficacy analyses of additional measures (such as vector control, ITN, and/or DEC-salt) in different vector–parasite situations.
- Strategies for eliminating LF in areas that are co-endemic for loiasis.

**MODELLING LYMPHATIC FILARIASIS TRANSMISSION AND THE EFFECTS OF MASS DRUG ADMINISTRATION**

Mathematical models provide useful tools to predict programme trends and, in principle, could facilitate decision-making by programme managers. Two models have been developed – Epiﬁl and Lymfasim; when tested against data, they give comparable predictions.\(^{14,15}\) The models for *Culex quinquefasciatus* have been studied most extensively. This work has generated findings that are important for all ongoing programmes; specifically, the number of rounds of MDA required for elimination is likely to exceed 4–6, the number used as the basis of programme implementation by many countries. As noted above, predictions about the intensity of control efforts (with respect to coverage and duration) strongly depend on the efficacy of the drugs and the pre-control prevalence of microfilaria. New information is needed to reﬁne these models, and efforts to validate them should be undertaken. Such a process would be facilitated by creating a common database for MDA programmes that includes both research and national programme monitoring data.

The overall transmission dynamics strongly depend on the dynamics at both interfaces, i.e. transmission from man to mosquito and from mosquito to man. A proper calibration of the model(s) requires data from mosquito feeding experiments. Therefore mosquito-feeding studies are needed for major vectors where existing data are insufﬁcient. It is important to generate these data to improve the utility of the models for predicting programme outcomes.

Refining and validating existing models is likely to be an iterative process. Throughout these efforts, there is a critical need to evaluate the utility of the models as tools for decision-making. Therefore, available models should be used to make predictions on several important issues:

- Definition of endpoints for stopping mass treatment based on results from available diagnostic tests (see below) for different vector/parasite combinations.
- Definition of optimal control strategies, i.e. optimal coverage for deﬁned endpoints and pre-control prevalence rates, and deﬁnition of whether the cost-effectiveness of control strategies can be improved by changing the frequency of treatment, the choice of drugs, or implementing vector control in the early or late phases of a programme.
- Identification of cost-effective strategies for monitoring during and after control.
- Analysis of the efﬁcacy of drug combinations on microfilaria and adult worms, especially at low levels of infection intensity.

**TOOLS FOR MONITORING MASS DRUG ADMINISTRATION PROGRAMMES**

A number of excellent tools have been developed in recent years for use in LF programmes. Briefly, these include tests for detecting circulating ﬁlarial antigen (bancroftian ﬁlariasis), assays
for IgG4 antibodies to recombinant filarial antigens (indicating infection or exposure), and methods for detecting filarial DNA in mosquitoes. These new tools complement the traditional diagnostic methods of detecting microfilaria and dissecting mosquitoes. However, there is no consensus on the comparative value of the new tools for documenting the endpoints for MDA programmes (i.e. when MDA can safely be discontinued with minimal risk of recrudescence).

The SWG endorsed one of the recommendations in the Essential Tools and Diagnostics section of the LF Research Forum Report. Briefly, this calls for studies to “define the comparative accuracy of available diagnostic strategies for monitoring the progress of LF elimination programmes and for deciding both when to stop MDA and how to initiate surveillance to detect potential recrudescence”. Such studies should include “longitudinal studies using all diagnostic tools concurrently in both high- and low- prevalence areas where LF elimination programmes are under way”. The studies should be closely linked to research scientists with interest and expertise in mathematical modelling for human filariasis.

There is also no consensus on sampling techniques for monitoring LF programmes or for post-MDA surveillance. Therefore, the group also endorsed the recommendation from the LF Research Forum to “validate sampling strategies for testing both vector and human populations for LF infection or exposure to infection”.

Improved tools (single-dose combination therapy and antigen detection tests) were important for the conceptualization and initiation of GPELF. Additional research is required to improve the existing tools and to develop new tools to support GPELF.

**Priority research needs identified by the Scientific Working Group:**

**Improve and test existing tools**
- Use existing tools to test guidelines for when to stop MDA.
- Validate antibody testing as a monitoring and evaluation tool for use by both brugian and bancroftian filariasis programmes.
- Further streamline filarial DNA assays and antibody tests to make them more user-friendly and accessible to endemic country laboratories.

**Develop new tools**
- Develop a sensitive *W. bancrofti* antibody assay for use in sub-Saharan Africa; there should be no cross-reactivity with sera from patients with loiasis or onchocerciasis.
- Develop a molecular assay for the specific detection of filarial infective larvae in mosquitoes.
- Develop and validate a new rapid-format filarial antigen detection test.

**SOCIAL SCIENCE AND FACTORS INFLUENCING THE SUCCESS OF MASS DRUG ADMINISTRATION**

Models predict and experience confirms that population coverage is a key determinant of the success of LF programmes. Use of the term ‘coverage’ implies that each person who receives the drugs actually takes them (i.e. they are compliant), but in several countries, most notably India, a gap between coverage and compliance has been observed. Intensified social mobilization can narrow this gap, at least to a degree; however, even in programmes where treatment is observed, compliance is not uniform. Unpublished surveys conducted after 3–5 rounds of MDA in Haiti and elsewhere have identified persons who are systematically noncompliant. The contribution

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**Lymphatic Filariasis**
of these persons to transmission is unknown, but systematic noncompliance may represent a potential threat to LF elimination. Despite the obvious importance of this issue, rigorous studies of compliance that are based on sound social science have not been conducted, perhaps because social scientists have been under-represented in the community of LF researchers. In order to understand why some people do not take the drugs during MDA, it is important first to understand why other people do take them. Systematic studies are needed to identify the perceived benefits of MDA from the community perspective. From this vantage point, it will be possible to study noncompliance and to define the most cost-effective strategies for social mobilization (e.g. communication for behavioural impact [COMBI] or others).

Other key operational research issues that have not been addressed have been identified by programme managers. Most LF programmes have been initiated, with great success, in rural communities, but a few programmes have extended into urban environments, in part because of concerns about the suitability of the MDA strategy for urban areas. Research is needed to determine whether new social mobilization and implementation strategies are in fact needed in urban areas. Similarly, the extent to which population migration impacts on MDA coverage, interruption of transmission and morbidity management is not clear. What are the social and epidemiological determinants of migration and how should these be addressed at the programme level?

Health system strengthening is a prerequisite to achieving health related goals; stronger health systems are key to achieving improved health outcomes. The evidence base to support efforts to strengthen health systems is very weak however, particularly when it comes to the effects that disease-specific programme may potentially have on these systems. The concerns are human resource shortages, constraints to scaling up health services, health financing, equity, human rights for disabled LF patients, to list but a few. Are MDA campaigns the best strategy for the health system? Research is needed to develop health system assessment tools and to measure the impact of the LF elimination programmes on health systems. In addition, as ministries of health move increasingly towards integration of programmes for neglected tropical diseases, what are the advantages and disadvantages of integration of LF programmes with other disease specific programmes?

The Scientific Working Group identified the following priorities for research:

- Systematic studies to identify cross-cutting factors affecting compliance and noncompliance from a comparative perspective.
- Determination of the best strategies for MDA and morbidity management in urban and conflict settings.
- Description of the effects/impact of LF elimination programmes on national health systems.
Lymphatic filariasis related morbidity and disability

Management and prevention of LF-related morbidity is an important component of the global programme. SWG discussions focused on four major areas: acute dermatolymphangiadenitis ("acute attacks"), lymphedema, hydrocele, and the impact of MDA on filarial morbidity.

ACUTE DERMATOLYMPHANGIO-ADENITIS

Research during the last decade has confirmed the importance of acute dermatolymphangiadenitis (ADLA) as a public health problem in filariasis endemic areas. Although some debate about the pathogenesis of ADLA continues, the central role of bacteria is generally accepted. Dramatic decreases in ADLA incidence have been noted following implementation of simple programmes of hygiene and skin care. Uncertainties remain about the role of inflammatory mediators or other triggers of ADLA, environmental risks factors, and best treatment practices.

LYMPHEDEMA

The current lymphedema management strategies of the GPELF are based on the central role of bacterial ADLA as a trigger for lymphedema progression. Simple intervention packages have been developed and are being used in many countries, although optimization of the components of these packages would benefit from further research. These interventions have resulted in dramatic reductions in ADLA rates in several studies. The key challenge now for GPELF in lymphedema management is how best to scale up, monitor, and evaluate programmes at the national level. Morbidity management programmes are generally in pilot project phase, with limited comparability among them. At least four different strategies are being employed or considered in different settings:

• Dissemination of information and reliance on patient self-motivation through the distribution of patient education booklets during MDA. This strategy has not been evaluated for effectiveness or impact because of funding limitations.
• Community-based care supervised by non-governmental organizations (NGOs), local health centres, or home-based disability prevention programmes. This strategy emphasizes care by patients, with support and assistance from family members and community health workers. This strategy appears to work well in areas where there is a low prevalence of lymphedema.
• Outpatient clinics open to lymphedema patients. This strategy depends on patient self-referral and allows for more thorough assessment of lymphedema severity and co-morbidity by doctors or nurses. In principle, such an approach permits collection of pre-intervention baseline data as well as follow-up assessments.
• Integrated approaches to general hygiene and health education for entire communities. This strategy attempts to encompass health education messages for control of other diseases such as trachoma, diarrhoeal diseases, soil-transmitted helminthiasis, and schistosomiasis.

These four strategies should be evaluated in different settings to determine the feasibility and efficiency of implementation, the degree of patient compliance, the factors that influence compliance, and the impact and cost of the interventions. In countries with over-stretched health services, it also may be useful to evaluate new strategies for delivering care and to assess the potential of alternate caregivers and support groups to improve access of patients to appropriate treatment. Finally, it is important to assess the impact of interventions in terms of quality of life of affected persons.
HYDROCELE

Of the clinical manifestations targeted by the disability alleviation component of the GPELF, hydrocele has been the focus of the least attention. Basic information is lacking on the effectiveness, complications, and risk of recurrence following hydrocele surgery in filariasis endemic areas. Similarly, there is little understanding of the social costs of hydrocele. The group identified two strategies that should be assessed to improve morbidity due to hydrocele:

- Short intensive surgical programmes several times a year, with hands-on training of local doctors by national specialists.
- Routine surgeries through local hospitals throughout the year.

These strategies should be evaluated to assess surgical outcomes (including post-surgical infections, recurrence, and quality of life), the cost of surgery, and secondary benefits, e.g. improved compliance with MDA.

EFFECT OF MASS DRUG ADMINISTRATION ON FILARIAL MORBIDITY

Data on the impact of MDA on filarial morbidity are inconsistent (Table 2). Several studies report reductions in adenolymphangitis, lymphedema, and/or hydrocele following MDA, but others report no such association. An overarching problem in interpreting these data is the lack of standardized case definitions. Assessing the public health impact of mass treatment with antifilarial drugs is an important issue for programme advocacy and for morbidity control strategies.

The Scientific Working Group identified the following priorities for research:

- Standardization of definitions (e.g. for ADLA, lymphedema, and hydrocele) and criteria for staging disease severity.
- Determination of how best to scale up morbidity management programmes.
- Definition of the impact of MDA on morbidity.
### Table 2 Summary of studies assessing the effect of antifilarial drug treatment on the clinical manifestations of acute attacks or lymphangitis, hydrocele, and lymphedema.

<table>
<thead>
<tr>
<th>Source</th>
<th>Acute attacks</th>
<th>Hydrocele</th>
<th>Lymphedema</th>
<th>Drug</th>
<th>Delivery</th>
<th>Follow-up interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bockarie</td>
<td>.</td>
<td>+</td>
<td>+ *</td>
<td>DEC, DEC+IV</td>
<td>Mass</td>
<td>5 years</td>
</tr>
<tr>
<td>Partono</td>
<td>+</td>
<td>.</td>
<td>+</td>
<td>DEC</td>
<td>Mass</td>
<td>11 years</td>
</tr>
<tr>
<td>March</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>DEC monthly</td>
<td>Mass</td>
<td>10 years</td>
</tr>
<tr>
<td>Fan</td>
<td>.</td>
<td>-</td>
<td>-</td>
<td>DEC</td>
<td>Mass (salt)</td>
<td>16–19 years</td>
</tr>
<tr>
<td>Bernhard</td>
<td>.</td>
<td>-</td>
<td>.</td>
<td>DEC</td>
<td>Mass, plus clinical trial **</td>
<td>1 year</td>
</tr>
<tr>
<td>Meyrowitch</td>
<td>.</td>
<td>+</td>
<td>+</td>
<td>DEC</td>
<td>Mass, salt</td>
<td>2 years</td>
</tr>
<tr>
<td></td>
<td>.</td>
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<td></td>
<td>Mass, salt</td>
<td>4 years</td>
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<tr>
<td>Beye</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>DEC</td>
<td>Mass, selective</td>
<td>16 months</td>
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<tr>
<td>Simonsen</td>
<td>-</td>
<td>- ****</td>
<td>-</td>
<td>DEC</td>
<td>Mass</td>
<td>1 year</td>
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<tr>
<td>Ciferri</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>DEC</td>
<td>Mass</td>
<td>2 years</td>
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<tr>
<td>Malecela, MacKenzie (pers. communication)</td>
<td>+</td>
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<td>+</td>
<td>IV + Alb</td>
<td>MDA</td>
<td>1–2 years</td>
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<tr>
<td>Pani</td>
<td>.</td>
<td>.</td>
<td>-</td>
<td>DEC</td>
<td>Clinical trial</td>
<td>1 year</td>
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<tr>
<td>Kerry</td>
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<td>.</td>
<td>+</td>
<td>DEC</td>
<td>Clinical trial</td>
<td>1–3 months</td>
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<tr>
<td>Moore</td>
<td>.</td>
<td>.</td>
<td>+</td>
<td>DEC</td>
<td>Case report</td>
<td>1 week–7 months</td>
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* = decrease from 5% to 4% prevalence
** = placebo-controlled
*** = 2 of 8 hydroceles resolved
* = decrease noted (not necessarily statistically significant)
- = no decrease noted (or if noted, not considered significant by authors)
. = not evaluated, or extremely small numbers
DEC = diethylcarbamazine
IV = ivermectin
Alb = albendazole
Conclusions

In order to execute the ambitious research agenda defined by the SWG, additional resources will be needed, both human and financial. Human resources must be developed at the country level through research capacity strengthening activities that complement parallel efforts to address other neglected tropical diseases. With the severe constraints on financial resources available to support LF research, renewed efforts to advocate for research on tropical diseases are needed. Also, greater coordination of research activities would help to diversify the research portfolio and increase the contribution of LF research to programmatic goals. Ultimately, the success of GPELF as a disease elimination programme requires a strong and engaged research community. Priorities identified by the SWG establish a framework that will help guarantee the success of GPELF.
References

Annex 1

AGENDA: Scientific Working Group on Lymphatic Filariasis
### Day 1, Tuesday 10 May 2005

<table>
<thead>
<tr>
<th>Time</th>
<th>Item</th>
<th>Speaker</th>
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</thead>
</table>
| 09.00–09:30  | • Welcome address  
• Introduction of participants                                | Dr. A. Asamoah-Baah, Assistant Director-General, Communicable Diseases (ADG/CDS)  
Dr. R. Ridley, Director UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)  
Dr. H. Endo, Director Strategy Development and Monitoring for Eradication and Elimination (CPE) |
| 09:30–09:45  | • Meeting objectives and process                                      | Dr. J.H.F. Remme, TDR                                                                   |
| 09:45–10:15  | • Global lymphatic filariasis (LF) elimination programme: progress and challenges | Dr. G. Biswas, CPE                                                                        |
| 10:15–10:30  | • Current strategic emphases for LF research in TDR                  | Dr. J.H.F. Remme                                                                          |
| 10.30–11.00  | Coffee break                                                          |                                                                                          |
| 11:00–11:30  | • Research needs of national LF elimination programmes               | National programme managers: Drs. Gyapong, Hernandez, Joshi, Kyelem, Milord                |
| 11.30–12.00  | • Needs and opportunities for research on lymphatic filariasis: summary of the LF Research Forum | Dr. E. Oettesen                                                                            |
| 12:00–12.30  | • Impact of mass drug administration (MDA) on LF transmission: *Culex*-transmitted, India | Dr. K.P. Ramalah/Dr. R. Rajendran                                                        |
| 12.30–14.00  | Lunch break                                                           |                                                                                           |
| 14:00–14.20  | • Impact of MDA on LF transmission: *Aedes*-transmitted, Pacific     | Dr. R. Speare                                                                             |
| 14.20–14.40  | • Impact of MDA on LF transmission: *Anopheles*-transmitted, Papua New Guinea | Dr. J. Kazura                                                                            |
| 15.00–15.20  | • Impact of MDA on LF transmission: *Anopheles*-transmitted, Africa  | 1. Prof. S.F. Traore  
2. Dr. J. Gyapong                                                                         |
| 15:20–15:40  | • Impact of MDA on LF transmission, Egypt                            | Dr. Ramsy                                                                                |
| 15.40–16.00  | Coffee break                                                          |                                                                                           |
| 16.00–16.20  | • Modelling LF elimination strategies                                | Dr. W. Stolk                                                                              |
| 16.20–16.40  | • Tools for measuring impact of filariasis control                   | Prof. G. Weil                                                                             |
| 16.40–17.00  | • Morbidity management: current status and research needs            | Dr. D.G. Addis                                                                            |
| 17.00–17.20  | • Social and behavioural aspects of MDA and morbidity management     | Dr. B.V. Babu                                                                             |

### Day 2, Wednesday 11 May

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<thead>
<tr>
<th>Time</th>
<th>Item</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>08.30–10.30</td>
<td>• Working groups (WG)</td>
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<tr>
<td>10.30–11.00</td>
<td>Coffee break</td>
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<tr>
<td>11.00–12.30</td>
<td>• Working groups: continued</td>
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<td>12.30–14.00</td>
<td>Lunch break</td>
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<tr>
<td>14.00–15:00</td>
<td>• Working groups: continued</td>
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<td>15.00–15.30</td>
<td>Coffee break</td>
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<tr>
<td>15.30–16.10</td>
<td>• Plenary report: Working Group I</td>
<td>WG rapporteur (presentation and discussion)</td>
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<tr>
<td>16.10–16.50</td>
<td>• Plenary report: Working Group II</td>
<td>WG rapporteur (presentation and discussion)</td>
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<tr>
<td>16.50–17.30</td>
<td>• Plenary report: Working Group III</td>
<td>WG rapporteur (presentation and discussion)</td>
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<td>Time</td>
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<td>08.30–10.30</td>
<td>Small group to review the overall prioritization, harmonize the recommendations, and outline a strategic plan</td>
<td>Small group: SWG chair and plenary rapporteurs, WHO secretariat</td>
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<tr>
<td>10.30–11.00</td>
<td>Coffee break</td>
<td>WGs</td>
</tr>
<tr>
<td>11.00–12.30</td>
<td>Small group report to the plenary meeting on overall priorities and draft strategic plan \ Plenary rapporteurs to finalize the SWG draft conclusions and recommendations</td>
<td>SWG chairperson/rapporteurs</td>
</tr>
<tr>
<td>12.30–14.00</td>
<td>Lunch break</td>
<td>All</td>
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<tr>
<td>14.00–15.30</td>
<td>Plenary discussion and amendment of conclusions, recommendations and draft strategic plan</td>
<td>All</td>
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<tr>
<td>15.30–16.00</td>
<td>Coffee break</td>
<td>All</td>
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<tr>
<td>16.00–16.30</td>
<td>Continuation of discussion on conclusions, recommendations and draft strategic plan \ Any other business</td>
<td>All</td>
</tr>
<tr>
<td>16.30–17.00</td>
<td>Concluding remarks \ Closure of the meeting</td>
<td>Chairperson, Director TDR</td>
</tr>
</tbody>
</table>

1 Unable to attend
2 Shift in presentation period between Drs Seaman (section II) and Ganguly (section III)
3 TDR definition of category I disease: epidemiological situation getting worse, and incidence of infection and disease increasing.
Annex 2
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Annex 3

WORKING PAPER:
Towards a strategic plan for research to support the global programme to eliminate lymphatic filariasis

Appendix A
Lymphatic Filariasis Forum: prioritized research needs .......................... 33

Appendix B
Participants and working groups .......................................................... 36
3: DEVELOPING A STRATEGIC PLAN FOR RESEARCH TO SUPPORT THE GLOBAL PROGRAMME TO ELIMINATE LYMPHATIC FILARIASIS

STEP 1: THE LYMPHATIC FILARIASIS RESEARCH FORUM

Eric A Ottesen
US LF Support Center
Task Force on Child Survival and Development
Decatur, Georgia, USA

1. BACKGROUND

1.1 The need for a research agenda

It was the dramatic research success in developing effective tools and strategies during the 1980s and 1990s that provided the foundation and rationale for the Global Programme to Eliminate Lymphatic Filariasis (GPELF). Yet, ironically, despite great progress in ‘scaling up’ this programme (currently active in 38 of the 80 endemic countries), or perhaps even because of this progress, one critical element for ultimate programme success – research – is increasingly being neglected.

It is widely appreciated that a mark of all successful public health programmes is the continuing involvement of an active research community capable of providing solutions both to programme problems as they arise and to anticipated problems or barriers that might arise during programme activities. Indeed, such research must be especially vigorous and focused in programmes (like the lymphatic filariasis [LF] programme) with a time-limited goal of disease elimination. In addition, for diseases like LF – the neglected ‘10/90 diseases’ of poverty – where research funds are particularly limited, it is especially critical that research needs and research initiatives be clearly identified and effectively prioritized. A strategic plan based on these identified needs is essential not only for the GPELF to develop cost-effective solutions to the problems it faces, but also for scientists to identify important research opportunities and for funding agencies to understand exactly how their investments fit into the overall horizon of LF research needs.

1.2 The three-step path to developing a strategic plan

In 2003, a progressive three-step process to develop a strategic plan for LF research was begun.

Step 1, the ‘brainstorming’ effort, was designed to provide an optimal opportunity for the filariasis scientific, research and public health communities first to explore, as freely and widely as possible, the research needs of the Global Programme (both today and in the future), then to identify the opportunities to meet those needs, and finally to prioritize the efforts required to pursue those opportunities. It culminated in the ‘LF Research Forum’ (appendix a).

Step 2, the period of reflection and focusing, was designed to allow analysis and debate of the many recommendations and opportunities identified through the brainstorming efforts in order to identify those research issues that would most help the Programme achieve its targets and goals, particularly in the near term but in the longer term as well. The conclusions have been captured in the report of an Informal consultation on issues arising out of five years of programme implementation.

Step 3 in this process of developing a strategic plan was perhaps the most important in that it required WHO/TDR to convene a scientific working group on lymphatic filariasis, first to reaffirm or improve on the conclusions from steps 1 and 2, and then to complete a strategic plan for LF research that would include not only recommendations, but also a real, viable action plan and funding strategy to ensure the strategic plan’s implementation.

2. STEP 1: DEVELOPING THE LYMPHATIC FILARIASIS RESEARCH FORUM

2.1 Approach and goals

The ‘ideal’ LF research forum was envisioned as one that would include all research-oriented members of the LF community from both the scientific and programmatic disciplines, with subgroups being formed to define the issues relevant to their disciplines. From these components, an overall research agenda could subsequently be developed. To come as close to this ideal as possible, the LF Research Forum was held in Philadelphia, USA (December 2003), at the time of two other activities where large numbers of filariasis-oriented researchers were congregating – the centennial meeting of the American Society of Tropical Medicine and Hygiene and a
filaria research summit’ where international scientists were convened for in-depth presentation and discussion of key, cutting-edge filariasis research issues.

During the LF Forum meeting, subgroups of researchers focused on defining the clinical, epidemiological and other scientific research issues most important to lymphatic filariasis, public health and the GPELF. These issues included pathogenesis, disease management, infection in children, drug utilization, drug development, diagnostic tools, strategies for employing these tools, modelling to define critical epidemiological endpoints, vector biology and others. Significantly omitted however (solely for reasons of logistics), were in-depth considerations of research needs related to social science, health economics, health systems and filarial genomics. (Since the latter two issues had been the subjects of other recent meetings of experts, they were also included in the final report from the LF Research Forum.)

2.2 Participants and funding

The inclusiveness of researchers participating in the Forum was limited only by the funds available to support people’s necessary travel expenses. Therefore, individuals (and their home institutions) were asked to support themselves if at all possible, with the remaining costs to be covered by a pool of funds from external donors.

Sixty-four senior scientists and experts in filariasis from 21 different countries participated in the LF Forum (appendix b). Another 24 invited participants from 11 countries (all but two represented by other attendees) were unable to attend but agreed to have an input into the process through review of the draft documents. A further list of nine potential invitees from five different countries (only one not otherwise represented) was developed but not acted upon because of budgetary constraints.

Instead of seeking a single donor to underwrite the costs of the Forum, it was decided to request smaller sums (US$ 5000 to US$ 20 000) from multiple organizations, both to decrease the burden on these organizations and to broaden the Forum’s support base. Indeed, eight organizations (three commercial, four non-governmental, and one governmental agency) contributed to its support. In addition, of the 64 participants, 42 investigators from 26 different organizations supported their own costs for meeting participation.

2.3 Organization

Initially an organizing committee representing six institutions (including the World Health Organization unit on Strategy Development and Monitoring for Eradication and Elimination [WHO/CEE] and WHO/TDR) identified ten sub-topics covering the range of scientific issues addressable at this Forum. These were the following: (1) chemotherapy, (2) LF infection and drug trials, (3) LF disease and treatment trials, (4) pathogenesis, (5) diagnostics, (6) epidemiology and parasite biology, (7) programme implementation, (8) programme monitoring and evaluation, (9) protective immunity, (10) vector biology.

Prior to the Forum, each participant was asked to select two of these sub-topics on which to focus in working groups at the Forum. Once the groups were constituted, a chairperson was designated who then contacted the working group members prior to the Forum itself.

During the two-day Forum, the ten working groups (6–15 individuals per group) met twice in five parallel sessions to determine the most important researchable questions in their topic areas and the priority that these questions should have with respect not only to the Global Programme but to other aspects of science and public health as well. Conclusions from all ten working groups were reviewed in plenary, and subsequently summaries of the sub-topics and conclusions were prepared by the group chairpersons and assembled into a draft document that was reviewed by all the Forum participants, invitees and others before finalization for publication.

3. STEP 1: PRINCIPAL OUTCOMES OF THE LYMPHATIC FILARIASIS RESEARCH FORUM’S ‘BRAINSTORMING’

The structure of the Forum allowed both issue preparation in advance of the meeting and ‘small-group’ informal interactions among experts during the meeting, all focused on specific topics and without severe time constraints. As a result, ample opportunity was provided for identification of the principal research needs, and the rationales underlying each of these needs could be defined and outlined in detail (see LF Forum final report and appendix a). As the organization of the meeting was by discipline, there was a measure of overlap in the research needs identified. Overall, however, the conclusions

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* Ellison Medical Foundation; The Geneva Foundation for Diseases of the Tropics; GlaxoSmithKline; Health and Development International; Merck & Company, Inc.; New England Biolabs; The US National Institute of Allergy and Infectious Diseases; The Wellcome Trust.
of the LF Research Forum could be generalized, as follows.

3.1 Operational research

To ensure success of the Global Programme, the operational research identified as being most important focused on finding solutions to four essential Programme needs.

The need to establish the tools and measures for programme success

This to be addressed by:
- Comparative evaluation of the diagnostics and sampling strategies available both in humans and in vectors.
- Testing the endpoints for defining transmission interruption.
- Creating/testing sets of indicators developed to monitor:
  - morbidity-control/disability-prevention efforts
  - multi-disease integrated programme activities
  - the GPELF impact on national health systems.

The need to ensure good clinical/morbidity management

This to be addressed by:
- Standardizing clinical terminology and technical approaches to patient assessment.
- Establishing best practices for home-based care for lymphoedema, surgical care for hydrocele/lymphocele, and treatment for individuals with LF infection.
- Assessing reversibility of clinical/subclinical LF disease, especially in children.

The need to protect effectiveness of drug-based programmes for elimination of lymphatic filariasis

This to be addressed by:
- Establishing a definition for diminished drug sensitivity.
- Developing parasite repositories and surveillance for genotypic signs of drug resistance.
- Continuing new and alternative drug development.

3.2 Basic, upstream research

In addition to these essential operational research issues, the need for ‘basic’ upstream research was also recognized as being critical for maintaining a strong science base for the GPELF. Not only might there be potential scientific ‘breakthroughs’ from these efforts that could entirely short cut the current LF elimination strategy but, just as importantly, such research activity will help ensure the existence of a cadre of knowledgeable investigators to serve as scientific ‘problem-solvers’ available even for assisting with the operational research needs of the Programme. The issues of particular importance for this upstream research study were identified as those defining:
- The effect of LF co-infections on clinical expression of other diseases and on responsiveness to routine vaccines.
- The mechanisms that determine the pathogenesis of lymphatic disease and its clinical expression.
- The susceptibility and resistance (immunity) to LF and the effect of MDA on natural immunity to LF in treated populations.
- The genomics and proteomics of filarial parasites.

4. DEFINING THE STRATEGIC PLAN AND AN ACTION PLAN TO IMPLEMENT IT

4.1 Step 3: Completion of the strategic plan for research to support the GPELF

It is essential that the WHO/TDR Scientific Working Group on Lymphatic Filariasis, responsible for step 3 of the process to develop a strategic plan, reviews all of the conclusions from steps 1 and 2 of this process and fills the gaps (particularly in the areas of social science and vector biology) that still remain. Once these gaps have been filled, the list of research needs must be thoughtfully distilled and prioritized in terms of both relevance to programme implementation and overall feasibility. Specific goals, targets and time frames can then be established.
4.2 The action plan

Having a strategic plan for LF research is an important step towards meeting the needs of the Global Programme, but without a concomitant action plan its value is much diminished. For LF research, however, the greatest barrier to developing a realistic action plan is not identifying what needs to be done or who can be engaged to do it, but rather, it is the critical lack of available funds to support the research. Therefore, the action plan needs to focus at least as much on implementing a funding strategy as it does on implementing research activities!

The traditional funding mechanisms are not now meeting the research needs of the LF community even as well as they did in the past. While one can hope that these traditional mechanisms (i.e. TDR support from its annual budget, investigator-initiated grants from national governments, international agencies or foundations) will begin to contribute again to a greater funding stream, it is clear that new approaches to stimulate funding of operational research for GPELF (and other global health initiatives) must be devised. Two obvious needs can be readily identified for developing new approaches to research funding – advocacy and leadership.

Advocacy really means making sure that the public and its decision-makers recognize the importance of the research that needs to be funded. From the humanitarian point of view, the efforts of GPELF and the research required to support it clearly address the poverty reduction, productivity and health objectives of the Millennium Development Goals. From a less humanitarian, practical point of view, decision-makers need to be made aware of the fact that society has already invested literally tens of millions of dollars in the Global Programme to Eliminate LF, and it is very much in the interests of protecting this investment that those hurdles (or potential hurdles) to the Programme’s achieving success be overcome through the necessary research efforts. Both these lines of advocacy (the humanitarian and the practical) are compelling, and it is important that they be disseminated as widely as possible.

Leadership must take on new attributes to meet the challenges of developing new funding strategies for LF and other ‘neglected’ tropical diseases. Many scientific funding institutions simply do not recognize how much of a difference support for the needed research for LF (and other similar diseases) would make to global health. Indeed, much of the research needed is relatively inexpensive. For a small proportion of the total budgets invested in the operational research needs of the LF Programme (and similar global health initiatives), the lives of an enormous number of the most underserved individuals in the developing world could be entirely transformed. Leadership in articulating such opportunities and in presenting both their cost-effectiveness and humanitarian implications is essential.

4.3 The challenge

But who will provide this leadership?

“Fundraising is everybody’s business.” Yet, still, it is WHO/TDR that has the most distinguished and enviable track record for understanding and investing wisely in research to overcome tropical diseases. Furthermore, it has the international convening authority and ‘honest broker’ image that make it an ideal candidate for the leadership role in pursuing a new, aggressive funding strategy.

It is fitting, therefore, to propose that TDR develops a portfolio describing the essential research needs for success of the LF elimination programme and similar global health initiatives, and that this includes the cost-benefit implications of the funded research. Convening a multinational council of research institutions and agencies, where specific research needs and their potential importance and value could be presented and debated, would ensure greater awareness of the global health community’s urgent needs for the real-world solutions that the supported research activities would generate. Establishing such a council would, moreover, foster a sense of global community partnership and a shared understanding among research institutions and agencies from different parts of the world (as well as provide an important forum for lobbying efforts), and it is likely that once the societal value of such research is recognized, a greater proportion of international research budgets would be devoted to it.

It is important that the strategic plan for LF research be completed by the SWG (step 3 of the three-step process), but it is just as important that an action plan for both implementation and funding of the identified research be generated. It is clear that the success of the Global Programme to Eliminate LF will require success of the action plan to implement the essential elements of the research agenda, and, in turn, this implementation will require the success of a new, aggressive funding strategy to generate the necessary funds to support it. For all of these challenges, WHO/TDR is in the best position to provide again that same measure of leadership and guidance that has led to its extraordinary success of the past 30 years.
References


Appendix A

LYMPHATIC FILARIASIS FORUM: PRIORITIZED RESEARCH NEEDS

1. RESEARCH DIRECTLY LINKED WITH GPELF ACTIVITIES (OPERATIONAL RESEARCH)

1.1 Essential tools: diagnostics

Prioritized research needs
• Develop effective, practical strategy for defining in field settings the areas and individuals with levels of Loa loa microfilaraemia so high as to be dangerous if MDA for concurrent LF were to be initiated (new tool; novel approach with available tools).
• Define the comparative accuracy of available diagnostics (antigen, antibody, DNA) and strategies for monitoring the progress of LF elimination programmes and for deciding both when to stop MDAs and how to initiate surveillance to detect potential recrudescence:
  – determine limits of sensitivity and specificity of available tests
  – carry out longitudinal studies using all diagnostic tools concurrently and in both high and low prevalence areas where LF elimination programmes are under way.
• Take advantage of new technologies to improve user-friendliness and efficiency of the LF diagnostics currently available (e.g. isothermal PCR, ‘multiplex’ antibody or PCR kits, use of oral fluids or urine for diagnostic tests).
• Validate sampling strategies for testing both vector and human populations for LF infection or exposure to infection.

1.2 Essential tools: drugs and clinical drug trials

Prioritized research needs
• Create a framework for monitoring for potential development of drug resistance, including:
  – defining criteria for the phenotype of reduced responsiveness and resistance
  – establishing a repository of microfilariae and/or adult worms to provide base-line data on the occurrence of drug-resistant genotypes
  – initiating a surveillance system for diminished responsiveness to antifilarial drugs.
• Initiate clinical trials of available antifilarial drugs in order to:
  – enhance microfilaria (mf) reduction (through alternative dosages, frequency regimens, etc.)
  – enhance adulticidal effectiveness
  – define ways to minimize patient treatment reactions at a population level
  – define a ‘standard treatment’ for individuals with LF.
• Ensure the safety of coordinated administration of drugs in ‘linked’ public health programmes (e.g. albendazole, ivermectin, azithromycin, praziquantel, etc.) or in other medical settings (e.g. used with HIV/AIDS or TB multidrug-therapy regimens).
• Establish a framework for seeking a macrofilaricide.
• Pursue discovery of anti-Wolbachia agent suitable for MDA and/or individual treatment.
• Develop broadly applicable implementation strategies for use of DEC-fortified salt (with or without concurrent albendazole administration).
• Evaluate use of moxidectin for LF.

1.3 Lymphatic Filariasis disease: clinical management

Prioritized research needs
• Investigate effects of MDA alone on progression or reversal of LF disease (LE, filaricele, ADL).
• Evaluate comparative studies of ‘filaricele’ surgical techniques for: a) relapse rates, b) surgical costs and duration, c) post-operative complications.
• Define epidemiology, risk factors, complications and optimal management of chyluria.

1.4 Programme implementation

Prioritized research needs
• Define the duration and coverage of MDA
necessary to achieve interruption of transmission in different epidemiologic/entomologic settings.

- Determine the effect of the rate of upscaling on:
  - duration of MDA necessary to achieve interruption of transmission
  - cost of the programme in the short and long term.

- Identify the most effective social mobilization strategies for MDA in different settings.

- Optimize MDA strategies for urban areas with low prevalence of infection.

- Determine the duration and coverage of DEC-salt administration necessary to interrupt transmission.

- Identify safe strategies for LF elimination in *L. loa* endemic areas.

- Assess the impact of LF elimination programmes on health systems.

- Identify the complementarities of specific targeted disease programmes that can promote linkages among the programmes for coordinated implementation, monitoring and evaluation.

- Review outcomes and “best practices” both from ongoing LF elimination programmes and from other, similar targeted disease programmes.

- Develop novel means of resource mobilization for upscaling national programmes.

**1.5 Monitoring and evaluation**

*J.O. Gyapong*

**Prioritized research needs**

- Initiate multicentre, longitudinal studies to define the relationship and comparative effectiveness of the available diagnostic monitoring tools (Ag, Ab, PCR) used in human or vector populations, to determine:
  - when to stop MDA
  - how to perform surveillance to ensure absence of resurgence
  - how to verify absence of transmission.

- Use data from this multicentre study to refine predictive models.

- Study the role of mobility and migration both in populations and by modelling to define their effects on LF transmission dynamics.

- Investigate the effects of non-compliance on the LF elimination programme, and the sociological reasons underlying non-compliance.

- Refine and validate tools for monitoring morbidity management programmes.

- Develop guidelines for monitoring multi-programme effectiveness and outcome in situations where LF elimination is coordinated (integrated) with other public health interventions (e.g. with onchocerciasis, intestinal parasite, trachoma or malaria control; and/or with vector control activities).

**1.6 Epidemiology, parasite biology, modelling**

*K.Y. Dadzie, M.-G. Basanez & F. Richards*

**Prioritized research needs**

- Define transmission dynamics for the various vector–parasite complexes, including the estimated reproductive lifespan of the adult worms.

- Determine end points at which MDA can be stopped with low probability of recrudescence, under different epidemiologic settings and using different diagnostic tests.

- Develop mathematical models to support decision-making on the duration of local MDA programmes in different epidemiological situations (e.g. initial endemicity, coverage rates, migration patterns, drug combinations).

- Define the comparative effectiveness of available tools and indicators for monitoring the progress of LF elimination programmes and for modelling to decide when to stop MDA and how to initiate surveillance to detect recrudescence.

**1.7 Vectors**

*T. Burkot & M. Bockarie*

**Prioritized research needs**

- Refine and evaluate the new tools for determining LF infection rates in mosquitoes.

- Develop and evaluate new tools for estimating the rate of contact between human and mosquito populations.

- Evaluate vector control strategies based on knowledge of vector biology for impact on LF transmission, including:
  - the effect of insecticide-impregnated mosquito nets on LF transmission by *Anopheles* and *Culex* vectors
  - breeding site reduction strategies on LF transmission by *Aedes* vectors
  - polystyrene beads and *Bacillus sphaericus* on LF transmission by *Culex* vectors.

- Conduct operational research on how to integrate successful vector control strategies for LF into ongoing programmes for other vector borne diseases (e.g. malaria, dengue).

**1.8 Health systems**

*D.A. McFarland & L.C. Barrett*

**Prioritized research needs**

- Test the current LF/health systems assessment tool (matrix) in a variety of endemic countries...
to determine if the data necessary for each proposed indicator can be feasibly acquired.
• Identify which health system function represents the best opportunity for assessing LF impact.
• Determine baselines for health systems performance in endemic countries at each level where the LF programme is likely to have an impact.
• Identify ways to disaggregate the health systems effects of the LF programme from those of other concurrent disease control programmes.

2. UPSTREAM (BASIC) RESEARCH TO SUPPORT THE GPELF

2.1 Pathogenesis
C.L. King & J.W. Kazura

Prioritized research needs
• Develop a revised, standardized set of definitions for lymphatic and urogenital pathology seen with LF.
• Utilize animal models and clinical studies to define the influence of LF parasites, molecules, endosymbionts and host-induced factors on lymphatic endothelium.
• Define the role of co-infections (local bacterial or systemic TB, HIV/AIDS, etc) in pathogenesis of LF disease.
• Define effects of the LF-altered host responsiveness on reactions to vaccines or to other infectious agents (malaria, HIV/AIDS, TB, etc).
• Explore roles of innate and adaptive immune responses to LF in the initiation, progression or reversal of lymphatic disease and disease of other organs.
• Define the role of the host immune response in the mechanism of action of the common antifilarial drugs (especially DEC).
• Define differential host susceptibility to development of disease caused by genetic, endocrinologic, nutritional and other types of heterogeneity.

2.2 Protective immunity: vaccines
A. Hoerauf & C. Steel

Prioritized research needs
• Define the changes to protective immunity among populations undergoing MDA programmes (requires longitudinal cohort studies in newborn infants and adults, the identification of markers of protective immunity [sterile and concomitant], and parallel observations in experimental animal models).
• Assess the impact of MDA-induced alteration of antifilarial immunity on efficacy of ‘routine’ vaccines and on co-infections with other helminths, malaria, TB and HIV/AIDS.
• Work towards an LF vaccine (as a tool for use post-2010) through:
  – identification of protective antigens and their product development
  – identification of the mechanisms underlying protective immunity
  – ‘piggy-backing’ observations on the anti-hookworm vaccine currently under development.

2.3 Filarial genomics
S. A. Williams

Prioritized research needs
• Collect materials:
  – before the opportunity is lost to preserve their genomes, collect geographically representative isolates of the various species and strains of human filarial parasites.
• Construct libraries:
  – construct updated and additional genomic and cDNA libraries to represent completely the different stages and species of filarial parasites.
• Sequencing:
  – expand EST sequencing from cDNA of a greater diversity of life cycle stages and parasites than currently available
  – complete the sequencing and annotation of the B. malayi genome
  – expand the sequencing of the W. bancrofti and O. volvulus genomes
  – complete the sequencing of the Wolbachia genome from B. malayi and the mitochondrial genomes from B. malayi and O. volvulus.
• Technical development:
  – develop transgenic methods useful for filarial parasites
  – utilize RNAi techniques for functional genomics studies
  – expand microarray assessments of gene expression with B. malayi and other filariae.
• Repositories:
  – develop and maintain all collections of genomes, libraries, sequences, microarrays, etc. in central repositories accessible to all interested investigators within and outside the filariasis research community.
### Appendix B

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WORKING PAPERS:
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4A: IMPACT OF MASS DRUG ADMINISTRATION ON CULEX-TRANSMITTED LYMPHATIC FILARIASIS IN INDIA

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1 INTRODUCTION

With more than 40% of its one billion population living in endemic areas and 48 million infected people (TDR, 1994), India accounts for 40% of the global lymphatic filariasis (LF) burden. Nearly 95% of the 48 million filarial infections in India are caused by Wuchereria bancrofti and transmitted by Culex quinquefasciatus, the tropical house mosquito. The other 5% of the infections are caused by Brugia malayi transmitted by Mansonia species.

Vector control combined with detection and treatment of people with microfilariae formed the core of the National Filaria Control Programme (NFCP) in India, which began in 1955 (NFCP, 1995). Its activities were confined to some urban areas with 11% of the total endemic population. Following the World Health Assembly resolution in 1997 calling for steps towards eliminating LF as a public health problem, India initiated a mass drug administration (MDA) programme. This programme was first implemented in 11 districts with a population of 32 million in 6 states; in 2001 it was extended to 20 more districts.

In a significant development, the MDA programme was expanded to include as many as 202 districts in 2004 (Sharma, 2004). The programme in India, except in a few districts, uses single-drug diethylcarbamazine (DEC) therapy. The merits of combination therapy with DEC + albendazole (ALB), recommended by WHO for use in LF elimination programmes, are being evaluated in pilot studies.

During the last decade, several studies have been initiated in India to address various issues that are directly or indirectly related to LF elimination, with more focus on MDA impact and process evaluation.

2 IMPACT OF MASS DRUG ADMINISTRATION

2.1 Impact on microfilaraemia

Longitudinal community-level trials in South Indian rural communities provided an insight into the potential of MDA to clear microfilaraemia in human populations. In one trial, five communities each received 8–9 cycles of DEC or ivermectin (IVM) mass administration at 12–15 month intervals over a period of 10 years. In these communities, nine cycles of DEC administration to 54%–75% of the population, except children under 15 kg body weight, resulted in a remarkable decrease in the microfilaria reservoir. The initial six cycles of treatment reduced the proportion of people with microfilariae from 13.2% to 1.9% (Ramaiah et al., 2002); three more cycles reduced the proportion from 1.9% to 0.8% (Ramaiah et al., unpublished). During the initial six-cycle duration, the geometric mean number of microfilariae declined from 0.66 to 0.06. During the seventh to ninth cycles, the mean number declined from 0.06 to 0.03. Thus, six cycles of treatment reduced the proportion of people with microfilariae and the geometric mean number of microfilariae by 86% and
91% respectively. Clearance of the remaining 15% microfilaria-positive infections was slow; it was not complete with three more cycles of treatment (fig. 1) and seems to require disproportionately more cycles of treatment. How many more cycles of treatment are required is unclear. Only 0.5% of children aged 1-15 years were positive for microfilariae after nine cycles of DEC treatment compared to 10.5% prior to the intervention.

With the other antifilarial drug, IVM, the results were slightly less impressive. Eight cycles of IVM administration decreased the proportion of subjects with microfilariae from 14.5% to 3.1%, and the geometric mean intensity of microfilariae from 0.62 to 0.07. Discontinuation of IVM administration after eight cycles led, within one year, to an increase in the microfilaria prevalence rate from 3.1% to 4.9%, and an increase in microfilaria intensity from 0.07 to 0.1 (Ramaiah et al., unpublished). Elsewhere also, an increase in the microfilaria-positive rate, from 1.81% to 4.74%, was observed one year after the cessation of two cycles of DEC + IVM mass administration (Sunish et al., 2002).

Villages may not respond uniformly to MDA. We observed variations in the microfilaria positive rate between villages after a given number of treatments. For example, after nine cycles of treatment, the microfilaria positive rate varied from 0% to 3.8% in the five treated communities. In another investigation, vector evaluation in 40 villages of a primary health centre (PHC) that received 5 cycles of MDA showed that 11 villages (28%) had a zero infection rate, that another 3 villages (8%) had a <1% infection rate, and that the remaining 64% villages had a 1%-19% infection rate. There are indications that smaller or low endemic villages show greater decreases in microfilaria positive rate and that larger or high endemic villages show lesser decreases. If these results are extrapolated to a district, which is an intervention unit in India and consists of more than one thousand villages with a population of 1.5 to 2.0 million, hundreds of endemic villages may become free from microfilaria positive infections after 6-10 treatments while others may require more cycles of treatment to decimate the microfilaria reservoir. In such a situation, it may be economical to ‘phase out’ the ‘successful’ villages from MDA over a period of time. Such a ‘phase out’ exercise appears to be complex because of uncertainties over: (i) the threshold criteria for stopping MDA; (ii) the threshold indicators and their measurement; and (iii) the sampling methodology for MDA impact assessment in an intervention unit with more than 1000 villages. These issues were recently elaborated by Lammie (2004) and Gyapong (2004).

With MDA alone and with 54% to 75% (or less than the recommended 80% of the population) undergoing treatment, 15% of microfilaria carriers continued to be microfilaria positive after six cycles of DEC treatment and 6% remained positive after nine cycles of treatment. Although the decrease in proportion of people with microfilariae is directly related to the number of treatments (Ramaiah et al., 2002), some people may not be able to clear microfilaraemia even after repeated treatments. For example, 1.6% of those who received 7-8 DEC treatments continued to show microfilaria in their blood. Thus, persistence of microfilaria carriers after 6-9 cycles of treatment may occur on two accounts: (i) treatment coverage of 54%-75% is inadequate; and (ii) though the efficacy of the drug is excellent, it falls slightly short of clearing microfilaraemia in all treated people. Therefore, improvement in peoples’ participation in treatment and some measures to improve the effectiveness of MDA seem to be necessary to achieve a zero per cent microfilaria positive rate in a 6-10 year time frame in large-scale or district-level elimination programmes, where treatment compliance is often much below 80% (Ramaiah et al., 2000).

Post-MDA microfilaria carriers and recrudescence of infection

Recrudesence of infection was shown to be a major threat to the control of Aedes transmitted LF in islands of the South Pacific. Recrudescence of infection is possible because of the persistence of microfilaria carriers in the community despite MDA. In some communities in our studies, 0.4% to 3.8% of the population continued to be microfilaria positive after nine cycles of treatment. These microfilaria positive people may be of two types: (i) those with intact infections owing to total non-compliance or poor compliance with treatment, as a result of semi-systematic treatment compliance patterns in their communities (Vanamail et al., 2005), and (ii) those left with what we call ‘residual microfilaraemia’ (or low density microfilaria carriers) resulting from the inability of the drug to clear 100% of the parasitaemia in every person (Eberhard et al., 1997). The number of such post-MDA microfilaria carriers, detectable using the blood smear technique, is expected to be approximately five in a village with a population of 1000 and a 10% microfilaria positive rate prior to MDA and a 0.5% positive rate after MDA. The microfilaria count of such carriers ranged from 1 to 38, and 60% of them had <5 microfilaria per 60 cu. mm of blood. The dangerous potential of these microfilaria carriers to perpetuate transmission and cause recrudescence of infection in humans is well documented in Aedes-transmitted LF (Esterre...
Microfilaria carriers with intact infections are likely to be an important source of infection to mosquitoes, at least for a few years. Hence it is necessary to ensure their treatment to prevent them contributing to transmission. Some information is available on the contribution of low density microfilaria carriers to transmission. A low density microfilaria carrier (1-6 microfilaria per ml of blood) can contribute to 0-15 infective stage larvae (L3) per year (McGreevy et al., 1982). Infected mosquitoes were also found in villages with zero or very low microfilaria positive rates (0.16% and 0.72%), estimated using the blood smear technique (Jayasekara et al., 1991; Ramaiah et al., 2003[a]). These studies clearly suggest that low level transmission is possible in the presence of residual microfilaraemia carriers in the communities. It is, however, not known whether this low level transmission is sufficient to cause recrudescence of infection in Culex-transmitted LF. In India, the proportion of subjects with microfilaria rose only marginally, from 0% to 0.03%, seven years after cessation of a DEC-fortified salt administration programme (G.S. Reddy, personal communication), indicating that recrudescence of microfilaraemia is not a serious problem. Partono (1978) is of the opinion that low levels of microfilaraemia detectable by the membrane filtration technique do not contribute to transmission. Some evidence for resurgence of infection was reported by Harb et al. (1993). Overall, the risk of recrudescence of infection in Culex-transmitted LF may not be as serious as in Aedes-transmitted LF. Some of the ongoing studies may provide opportunities to examine the ‘recrudescence’ issue.

2.2. Effect on transmission

The decline of transmission in treated communities was along expected lines, following the reduction of microfilaraemia prevalence and intensity in the human population. After six cycles of mass DEC administration, the annual infective biting rate (AIBR) per person fell from the pre-MDA level of 735 to 93, and the annual transmission potential (ATP) fell from 2514 to 125 (Ramaiah et al., 2003[a]), which is equivalent to reductions of 87% and 95% respectively. Monitoring of the resting vector population confirmed what we observed with microfilaraemia – residual parasitaemia persists even after nine cycles of MDA (fig. 2) (K.D. Ramaiah, unpublished). About 2% of resting mosquitoes were found with infection and 0.06% with L3 larvae after nine cycles of DEC treatment, compared to 18% and 1% respectively before the start of the study. This is equivalent to a 90% reduction in the infection rate and 94% in the infectivity rate. The transmission intensity index (resting vector density x proportion of mosquitoes with L3 x average number of L3/infective mosquito) declined by 97%. After nine cycles of MDA, while mosquitoes with microfilariae or first or second stage larvae were found in four out of five villages, mosquitoes with infective stage larva (L3) were found in only one out of five villages. Persistence of mosquitoes with infection was relatively higher in villages with high microfilaria positive rates. Intensive searches in a couple of villages where no mosquitoes with L3 had been found during routine evaluation for four consecutive years led to the detection of a single mosquito with L3 in one village. It is debatable whether MDA should be continued or withdrawn in those villages without (or with only ‘stray’) infective mosquitoes but with mosquitoes containing pre-L3 stage parasites. The decline in vector infection rate is similar to that observed with the microfilaria prevalence rate – it was consistent initially but meagre during
the seventh to ninth cycles of treatment. The impact of MDA on transmission intensity was also greater in smaller/low endemic villages compared to larger/highly endemic villages.

Mass IVM administration led to equally good results. Eight cycles of mass IVM administration led to a decline in resting vector infection rate from the pre-intervention value of 18.7% to 2.8%, and to a decline in infectivity rate from 1.71% to 0.31%, reductions of 85% and 82% respectively. Withdrawal of IVM administration led to a surge in infection rate from the reduced level of 2.8% to 5.1%, and in infectivity rate from 0.31% to 0.74, within one year (Ramaiah et al., unpublished). Sunish et al. (2002) reported an increase in ATP from 21 to 632 when administration of DEC + IVM was stopped after two treatments.

The possibility of recrudescence of infection in MDA-implemented communities is partly determined by the ‘limitation’ and ‘facilitation’ phenomena observed in vector species. Culex and Aedes exhibit limitation, in which transmission efficiency of the vector increases at low microfilaria densities; this is often seen after MDA programmes. Anopheles vectors however exhibit facilitation – they sustain transmission at higher densities of microfilariae than Culex (Southgate, 1992). As the critical density of microfilariae required to sustain transmission in Culex is less than in Anopheles, more efficient control of microfilaraemia is necessary in Culex vector areas than in Anopheles vector areas.

2.3. Effect on antigenaemia

The level of circulating filarial antigen indicates the burden of infection with adult or pre-adult worms, and assessment of antigenaemia after MDA is useful for finding out if transmission is totally interrupted. However, in large-scale MDA programmes the timing of antigenaemia assessment appears to be important – it may depend on the efficiency of the programme in terms of compliance with treatment. With poor or moderate treatment compliance (40% to 60%), some amount of transmission is always possible during the initial cycles (1-4) of MDA. For example, we estimated the total transmission during the first to fourth cycles of MDA to be 524 infective bites per person. This may explain the presence of antigenaemia in as many as 18.9% of children in the 0-5 year age group after six cycles of DEC treatment, compared to 22.4% in placebo villages (p>0.05) (Ramaiah et al., 2003[b]). These results suggest that a significant effect of MDA on the antigenaemia positive rate is possible only with very high levels of (>80%) treatment compliance from the beginning of the programme.

2.4. Impact on acute and chronic disease

Community level trials suggest that up to four cycles of mass administration of DEC or IVM will have no impact on incidence of the acute form of the disease (Das et al., 2001), which is a significant health problem in endemic communities. This confirms earlier findings that foot care combined with local application of antibiotic and antifungals is more important for containing the incidence of ADL episodes than treatment with antifilarial drugs (Shenoy et al., 1998).

Studies carried out in India showed a dramatic impact of MDA on frequency of hydrocele, which constitutes about 60% of the total chronic disease burden (TDR, 1994). The proportion of people with hydrocele was 20.5% prior to intervention, compared to 5.1% (= 75% reduction) after seven cycles of DEC mass administration. The impact was more appreciable in the <40-year age group, in which the frequency of hydrocele cases declined from 13.6% to 1.5% (= 90% reduction). In villages administered seven cycles of IVM, the overall frequency of hydrocele decreased from 23.9% to 10.4% (= 56% reduction) and the frequency in the <40-year age group decreased from 15.8% to 6.0% (= 62% reduction). However, these optimistic results need to be viewed in the light of the 47% (20.4%-10.9%) and 48% (13.5%-7.1%) reductions observed in placebo villages in the entire population and <40-year age group respectively (Vector Control Research Centre, annual report 2003). Meyrowitsch et al. (1996) and Bockarie et al. (2002) also reported a very appreciable impact of MDA on prevalence of hydrocele. It is not known if a few more cycles of MDA or better treatment compliance would further reduce the prevalence of hydrocele, or if MDA caused ‘cure’ of hydrocele is irreversible. Because of the close association between the chronic and acute disease, such a drastic reduction in the proportion of people with hydrocele should also lead to some relief for the patients from acute disease episodes.

MDA is unlikely to provide much relief to lymphoedema patients in the Indian situation. The pre-intervention lymphoedema frequencies of 3.7% in the population administered with DEC and 4.6% in the population administered with IVM remained almost unchanged after seven cycles of treatment (Vector Control Research Centre, annual report 2003). Hence, the importance of a foot-care-based morbidity-management strategy for lymphoedema patients assumes greater significance for the Indian programme.
3. COMBINATION THERAPY VERSUS SINGLE DRUG THERAPY

Data are now available from four research studies on the impact of combination therapy (DEC + albendazole) on microfilaria prevalence and geometric mean number of microfilaria. In all four studies, combination therapy yielded greater reduction in the microfilaria positive rate than single drug (DEC) therapy. Two to three cycles of mass administration of DEC + ALB decreased the proportion of microfilaria positive subjects by 37%–61%, and DEC alone decreased the proportion by 3%–42%. The difference in microfilaraemia clearance rate between the two regimens was in the range 11%–34% (p>0.05) (Rajendran et al., 2004; Ramaiah et al., unpublished; Vector Control Research Centre, annual report 2003). There was a difference in impact on geometric mean microfilaria count between the two regimens – two studies showed only a marginal difference, while the other two studies showed that a 27%–61% greater reduction in the count is possible with combination therapy. Comparable data on the effect of the two regimens on the antigenaemia positive rate is available only from one study – the rate decreased from 23.8% to 10.1% in the population treated with three cycles of combination therapy and from 17.0% to 16.3% in the population treated with single drug therapy, equivalent to 57% and 4% respectively (p<0.05) (Rajendran et al., unpublished). As expected, the combination therapy was very effective against intestinal helminths – 76% of the population became free from infection, compared to 15% with DEC alone, after two cycles of MDA. The intensity of infection was reduced by 98% with combination therapy compared to 58% with DEC alone (Mani et al., 2004), and these reductions are sustainable for one year in the people treated with DEC + ALB (Rajendran et al., 2003).

After six rounds of MDA, the impact of DEC + IVM combination on microfilaraemia and transmission was found to be almost similar to that of DEC alone (Ramaiah et al., unpublished).

4. COST–BENEFIT AND COST–EFFECTIVENESS ANALYSES

Recent analyses suggest that benefits to the community expected to accrue from the use of MDA far outweigh its costs. Prevention of chronic disease by spending US$ 8.41 leads to savings of 58 working days per case per annum, equivalent to US$ 449 over a period of 11 years, the duration of productive life lost by a patient. This gives a cost–benefit ratio of 0.019 (Ramaiah and Das, 2004). Cost–effectiveness analysis revealed that the predicted cost per DALY averted with DEC-medicated salt, MDA and vector control is US $3.3, 8.1 and 84.3 respectively (Remme and Ramaiah, unpublished). These studies clearly suggest that MDA is a very cost-effective option.

5. OPERATIONAL ISSUES

Experience from large-scale MDA programmes suggests that, with reasonable efforts, LF drugs could be distributed to >80% of the population. However, based on some strong beliefs, 1/3 to 1/4 of the population is reluctant to consume the drug (Ramaiah et al., 2000; Babu and Kar, 2004); this is one of the most important issues for the Indian programme. Changing the behaviour of the reluctant, and sustaining the interest of the willing, through appropriate community mobilization strategies – notwithstanding the costs – is a major challenge, particularly in the wake of the severe side reactions and even some deaths attributed to MDA (Ramaiah et al., 2005[a]). Failure to do this will have significant negative implications for the duration and impact of the LF elimination programme. A social mobilization strategy to improve people’s participation in MDA programmes yielded some positive results (Ramaiah et al., unpublished).

Some workers question the rationale of adopting a district (Sabesan et al., 2005), which consists of 30–50 PHCs and more than 1000 villages, or an entire urban area as an ‘intervention unit’ because of the sheer size and variation in endemicity level; these workers argue for a ‘stratification’ approach. Studies in urban areas suggest that LF is steadily decreasing, particularly in higher income groups, owing to better health care and awareness and use of ‘self protection’ measures against the mosquito nuisance (primarily the LF vector C. quinquefasciatus) in almost all households (Snehalatha et al., 2003). It is not clear whether such groups should be included in MDA at all (Ramaiah et al., 2005[b]).

The quality of drugs has become a major issue after allegations of death due to DEC in the southern state of Tamil Nadu (Ramaiah et al., 2005[a]).

6. CONCLUSIONS

• Evidence suggests that nine cycles of mass DEC administration are able to: (a) clear microfilaraemia in 94% of subjects; (b) cut down transmission very drastically; (c) prevent incidence of new infections; (iv) appreciably reduce the proportion of cases with hydrocele in Culex-transmitted LF. These remarkable results were achieved with less than the recommended 80% treatment compliance.
• Microfilaria prevalence declines consistently from a level of >10% to 1–2% with the initial cycles of treatment. Further decline to zero per cent appears to be slow and possible only with multiple cycles of MDA.
• After nine cycles of treatment, in most villages the microfilaria positive rate declines to <1% with virtually no infective mosquitoes. However, most of these villages are likely to have a few microfilaria carriers, many people with antigenemia, and mosquitoes with infection, making it uncertain whether the villages qualify for stopping MDA.
• The outcome of MDA and the number of cycles of treatment required is likely to vary with the endemicity and population size of the village. Low endemic villages are more amenable and require fewer cycles of treatment to reduce the proportion of people with microfilaraemia to zero per cent.
• Combination therapy achieves better clearance of microfilaraemia than single drug therapy, as well as appreciable reduction in intestinal helminth infections.
• Evidence from large-scale programmes suggests that a considerable proportion of people accept the drugs but are reluctant to consume them.

7. RESEARCH NEEDS
• Assess critically the potential of the last few and persistent microfilaria carriers to cause recrudescence of infection in communities that have progressed to a near zero rate of microfilaria positivity.
• Explore various options such as vector control, new treatment regimens, and DEC-medicated salt, to improve the effectiveness of MDA in eliminating the residual microfilaria reservoir with fewer cycles of treatment.
• Determine the threshold indicator to be used in LF elimination programmes and define the threshold levels for stopping MDA with no probability of transmission and recrudescence of infection.
• Develop user-friendly and cheaper molecular tools for health workers to monitor the impact of MDA at PHC level and facilitate decision-making about stopping or continuing MDA.
• Develop and validate sampling strategies to: (a) monitor the impact of MDA, (b) stop MDA, and (c) monitor the recrudescence of infection.
• Develop and test strategies to bridge the gap between receiving and consuming the drug in MDA programmes.
• Investigate the collateral benefits of MDA.
• Define the socioeconomic and epidemiological criteria for excluding low-risk populations in urban areas from active MDA programmes, and assess the advantages and disadvantages of their exclusion.
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OVERVIEW OF LYMPHATIC FILARIASIS CONTROL / ELIMINATION IN THE REGION

Vector control was the primary tool for controlling filariasis in the Pacific when effective antifilarial drugs were unknown and, even after effective antifilarials became available, was preferred because mass drug administration (MDA) campaigns were considered too labour intensive (Burkot and Ichimori, 2002). Beginning in the 1950s, various diethylcarbamazine (DEC)-based population treatment strategies were undertaken to control lymphatic filariasis (details below). These campaigns often succeeded in achieving significant reductions in microfilariae (mf) rates and densities. However, mf rates frequently rebounded due to: (1) poor compliance; (2) inadequate duration of campaigns; and (3) failure of DEC to completely kill or sterilize adult Wuchereria bancrofti in all people treated, despite repeated administration (Chow, 1974).

The present Pacific Programme for the Elimination of Lymphatic Filariasis (PacELF) relies on repeated annual mass drug administration (MDA) of diethylcarbamazine (DEC) and albendazole, with nearly universal coverage of affected populations. Evidence that the present DEC/albendazole combination will be more successful than monotherapy with DEC against adult worms is supported by falling adult worm antigen levels and clinical reactions in infected humans receiving the drug combination (Ottesen, Ismail and Horton, 1999). A number of the PacELF countries have now completed five annual rounds of MDA but their impact has not yet been fully evaluated. There is, however, evidence from Samoa and French Polynesia where Aedes polynesiensis is an important vector that, despite high coverage with MDA campaigns, transmission was not interrupted by the DEC-based campaigns as there were increases in microfilaria (mf) prevalence after the campaigns. There may well be a need for adjunct control measures, including vector control, to accomplish disease elimination where mf levels are not adequately suppressed by MDA alone.

VECTOR CONTROL AS AN ADJUNCT TO MDA FOR LYMPHATIC FILARIASIS ELIMINATION

Success in the control and elimination of filariasis based only on anti-vector activities has been demonstrated in the Pacific. In Papua New Guinea and the Solomon Islands, where species of Anopheles are the vectors of malaria and filariasis, filariasis was eliminated from areas where DDT spraying campaigns to control malaria were undertaken (Bockarie, 1994; Webber 1977, 1979). Similarly, W. bancrofti was eliminated from Australia, primarily by sanitation campaigns against C. quinquefasciatus (Boreham and Marks, 1986). Comparable vector control based successes in the areas where Ae. polynesiensis is the vector do not exist. Ae. polynesiensis is a notoriously efficient vector due to ‘limitation’, a characteristic whereby the efficiency of transmission increases with decreasing densities of mf (Pichon, 2002).

In areas where W. bancrofti is subperiodic, lymphatic filariasis (LF) transmission can be complex due to the presence of multiple vectors; in the region from Fiji

| Table 1. Reported Aedes vectors of lymphatic filariasis in the Pacific |
|-----------------------------|-----------------------------|
| Vector                      | Countries where found       |
| Aedes cooki                 | Niue                        |
| Aedes fijiensis             | Fiji                        |
| Aedes horrensces            | Fiji                        |
| Aedes kochi                 | Papua New Guinea            |
| Aedes marshallensis         | Kiribati                    |
| Aedes oceanicus             | Tonga                       |
| Aedes polynesiensis         | American Samoa, Samoa, Cook Islands, Tokelau, Tuvalu, French Polynesia, Wallis and Futuna, Fiji |
| Aedes pseudoscütellaris     | Fiji                        |
| Aedes rotumae               | Rotuma Island in Fiji       |
| Aedes samoanus              | Samoa                       |
| Aedes tabu                  | Tonga                       |
| Aedes tutuilae              | Samoa                       |
| Aedes upolensis             | Samoa                       |
| Aedes vigilax               | New Caledonia, Fiji         |
to French Polynesia, there are 14 reported *Aedes* vectors (six LF vectors are found in Fiji) (table 1). With the exception of *Ae. polynesiensis* and *Ae. vigilax*, little is known about the ecology of these mosquitoes and there is almost no documentation of attempts to control them. *Ae. polynesiensis* is believed to pose the greatest challenge to LF elimination and is the most important *Aedes* LF vector in the Pacific, and is thus the focus of this manuscript.

**VECTOR CONTROL STRATEGIES FOR **

**Aedes**

Mosquito surveillance and control is an integral part of filariasis elimination plans in many Pacific islands. Among these island countries, larval surveys for filariasis vectors are often advocated with environmental sanitation to reduce mosquito breeding sites, as are bednets and ultra-low-volume (ULV) spraying against adult mosquitoes. Unfortunately, the effectiveness of these interventions at the population level has rarely been evaluated. For example, many studies on controlling *Ae. aegypti* for dengue have shown that treating rainwater drums with larvicides dramatically reduces the numbers of mosquitoes breeding in these drums, but there are only a few studies showing the impact that elimination of drums has on the number of adult mosquitoes.

There have not been any studies on controlling *Ae. vigilax* in the Pacific. The long flight range of this vector means that focal larviciding is unlikely to be feasible or cost-effective. However, as *Ae. vigilax* breeds in salt marshes, runnels (ditches designed to allow flushing of salt marshes by tides) had some impact on larval numbers in Australia (Dale et al., 1993). Unfortunately, the impact on biting rates was not measured in this study.

More operational research for control of *Ae. polynesiensis* at population level has been conducted in the Pacific (table 2). *Mesocyclops aspericornis* reduced by 98% the number of *Ae. polynesiensis* larvae in treated crab holes. However, despite treating more than 14 000 crab holes on one French Polynesian island, no measurable impact on the number of biting *Ae. polynesiensis* was demonstrated (Lardeux et al., 1992). Insecticide fogging and spraying campaigns have had minimal impacts on *Ae. polynesiensis* biting rates, with reductions of less than 64% in three trials (Suzuki and Stone, 1976; Chow, 1974; Wharton and Jachowski, 1980).

Table 2. Summary of field trials for controlling *Aedes* in the Pacific

<table>
<thead>
<tr>
<th>Vector*</th>
<th>Breeding site</th>
<th>Country</th>
<th>Control method</th>
<th>% Reduction in Breeding sites</th>
<th>% Reduction in Mosquitoes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ae. polynesiensis</em></td>
<td>Tree holes</td>
<td>Fiji</td>
<td>Destroying tree holes</td>
<td>87%</td>
<td>?</td>
<td>Burnett GF, 1960[a]</td>
</tr>
<tr>
<td><em>Ae. polynesiensis</em></td>
<td>Crab holes</td>
<td>Fiji</td>
<td>1% Lindane and plugging of crab holes</td>
<td>?</td>
<td>0% on biting</td>
<td>Burnett GF, 1960[a]</td>
</tr>
<tr>
<td><em>Ae. polynesiensis</em></td>
<td>All types</td>
<td>French Polynesia</td>
<td>Breeding site elimination within 100 yd. of village</td>
<td>?</td>
<td>80% to 90%</td>
<td>Kessel JF, 1965</td>
</tr>
<tr>
<td><em>Ae. polynesiensis</em></td>
<td>All types</td>
<td>French Polynesia</td>
<td>Breeding site elimination within 100 yd. of village</td>
<td>?</td>
<td>90% of larvae</td>
<td>Laigret J, 1958</td>
</tr>
<tr>
<td><em>Ae. polynesiensis</em></td>
<td>All types</td>
<td>French Polynesia</td>
<td>Breeding site elimination; vegetation control</td>
<td>?</td>
<td>81% biting</td>
<td>Byrd EE, St Amant LS, 1959</td>
</tr>
<tr>
<td><em>Ae. polynesiensis</em> and <em>Ae. samoanus</em></td>
<td>All types</td>
<td>Samoa</td>
<td>DDT spray of breeding site and fogging of houses/bush</td>
<td>?</td>
<td>64% biting</td>
<td>Suzuki T, Stone F, 1976</td>
</tr>
<tr>
<td><em>Ae. polynesiensis</em> and <em>Ae. samoanus</em></td>
<td>Not known</td>
<td>Samoa</td>
<td>Abate larvicide and malathion fog</td>
<td>?</td>
<td>60%</td>
<td>Chow CY, 1974</td>
</tr>
<tr>
<td><em>Ae. polynesiensis</em></td>
<td>Not available</td>
<td>American Samoa</td>
<td>DDT house spraying; aerial spraying every 14 days</td>
<td>Not available</td>
<td>0% at 14 days</td>
<td>Wharton and Jachowski, 1980</td>
</tr>
<tr>
<td><em>Ae. aegypti</em> and <em>Ae. samoanus</em></td>
<td>Cisterns, wells, drums</td>
<td>French Polynesia</td>
<td>Integrated control (Abate, sealing drums, polystyrene beads, <em>Poecillia reticulata</em>)</td>
<td>94%</td>
<td>84%</td>
<td>Lardeux F et al, 2002(a)</td>
</tr>
<tr>
<td><em>Ae. polynesiensis</em></td>
<td>Crab holes</td>
<td>French Polynesia</td>
<td><em>Mesocyclops aspericornis</em></td>
<td>98% of larvae</td>
<td>0% of adults</td>
<td>Lardeux F et al, 1992</td>
</tr>
<tr>
<td><em>Ae. polynesiensis</em></td>
<td>Crab holes</td>
<td>French Polynesia</td>
<td>Insecticide impregnated crab bait</td>
<td>86%</td>
<td></td>
<td>Lardeux F et al, 2002(b)</td>
</tr>
</tbody>
</table>

* References in the literature to *Ae. pseudoscutellaris* prior to 1960 are believed to be *Ae. polynesiensis* and are listed as *Ae. polynesiensis*. *Ae. polynesiensis* was described by Marks as a separate species in 1962.
The effectiveness of larval source-reduction campaigns against *Ae. polynesiensis* has been repeatedly demonstrated in French Polynesia (Kessel, 1965; Laigret, 1965), particularly when integrated with other measures (Lardeux et al., 2002[a]) including removal of vegetation to facilitate discovery of breeding sites (Byrd and St Amant, 1959). However, the sustainability of source reduction is unproven. A Fijian study documented the rapidity with which breeding sites reappear after clean-up campaigns. Within 4.5 months, 3906 destroyed containers were replaced with 2040 new breeding sites and 2544 destroyed tree holes were replaced with 388 new tree holes demonstrating breeding (Burnett, 1960[b]). These efforts are labour-intensive. Hairston (1973) estimated that one man-month of work was needed to eliminate breeding sites around each village, and that only 77% of breeding sites were amenable to destruction.

Targeted source reduction of *Ae. polynesiensis* will only be possible if we have more complete knowledge on the importance of different breeding sites. Although studies show that *Ae. polynesiensis* will breed in a large variety of man-made (storage drums, tyres, rain gutters) and natural (crab holes, tree holes, leaf axils, rat-damaged coconuts) containers, their relative importance in different areas is not known. Specific local studies are required to guide control efforts. In American Samoa, for example, Lambdin (Masters in Public Health [MPH] thesis, Emory University, unpublished) found that almost 70% of *Ae. polynesiensis* pupae were present during the wet season in five container categories (drums, tyres, buckets, ice cream containers, folded plastic sheets). Similar results were obtained during the dry season, with 66% of *Ae. polynesiensis* pupae produced in buckets and plastic containers (Burkot, unpublished) although buckets and plastic containers were only 27% of all containers surveyed.

Anti-dengue campaigns worldwide are now primarily based on larval source reduction and, while important behavioural differences exist between *Aedes aegypti* and *Ae. polynesiensis*, there are sufficient similarities between the two species (both bite in the daytime and breed in containers) to allow us to draw some lessons from the anti-*Ae. aegypti* campaigns for *Ae. polynesiensis* control. Of particular importance is the need for local information on breeding sites and community practices prior to the implementation of health education campaigns aimed at encouraging the community to reduce the number of breeding sites.

There are very few data on control strategies targeting adult *Ae. polynesiensis* mosquitoes. A trial is being conducted in Fiji to evaluate the impact of insecticide-treated curtains and bednets on transmission by *Ae. polynesiensis* (Koroivueta, Ichimori and Burkot, personal communication). There is clearly a need to investigate the potential of additional personal protection measures, including naturally occurring botanical extracts, as components of an integrated *Ae. polynesiensis* control strategy. University of Kentucky researchers are conducting trials using Wolbachia-induced cytoplasmic incompatibility for *Ae. polynesiensis* elimination (Dobson, personal communication).

From the above review, it is clear that much of our understanding of *Aedes* behaviour and transmission of *W. bancrofti* is based on studies conducted many decades ago, and that there has been limited investment in recent years in operational research to guide an integrated approach to LF control and elimination.

**IMPACT OF MASS DRUG ADMINISTRATION ON TRANSMISSION**

Prior to the 1950s, LF control in the Pacific relied almost exclusively on vector control. With the discovery of the anti-microfilaricidal activity of DEC, emphasis shifted to MDA campaign-based control. These campaigns, particularly in Samoa and French Polynesia, achieved significant reductions in mf rates and densities (Ichimori, 2001; Esterre et al., 2001; Laigret et al., 1980). In Samoa, five extensive campaigns using DEC, including 12–18 month treatments in 1966 and 1971, and single annual doses in 1982, 1983 and 1986, reduced the mf rate from 21% in 1964 to 2.3% in 1987. Mf rates declined to 0.14% in 1974, following the second DEC campaign, but rebounded to 2.1% within two years (Ichimori, 2001).

In French Polynesia, since 1955 but excluding the years 1960–67 and 1970–74, twice yearly DEC chemotherapy (6 mg/kg) was administered to an average of 85% of the population on Maupiti island (Esterre et al, 2001). In addition, mosquito control using DDT (1955–1957) and larval breeding source destruction (1955–1970) were implemented. Despite these efforts, a comprehensive survey in 2000 found that 0.4% of residents had mf and 4.6% had antigenaemia (Esterre et al, 2001).

After cessation of the MDA campaigns in Samoa and French Polynesia, mf rates increased (Kimura et al., 1985; Ichimori, 2001). While the extensive campaigns succeeded in minimizing filariasis as a public health
problem by significantly reducing the number of clinical cases of the disease, elimination of the parasite was not achieved. A subsequent analysis of LF positives on Maupiti suggests that residual positives may have persistently not complied with the MDA programme (Nguyen, personal communication).

Under the PacELF MDA programme, annual administration of DEC and albendazole has been undertaken in the following countries where *Aedes* species are important vectors: American Samoa, Cook Islands, Fiji, French Polynesia, Niue, Samoa, Tokelau, Tonga, Tuvalu, and Wallis and Futuna. By the end of 2005, five rounds of MDA will have been completed in the Cook Islands, French Polynesia, Niue, Samoa and Tonga. Samoa is the only country to have completed its prevalence assessment after five rounds of MDA, with annual coverage ranging from 57% to 90%, but the results of this assessment are not yet available.

**FEASIBILITY OF TERMINATING TRANSMISSION BY MDA OR OTHER INTERVENTIONS, AND RISK OF RECURRENCE**

Despite phenomenal progress in the Pacific towards elimination of LF, several major challenges remain. Firstly, we do not know the exact level of suppression of mf that needs to be achieved in order for elimination to be realized. This obstacle is even more vexing where *Aedes* is the vector. The implications of Pichon’s (2002) ‘limitation’ models have been verified by observations on mf rates following MDA campaigns with DEC in Samoa. Despite reducing mf rates to less than 0.33% between 1972 and 1974, LF rates rose afterwards. It is likely that ‘pockets of infection’ capable of initiating resurgence of LF will remain and that relatively low levels of microfilaraemia may permit resurgence and pose a formidable challenge to traditional surveillance techniques. New surveillance tools will certainly be necessary where *Aedes* mosquitoes are the vectors if MDA is used alone for elimination of LF.

A second significant challenge is the mobility of Pacific islanders; migration is particularly common in many of the Pacific islands where *Aedes* is an important LF vector. More Cook Islanders live in New Zealand than on the main island of Rarotonga, and thus may have missed annual MDA treatment. Frequent travel back to the Cook Islands carries with it the possibility of reintroduction of LF. Similarly, Samoans frequently travel between Samoa and American Samoa for economic opportunities and to visit relatives and friends living in the neighbouring country. Thus, the PacELF regional approach to LF in the Pacific is appropriate but migration between the various Pacific countries, including Australia and New Zealand, must be taken into consideration.

A third challenge is the presence of individuals whose behaviour places them at risk of infection or who do not regularly participate in MDA, placing their communities at risk of ongoing transmission (Gyapong et al., 1996). Merely increasing the number of years of MDA campaigns will not reach these individuals, but a better understanding of their perceptions and priorities will allow tailoring of messages and interventions so that they are locally appropriate and acceptable (Durrheim et al., 2004).

A fourth challenge is the potential for *W. bancrofti* to develop resistance to either DEC or albendazole. Albendazole resistance is already common amongst helminths of veterinary importance. Although there is currently no evidence of resistance to DEC or albendazole in areas where LF elimination programmes are under way, no reliable assay system is currently available to allow assessment of resistance. Resistance is more likely to appear late in an MDA programme when success appears feasible.

These challenges can be reduced by integrating vector control with MDA for LF elimination (Burkot et al., 2002). A country-wide vector control programme can: suppress LF transmission without the need for identifying all individual ‘pockets of infection’; minimize the risk from imported mf positives; and reduce the spread of any DEC or albendazole resistant *W. bancrofti*. Furthermore, control measures targeting *Aedes* vectors may also decrease the risk of dengue transmission. Vector control strategies as adjuncts to the MDA campaigns are certainly needed in the next five years to ensure success of the elimination efforts.

**IMPACT OF MDA ON DISEASE, AND ELIMINATION OF LF AS A PUBLIC HEALTH PROBLEM**

Clinical presentations, now known to be consistent with LF infection, were first reported in Polynesia by early European explorers, including Captain Cook. In recent years there have been relatively few cross-sectional surveys on prevalence of LF disease; however, overt pathology was seen to diminish concurrently with previous widespread DEC-based MDA. The most recent data available from Pacific countries in *Aedes* transmission areas include:
- In Samoa in 1954, an elephantiasis rate of 3.6% and a lymphadenitis rate of 15%-20% were reported (Sasa, 1976).
- In Tonga in 1977, a 0.39% prevalence of elephantiasis and a 2.4% prevalence of hydrocele were found.
- In Tuvalu in 1928, 23% of men surveyed had hydroceles and there was an 8.1% elephantiasis rate (Sasa, 1976).
- In Tokelau during a 1994 survey, a single case of elephantiasis was found (Tokelau country report to the PacELF annual meeting, Apia, Somoa, 1994).
- In Niue in 1960, a clinical survey found 5.5% of the population with symptoms of LF (Ichimori, unpublished).
- In French Polynesia, the most recent data report a 1.3% prevalence of elephantiasis (Sasa, 1976).
- In Fiji between 1991 and 1995, a countrywide clinical survey of 18 253 people found 16% of people had lymph node enlargement, 0.9 % had hydrocele, and 0.2% had elephantiasis (Fiji MOH, unpublished).
- In the Cook Islands during 1965, a survey found that 3.8% of 498 people examined had elephantiasis (Sasa, 1976).

SUMMARY OF THE MAJOR REMAINING UNCERTAINTIES, RESEARCH QUESTIONS AND SUGGESTIONS FOR SPECIFIC STUDIES

The ability of *Ae. polynesiensis* to sustain LF transmission at low mf levels demands an integrated approach to control that is sensitive to local vector and human characteristics and behaviour. The following conclusions may be drawn from the limited number of population-based studies of *Aedes* control strategies:

- The contribution of human behaviour and perceptions to achieving and sustaining adequate MDA coverage, and to placing individuals at risk of infection, needs to be better understood and probably poses the biggest threat to achieving elimination of LF.
- As well as benefits in eliminating LF transmission, *Ae. polynesiensis* control strategies offer potential in preventing and controlling dengue through their concurrent impact on *Ae. aegypti*.
- Source reduction of *Ae. polynesiensis* breeding sites has demonstrated the most consistent success in reducing *Ae. polynesiensis* numbers.
- When source reduction is integrated with other control measures, for example use of insecticide-treated crab baits where crab holes are the major breeding sites, then the impact on biting rates and possibly transmission is enhanced.
- While insecticide-treated bednets have been shown to effectivelly control filariasis where it is transmitted by anophelines, their impact on the day-time biting *Aedes* vectors in the Pacific is unknown. It may be that insecticide-treated materials, including curtains, could have a significant impact in either killing vectors or repelling vectors from houses.
- Insecticides have not been effective in reducing adult *Ae. polynesiensis* populations when used alone.
- The demonstrated ability of LF to rebound in *Ae. polynesiensis* transmission areas, even at very low mf rates, and the high mobility of Pacific island peoples makes recrudescence a real threat:
  - surveillance systems are needed to promptly detect mf positive individuals
  - vector control can reduce the risk of LF resurgence.
- Little is known about the impact of the PacELF MDAs on the prevalence of LF disease.

RECOMMENDATIONS FOR SPECIFIC STUDIES

- As a large number of countries with *Aedes* vectors of LF have completed five rounds of MDA, there is an urgent need for population-based trials of *Aedes* control strategies for implementation as adjunct measures to MDA. Strategies that deserve further evaluation include:
  - novel biological, chemical and mechanical source reduction measures, including the use of crab baits impregnated with insecticides
  - use of insecticide-treated materials, including clothing and curtains
  - personal protection measures.
- Control strategies that integrate a combination of approaches consistent with the ecology of local vectors should be encouraged.
- Simple survey methods for trapping adult *Aedes* that can be implemented at local level need to be evaluated, as standard traps are not effective.
- Pupal surveys need to be undertaken to identify the most productive containers for producing adult *Aedes*.
- Qualitative studies are required to provide a better understanding of human behavioural and perceptual contributions to ongoing transmission.
- Surveys of remaining LF pathology are needed to determine the impact of the MDA strategy where *Aedes* species are the vectors.
References


4C: LONG-TERM IMPACT OF MASS DRUG ADMINISTRATION ON BANCROFTIAN FILARIASIS IN DREIKIKIR, PAPUA NEW GUINEA

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¹ The Papua New Guinea Institute of Medical Research, Madang, Papua New Guinea
² Case Western Reserve University School of Medicine, Cleveland, USA

INTRODUCTION

A crucial unresolved issue in chemotherapy-based elimination programmes against bancroftian filariasis is the level to which the parasite population density must be reduced in order to stop the intervention with minimal risk of recrudescence. In ecological terms, the goal is local, and ultimately global, extinction of lymphatic filariasis (LF). Mass drug administration (MDA) programmes that are too short in duration, interrupted, have inadequate population coverage, or in which drug resistance arises, will eventually lead to parasite population recovery and recrudescence. On the other hand, MDA given for too long a period of time is wasteful of financial and human resources, and inappropriate since individuals will be given drugs that are not indicated for personal or public health reasons.

EARLIER MDA STUDIES IN DREIKIKIR, PAPUA NEW GUINEA

From 1993 to 1998, we examined the impact of four annual single doses of MDA (block randomization of DEC alone [6 mg per kg body weight] vs. DEC + ivermectin [400 µg per kg]) on anopheline-transmitted W. bancrofti in Dreikikir, East Sepik Province, Papua New Guinea. These data have been published.¹² The key findings were that: a) transmission by Anopheles punctulatus and An. koliensis, the major vectors of LF in Papua New Guinea, was reduced by 96.7% in the low transmission zone one year after the fourth cycle of MDA; b) the human microfilaria+ (mf+) rates were reduced by 86%–98% one year after the fourth cycle of MDA; c) there was no significant difference in reduction of transmission and human infection after the third cycle of MDA; d) the impact of MDA on mosquito and human infection levels was greatest in areas where the pre-treatment level of transmission was moderate (annual transmission potential [ATP] 45–404 L3/person/year) vs. areas where transmission was relatively higher (ATP 704–2518 L3/person/year). Salient data supporting these claims are presented in table 1 and figure 1.

### Table 1. Effect of four annual treatments with diethylcarbamazine plus ivermectin or diethylcarbamazine alone on the reservoir of microfilariae in treatment units with a moderate rate of transmission and treatment units with a high rate of transmission, according to year*

<table>
<thead>
<tr>
<th>Treatment and Variable</th>
<th>Moderate Transmission Rate</th>
<th>High Transmission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethylcarbamazine plus ivermectin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects examined</td>
<td>797</td>
<td>756</td>
</tr>
<tr>
<td>No. of microfilariae-positive subjects (%)</td>
<td>376 (47)</td>
<td>156 (21)</td>
</tr>
<tr>
<td>Geometric mean no. of microfilariae/ml</td>
<td>9.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Diethylcarbamazine alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects examined</td>
<td>903</td>
<td>815</td>
</tr>
<tr>
<td>No. of microfilariae-positive subjects (%)</td>
<td>381 (42)</td>
<td>238 (29)</td>
</tr>
<tr>
<td>Geometric mean no. of microfilariae/ml</td>
<td>8.8</td>
<td>2.6</td>
</tr>
</tbody>
</table>

*Four treatment units with a moderate transmission rate were randomly assigned to receive diethylcarbamazine plus ivermectin, and four were assigned to receive diethylcarbamazine alone; three treatment units with a high transmission rate were randomly assigned to receive diethylcarbamazine plus ivermectin, and three were assigned to receive diethylcarbamazine alone.

††p<0.001 for the comparison with all other years.

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**Figure 1.** Odds of microfilariae-positive infection over the five-year study period among subjects in treatment areas with moderate and high rates of transmission randomly assigned to receive diethylcarbamazine plus ivermectin or diethylcarbamazine alone.

The first annual dose of each drug regimen was given immediately after the determination of microfilarial status in 1994. The odds of microfilariae-positive infection were less than 0.1 in 1998, regardless of the drug regimen or the base-line transmission potential.

[Diagram showing the odds of microfilarial infection over the five years of study.]

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**Table 2.** Og4C3 antigen status of children one year after the fourth cycle of MDA

<table>
<thead>
<tr>
<th>Age</th>
<th>Age 4</th>
<th>Age 5</th>
<th>Age 6</th>
<th>Age 7</th>
<th>Age 8</th>
<th>Age 9</th>
<th>Age 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1(0.1)</td>
<td>5(3.2)</td>
<td>18(9.9)</td>
<td>16(10.6)</td>
<td>21(14.7)</td>
<td>21(11.10)</td>
<td>7(3.4)</td>
</tr>
<tr>
<td>Antigen positive (low, high)*</td>
<td>2(66%)</td>
<td>18(78%)</td>
<td>23(56%)</td>
<td>31(65%)</td>
<td>54(72%)</td>
<td>61(74%)</td>
<td>46(86%)</td>
</tr>
<tr>
<td>Antigen negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>3</td>
<td>23</td>
<td>41</td>
<td>47</td>
<td>75</td>
<td>82</td>
<td>53</td>
</tr>
</tbody>
</table>

* Numbers in parentheses indicate number of children with low or high antigen levels.

---

**UNPUBLISHED ANALYSES OF IMPACT OF MDA FOLLOWING CESSION OF SYSTEMATIC DRUG DISTRIBUTION**

Formal studies of LF ceased in the Dreikikir area in 1998 because of financial constraints. Antifilarial drugs, bednets and other potential interventions have not been available to the population from either the investigators or the Papua New Guinea Ministry of Health. We have however been able to initiate work that will enable us to assess the long-term effects of the MDA trial to aid in planning for future interventions.

**CHILDHOOD INFECTION**

In order to determine the immediate impact of MDA on infection in persons with limited exposure to L3, we measured Og4C3 antigen levels of under-10-year-old children one year after the fourth cycle of MDA (1998). Three hundred and twenty-four children were examined, and 89 (27%) were infected (titre group ≥4). The distribution of infection according to age and antigen level scored as ‘low’ or ‘high’ (titre group 4–5 and 6–7, respectively) are shown in table 2. Of children 4–6 years of age, born at most two years before initiation of MDA in 1994 and therefore unlikely to have been infected prior to the initiation of the study, 24 of 67 (36%) were antigen positive. These data suggest that transmission continued following initiation of MDA.

A subset of 36 children in this group was examined again in 2003 in order to assess whether ‘new’ infections might have been established after cessation of MDA six years earlier. In 1998, 28 children were antigen negative and 8 were antigen positive. All 36 were antigen negative in 2003.
COMMUNITY INFECTION RATES SIX YEARS AFTER CESSION OF MDA

We obtained blood samples in 2003 from 538 residents of three moderate transmission villages that were part of the MDA trial. The prevalence of mf+ samples (mf quantified after nucleoprotein filtration of 1 ml blood obtained between 22.00 hrs and 02.00 hrs) had been 34% prior to initiation of MDA (1993–4), and 0.4% one year after the final year of four annual treatments with MDA. Upon re-examination in 2003, only three of the 538 individuals (0.5%) were mf+. Two of the three mf+ persons had not participated in the MDA programme and had never received antifilarial drugs (although recorded as residents of the villages, they were absent when distribution of the drugs occurred). The remaining mf+ individual was an immigrant from a surrounding area where MDA had not been used.

Og4C3 assays have been completed for 132 study participants from whom plasma was available in 1998 and 2003 (the assays were performed on matched samples using the same plate). As indicated in table 3, among individuals who were antigen positive in 1998, 23% remained positive six years later. Only one individual who was antigen negative in 1998 was antigen positive in 2003. When antigen status was examined as a continuous variable, 98% of individuals who were antigen positive in 1998 had lower or undetectable levels in 2003.

Table 3. Long-term effect of MDA on infection as determined by filarial antigenaemia

<table>
<thead>
<tr>
<th>Number</th>
<th>Antigen positive six years post-MDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigen negative one year after final MDA</td>
<td>71</td>
</tr>
<tr>
<td>Antigen positive one year after final MDA</td>
<td>61</td>
</tr>
</tbody>
</table>

Taken together, these data suggest that human LF infection remained reduced with no evidence of recrudescence six years after cessation of MDA and in the absence of other systematic interventions against LF.

ENTOMOLOGICAL INDICATORS OF LF TRANSMISSION

In order to assess the long-term impact of the four cycles of MDA on entomological indicators of transmission, Anopheles punctulatus and An. koliensis mosquitoes attempting to feed on human volunteers between 18.00 hrs and 06.00 hrs were captured and the proportion infected with any larval stage or L3 enumerated. Table 4 below presents results for the pre-treatment period (1993/4), selected years during the MDA study, and for 2003/4, six years after cessation of MDA in the three villages where mf and Og4C3 antigen levels were determined. Following reductions in the proportions of infected and infective mosquitoes after the first and second cycles of MDA, these values continued to decrease with no recrudescence six years after cessation of MDA. Only one infected mosquito and no mosquitoes with L3 were identified in 2003/4. These results parallel those for human infection indicators, suggesting that LF transmission may be extinguished by the four cycles of MDA completed six years earlier.

Table 4. Anopheles mosquitoes containing any larval stage and L3 in three study villages

<table>
<thead>
<tr>
<th>Year</th>
<th>No. dissected</th>
<th>No. infected (%)</th>
<th>No. with L3 (%)</th>
<th>Months with MTP&gt;0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993/4</td>
<td>1195</td>
<td>89 (7.50)</td>
<td>22 (1.8)</td>
<td>8</td>
</tr>
<tr>
<td>1994/5</td>
<td>1500</td>
<td>14 (0.93)</td>
<td>2 (0.13)</td>
<td>1</td>
</tr>
<tr>
<td>1995/6</td>
<td>1172</td>
<td>8 (1.68)</td>
<td>3 (0.26)</td>
<td>1</td>
</tr>
<tr>
<td>2003/4 (Aug 03–Jan 04)</td>
<td>764</td>
<td>1 (0.10)</td>
<td>0 (0.00)</td>
<td>0</td>
</tr>
</tbody>
</table>
POINTS FOR DISCUSSION

- Evaluation of villages where pre-treatment transmission intensities are higher than those examined to date is necessary to evaluate more fully the impact of these earlier MDA studies conducted in Papua New Guinea.
- The promising results of our earlier MDA trial suggest that additional interventions such as insecticide-impregnated bednets may be useful to accelerate reduction of transmission and possibly eradication of LF in areas where anopheline mosquitoes are the primary or exclusive vectors.
- The importance of facilitation in the vector-parasite relationship may account in part for the sustained reduction in transmission observed to date.
- Variables such as population coverage with MDA and pre-existing transmission level may influence the success of LF control in Papua New Guinea and other areas of anopheline-transmitted filariasis. Deterministic and stochastic models may be helpful in this context.
- These earlier studies in Papua New Guinea used single annual doses of DEC alone or DEC + ivermectin, combinations that predated the current recommendation of DEC plus albendazole. It will be useful to determine the potential added benefit of albendazole to DEC in future work.

References


INTRODUCTION

Recent evidence suggests that anopheline transmitted lymphatic filariasis can be eliminated worldwide because of the phenomenon of facilitation. This hypothesis indicates that, at low microfilaria densities, Anopheles vectors of filariasis are less efficient in transmitting Wuchereria bancrofti. This has been borne out by observations in Papua New Guinea where the vector is Anopheles punctulatus (Bockarie et al., 1998). However, it may not be practical to generalize this observation worldwide since the threshold levels of microfilaraemia needed for elimination of anopheline transmitted W. bancrofti lymphatic filariasis (LF) might differ from species to species (Southgate, 1992[a], 1992[b]; Southgate and Bryan, 1992). For example, results from earlier studies in sub-Saharan Africa, on the quantitative relationship between transmission intensity and microfilarial reservoir, indicated variation among members of the An. gambiae complex and An. funestus (Bryan and Southgate, 1988[a], 1988[b]); McCreavy et al., 1982; Bryan, McMahon and Barnes, 1990).

In Ghana, several sympatric Anopheles species are vectors of Wuchereria bancrofti (Dzodzomenyo et al., 1999); these species are likely to differ in their vectorial role and capacity to transmit low density microfilaraemia. For example, Appawu et al. (2001) observed that no An. arabiensis (a member of the An. gambiae complex) was positive for W. bancrofti although this species formed 9%-14% of An. gambiae s.l. Furthermore, analysis of pooled data for Anopheles mosquitoes from a recent study by Boakye et al. (2004) indicated presence of the ‘limitation’ process, although larger samples need to be investigated to determine whether this process occurs only in An. gambiae s.l. or An. funestus or in both of these taxa.

Although the impact of treatment on transmission of LF has not been studied in Ghana, there have been some transmission studies and investigations on the efficacy of different treatment regimes (Appawu et al., 2001; Dunyo et al., 2000). Concerning treatment efficiency, Dunyo and Simonsen (2002) observed that re-treatment of Wuchereria bancrofti microfilaraemia with a combination of ivermectin and albendazole resulted one year later in an overall mean reduction in microfilarial intensity of 76.2%. The efficacy of the combination treatment thus appeared to be largely independent of the type of primary treatment given and was multiplicative when used repeatedly. Gyapong (2000) evaluated the impact of a single dose of ivermectin in six communities in Ghana after two years (due to unavailability of the drug for re-treatment in the second year); this showed the community microfilaraemia prevalence and intensity to be reduced, respectively, by only 25.5% and 39.5% of pre-treatment levels.

Although LF has been known in Mali since 1912 (Thiroux), only a few studies have been aimed at determining disease burden and transmission patterns (Touré, 1979; Keita, 1979). The data show, however, that the LF infection rate increases from the northern to the southern part of the country, and they confirm the nocturnal periodicity of W. bancrofti. Entomological data have identified the gambiae and funestus complexes as the main vectors of LF in Mali. Recently Coulibaly (2002) reported a survey carried out 20 years after a previously reported study in the same endemic area (savannah area). The data show a significant decrease of infection rate in both human and vector in the absence of any control measures. Data from Keita (2002) however, on the prevalence of elephantiasis in the country, show that LF is a major public health problem in Mali.

The Ministry of Health (MOH) coordinating group undertook mapping of LF in eight regions of the country in 2002, and in Bamako, the capital city, in 2004 (supported by WHO). In the eight regions, the infection rate by the immunochromatographic card test (ICT) ranged from 1% in Timbuktu (northern part) to 18.6% in Sikasso (southern part) with a mean infection rate of 7.07% (n = 100 per community). In the capital city (six communes), the average infection rate was 1.5% (n = 5990); four communes were found positive using ICT.

The Lymphatic Filariasis Elimination Programme of the Ghana Health Service and the Malian MOH are undertaking elimination of LF using mass drug
administration (MDA) with ivermectin and albendazole. The elimination programmes have been set up in both countries as part of the Global Programme to Eliminate Lymphatic Filariasis using the following strategies:

- Information, education and communication (IEC).
- Mass drug administration to the populations at risk.
- Prevention of disabilities.
- Integration into other programmes at operational, intermediate and central levels.

This provides the opportunity to investigate the impact of MDA on transmission by members of the An. gambiae complex and An. funestus group.

CURRENT STATE OF KNOWLEDGE AND AVAILABLE EVIDENCE ON IMPACT OF MDA ON TRANSMISSION

These studies were organized as multicountry studies with the aim of evaluating the effect of community-based mass chemotherapy on the transmission of LF. The specific objectives were to:

- Determine the infection rates in mosquitoes after two rounds of community-based mass treatment.
- Determine the prevalence of W. bancrofti infection and associated clinical signs after one round of community-based mass treatment.
- Identify and determine the prevalence of adverse events (side effects) associated with mass treatment with albendazole-ivermectin.
- Determine the trend of major entomological and parasitological parameters after two rounds of treatment.

In Ghana, the study sites included eight villages in a district with a record of filariasis endemicity where there had not been any community-wide treatment but which had been earmarked for treatment with ivermectin and albendazole. A census was carried out in all eight villages: all houses were enumerated and demographic data of the inhabitants recorded, including the use of bednets. In Mali, similar baseline data were collected using a common protocol.

Entomological studies (assessing transmission)

Mosquito collection

Each village was divided into four sections and one house per section selected randomly for overnight mosquito collection using the man-landing catch method. Four houses were sampled in each village per night (from July to December, from 2001 to 2004); the mosquitoes were later dissected in the laboratory.

Parasitological studies

Inhabitants surveyed for W. bancrofti infection were randomly selected by computer. The first prevalence survey was conducted during February 2002 before mass treatment of the inhabitants (in March 2002). Subsequent surveys were done in 2003, 2004 and 2005. Each time, the surveys preceded MDA in the communities.

Results

Ghana

The average coverage by MDA in the three years for the eight villages was around 66% (table 1). The lowest coverage was 13.9% in the village of Fawomanye in 2002; this situation improved to 62% and 65% in subsequent years (2003 and 2004, respectively). At the time of writing, treatment had been completed at all sites for 2005 and data were being collected.

<table>
<thead>
<tr>
<th>Community</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obiri</td>
<td>90.3</td>
<td>65</td>
<td>58</td>
</tr>
<tr>
<td>Hwida</td>
<td>87.4</td>
<td>79</td>
<td>73</td>
</tr>
<tr>
<td>Dego</td>
<td>85</td>
<td>60</td>
<td>51</td>
</tr>
<tr>
<td>Ayensuano</td>
<td>78.3</td>
<td>97</td>
<td>86</td>
</tr>
<tr>
<td>Fawomanye</td>
<td>13.9</td>
<td>62</td>
<td>65</td>
</tr>
<tr>
<td>Kyiren</td>
<td>75.8</td>
<td>52</td>
<td>79</td>
</tr>
<tr>
<td>Amanful</td>
<td>76.5</td>
<td>62</td>
<td>58</td>
</tr>
<tr>
<td>Mampong</td>
<td>-</td>
<td>55</td>
<td>63</td>
</tr>
<tr>
<td><strong>% Mean coverage</strong></td>
<td><strong>63.4</strong></td>
<td><strong>66.5</strong></td>
<td><strong>66.625</strong></td>
</tr>
</tbody>
</table>

Table 1. Mass drug administration treatment coverage (%) with ivermectin and albendazole in the study communities (Ghana)
Parasitological examination of blood smears has shown a decrease in proportion of positive individuals in the population. In 2002, the proportion was 4.6%; in the most recent survey, in January 2005, this had declined to 0.9% (fig. 1 and table 2).

Final analysis of the entomological data for 2005 is being compiled. Data for the first three years showed an overall decreasing trend in the annual transmission potential (ATP) (from 356.2 in 2001, through 296.6 in 2002, to 229.4 in 2003) (fig. 2). However, when this was broken down to the contributions made by different *Anopheles* species, it was realized that, while the ATP of *An. funestus* had significantly decreased, that for *An. gambiae* had not. A critical examination of the data indicated that the ATP is being influenced by collections from one site (Mampong); the current analysis will take this into account. The ATP is mirrored in the annual infective biting rate (fig. 3).

### Table 2. 2001–2004: blood sampling results for infections with *W. bancrofti* (Ghana)

<table>
<thead>
<tr>
<th>VILLAGE</th>
<th>NUMBER EXAMINED</th>
<th>NUMBER POSITIVE</th>
<th>RANGE OF DENSITIES (mf/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G. Mampong</td>
<td>50</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>Kyeren</td>
<td>120</td>
<td>58</td>
<td>54</td>
</tr>
<tr>
<td>Anamful</td>
<td>44</td>
<td>30</td>
<td>43</td>
</tr>
<tr>
<td>Fawomanyo</td>
<td>53</td>
<td>28</td>
<td>36</td>
</tr>
<tr>
<td>Obiri</td>
<td>80</td>
<td>38</td>
<td>48</td>
</tr>
<tr>
<td>Hwida</td>
<td>100</td>
<td>47</td>
<td>50</td>
</tr>
<tr>
<td>Dago</td>
<td>442</td>
<td>112</td>
<td>105</td>
</tr>
<tr>
<td>Ayensuano</td>
<td>52</td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>941</td>
<td>380</td>
<td>397</td>
</tr>
</tbody>
</table>

**Figure 1.** Mean prevalence of microfilaraemia over a four-year period (Ghana)

**Figure 2.** Annual transmission potential (ATP) trends for the main *Anopheles* vector species from 2001 to 2004 (Ghana)

**Figure 3.** Annual infective biting rate (AIBR) trends for the main *Anopheles* vector species from 2001 to 2004 (Ghana)
**Mali**

The treatment coverage based on total study population was 67% with 0.6% having side effects in 2002, and 69.4% with 0.4% having side effects in 2003.

**PARASITOLOGICAL AND CLINICAL STUDIES**
- 2001 sample size: 1141 people, with 29.7% loss to follow-up in 2004.
- Average infection rate: 9.3% reduction between 2002 and 2004 (fig 4).
- Side effects: 0.6% in 2002 and 0.4% in 2003.

**ENTOMOLOGICAL STUDIES**
- Main vectors: *An. gambiae s.l.* (>86%) and *An. funestus* (table 3).
- Infection rate: 73.8% reduction between 2001 and 2004 (after two MDAs) (fig 5).
- Infectivity rate: 94.8% reduction between 2001 and 2004 (after two MDAs) (fig 5).
- Man-biting rate: not affected by the treatment (after two MDAs) (fig 6).
- Annual transmission potential: 97.25% reduction between 2001 and 2004 (fig 7).

---

**Table 3. Species composition (Mali)**

<table>
<thead>
<tr>
<th>Year</th>
<th>An. funestus</th>
<th>An. gambiae s.l.</th>
<th>Total no. of mosquitoes examined</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>9.9%</td>
<td>90.1%</td>
<td>23 265</td>
</tr>
<tr>
<td>2002</td>
<td>14.0%</td>
<td>86.0%</td>
<td>12 986</td>
</tr>
<tr>
<td>2003</td>
<td>3.1%</td>
<td>96.9%</td>
<td>18 394</td>
</tr>
<tr>
<td>2004</td>
<td>9.2%</td>
<td>90.8%</td>
<td>13 021</td>
</tr>
</tbody>
</table>

---

**Figure 4.** Parasitological data variation before and after treatment (Mali)

**Figure 5.** Vector infection and infectivity rates, 2001–2004 (Mali)

**Figure 6.** Vector man-biting rates (MBR) and entomological inoculation rates (EIR), 2001–2004 (Mali)

**Figure 7.** Vector annual transmission potential, 2001–2004, expressed in number of infective bites per man per year
SUMMARY OF THE MAJOR REMAINING UNCERTAINTIES AND RESEARCH QUESTIONS, AND SUGGESTIONS FOR SPECIFIC STUDIES

The observation that Anopheles-transmitted W. bancrofti in the Bongo area of Ghana shows the process of limitation (Boakye et al. 2004) indicates that the situation needs clarification in terms of the species involved in transmission. A similar study to look at specific Anopheles species is necessary.

The study on trends in transmission after MDA in the eight communities in Ghana indicates that some of the vectors (An. gambiae s.s.) are able to pick up the infection and transmit infective larvae at very low levels of microfilaraemia in humans. Although the 2004 entomological analysis is yet to be completed, it may be necessary to consider continuing the study for longer than the five years of MDA planned by the national programme. As now planned, the study will end after four years of MDA, but this may not be enough to arrive at a definite conclusion.

Pichon (2002) postulated that low level prevalence and intensity of microfilaraemia may increase the mean lifespan of some of the local Anopheles species and may worsen the problem posed by malaria. How this increase in mean lifespan affects the transmission of W. bancrofti has not, however, been examined.

Issues to be addressed to increase the chances of eliminating lymphatic filariasis by mass drug administration

• Treatment coverage required to have maximum impact and reduce the duration of intervention.
• Untreated people (persistent refusals, migration) as a source of vector infection.
• IEC for better involvement of the population.
• Vector control as an adjunct to MDA.

Suggestions for specific studies

• Impact of insecticide-treated nets on LF transmission: effect of intense use during MDA in high, middle and low transmission areas.
• Finding a good macrofilaricidal drug: other drugs (e.g. if combined with antibiotics) with effects on adult worm (as deduced by sono-graphic assessment).
References


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Southgate BA. The significance of low density microfilaraemia in the transmission of lymphatic filarial parasites. *Journal of Tropical Medicine and Hygiene*, 1992[a], 95:78-86.


4E: IMPACT OF MASS DRUG ADMINISTRATION ON INFECTION AND TRANSMISSION OF LYMPHATIC FILARIASIS IN EGYPT

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2 Barnes-Jewish Hospital and Washington University School of Medicine, St. Louis, Missouri, USA

ABSTRACT

Egypt was among the first countries to implement a national filariasis elimination programme based on annual mass drug administration (MDA) with diethylcarbamazine (DEC) and albendazole (target population about 2.5 million in 181 endemic towns and villages). We evaluated the impact of four rounds of MDA in four sentinel villages. Circulating filarial antigen (CFA, immunochromatographic card test [ICT]), microfilaraemia (mf) prevalence rates and levels, and MDA coverage were assessed in randomly selected households before and 6–8 months after each round of MDA. Mf testing (by membrane filtration of night blood) was limited to those with positive CFA tests. MDA coverage rates were 86.7%, 95.5%, 90.1% and 88.8% for rounds 1 to 4, respectively, in our study villages. Pretreatment infection rates varied significantly among the study villages. Overall mf prevalence decreased 98%, from 8.0% to 0.16%, after four MDA rounds. Mf/ml/population fell 96.9%, from 13.0 to 0.4. CFA prevalence decreased 86.4%, from 15.7% to 2.3%. The smaller reduction in CFA prevalence (compared to mf) may indicate survival of adult worms in some subjects who cleared mf. We also assessed antibody prevalence rates (IgG4 to Bm14) in primary school children in study villages before and after MDA. Antibody rates decreased from 20.6% before MDA to 2.7% six months after the fourth round of MDA. Indoor-resting mosquitoes were collected before and after MDA at night, pooled by house, and infection rates assessed by the 5spa-PCR assay. The overall minimum mosquito infection rate (assuming that a positive mosquito pool contained one infected mosquito) decreased 90.8%, from 2.8% before MDA to 0.2% after four rounds of MDA. Elimination targets were achieved more quickly in the villages with low rates. Since most of the 181 localities included in the MDA programme had low baseline infection parameters, our results suggest that filariasis would be eliminated in most endemic villages of Egypt by five rounds of MDA.

INTRODUCTION

Bancroftian filariasis, a deforming and disabling parasitic disease caused by the filarial nematode Wuchereria bancrofti, is endemic in some 80 countries with an estimated 100 million infected people (TDR, 1997). In 2000, the World Health Organization (WHO) initiated a Global Programme for Elimination of Lymphatic Filariasis (GPELF), which is based on repeated annual cycles of mass drug administration of single-dose drug combinations to at-risk populations. By such an approach, the GPELF aims to interrupt transmission of filariasis by attacking the reservoir of microfilariae (mf) and thereby reducing the uptake of parasites by mosquitoes. Recent reports indicate that the programme has expanded rapidly to cover approximately 60 million people in 34 countries in 2002 (Molyneux and Zagaria, 2002).

Nocturnally periodic lymphatic filariasis caused by Wuchereria bancrofti has been endemic in Egypt for a long time (Harb et al, 1993). Culex pipiens is the main mosquito vector responsible for transmission of filariasis in Egypt (Southgate, 1979). Filariasis has a highly focal distribution in Egypt with most cases in the densely populated governorates in the Nile Delta. There are also foci of infection in Giza and Asiut governorates in Upper Egypt (Harb et al, 1993). Recent spot surveys (Weil et al., 1999) have shown that mf prevalence rates and intensity of infection are low.

Egypt was among the first countries to join the WHO global efforts and develop a national programme to eliminate LF (NPELF) as a public health problem. The NPELF has a major goal: to interrupt transmission by decreasing mf prevalence rates to less than 0.1% by MDA of an annual dose of DEC (6 mg/kg) in combination with albendazole (400 mg). A total of 181 villages (implementation units) with mf smear or filarial antigen prevalence rates of 1% or more are included in the programme. To be successful, the NPELF aims to achieve an MDA coverage rate of about 80% of the at-risk population in the target villages. However, children below two years of age and pregnant women are excluded from MDA.

Although several studies have documented the effects of community-based single-dose DEC on microfilaria prevalence rates and levels (Ramzy et al., 2002), so far studies to evaluate the effects of MDA based on combined regimens are lacking. Over the last decade, our group has been actively
involved in developing and evaluating various epidemiological tools for monitoring the effect of treatment on infection rate and transmission parameters. These include detecting serological markers such as circulating filarial antigen (CFA) by the ICT (Weil et al., 1997; Ramzy et al., 1999) and Bm14-IgG4 antibodies by the ELISA, and a molecular marker, the Ssp1-PCR assay, for detecting *W. bancrofti* DNA in the mosquito vector (Ramzy et al., 1997).

As of October 2004, the NPELF had completed five cycles of MDA in 161 endemic villages (and 1 to 4 cycles of MDA in an additional 20 villages) covering over 2.5 million people. Consequently, the present study was designed to assess the impact of these MDA rounds in four different sentinel villages from two governorates, and to compare different methods for monitoring the effects of MDA on infection rate and transmission. In particular, we assessed CFA by the ICT, mf prevalence rates and levels, and MDA coverage in randomly selected households before and 8–10 months after each round of MDA. Furthermore, as a marker of exposure to infection, we compared antibody prevalence rates (IgG4 to Bm14) in primary schoolchildren in the study villages before and after MDA. In addition, for monitoring transmission, mosquito infection as determined by the Ssp1-PCR assay were compared in indoor-resting mosquitoes collected at night before and after MDA.

**MATERIALS AND METHODS**

To achieve the objectives of the present study, three types of survey were conducted in four sentinel villages representing two governorates (Giza and Qalyubia). These included a village survey to assess MDA coverage, CFA prevalence, and mf prevalence rates and levels; a school survey to measure Bm14-IgG4 antibodies in primary schoolchildren; and a vector survey to determine mosquito infection rates before and after each round of MDA.

The study was approved by institutional review boards at Ain Shams University in Cairo and Barnes-Jewish Hospital in St. Louis.

**Village surveys**

Two (Kafr Tahoria [KT] and Tahoria [TH]) of the four study villages are located approximately 35 km north-east of Cairo, in Shebin El Kanatar District, Qalubia Governorate. These villages had low mf prevalence and intensity of infection prior to MDA and are typical for endemic villages in Egypt. The other two villages (Kafr El Bahary [KB] and Kafr El Qebly [KQ]) are located approximately 40 km south-west of Cairo, in El Badrasheen District, Giza Governorate; they had relatively high mf prevalence and intensity of infection prior to MDA.

Annual surveys were performed in 10% of randomly selected households; a different household sample was tested each year. Surveys were performed before the first round of MDA and approximately 6–8 months following each round of MDA. Field teams, comprised of a physician, a technician, and a local health worker, visited houses at night (21.00–23.00 hrs). After obtaining informed consent, the teams recorded demographic and MDA information on pre-printed forms. Finger prick blood samples were collected for performance of the ICT filariasis (antigen) test according to the manufacturer’s instructions. Note that AMRAD ICT cards were used for three cycles (before MDA and after the first and second MDA rounds), and Binax ICT cards for the last survey. If a card test turned positive, then venous blood samples were collected for mf detection by membrane filtration of 1 ml blood.

**Mosquito study**

The prevalence of infected mosquitoes was also assessed in the same study houses. Houses were visited late at night and indoor-resting mosquitoes collected by aspiration by trained field workers. Fed and gravid *Culex pipiens* mosquitoes were pooled by house, and mosquito pools were stored at -70°C until tested for *W. bancrofti* DNA by polymerase chain reaction (PCR) with primers specific for the Ssp1 repeat, as previously described (Ramzy et al., 1997). Details of the mosquito survey methods are reported elsewhere (Farid et al., manuscript in preparation).

**School study**

To assess the prevalence of IgG4 antibodies to the recombinant filarial antigen Bm14, finger prick blood samples (approximately 300 μl) were collected, in Eppendorf tubes containing 30μl EDTA, from all children in grades 1 and 5 at primary schools in the study villages. Plasma samples were separated and tested by ELISA as previously described (Ramzy et al., 1995).

**DATA ANALYSIS**

Data management and statistical analysis were performed using a statistical software package (SPSS, Chicago, IL). Proportions were compared by chi-square or Fisher’s exact test (two-tailed). The Kruskal-Wallace test was used to assess the significance of group differences for continuous variables.
Tests were two-tailed and a p-value of less than 0.05 was considered significant.

RESULTS

Mass drug administration coverage rates

The overall MDA coverage rates in our study population were, relative to the target population and for the four rounds respectively, 86.7%, 95.5% 90.1% and 88.8% (table 1). These coverage rates were relatively high and exceeded the MDA target (80%) of the elimination programme. In general, our coverage rates were not different from those rates estimated by the national programme for the entire governorates of our study villages (table 1).

Impact of four rounds of MDA on microfilaraemia rate and level

Pretreatment mf rates ranged between 13.1% and 0.75% in the study villages (fig.1). Note that eligible residents of the village with the lowest mf prevalence (approximately 75% of subjects aged over four years and not pregnant) were treated with DEC in 1998. Pretreatment age-specific mf rates increased with age, reached a peak (13.3%) in the 21–30 year age group, then declined thereafter (table 2). Pretreatment microfilaraemia was significantly higher in males than females ($X^2 = 4.29, p = 0.038$). This was also true following the first ($X^2 = 4.12, p = 0.04$) and second ($X^2 = 4.15, p = 0.04$) rounds of MDA.

Table 1: Estimated percentage coverage rates$^1$ of four rounds of mass drug administration among the study villages

<table>
<thead>
<tr>
<th>Locality</th>
<th>Year one</th>
<th>Year one</th>
<th>Year two</th>
<th>Year three</th>
<th>Year four</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Our estimate</td>
<td>MOPH$^2$</td>
<td>Our estimate</td>
<td>MOPH</td>
<td>Our estimate</td>
</tr>
<tr>
<td>Giza gov.</td>
<td>86.7</td>
<td>86.8</td>
<td>95.5</td>
<td>96.6</td>
<td>90.1</td>
</tr>
<tr>
<td>K. Bahary</td>
<td>89.5</td>
<td>91.8</td>
<td>96.3</td>
<td>93.7</td>
<td>90.7</td>
</tr>
<tr>
<td>K. Qebly</td>
<td>81.8</td>
<td>90.2</td>
<td>86.3</td>
<td>91.3</td>
<td>93.4</td>
</tr>
<tr>
<td>Qalyubia</td>
<td>82.0</td>
<td>85.7</td>
<td>98.5</td>
<td>95.2</td>
<td>89.9</td>
</tr>
<tr>
<td>K. Tahoria</td>
<td>91.3</td>
<td>98.6</td>
<td>96.6</td>
<td>90.1</td>
<td>95.9</td>
</tr>
<tr>
<td>Total</td>
<td>86.7</td>
<td>86.8</td>
<td>95.5</td>
<td>96.6</td>
<td>90.1</td>
</tr>
</tbody>
</table>

$^1$ These coverage rates are in relation to the target population.

$^2$ MOPH estimated coverage rate is the mean for the entire governorate.
The overall mf prevalence decreased significantly (98%), from 8% to 0.16%, after four MDA rounds ($X^2=146.6, \ p<0.001$). Microfilaraemia prevalence rates decreased in all study villages after each MDA round, and no mf carriers were identified in KT, TH and KB after the first, second and third MDA rounds respectively (fig. 2).

The overall median mf/ml in mf-positive cases were: 42 (pretreatment), 19 (year 1), 9 (year 2), 23.5 (year 3) and 35 (year 4). Mf/ml/population decreased significantly in all study villages (fig. 3), with an overall mf/ml/population decrease of 99.5% (from 13 to 0.07) (fig. 4).

Impact of four rounds of MDA on circulating filarial antigen prevalence rate

Pretreatment CFA rates ranged between 23.4% and 13.0% in the study villages (fig. 1). CFA prevalence rates decreased in all study villages after each round of MDA. The overall CFA prevalence rate decreased significantly (86.4%), from 16.9% to 2.3%, after the four MDA rounds ($X^2 = 230.48, \ p<0.001$). The reduction in CFA prevalence relative to the baseline was

<table>
<thead>
<tr>
<th>Age group</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number examined</td>
<td>Mf rate (year 1)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>108</td>
<td>1.9</td>
</tr>
<tr>
<td>11–20</td>
<td>345</td>
<td>6.1</td>
</tr>
<tr>
<td>21–30</td>
<td>239</td>
<td>10.5</td>
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<tr>
<td>31–40</td>
<td>125</td>
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<tr>
<td>41–50</td>
<td>93</td>
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<tr>
<td>&gt;60</td>
<td>41</td>
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</tr>
<tr>
<td>Total</td>
<td>1009</td>
<td>6.7</td>
</tr>
</tbody>
</table>

$Mf = \text{microfilaria}$

$CFA = \text{circulating filarial antigen}$
less dramatic after each MDA than that observed for mf prevalence (fig. 3). This may suggest that the treatment employed for MDA is more effective against mf than against adult worms.

Impact of four rounds of MDA on anti-Bm14 antibody rate in schoolchildren

Results from schools in the two Giza villages were pooled and compared to results from schools in the two Qalyubia villages. Pretreatment antibody rates were higher in Giza (23.8%) than Qalyubia schools (10.15%) ($X^2=35.19$, $p<0.001$), and higher in grade five (25.2%) than grade one (15.4%) ($X^2=20.24$, $p<0.001$) (fig. 5). The overall antibody rates decreased (86.9%) from 20.6% before MDA to 2.7% after the fourth round of MDA. Antibody prevalence in Qalyubia schools grade one declined to zero after two MDA rounds. The antibody prevalence rate in Giza schools grade one (GS1) decreased significantly after each MDA round, and four MDA rounds reduced the antibody rate in GS1 significantly (94.1%), from 18% to 1% (fig. 5).

The overall mean antibody level decreased from 80.5 units (range 15–263 units, median 81.1 units) to 59 units (range 15.6–380.0 units, median 44.6 units) after four MDA rounds ($Z=-3.725$, $p<0.001$).

Impact of MDA on W. bancrofti infection of wild caught mosquitoes

Indoor-resting mosquitoes were collected each year from the four study villages, and pooled by household. The minimum infection rate before MDA, assuming that a positive mosquito pool contained only one infected mosquito, ranged from 2.3% to 4.0%. The overall minimum infection rate decreased significantly (90.8%), from 2.8% before MDA to 0.26% after four MDA rounds. The mosquito data are reported elsewhere in detail (Farid et al., manuscript in preparation).

DISCUSSION

The present study was designed to evaluate the impact of four rounds of MDA in four different sentinel villages selected from two governorates. Two of our study villages (in Giza governorate) represent the most highly filariasis-endemic villages, whereas the other two (in Qalyubia governorate) have relatively low prevalence and intensity of infection and are typical of most filariasis-endemic villages in Egypt.

Our data strongly suggest that filariasis has been eliminated, with interruption of transmission, in the two study villages in Qalyubia governorate. This is supported by the absence of microfilaria carriers (by the stringent membrane filtration test) (fig. 3), the absence of antifilarial antibodies in first grade children (fig. 5), and the absence of positive mosquito pools by PCR (data not shown) after four rounds of MDA. Four rounds of MDA also resulted in dramatic decreases in infection and transmission parameters in the two study villages in Giza governorate. Such findings suggest that residual infection and transmission rates in the 181 localities included in the NPELF programme are likely to be very low.
following the four rounds of MDA. The goal of filariasis elimination has probably been achieved in many treated villages. However, additional studies, with broader sampling, are needed to determine whether filariasis has been eliminated in Egypt by five rounds of MDA.

Our independent assessments confirmed the government claims of high coverage rates in the MDA programme. High MDA coverage rates (>85%) achieved for the four implemented rounds have greatly contributed to the clearance and significant reduction in mf intensity and prevalence rates. Computer-based models have indicated that the number of treatment rounds necessary to achieve elimination depends to a large extent on treatment coverage, drug efficacy, and disease endemicity level. Predictions based on simulation analysis suggest that 90% coverage is required to achieve the goal of elimination with five annual rounds of DEC-based MDA (Das and Subramanian, 2002). It is likely that the reported coverage rate (>85%) for the NP ELF programme would be sufficient to achieve LF elimination with five annual MDA rounds using the more efficient combination treatment (DEC + albendazole) rather than DEC alone, especially as levels of endemicity are low.

A second goal of the present study was to compare different methods for monitoring the effects of MDA on infection rate and transmission. Microfilaraemia was assessed by a stringent test, membrane filtration of 1ml blood, which showed low residual mf counts (median 35) in less than 1% of subjects tested after MDA. It is more likely that such subjects, with relatively low mf counts by membrane filtration (<100 mf/ml), would be free of mf by the thick blood smear (20–50 μl blood), a method usually used for routine surveys. Data from a previous study by our group (Farid et al., 2003) have suggested that filariasis elimination programmes should aim to achieve mf smear rates of zero. This is because few mf were ingested, and very few L3 were produced, by mosquitoes which had been fed on infected subjects who were microfilaraemic by the 50 μl thick smear. Additional studies are needed to further establish the relationship between low mf count by membrane filtration and the thick blood smear after MDA.

As anticipated, the overall decrease in the CFA prevalence rate (86.4%), as measured by the ICT, was smaller than the overall reduction in mf prevalence rate (98%). The single-dose combination regimen (DEC + albendazole) is known to be effective for reducing the blood mf count; however, it is only partially effective at killing adult *W. bancrofti*. For such methods (as assessment of CFA prevalence by the ICT) to be cost effective, we believe they should be employed at wider intervals than those used for mf assessment. For surveillance of elimination programmes, we suggest assessing CFA prevalence by the ICT before MDA to obtain baseline rates, then repeating the assessment after every three rounds of MDA.

As a marker for interruption of transmission, we used a xenomonitoring approach to assess the presence of *W. bancrofti* DNA by PCR in indoor-resting mosquitoes. The Spel-PCR method has gained much attention as a powerful epidemiological tool (Farid et al., 2001) and was proposed as a useful means for monitoring of filarial transmission during control campaigns (Ramzy, 2002). Data from the present study provided empirical proof for this proposal. However, considering that, as the elimination programme progresses, the parasitic load in treated populations will decrease to a level where transmission will be interrupted, few mf will be available for ingestion by mosquitoes. Consequently, thousands of female mosquitoes would need to be collected for active surveillance of elimination programmes. In such cases, collecting blood-fed resting mosquitoes may not provide enough mosquitoes to estimate the vector infection rate after multiple rounds of MDA; additional studies are required to determine whether other methods for mosquito collection (Service, 1993) would fulfil such a need.

We measured antibody prevalence in primary schoolchildren (first and fifth grades) as another marker for interruption of transmission. Antibody rates in adults may reflect exposure or infection prior to the initiation of the MDA programme; it may take many years for antibody rates to fall in adults even after effective MDA. We favoured sampling of schoolchildren, assuming that their exposure to infective mosquitoes reflects the transmission status in their communities after MDA. The dramatic reduction in antibody prevalence in Giza schools grade 1 following four MDA rounds (94.1%) validates our assumption and indicates that transmission in our study areas became very low consequent to MDA. Such a finding renders this approach – successive assessment of specific antifilarial antibodies in primary schoolchildren – to be the most appropriate and valuable strategy for monitoring elimination programmes.

We conclude that four rounds of MDA have dramatically decreased filariasis infection rates, infection intensity, and transmission in our study villages. The method of choice to evaluate interruption of transmission is assessment of antibody in primary,
preferably first grade, schoolchildren. If our study villages are representative of the 181 localities included in the MDA programme, our results suggest that the five-year programme may lead to elimination of filariasis as a public health problem in Egypt.

References


Annex 5

WORKING PAPER:
Advances and challenges in predicting the impact of lymphatic filariasis elimination programmes
5: ADVANCES AND CHALLENGES IN PREDICTING THE IMPACT OF LYMPHATIC FILARIA ELIMINATION PROGRAMMES

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INTRODUCTION

Lymphatic filariasis is a mosquito-borne parasitic disease and an important cause of chronic morbidity in tropical countries. In 1998, the Global Programme to Eliminate Lymphatic Filaria (GPELF) was initiated, aiming at worldwide elimination of this parasitic disease as a public health problem. The main strategy in the global programme is to interrupt transmission by annual population treatment with antifilarial drugs (diethylcarbamazine or ivermectin plus albendazole). In addition, morbidity management should reduce the suffering of patients who have chronic manifestations. Thirty-two countries had started elimination programmes in 2002 and this number is still growing.

The goal of elimination is ambitious. Past mass treatment programmes had varying degrees of success. In some areas transmission was apparently interrupted. In other areas elimination was not achieved, in spite of long-term control programmes. How strategic choices, and operational or biological factors, contribute to success or failure is poorly understood. It is unknown what coverage and duration of mass treatment (and possible additional measures) are required to achieve elimination and how this depends on the vector and parasite strain, endemicity level, and drugs used. Mathematical models can help to clarify these issues and application of such models is considered important for support of GPELF.

Mathematical models have been used widely in parasitology. They help to understand the complex transmission dynamics of parasitic diseases and are useful tools for planning and evaluating control programmes. Models have also played an important role in lymphatic filariasis research. Targeted models, which consider part of the processes involved in transmission, helped, for example, to clarify the role of acquired immunity and the macrofilaricidal effects of treatment. This paper concentrates on so-called ‘full transmission models’, which relate the rate of transmission to the intensity and distribution of infection in a human population and can be used to predict the impact of interventions on transmission and the probability of elimination.

To our knowledge, three full transmission models have been described in the literature. The first was specifically developed for the evaluation of a vector control programme and is not considered here. The two other models, called EPIFIL and LYMFASIM, are both being used for planning and evaluation of elimination programmes. After a brief introduction of the processes involved in transmission and control of lymphatic filariasis, we describe the basic structure of these models, compare and discuss some critical model predictions, and outline future research priorities.

PROCESSES IN LYMPHATIC FILARIA ELIMINATION TRANSMISSION AND CONTROL

Models for lymphatic filariasis control basically describe the main biological processes involved in transmission (fig. 1). To study the dynamics of transmission and how intervention affects transmission, it is specifically important to take account of density dependence and heterogeneities.

Density dependence means that the outcome of a process depends on the abundance of the parasite stages involved. Several limitation mechanisms may reduce transmission when the average worm burden increases. For example, the proportion of microfilariae (mf) that develop into infectious L3 larvae saturates in Culex quinquefasciatus when the mf intake is higher, limiting the transmission of infection. Further, the survival probability of mosquitoes is reported to reduce with their infection load. Acquired immunity may limit infection intensity in the human host. Different mechanisms for this have been proposed, but evidence for the operation of such immunity is inconclusive. These limitation mechanisms all negatively affect the impact of interventions, because transmission becomes relatively more efficient when infection levels are lower. Density dependence, however, may also occur in the opposite direction (called facilitation). The probability that a female worm mates with a male worm increases with higher worm burdens. Further, in some anopheline mosquito species, larval development might increase with higher mf intake. It is unknown whether density dependence, either limitation or facilitation, occurs in parasite establishment...
and survival in humans, their fertility, and mf survival.

The term heterogeneity points at variation between individuals. Individuals differ for example in genetic background, nutritional status and behaviour, which may cause differences in exposure to mosquitoes, susceptibility to infection, and survival, maturation and fecundity of parasites. Therefore individuals may be predisposed to heavy or light infection, leading to an aggregated or overdispersed distribution of parasites (with a few hosts harbouring the majority of the parasites). Individuals also differ in compliance and responsiveness to treatment, which may also contribute to aggregation of parasites. This aggregation enhances transmission because it increases the probability that female and male worms mate. Heterogeneity may also occur in the parasite population, e.g. with respect to the lifespan and resistance to treatment.

**AVAILABLE MODELS**

The two available models for lymphatic filariasis transmission and control, EPIFIL and LYMFA SIM, mainly differ in the amount of detail included. Specific variants of both models have been developed for *Wuchereria bancrofti* transmitted by *Culex quinquefasciatus*, using data from an integrated vector management control programme carried out in Pondicherry, India, 1981–1985. These ‘Pondicherry model variants’ are described below. Table 1 gives the quantification of several key biological parameters of the models. Figure 2 illustrates the good fit of both models to the precontrol (1981) data from Pondicherry.
Table 1. Quantification of several key biological parameters in the EPIFIL and LYMFASIM model variants for Pondicherry, where Wuchereria bancrofti is transmitted by Culex quinquefasciatus

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EPIFIL</th>
<th>LYMFASIM</th>
<th>LYMFASIM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Anti-L3 immunity</td>
<td>Anti-fecundity immunity</td>
</tr>
<tr>
<td>Parasite lifecycle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average adult worm lifespan in years (type of distribution)</td>
<td>8</td>
<td>10.2</td>
<td>11.8</td>
</tr>
<tr>
<td>(type of distribution)</td>
<td></td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>Average mf lifespan in months (type of distribution)</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>(type of distribution)</td>
<td></td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>Premature period in months</td>
<td>-</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Exposure variation by age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure at age zero as fraction of maximum exposure</td>
<td>0</td>
<td>0.26</td>
<td>0.40</td>
</tr>
<tr>
<td>Age in years at which maximum exposure is achieved</td>
<td>9</td>
<td>19.1</td>
<td>21.3</td>
</tr>
<tr>
<td>Density dependence in mosquitoes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum number of L3 larvae that can develop in mosquitoes at high mf intensities</td>
<td>6</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>(type of distribution)</td>
<td></td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>Acquired immunity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of acquired immunity in years</td>
<td>lifelong</td>
<td>9.6</td>
<td>11.2</td>
</tr>
<tr>
<td>(type of distribution)</td>
<td></td>
<td>f</td>
<td></td>
</tr>
<tr>
<td>Other parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly biting rate</td>
<td>5760</td>
<td>2200</td>
<td></td>
</tr>
<tr>
<td>Proportion of L3 larvae in mosquitoes that enter the human host when a mosquito bites</td>
<td>0.414 x</td>
<td>0.32</td>
<td>0.1</td>
</tr>
<tr>
<td>Proportion of inoculated L3 larvae that develop successfully into adult worms (×10^3)</td>
<td>0.113</td>
<td>1.03</td>
<td>0.42</td>
</tr>
<tr>
<td>Mf production per worm</td>
<td>2</td>
<td>0.61</td>
<td>4.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>h,i</td>
<td></td>
</tr>
</tbody>
</table>

- Not considered in the model
- When only one number is given, this is the same for both model variants.
- Assuming a negative exponential distribution.
- Assuming a Weibull distribution with shape parameter = 2.
- Exponential saturating function with initial increase when mf intake increases from zero = 0.047
- Hyperbolic saturating function with initial increase when mf intake increases from zero = 0.09
- This parameter defines the period in which the strength of the immune response is halved in the absence of boosting
- In the absence of anti-L3 immunity
- In the presence of at least one male worm, scaled to the number of mf per 20 μl peripheral blood
- In the absence of anti-fecundity immunity

Figure 2. Comparison of model predictions with microfilaraemia prevalence by age observed before the start of vector control in Pondicherry, India, in 1981. (A) LYMFASIM predictions for models with anti-L3 immunity (solid line), anti-fecundity immunity (dashed line), and a model variant without immunity (dot-dashed line); the latter model does not fit the data and was therefore rejected. (B) EPIFIL predictions of a model with acquired immunity. Symbols in both graphs indicate the observed prevalence levels with corresponding confidence intervals.
EPIFIL

EPIFIL simulates the average course of infection over age and time in a human population by a set of differential equations. The human population is constant in size and age-structure. Limitation in the transmission of infection by culicine mosquitoes is taken into account, so that the number of infectious L3 larvae that can develop in mosquitoes saturates at higher mf intensities. Acquired immunity is included as a second limitation mechanism: it is triggered by incoming L3 larvae and reduces the probability that new larvae develop into adult worms. Heterogeneity is only included by age-related exposure to mosquitoes, i.e. the risk of infection increases with age, until a maximum level is reached at the age of 9 years. The mf prevalence is calculated using a negative binomial distribution, assuming a certain amount of aggregation of parasites in the human population.

The model can be used to simulate the impact of vector control or mass treatment. Vector control is assumed to reduce the mosquito biting rate. Mass treatment leads to killing of a proportion of adult worms or mf and to temporal infertility of worms, depending on the proportion of the population that receives treatment and characteristics of the treatment regimen.

The design of this population-based, deterministic model is based on a general differential equation framework describing the dynamics of macroparasitic infections.\(^{19,27,28}\)

LYMFASIM

LYMFASIM simulates the acquisition and loss of worms over age and time in a discrete number of human individuals, using stochastic microsimulation. Individuals interact through biting mosquitoes and together they form a dynamic population of which the size and age-structure may change over time. Like EPIFIL, LYMFASIM takes account of limitation in the proportion of engorged mf that develop into L3 larvae inside the mosquito and of acquired immunity in human hosts. Two model variants were developed for Pondicherry, which differed with respect to the type of acquired immunity: ‘anti-L3’ immunity is triggered by incoming L3 larvae and reduces the probability of successful adult worm establishment; ‘anti-fecundity’ immunity is triggered by the presence of adult worms and reduces the rate of mf production by female worms. By considering individual worms in individual hosts, the model automatically takes account of the declining mating probability of female and male worms with lower average infection intensities. Age-dependent exposure is included, assuming that exposure increases until a maximum is reached at about 20 years of age. Other factors contributing to heterogeneity are variation in exposure to infection within age groups, inclination to participate in treatment programmes, the response to treatment, and the ability to develop immune responses. Parasites may vary with respect to their lifespan (about ten years on average). Individual mf intensities are translated into the number of mf that would be counted in a 20 μl blood smear, taking account of random variability in these counts and reduced sensitivity of diagnostic tests at lower mf densities. The mf prevalence and (geometric or arithmetic) mean mf intensity can be directly calculated from the smear counts, using data from all simulated individuals or specific subgroups.

Similar to EPIFIL, LYMFASIM simulates the impact of vector control by reducing the mosquito biting rate. Treatment takes place at the individual level, and results in killing (part) of adult worms or mf and a temporal or permanent reduction in the fertility of female worms. Selective or mass treatment can be simulated.

This individual-based model uses the technique of stochastic microsimulation, which was earlier applied in the modelling of onchocerciasis transmission and control.\(^{29,30}\)

COMPARISON OF MODEL PREDICTIONS

Both EPIFIL and LYMFASIM have been used to predict the impact of control measures.\(^{9,10,31,32}\) In this report, we focus on predictions of the coverage and duration of annual mass treatment programmes that will be required for elimination. All published predictions were based on the Pondicherry variants of the model, although acquired immunity was left out of the model in the EPIFIL predictions. From the predictions of both models we can conclude that it is possible to eliminate lymphatic filariasis by yearly mass treatment, but the number of treatment rounds largely depends on coverage, precontrol mf prevalence, and the macrofilaricidal effects of drugs. This is illustrated in tables 2 and 3, and figure 3. Often the required number of yearly treatment rounds is predicted to be higher than 4–6, which was hoped to be sufficient when GPELF was initiated. As an alternative to longer programmes, one might consider more frequent mass treatment (e.g. half-yearly) or applying vector control in addition to mass treatment (fig. 4).
Table 2. LYMFA SIM: predicted number of annual rounds of mass drug treatment required to achieve elimination in 99% of the simulation runs in an area like Pondicherry, for four different drugs or drug combinations and two coverage levels. Predictions are based on the anti-L3 variant of the model for Pondicherry, with a precontrol microfilaraemia prevalence of 8.5%. Elimination is defined as zero microfilaraemia prevalence 40 years after the start of treatment.12

<table>
<thead>
<tr>
<th>Drug (combination)</th>
<th>Assumed treatment effects (proportion killed)</th>
<th>Predicted number of rounds required for elimination with coverage of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>adult worms</td>
<td>microfilariae</td>
</tr>
<tr>
<td>Ivermectin + albendazole</td>
<td>35%</td>
<td>100%</td>
</tr>
<tr>
<td>Diethylcarbamazine</td>
<td>50%</td>
<td>70%</td>
</tr>
<tr>
<td>Diethylcarbamazine + albendazole</td>
<td>65%</td>
<td>70%</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>80%</td>
<td>0%</td>
</tr>
</tbody>
</table>


Figure 3. LYMFA SIM: prediction of the duration of yearly mass treatment with ivermectin required to reach elimination (zero microfilaraemia prevalence 40 years after the start of treatment) with 99% certainty, in relation to coverage. Ivermectin is assumed to permanently sterilize 77% of female worms and to kill all microfilariae. Results are shown for two variants of the LYMFA SIM model for Pondicherry that differ in the type of acquired immunity assumed, assuming a precontrol microfilaraemia prevalence of 8.5%. The ‘drop lines’ (i.e. the intersecting horizontal and vertical lines) indicate the number of treatment rounds that would be necessary to achieve a 99% probability of elimination when the population coverage is 65% 13

Table 3. Prediction of number of yearly mass treatment rounds required to reach a 0.5% microfilaraemia prevalence threshold, using a combination of diethylcarbamazine plus albendazole in relation to endemicity and coverage. The combination treatment is assumed to kill 95% of all adult worms and 95% of the microfilariae, and to interrupt microfilaria production for six months. EPIFIL simulations were published10 and concerned a model without acquired immunity. LYMFA SIM results from the model with anti-L3 immunity were added for comparison for an average pretreatment microfilaraemia prevalence of 10%.

<table>
<thead>
<tr>
<th>Pretreatment mf prevalence</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60%</td>
</tr>
<tr>
<td><strong>EPIFIL</strong></td>
<td></td>
</tr>
<tr>
<td>2.5%</td>
<td>2.5</td>
</tr>
<tr>
<td>5%</td>
<td>5</td>
</tr>
<tr>
<td>10%</td>
<td>10</td>
</tr>
<tr>
<td>15%</td>
<td>12</td>
</tr>
<tr>
<td><strong>LYMFA SIM</strong></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>10</td>
</tr>
</tbody>
</table>

* Based on the average trend in microfilaraemia prevalence of 100 simulation runs.
The predictions of EPIFIL and LYMFASIM cannot be compared directly because the original publications reported results for different treatment regimens, with different assumptions on efficacy of the drugs, and different precontrol mf prevalence levels. Further, different criteria for elimination were used: in EPIFIL elimination was assumed to occur if the mf prevalence after treatment was below 0.5%; in LYMFASIM elimination was defined as a zero mf prevalence 40 years after the start of control. To allow better comparison of the models, we did a series of additional simulations with LYMFASIM for mass treatment with the combination of diethylcarbamazine plus albendazole, using the same assumptions on drug efficacy and the same criterion for elimination as in published EPIFIL predictions (table 3). Simulations were done with the anti-L3 variant of the LYMFASIM model.

It is reassuring that both models come to comparable conclusions regarding the number of treatment rounds required to achieve elimination, although LYMFASIM predictions are slightly more optimistic than EPIFIL predictions when population coverage is high. This finding of nearly equal predictions is not straightforward. The LYMFASIM model contains several assumptions and mechanisms, which, relative to EPIFIL, limit the impact of the intervention on transmission: 1) a longer adult worm lifespan (about 10 years vs. 8 years); 2) acquired immunity; 3) heterogeneities in exposure to mosquitoes, compliance to mass treatment, and adult worm lifespan. However, the limiting effect of these assumptions and mechanisms on the impact of mass treatment is apparently counteracted by the enhancing effect of a reduced mating probability of worms at lower average worm burdens in LYMFASIM.

CRITERIA FOR ELIMINATION

EPIFIL predictions were based on the assumption that transmission will not continue when the mf prevalence falls below 0.5%. The choice for this threshold is somewhat arbitrary in the absence of evidence from the field. Given its individual-based structure, LYMFASIM is more suitable for examining in how many runs infection is ‘truly’ eliminated, as indicated by zero mf prevalence 40 years after the start of control. For example, in the runs with 10% precontrol prevalence, 8 rounds were required to bring the average mf prevalence below 0.5% (table 3). However, in only 87% of the runs did this result in zero mf prevalence 40 years after the start of control. It is clear that to be 99% certain of elimination (as was the criterion in table 2), much longer continuation of mass treatment would be required. More extensive simulation studies are required to determine a more precise threshold level below which elimination would occur. This threshold level (or threshold levels) will depend on local transmission dynamics and mosquito biting rates, immigration of parasite carriers or infected mosquitoes, but also on heterogeneities and population size in view of the stochastic processes involved.

APPLICATION OF MODELS FOR OTHER REGIONS

The existing model variants were all quantified for transmission of *W. bancrofti* by *Culex quinquefasciatus* and tested against data from Pondicherry.\(^ {27,26} \) The basic structure of the models is generalizable to other areas, but various model parameters may take different values. Most importantly, this concerns the relationship between mf density in the human blood and the number of L3 larvae developing in mosquitoes. Unfortunately, few data are available to quantify this relationship for the different mosquito species involved.\(^ {35} \) Especially for the anopheline mosquito species responsible for transmission in large parts of Africa, more field research is needed. Other parameters that may need requantification relate to the composition of the human population, mosquito biting rates and heterogeneity in exposure, and operational characteristics of interventions.

Biological parameters are not expected to vary much between regions. However, our understanding of the biology of infection (in spite of in-depth model-based analysis of the Pondicherry data) is incomplete and there is uncertainty about the quantification of several key parameters, such as the parasite lifespan or role of acquired immunity. Therefore, it is crucial to continue testing the validity of existing and new model variants against epidemiological data. Testing models against age-specific data may help to determine the role of acquired immunity or other processes.\(^ {34} \) Trends during vector control are especially informative about the adult worm lifespan.\(^ {26,35} \) Trends during mass treatment may give information about the effects of drugs on worm survival and productivity. And trends after cessation of control may help to determine whether density-dependent mechanisms have appropriately been included in the model. Better information on all these aspects should eventually come from field research: using combinations of available diagnostic tests (mf and antigen detection, ultrasound to visualize adult worms), it may be possible to further increase the validity of our existing models.

Some work has already been done to prepare
models for use in other areas. The LYMFASIM model has been applied to age-patterns observed in an area of South-East India that has the same vector-parasite combination and presumably the same transmission dynamics as Pondicherry. This led to the development of new model variants with less strong or no immunity (Subramanian, unpublished data). Comparison of predictions from the new LYMFASIM model variant and EPIFIL with observed trends during mass treatment in this region indicated that assumptions regarding efficacy of drugs or possibly coverage and compliance patterns had to be adapted (Subramanian, unpublished data). Using published data of uptake and development of mf in Anopheles mosquitoes, LYMFASIM was adapted for transmission in Africa (Stolk, unpublished data). Model parameters were adapted so that the predicted age-prevalence reflects the observed data from this region.

CHALLENGES IN THE EVALUATION OF CURRENT ELIMINATION PROGRAMMES

The available models soon have to face new challenges in the ongoing programmes for elimination of lymphatic filariasis. Predictions of the number of treatment rounds required for elimination were only a first step. However, specific programmes also need to be monitored and evaluated. For example, the observed results can be compared with model predictions to see whether progress is as expected. If results lag behind, programmes can be adapted. Also, the models could help to determine when mass treatment can be stopped with low risk of recrudescence, taking account of the specific local conditions, local coverage and compliance levels, and the achieved reduction in mf prevalence and intensity. Analogously, models can help to determine cost-effective surveillance strategies for early detection of recrudescence of infection after cessation of control, and measures to be taken to stop this recrudescence.

To address the discussed issues on monitoring and surveillance, the models must be extended to include the results of antigen detection, which is widely used in monitoring and surveillance by ongoing control programmes. Other possibly useful extensions of the model include migration of parasite carriers and infected mosquitoes and development of resistance to available drugs.

Although discussion until now focused on the elimination of transmission, this goal may be difficult to achieve in some areas. In some situations focus may shift to reducing the public health problem without explicitly eliminating infection. To address this with the models, more attention is required for the development of disease. Simple mechanisms of disease development are included in both models, but this has received little attention in published work until now.

CONCLUSIONS

There are currently two models for lymphatic filariasis transmission and control, LYMFASIM and EPIFIL, that have been used in predicting the impact of mass treatment programmes. These models give more or less similar predictions on the number of treatment rounds that will be required for elimination, at least in Pondicherry-like situations. The models differ however in defining when elimination occurs, which leads to different advice on the duration of mass treatment. In view of current elimination programmes, it is crucial to obtain better criteria for when to stop control, taking account of stochasticity in the eventual outcome of elimination. Antigen tests should be included in the model, and the disease part of the models may need more attention. Model variants that are adjusted to local situations are powerful tools to aid decision-making in current control programmes.
References


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Annex 6

WORKING PAPER:
Diagnostic tools for filariasis elimination programmes

Appendix
Primer: diagnostic options for monitoring the effects of mass drug administration in programmes for elimination of lymphatic filariasis

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6: DIAGNOSTIC TOOLS FOR FILARIASIS ELIMINATION PROGRAMMES

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INTRODUCTION

In the not so distant past, diagnostic tools for filariasis were limited to clinical diagnosis (insensitive for active infections, low specificity), detection of microfilariae (mf) (insensitive for infection, impractical in many areas), and detection of antibodies to crude native antigen preparations (poor specificity). These tools were inadequate for answering basic questions that are crucial to programmes for elimination of lymphatic filariasis (PELFs). There have been significant advances in diagnostic tools in recent years. It is obvious that the thoughtful use of these tools may be more important than their intrinsic properties. The Japanese PELF succeeded with mf testing alone as an assessment tool. It is also possible to cut a piece of wood in two with a hammer! The purpose of this working paper is to critically review the current state of filarial diagnostics as they apply to PELFs. This review summarizes the work of many scientists (much of which is unpublished). I have inserted a primer on diagnostic options as an appendix to help bring the non-specialist reader up to speed in this important area.

Different tools may be needed for key stages in ELF programmes. I have used the metaphor of a ship sailing from her home port to a distant destination to illustrate this point.

STARTING POINT

Obviously, a navigator needs to know the point of origin to properly plan the journey. The first stage of a PELF requires a sensitive, specific, and convenient method for detecting filariasis endemicity that can be used to map endemic areas for inclusion in the programme. Overdiagnosis that includes nonendemic areas can greatly increase programme expenses and decrease the chances for success. Underdiagnosis and exclusion of endemic areas is also not acceptable. There are several viable diagnostic options for this early stage. Some programmes have used traditional mf testing (usually with thick blood smears collected at night). This method is insensitive for active infections; it misses people with low mf counts and those with amicrofilaraemic infections that have the potential to contribute to future transmission. Thus, reliance on mf testing may lead to underdiagnosis and exclusion of areas with sustainable LF transmission from PELFs. It is tempting for programme managers to focus on the potential advantages of mf testing, namely that it is specific, inexpensive, and low tech (low infrastructure requirement). I have emphasized ‘potential’ because, in practice, mf testing may not have any of these desirable features. It is often very difficult to obtain representative samples of night blood from endemic communities for mf testing. Specificity requires proper staining procedures and skilled microscopists with good equipment to differentiate mf from artefacts and to distinguish different filarial species. These attributes are not inexpensive to implement or maintain. Any money saved by reliance on technically poor mf testing to classify implementation units early in a PELF is lost with interest paid later in the programme when the ostrich withdraws from its hole to find untreated endemic areas.

Antibody detection and molecular xenomonitoring could easily be used for identifying areas that are endemic for bancroftian filariasis. However, these tools have not been widely used for this purpose to date. This is probably because they have not been widely available in a convenient, user-friendly format. This conclusion is supported by experience with antigen detection for filariasis (reviewed below and in the appendix).

Several laboratories described methods for detecting soluble filarial antigens in human blood in the late 1970s and early 1980s. However, no filarial antigen test was sensitive or convenient enough to be practically useful outside the developer’s home laboratory until the Weil laboratory developed a monoclonal antibody-based ELISA (using monoclonal antibody AD12) for detecting circulating W. bancrofti antigen in 1984. Early studies with this test showed that it was more sensitive for active infection than mf tests, specific for W. bancrofti infection, and that serum antigen levels decreased following treatment with diethylcarbamazine (DEC). Although this ELISA was a useful research tool, it was not practical for use by public health programmes. (This is also largely true of the TropBio CELISA for W. bancrofti antigenaemia that was marketed in the early 1990s. The TropBio kit has been widely used in research projects, but it has not caught on as a tool for mapping or monitoring ELF programmes.) This situation changed in 1997 with the introduction of a lateral flow, rapid-format card test for detecting filarial antigenaemia (the ICT Filariasis Test). It took a few years for this test to gain acceptance.
However, by 2000 the ICT test was recommended by international authorities as the diagnostic method of choice for mapping the distribution of bancroftian filariasis, and this test is now widely used around the world for this purpose in ELF programmes. Its virtues are that it is quick (ten minutes), minimally invasive (100 μl blood from a finger prick), easy to perform, and widely available. The last points are particularly important, because these features freed filarial antigen testing from the confines of research laboratories so that it could be used in field sites around the world. Please see the appendix for more information on this test.

**Options for mapping areas with Brugian filariasis**

Despite the limitations of mf testing listed above, lack of a sensitive antigen test for *Brugia* infections means that good quality mf testing is still a very useful option for identifying *Brugia*-endemic areas. Parasite DNA detection (either in mosquitoes or in human blood samples) and antibody testing could also be used for this purpose. Antibody test kits (a dip-stick and a cassette test) based on recombinant antigen BmR1 have recently become commercially available. These tests have been reported to be sensitive for *Brugia (malayi and timori)* infection/exposure. They have not yet been validated as tools for mapping the distribution of brugian filariasis for PELFs; in my opinion, additional studies would be needed to determine how antibody prevalence rates correspond to mf rates that merit inclusion in PELFs.

**MONITORING PROGRESS DURING AN ELF PROGRAMME**

Let us assume that baseline information was adequate for our ELF ship to leave port pointed in the correct direction. We cannot expect a ship to reach its destination without periodic navigational readings en route. These are important to show that we are on course, and also important for identifying problems that can be solved by mid-course corrections. The same can be said of ELF programmes. Interim measurements of progress may be crucially important for identifying problems that can be solved while funding is available and also for securing resources needed to complete the programme.

Considerations for tools for this purpose are somewhat different from those used for mapping endemicity. For example, consider mf testing. Microfilaraemia rates and intensities typically fall shortly after initiation of MDA programmes, and this is gratifying to programme managers. While we would agree that this is a positive change and evidence of good MDA coverage, it can also be misleading. This is because decreases in mf rates can be transient if the treatment regimens employed are either not highly macrofilaricidal (consider changes in mf rates that would occur a few months after a first round of MDA with ivermectin alone) or do not interrupt transmission of the infection for a period that is longer than the lifespan of most adult filarial worms. In addition to the limitations of mf testing mentioned above, this method does not provide much information on changes in filariasis transmission during an ELF programme. Therefore, while mf testing will be employed in many areas for historical or practical reasons, it is not recommended as a single tool for monitoring ELF programmes (author’s opinion). While I endorse the use of antigen testing for mapping endemicity, this may not be an optimal tool for interim assessments of ELF programmes (especially early on). This is because antigen rates tend to fall relatively slowly following effective MDA, and antigen testing, in isolation, will tend to underestimate the effects of MDA on microfilaraemia and transmission. However, antigen prevalence rates do fall sharply after several rounds of effective MDA. We have seen rates (card test) fall from 19% to ~2% after only four years of MDA. If very low residual antigen rates are achieved, the risk that filariasis will reappear in an area should be very low (assuming no reintroduction due to migration). Therefore, I believe that antigen monitoring is preferable to mf testing as a monitoring tool. Either method is clearly preferable to no monitoring at all. Antigen monitoring in the context of PELFs should not be done more frequently than every two years (author’s opinion).

**ALTERNATIVES TO ANTIGEN MONITORING**

Recent studies in Egypt and Papua New Guinea have shown the value of antibody testing and molecular xenomonitoring (MX) as monitoring tools for interim assessment of ELF programmes. These tests are sensitive to changes that occur during a successful ELF programme that indicate the programme is on course. They provide information on changing rates of filariasis transmission and the potential risk of transmission, respectively.

However, these tests are now where antigen testing was before the ICT card test appeared – interesting research tools not quite ready for broad programme use. There is a ‘Catch 22’ situation here. While it is true that antibody testing will not be widely practiced until commercial kits become available, kits will not appear until enough people become available.
The situation is somewhat different for MX, because it is a breakthrough technology that does not depend on availability of commercial kits; it is very unlikely that commercial kits will be developed for filarial MX. Despite the excitement and potential value of this technology, MX has not been a practical choice for use by endemic countries for monitoring ELF programmes to date; no government’s national ELF programme uses this method for monitoring at this time. Again the issue is accessibility. However, we believe that recent technical advances have made MX a realistic choice for practical field use in monitoring large-scale ELF programmes. These include use of traps for more efficient collection of mosquitoes ( gravid traps for *Culex*, light traps for *Anopheles*), improved methods for isolating DNA from mosquito pools, software ( Poolscreen2) for calculating mosquito infection rates from qualitative PCR results, and real-time PCR (Dr R. Rao, unpublished data) for specific amplification of parasite DNA and detection of amplified DNA product. Real-time PCR is more sensitive than conventional PCR; other advantages are higher throughput, reduced risk of contamination in the laboratory, and the ability to perform other tests (e.g. HIV viral loads) with the same instrument. The cost per test for real-time PCR is comparable to conventional PCR (apart from the initial cost of the equipment).

More research is needed to determine the relative value of antibody and MX testing as monitoring tools. Each has advantages, and the two approaches are complementary. Antibody monitoring of sentinel populations provides information on the cumulative lifetime exposure of the sampled cohort to filarial infection. This method requires collection of finger-prick blood from a representative sample (often primary school children). MX is based on the ability of mosquitoes to collect human blood, which these flying syringes do this for a living. MX provides information on the point prevalence of filarial parasites in mosquitoes in the area of interest. In practice, most parasite DNA detected by MX in mosquitoes is from pre-infective stages. Therefore, MX should be thought of as a means of efficiently sampling endemic populations for the presence of microfilariae. It is not a measure of infectivity or current rates of transmission.

**On the horizon: molecular assays for infectivity**

Bedbugs probably ingest mf during blood meals, but filarial DNA rates in bedbugs (and even mosquitoes) would provide a cloudy picture of filariasis transmission in a community. This is because mf cannot develop to the infective L3 stage in bedbugs, and bedbugs cannot transmit the parasite. Thus, bedbugs may be infected, but they are not infective. Entomologists and modellers are looking for better information on infectivity of mosquitoes. Pilot studies performed by Dr. Steven Williams’ group suggest that this is feasible by using reverse transcriptase PCR (RT-PCR) to amplify messenger RNA for genes preferentially expressed by L3. This work is ongoing, and it remains to be seen whether this tool will be practical and useful for use in ELF programmes.

**ENDPOINTS FOR PELFs AND EARLY DETECTION OF RESURGENCE**

More information is needed on how to use antigen, antibody, and MX tests to inform decisions on when it is safe to discontinue MDA. There is no consensus on this issue at this time. We (Weil and Egyptian colleagues) favour an evidence-based approach to this question rather than adoption of arbitrary targets. In particular, we do not agree with the target sometimes mentioned of reducing mf prevalence rates to below 0.1% or the current WHO recommendation to require implementation units to undertake additional rounds of MDA if 1 in 3000 children born after the initiation of MDA have positive antigen tests. We believe that these targets are well beyond what is needed to eliminate LF (or reduce transmission to unsustainable levels (at least in areas with transmission by *Culex* or *Anopheles* mosquitoes).

It is difficult to demonstrate the absolute absence of infection or transmission. The assessment tools are not perfect, and financial constraints place limits on the number of samples that can be collected and tested. Therefore, we favour using statistical criteria for targets: sample sizes should be calculated to provide 95% certainty that the true rate is less than the target rate (with power = 0.8). Target rates do not need to be zero; they should be rates that are below those needed for sustained transmission of LF. A few new cases can be accepted if the incidence rate is well below the natural attrition rate for LF infections.

Data from Egypt are again helpful in this regard. Seven per cent of our sample from localities with high baseline infection prevalence rates denied taking DEC/albendazole in any of the first four rounds of MDA. As expected, antigen and mf prevalence rates in these people were significantly higher than in people who reported taking at least one round of DEC/albendazole. However, infection rates in the systematically noncompliant people were about...
75% lower than baseline rates in the same population prior to MDA. We believe that these data indicate that effective MDA programmes have a herd treatment effect (analogous to herd immunity seen in vaccine programmes) in that they benefit those who fail to participate in the programme. If transmission is greatly reduced by MDA, old infections die out at a much faster rate than new infections can be established. This should be obvious to anyone who has thought about MDA in LF, but we were happy to see actual data to support this hypothesis.

Returning to targets, we favour adoption and testing of targets derived from population-based studies of PELFs. For example, our studies in Egypt suggest targets for treated populations following four years of effective MDA: < 2% for antigenaemia (or < 1% to be conservative), < 2% for antibody prevalence in first year primary school children, and < 0.25% infection rates by PCR/Poolscreen. We are about to initiate a study that will test whether communities that have achieved these targets have reduced transmission below sustainable levels. Different targets may be needed in different areas, depending on vector species, seasonal transmission patterns, biting rates, drugs used for MDA, etc. How can we determine targets for different areas?

We favour the use of antibody testing and MX as surveillance tools for early detection of resurgent transmission. Fairly large samples are needed to show statistically significant increases in these measures when baseline rates post-cessation of MDA are very low. There is no consensus at this time on how these or other tests should be used for post-MDA surveillance. Research is required to provide data on this important question.

ADVANCED DATA ANALYSIS AND MODELLING

Modelling studies have the potential to help the navigator by clearly defining the destination and by developing tools that can tell the captain when the ship has reached the destination (ideally with a pre-defined, finite degree of certainty). While it has been useful, we will now leave the ship metaphor behind and speak seriously about modelling.

Research projects and ELF programmes around the world are generating reams of data on events in specific villages, regions, and countries. Mathematical analysis and modelling efforts are needed to identify patterns in the data so that we can move from the specific to the general. Dr. Wilma Stolk (personal communication) has commented on this situation as follows: “While field studies are useful, there are few good ones, and even the best of them are limited in scale and time by budget constraints. Moreover, it is not possible to test every intervention in every situation. Modelling can help overcome these limitations by intelligently predicting outcomes of studies that have not been conducted”.

I believe that modelling has the potential to be very helpful for people in the real world who are responsible for making tough decisions about PELFs. Models should have practical outputs so that they can help ELF programme managers to manage. Managers need guidance on criteria for including areas in MDA programmes, on when it is reasonable to stop MDA, on how to look for early evidence of LF re-emergence, and on options for managing this unhappy situation if it happens.

Modelling studies depend on the quality of the data available for analysis, and this has been a significant limitation in some prior modelling efforts for LF (author’s opinion). Existing models should now be refined by incorporating new types of data (antigenaemia, antibody rates, mosquito infection rates) to analyse relationships between infection and transmission parameters. While it may not be possible to do this for every combination of vector, parasite, and environment, I think that this should be done with real data from several of the major epidemiological situations for LF transmission. The hope is that improved models will be able to use these new variables (alone and in combination) to improve understanding of the effects of MDA on filariasis transmission and to develop practical targets for ELF programmes.
Appendix

PRIMER: DIAGNOSTIC OPTIONS FOR MONITORING THE EFFECTS OF MASS DRUG ADMINISTRATION IN PROGRAMMES FOR ELIMINATION OF LYMPHATIC FILARIASIS

Several options are available:

Disease rates

Disease rates (prevalence rates for hydrocele, lymphedema, or elephantiasis) are not useful for this purpose because most clinically evident filariasis is chronic and develops over a period of many years. Chronic filariasis, like a layer of coloured stone on the face of a cliff, reflects events from many years past. Thus, disease prevalence rates are not sensitive indicators of changes in infection prevalence or transmission following MDA.

Microscopic detection of microfilariae (mf testing)

This provides data on infection prevalence and parasite density, both of which should fall following effective MDA programmes. However, mf testing is labour-intensive and requires collection of blood at night in many endemic areas. It is not very sensitive for active infections, and is impractical in some settings. Thus, while membrane filtration of venous blood is more sensitive than thick smears for detecting mf, this method requires expensive materials and unpopular venipuncture. In addition, relatively large population samples are needed to demonstrate that mf prevalence rates are below the very low targets suggested for ELF programmes. On top of these problems, it is very difficult to obtain large, representative samples in night blood surveys in filariasis-endemic areas.

Despite these limitations, mf testing has certain advantages (it is low tech and inexpensive) and a long track record. Unfortunately, the availability of high quality mf testing is often taken for granted, although it is often not done well. It is a dying (or dead) art in many areas. Mf detection requires lots of work, training, and attention to detail (M. Sasa is a good resource on this). Proper sampling of populations, preparation of smears, staining and microscopy is very labour intensive. Despite these challenges, there may well be situations where mf testing could and should be the method of choice for assessment. If programmes choose this approach, they should not focus on young schoolchildren for sampling, because mf rates are often very low in this group even in the setting of ongoing transmission prior to MDA.

More information is needed to determine residual mf prevalence rates that correspond to interruption of transmission in different situations (i.e. reduction of incidence rates to well below rates of spontaneous clearance of filarial infections). These may vary in different epidemiological settings. If the mf threshold rate of < 1% reported from China is not completely accepted, is there any evidence that a mf rate of under 0.5% can sustain transmission in non-Aedes areas? If we accept a mf target of < 0.5%, this is much easier to demonstrate (because of sample size requirements) than < 0.1%.

Detection of filarial antigenaemia

Sensitive immunological tests (the original AD12 ELISA and a commercial test based on monoclonal antibody Og4C3 and marketed as the TropBio Filaria Antigen CELISA) and a lateral flow card test based on mAB AD12.1 (now marketed as the Filaria Now ICT Test by Binax) detect antigens released by living adult *W. bancrofti* worms in sera/plasma/whole blood from infected subjects. These tests do not detect antigenaemia in sera from subjects infected with other parasites including other filarial species. While positive tests may be seen in subjects with other parasitic infections if they have a history of residence in an area that is endemic for bancroftian filariasis, positive tests should not occur with sera from people with no history of exposure to *W. bancrofti*. Antigen tests have sensitivities of 95% or higher in untreated subjects with *W. bancrofti* microfilaraemia, and they also detect infections in subjects with afilarial infections.

Several lines of evidence support the notion that amicrofilaraemic subjects with positive antigen tests are truly infected: their sera contain the same 200 kDa parasite antigen (detectable by Western blot) that is present in sera from mf carriers; their very high antifilarial antibody prevalence rates are comparable to those seen in mf carriers; their antigen levels decrease or disappear following treatment; they are at increased risk of developing microfilaraemia relative to antigen-negative subjects in the same community; like mf carriers, mf-negative men with positive filarial antigen tests often have motile adult worms in scrotal lymphatic vessels that are visible by ultrasound. In contrast, most
amicrofilaraemic subjects with clinical filariasis have negative filarial antigen tests and no motile worms visible by ultrasound; we believe that such subjects are no longer infected with adult filarial worms.

The sensitivity of antigen tests in subjects with persistent microfilaraemia following treatment is lower than in untreated subjects (in the range of 85% for the card test relative to membrane filtration with higher sensitivity in persons with mf detected by thick smear). Prior studies have shown that mf prevalence rates (by thick smear) are much lower than filarial antigen prevalence rates in untreated populations (ratio mf rate/antigen rate approximately 0.5). This ratio tends to decrease to 0.25 or lower following several rounds of MDA (which is more effective against mf than adult worms). More data are needed on the relationship between antigen and mf prevalence rates in treated populations.

Antigen testing has certain advantages over mf testing for detecting active filarial infections: (1) it is more sensitive than mf detection, and (2) blood collected by finger prick during the day or night can be used. Based on data from filarial infections in animals, filarial antigen levels are believed to be related to the number of adult filarial worms in the human host.

Unfortunately, antigen testing alone is not very good for monitoring progress in the first few years of ELF efforts based on MDA. This is because many infected subjects remain antigen-positive for years after treatment, even if they achieve sustained clearance of microfilaraemia. Thus, major early changes in mf prevalence and density, and decreases in filariasis transmission, are likely to be missed by monitoring programmes that are based solely on antigen testing. Antigen rates do however decrease sharply to levels that can approach zero following several rounds of effective MDA. While amicrofilaraemic, treated subjects with persistent antigenaemia are theoretically at some risk of redeveloping microfilaraemia and potentially reinitiating transmission in the future, the magnitude of this risk is unknown. The risk that mf might reappear following MDA is likely to depend on the drug combination used and the number of rounds of treatments taken. The author considers this question (rates of recurrence of microfilaraemia in subjects with persistent antigenaemia following MDA) to be a high research priority.

Additional notes on filariasis antigen card tests

The card test was transferred from AMRAD ICT to Binax, Inc. in 2000. The Binax Filariasis Now test has generally performed very well, although technical problems with certain test lots caused an interruption in availability of the test in early 2005. Binax officials have told the author that they have solved the problem and are scheduled to resume sales of the test in May 2005. It is very important to read the Binax card test result at ten minutes. Falsely positive tests can occur if the tests are read after the recommended time point, and this problem increases with time (with up to 50% false positives after several hours). Simonsen and Magesa recently reported that late false positive lines can be distinguished from true positive tests. Late-appearing false positive lines tend to be grey instead of purple, and they have indistinct margins that are strongest on the lateral edges of the nitrocellulose membrane (in contrast to true positive lines that are purple, sharp, and fairly uniform across the membrane). In our experience, it is sometimes difficult to distinguish late false positive tests from weak true positive tests when the cards are read one or more days after test performance.

Detection of filarial parasites in mosquitoes

One commonly used traditional method is dissection of host-seeking mosquitoes (collected with CO2/light traps) to look at changes in infection (any filarial larvae present) and infectivity (infective larvae present) rates over time. Mosquitoes can also be collected with human bait to estimate annual transmission potential; this method was used to document dramatic decreases in filariasis transmission after MDA with DEC and ivermectin in villages in Papua New Guinea. Unfortunately, human bait studies are labour intensive, and some have questioned the ethics of this mosquito collection method. In addition, dissection of mosquitoes collected by any method is insensitive for detection of parasites in areas with very low mosquito infection rates following MDA. Molecular xenodiagnosis (MX) detects filarial DNA in mosquitoes by PCR. MX is much more sensitive for detecting filarial parasites in mosquitoes than dissection. Unfortunately, MX by PCR is beyond the capabilities of many laboratories in filariasis-endemic countries.

However, recent advances in mosquito collection strategies, DNA isolation, and DNA detection have the potential to change MX from a research tool to a monitoring tool that can be used by PELFs around the world. Because of high infrastructure requirements, we favour the model of establishing regional
Antibody monitoring

Early antibody diagnostic tests for LF were plagued by poor specificity. Our group achieved greatly improved specificity by testing for IgG4 antibodies to a recombinant filarial antigen, Bm14 (ORF 459 bp, expressed in pGex as a GST fusion). This antigen is similar to Bm SXP-1 reported by Piessens’s group. Numbers studies have shown that the Bm14 antibody test is sensitive for infection with (or heavy exposure to) *B. malayi* and *W. bancrofti* (generally positive in over 90% of mf carriers). A recent blinded multicentre study confirmed this finding. Primates produce antibodies to Bm14 a few weeks after they are infected with *Brugia* (i.e., during the pre-patent period). Humans with pre-patent infections also have antibodies to Bm14; a prospective study showed that antibody to Bm14 was a significant risk factor for incidence of microfilaraemia over the next year. While a positive antibody test does not prove current infection, this test is specific for infection or heavy exposure to filarial parasites (i.e., no false-positive tests are seen with sera from people with or without other nematode infections who have not been exposed to filarial parasites). Prior studies have shown that antibody prevalence rates are much higher than mf and antigen prevalence rates in low-prevalence settings (pre-MDA Egyptian villages), but these three measures of filariasis activity varied in parallel in untreated populations. Antibody rates also tend to be much higher in young children in areas with low-level LF transmission than antigen or mf rates. For this reason, mf and filarial antigen tests are not as useful as antibody testing of sentinel children for assessing changes in LF transmission following MDA; preliminary studies have shown that antibody rates in young children fall fairly rapidly in the years following initiation of effective MDA programmes.

Antibody testing is complementary to molecular xenomonitoring as a tool for monitoring changes in LF transmission during and after ELF programmes. MX typically tests mosquitoes collected over a short period of time (sometimes from a single night per sampling site). This is not a problem, because MX is primarily a method that uses mosquitoes to detect mf in the human population; it is not used to measure transmission rates. Even so, mosquito populations vary with weather and season in many areas, and sometimes conditions are not suitable for collection of representative samples of fed or gravid mosquitoes preferred for MX studies. On the other hand, antibody responses in a child reflect or integrate the child’s lifetime exposure to LF infection, and antibody testing can be performed in any season. Antibody testing is also useful in locations where MX is not feasible because of technical difficulties in collecting mosquitoes or lack of laboratory facilities.

One limitation of the Bm14 antibody test is that it often gives weak positive results with sera from patients with loiasis and onchocerciasis. This limits the utility of the test in areas of sub-Saharan Africa where LF is co-endemic with these infections. Unfortunately, the WHO AFRO region contains as much as 40% of the world’s LF burden.

Therefore, we consider development of a LF-specific antibody test for use in sub-Saharan Africa to be a high research priority.

While this review has concentrated on Bm14, antigens such as Bm5, Bm serpin, Bm shp-1, BmR1, and others have been reported to have potential as diagnostic reagents. Of these, only BmR1 has been studied extensively. Numerous studies have shown that antibody tests based on BmR1 are sensitive for *Brugia* infections. The sensitivity of BmR1 for *W. bancrofti* infection (generally low to middling) has been reported to vary with sera from different areas. BmR1 antibody assays have less cross-reactivity with sera from subjects with loiasis or onchocerciasis than Bm14 antibody assays.
References


Annex 7

WORKING PAPER:
Morbidity management in the global programme to eliminate lymphatic filariasis:
a review of the scientific literature
7: MORBIDITY MANAGEMENT IN THE GLOBAL PROGRAMME TO ELIMINATE LYMPHATIC FIlARIASIS: A REVIEW OF THE SCIENTIFIC LITERATURE

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SUMMARY

The goal of this review is to assess the state of scientific knowledge regarding current management of filariasis-associated morbidity within the Global Programme to Eliminate Lymphatic Filariasis (GPELF). The review focuses on four major areas: acute inflammatory episodes (principally acute dermatolymphangioadenitis); lymphoedema; hydrocele; and the impact of mass drug administration on filarial morbidity.

Acute dermatolymphangioadenitis

Research during the last decade has confirmed the importance of acute dermatolymphangioadenitis (ADLA) in filariasis-endemic areas. Although some debate continues, a central role for bacteria is generally accepted. Evidence includes isolation of bacteria and increased antibody titres to Streptococcal antigen; comparable data from the general lymphoedema and dermatological literature; and dramatic decreases in ADLA incidence with hygiene and skin care, as well as with prophylactic antibiotics. Several studies document the economic burden of ADLA and its impact on quality of life.

Lymphoedema

The current strategies of the GPELF for lymphoedema management are based on the central role of bacterial ADLA as a trigger for lymphoedema progression. Simple intervention packages have been developed and are being used in many countries, although optimization of the components of these packages would benefit from further research. These interventions have resulted in dramatic reductions in ADLA rates in several studies. Lymphoedema management has also been shown to reduce chronic inflammatory cells in the skin and improve quality of life. During the past decade, the socioeconomic impact of lymphoedema in filariasis-endemic areas has received increasing attention. A key challenge for the GPELF is how best to scale up, monitor, and evaluate lymphoedema management programmes at the national level. Numerous operational research questions remain to be answered in this regard.

Hydrocele

Of the clinical manifestations targeted by the disability alleviation component of the GPELF, hydrocele has been the focus of the least attention. Basic information is lacking on the effectiveness and complications of hydrocele surgery and risk of postoperative hydrocele recurrence in filariasis-endemic areas. While there has been a steady increase in the number of papers addressing health-seeking behaviour, beliefs, quality of life, and productivity losses to hydrocele, few have evaluated the impact of surgery on quality of life and productivity.

Effect of mass drug administration on filarial morbidity

Data on the impact of mass drug administration (MDA) on filarial morbidity are inconsistent. Several studies report reductions in acute inflammatory episodes, lymphoedema, and/or hydrocele following MDAs, but a roughly equal number of studies report no such association. Many of these studies are limited by inadequate or non-standardized case definitions and intermittent or incomplete follow-up. Few studies included control groups. Assessing the public health impact of mass treatment with antifilarial drugs is an important issue for programme advocacy and for morbidity control strategies.

1. BACKGROUND

The objectives of this review are to summarize the scientific basis for morbidity management within the Global Programme to Eliminate Lymphatic Filariasis (GPELF) and to identify priorities for research. Lymphatic filariasis causes a wide range of clinical signs and symptoms, including lymphoedema, hydrocele, lymph scrotum, chyluria, tropical pulmonary eosinophilia (TPE), adenopathy, haematuria, and various manifestations of worms in ectopic sites, among others. This document does not focus on the clinical management of individual patients with these various forms of filarial disease. Rather, it examines the scientific evidence for the morbidity management strategies that have been adopted by the GPELF to reduce the public health burden from the major forms of morbidity in persons with lymphatic filariasis, both acute (inflammatory episodes)
During World War II, clinical and pathologic studies suggested that the pathogenesis of disease in lymphatic filariasis (e.g., chyluria) lack public health significance, but rather, that no coordinated public health approach to these other problems has yet been established.

Our understanding of lymphatic filariasis morbidity has evolved considerably during the last 20 years, and this new understanding has led to the current strategies for morbidity management—especially for lymphoedema and adenolymphangitis. It seems clear that the clinical manifestations and factors leading to progression of so-called ‘filarial lymphoedema’ are similar, if not identical, to those for lymphoedema in non-filarisis-endemic areas. Indeed, given the absence of a diagnostic marker for ‘filarial lymphoedema’, as well as its multifactorial aetiology, some have argued that the use of this term should be avoided. The literature on management of lymphoedema in filariasis-endemic areas is relatively limited; considerably more is known about the pathogenesis, clinical management, and psychosocial impact of ‘non-filarial’ lymphoedema in Europe, Australia, and North America. It is outside the scope of this document to systematically review the literature on lymphoedema and hydrocele from non-endemic areas, but we will refer to this literature in passing.

The document is divided into three sections corresponding to the three major clinical manifestations to be addressed: acute inflammatory episodes, lymphoedema, and hydrocele. After a brief introduction, the available data are reviewed for the following topics: pathogenesis, epidemiology, economic and social impact, and treatment. A fourth section addresses the impact of mass treatment with antifilarial drugs on all three forms of morbidity.

2. ACUTE INFLAMMATORY EPISODES (ACUTE ATTACKS)

The aetiology of acute inflammatory episodes in lymphatic filariasis has long been a subject of debate and confusion. Indeed, a variety of terms have been used in the literature to describe them, including ‘adenolymphangitis (ADL)’, ‘acute attack’, ‘filarial attack’, and ‘endemic lymphangitis’, among others. As early as the 1920s, some scientists argued that bacterial infections were the primary cause of ‘filarial’ lymphangitis. In 1924, the British Filariasis Commission went so far as to state that “all the pathological manifestations” of lymphatic filariasis were caused by secondary bacterial infections. During World War II, clinical and pathologic studies of soldiers with adenolymphangitis and other early clinical manifestations demonstrated the importance of Wuchereria bancrofti adult worms or 4th-stage larvae. The debate continued after World War II, when the role of the immune system in triggering adenolymphangitis, as well as other forms of filarial pathology, was emphasized.

One of the major factors contributing both to the debate and the confusion during the latter half of the 20th century was the relative lack of emphasis on careful clinical observation and case definitions. In 1999, Gerusa Dreyer and colleagues, working in Brazil, defined two distinct clinical syndromes: acute filarial lymphangitis (AFL), caused by death of the adult worm, and acute dermatolymphangioadenitis (ADLA), caused by secondary bacterial infection. AFL is characterized by lymphangitis that progresses distally or in a ‘retrograde’ fashion, along the lymphatic vessel, producing a palpable ‘cord’. Rarely, AFL is accompanied by mild fever, headache, and malaise. Distal lymphoedema may occur, but is usually mild and reversible, i.e. self-limited. In contrast, ADLA (a term used by Olszewski), develops in a reticular or circumferential pattern, and is clinically similar to erysipelas or cellulitis. Symptoms of local pain and swelling, as well as fever and chills, are present. In filariasis-endemic areas, ADLA occurs much more commonly than AFL.

Although there is general agreement within the GPELF on the two syndromes as described by Dreyer et al., investigators have suggested that exposure to 3rd-stage filarial larvae also causes lymphangitis and triggers the onset or progression of lymphoedema. A role for 3rd or 4th-stage larvae in lymphangitis or lymphoedema is supported by animal studies, experimental infections, reports of disease in individual patients travelling from non-endemic areas, and epidemiologic observations that associate incidence of acute adenolymphangitis with filarial transmission intensity. However, a case definition has not been established for larva-associated lymphangitis, which might distinguish it from either AFL or ADLA; this makes it difficult to count cases. Additional work is needed to clarify the incidence, possible mechanisms, and clinical expression of larva-associated filarial lymphangitis and to assess its public health importance in filariasis-endemic areas.

Recent speculation also has focused on a potential role for Wolbachia in the pathogenesis of filaria-related disease. Lammie and colleagues have suggested that the pathogenesis of disease in lymphatic filariasis is multifactorial, and have proposed
a model that involves the immune system and also allows for a variety of possible causes.3

Limited attention has been paid to the differences in pathogenesis and clinical manifestations of brugian and bancroftian filariasis. Obvious differences have been noted, such as the absence of male urogenital involvement and chyluria, and the much more frequent occurrence of abscesses at the site of lymph nodes in brugian filariasis. However, the reasons for these differences are poorly understood.

The following two sub-sections review the scientific data on ADLA and AFL.

2.1 Acute dermatolymphangioadenitis

2.1.1 Pathogenesis

Evidence for a bacterial aetiology of ADLA in filariasis-endemic areas comes from the distinctive clinical signs and symptoms, isolation of bacteria at the time of the acute episode, and changes in antibody titres between acute and convalescent serum specimens.20–22 In India, the bacteria most frequently associated with ADLA are Group A Streptococcus. Other bacteria are often found in cultures, including those that are usually regarded as non-pathogenic.21, 23, 27

The role of the immune system in amplifying or modulating ADLA is not entirely clear. The relative infrequency with which bacteria are isolated from patients with ADLA,21, 26, 31 as well as from persons with cellulitis in areas not endemic for lymphatic filariasis,32, 33 suggests a role for inflammatory mediators.32–34

Little has been published on the antimicrobial sensitivity of bacteria isolated from persons with ADLA in filariasis-endemic areas. Available experience suggests that the organisms most commonly involved are sensitive to penicillin; thus, penicillin is usually recommended for treatment.35

The clinical description of ADLA in filariasis-endemic areas is remarkably similar – if not identical – to that for erysipelas, about which much has been written in the dermatologic literature. Group A Streptococcus is the classical causative organism for erysipelas, and lymphoedema is a well-recognized risk factor for erysipelas and cellulitis in areas not endemic for lymphatic filariasis.34

2.1.2 Epidemiology

In the early 1990s, TDR sponsored a series of population-based studies on the incidence of ‘acute attacks’ among the general population in filariasis-endemic areas. These studies were done before the bacterial aetiology of ADLA was widely appreciated. However, the case definition – localized pain, lymphadenitis and/or lymphangitis and/or cellulitis and local warmth, with or without systemic manifestations of fever, nausea, and vomiting (in some studies, lasting for at least three days) – is consistent with ADLA. In these studies, the overall incidence of ADLA ranged from 33 per 1000 per year to 97 per 1000 per year.36–39 A study from Papua New Guinea, which found an incidence of 31 attacks per 1000 population per year, included only cases with fever.40 The one such study in an area endemic for Brugia malayi, which also included only cases with fever, found an incidence of 371 episodes per 1000 people per year.41 It is unclear whether these episodes were ADLA or AFL, or both. Taken as a group, these studies indicate that the rate of ADLA is higher in persons with chronic filarial disease, principally lymphoedema. Among lymphoedema patients in filariasis-endemic areas, the mean annual reported incidence of ADLA ranges from 0.5 to more than ten episodes per patient.14, 38, 42–44

The duration of ADLA, primarily based on patient self-reporting, ranges from 3 to 11 days.20, 31, 36–39, 42, 43, 45–47 Recurrent ADLA episodes result in significant short-term disability (see section 2.1.3.2), and are of much greater concern to patients than is lymphoedema per se.48 Studies in Ghana indicate that patients with ADLA are incapacitated for 3 of the 5.1 days of ADLA duration;37 in Tanzania, patients are incapacitated for 3.7 of the 8.6 days of ADLA.36 In India, total disability from ADLA lasted no more than 3 days in an area with brugian filariasis area.41 However, preliminary data from Haiti42 and Togo49 suggest that the number of workdays lost may exceed the duration of the acute ADLA episode itself.

Among persons with lymphoedema, risk factors for ADLA include increasing patient age,36–38 poor hygiene50 and illiteracy.51 Gender, lymphoedema severity, and the presence of entry lesions are additional risk factors. Females tend to experience higher rates than males, although exceptions have been noted.35 The relationship between lymphoedema stage and incidence of ADLA is not consistent among all studies. It is complicated, in part, by the use of different systems to stage lymphoedema. Most studies show a positive association between lymphoedema stage and observed or patient-reported incidence of ADLA.6, 13, 31, 44, 52–54 However, some studies – all of which relied on patient recall of ADLA incidence – found no such association.36, 37, 42, 43 Data from Brazil, India, and Guyana indicate that the presence of interdigital skin lesions increases the risk of ADLA13, 50,55 (G. Dreyer, personal communication).
The epidemiologic association between ADLA frequency and stage, as well as extensive clinical experience from both filariasis-endemic and non-endemic areas, strongly suggest that ADLA episodes are a major – likely the most important – factor in lymphoedema progression, particularly in filariasis-endemic areas.

### 2.1.3 Economic and psychosocial impact

#### 2.1.3.1 COST

Studies from India, Ghana and Haiti indicate that ADLA treatment costs to patients range from US$ 0.25 to US$ 1.62 per episode, as much as two days’ wages. In Sri Lanka, Chandrasena reported costs of US$ 7.38 per episode for care from private practitioners, although most patients received free treatment at government clinics. These costs include direct costs of treatment, including self-medication, as well as travel. Two studies also included costs of food and accommodation. In all cases, except for consultations with herbalists in Haiti, patients seeking care from health centres or private practitioners spent more money, primarily because these providers had higher consultation charges. In addition, payment is often provided in-kind when care is given by members of the extended family or traditional practitioners. At the upper end of the spectrum, Kron et al. calculated costs for personal expenses in the Philippines as high as US$ 25 per ADLA episode, excluding lost wages.

#### 2.1.3.2 PRODUCTIVITY

The true burden of ADLA comes not from treatment costs, but from indirect costs due to lost productivity. ADLA episodes significantly affect patients’ abilities to carry out both economic (farming, market activities, building) and domestic (household chores, cooking, taking care of children) activities. ADLA episodes are more disabling than other febrile illnesses. This incapacitation results in productivity losses; studies in India and Tanzania showed that patients undergoing ADLA spent an average of 2.7–3.6 hours less per day on economic activities than controls.

Studies indicate that ADLA episodes reduced potential community labour supply in Ghana by 0.79% and in Indian communities by approximately 0.1%. While these figures represent a much smaller loss than that from chronic filarial disease (7% of potential labour lost), they do not adequately capture impact at the level of the household. Household-level effects, including time lost from work and school for caregivers, have not been studied in detail.

Even with these modest estimates, the productivity lost due to ADLA represents a significant loss of potential income. Sabesan estimated that US$ 160 000 per year was lost to ADLA among persons with lymphatic filariasis in Pondicherry, India, while other studies in India estimate a national figure of US$ 60–85 million lost per year. Kron estimated that US$ 38 million is lost annually due to ADLA in the Philippines.

#### 2.1.3.3 QUALITY OF LIFE

Most information collected on quality of life has not differentiated the effect of chronic disease from that of ADLA. A study of patients at a filariasis clinic in Haiti found that ADLA affected several quality of life indicators, including how much one thinks about the disease and the ability to work. A qualitative study in the Dominican Republic found that the greatest physical and psychological distress occurs during ADLA, regardless of stage of lymphoedema. A study of lymphatic filariasis on schoolchildren in India found that ADLA led to common absenteeism and impaired performance.

In another recent study, patients in India ranked ADLA higher than lymphoedema and hydrocele in terms of severity, with an average severity score of 25–27 on a scale of 0–28. Patients also cited ‘very severe problems’ in the domains of mobility, self-care, usual activities, pain, anxiety/depression and social participation on an extended EuroQol scaling system. They reported curtailing their activities and interactions with others in an attempt to prevent other ADLA attacks from occurring. Other studies have remarked on the pain, restrictions and dependency that result from ADLA episodes, but have not translated this into standard quality-of-life indicators.

#### 2.1.3.4 HEALTH CARE SEEKING BEHAVIOUR

Studies in India found that 49%-98% of lymphoedema patients sought treatment for ADLA during the previous 6–12 months, either by consulting government or private health personnel or self treatment. Patients in urban areas were more likely to seek treatment. In a study in rural Haiti, approximately 50% of people experiencing an ADLA episode sought treatment from health clinics, traditional healers, or by self-treating. In rural Ghana, Gyapong et al. found that 55% of those suffering ADLA episodes sought care (with only 1% going
to government health facilities), compared to 88% of those with other febrile illnesses. Because of distance to health facilities, difficult terrain, and the pain associated with ADLA, many patients do not seek treatment outside the home until the episode is almost over. In addition, many patients believe that ADLA is not preventable, since it recurs even with treatment, so they stop seeking treatment. **Preliminary data from Togo confirm this impression, and indicate that many patients have sought help in the past for ADLA from a wide variety of sources, but currently either self-medicate or do not seek help.**

Traditional practices for ADLA include herbal preparations which are smeared on the affected limb, scarification or cutting the skin, and analgesics bought from local drug peddlers.

### 2.1.4 Treatment and prevention

#### 2.1.4.1 TREATMENT

Treatment recommendations for ADLA include rest, cooling the affected area to relieve pain and limit thermal-related damage to the skin, analgesics and antipyretics to relieve pain and fever, systemic antibiotics, and elevation of the affected limb. Little is known about the degree to which antibiotics shorten the duration of ADLA episodes, but as with erysipelas and cellulitis in areas not endemic for lymphatic filariasis, antibiotic treatment is recommended.

#### 2.1.4.2 PREVENTION

**Basic lymphoedema management**

An increasing number of studies have documented the effectiveness of basic lymphoedema management, as recommended by WHO, in reducing the incidence of ADLA episodes. In Guyana, McPherson found that none of 11 patients reported ADLA during the six months after hygiene education, whereas 10 had reported ADLA during the preceding six months. A recent evaluation by WHO reported even more dramatic reductions in incidence of ADLA in Sri Lanka, Zanzibar (United Republic of Tanzania), and Madagascar. In India, several placebo-controlled studies have observed significant decreases in ADLA incidence among lymphoedema patients who only received instruction in foot care.

Reductions in ADLA frequency can be maintained for several years through home-based care. In Haiti, the reported incidence of ADLA during the year before beginning treatment was 2.1 episodes per year; this decreased to 0.6 episodes after hygiene and skin care were emphasized. A follow-up assessment 18 months after the patients ‘graduated’ from clinic visits, but continued lymphoedema care at home, showed an annual incidence of 0.5 ADLA episodes per year. Suma and colleagues reported sustained practice of self-care among patients in an area endemic for Brugian filariasis; some two years after patients had received ‘foot care’ education, 95.3% reported having fewer or less severe ADLA episodes, with a mean incidence of 2.8 acute attacks per year.

**Prophylactic antibiotics**

For patients who continue to experience frequent episodes of ADLA despite basic measures of hygiene and skin care, prophylactic antibiotics are recommended. This practice is also recommended in non-endemic countries for patients with lymphoedema who have recurrent ADLA. The effectiveness of prophylactic antibiotics has been evaluated in several studies. Olszewski examined the effect of benzathine penicillin, given at three-week intervals for one year, on the incidence of ADLA, and reported a dramatic decrease, with recurrent episodes occurring only in 9% of patients. In a placebo-controlled trial in Vellore, India, lymphoedema patients who received prophylactic penicillin experienced greater decreases in ADLA incidence than those who only received training in foot care. In similar studies in Kerala, India, Shenoy and colleagues found that, for most patients, antibiotics provided little additional benefit if foot care was regularly practiced. Kerketta and colleagues, in Orissa, India, observed lower rates of ADLA among patients who were randomized to receive foot care and penicillin prophylaxis than among patients not receiving penicillin, although the difference was not statistically significant. A recent Cochrane review concluded that although penicillin and foot care appear to reduce the frequency of ADLA, further studies are needed to document the effectiveness of these measures.

**Antibiotic soap**

An unpublished study from Haiti found that the incidence of ADLA in lymphoedema patients decreased to a similar extent (from 1.1 episodes to 0.4 episodes per year) in patients who washed with antimicrobial soap and those who received standard soap, suggesting that hygiene itself was more important than the antimicrobial content of the soap.

**Participation in patient support groups**

Participation in patient support groups has been shown to decrease the number of ADLA episodes and improve quality of life among lymphoedema patients in Haiti.
Table 1. Matrix of published studies on acute dermatolymphangioadenitis (ADLA) in filariasis-endemic areas

<table>
<thead>
<tr>
<th>Study or publication</th>
<th>Aetiology</th>
<th>Epidemiology</th>
<th>Socioeconomic impact of ADLA</th>
<th>Impact of treatment</th>
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<td>Economic Impact of disease</td>
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<td>Hygiene and foot care</td>
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<td>Alexander 1999</td>
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<td>Ananthakrishnan 2004</td>
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Risk of death

Fatal outcomes for ADLA are thought to be uncommon, but most programme managers and clinicians who care for patients with lymphoedema are aware of at least a few cases in which ADLA progressed to septicemia and death. The actual incidence of fatal outcomes with ADLA is unknown, as are the risk factors for severe or fatal ADLA. The clinical experience of Dreyer and others indicates that elderly patients, alcoholics, and patients with malnutrition, hypertension, diabetes, or chronic cardiac or pulmonary disease may be at increased risk of severe ADLA.\textsuperscript{35}

Table 1 summarizes, in a matrix format, studies published on ADLA.

### 2.2 Acute filarial lymphangitis

#### 2.2.1 Pathogenesis

As noted above, among persons born and raised in areas endemic for bancroftian filariasis, episodes of AFL, due to death of the adult worm or 4th-stage larva, are less severe and have less systemic involvement than ADLA. Systemic involvement may be greater in ‘immune-naïve’ immigrants to endemic areas. Classical AFL was described extensively in US and European soldiers during World War II.\textsuperscript{31, 78–81} AFL has been reported widely following treatment with DEC; indeed, such reactions are considered evidence of the drug’s macrofilaricidal efficacy.\textsuperscript{82–84} AFL is commonly observed following mass treatment with DEC.\textsuperscript{85, 86}
2.2.2 Treatment

Treatment of AFL is supportive. Cold compresses, rest, and analgesics are recommended. Treatment with antifilarial drugs during acute inflammatory episodes used to be recommended, but now is considered contraindicated. 26, 35, 87

2.2.3 Acute filarial lymphangitis and clinical disease

The degree to which AFL triggers or hastens the development of hydrocele in bancroftian filariasis has been investigated by several authors. Norões and colleagues reported a 22% incidence of acute hydrocele following a single ‘scrotal nodule event’, whether spontaneous or induced by DEC. 88 Overall, 5% of men with scrotal nodules (adult worm death) developed hydrocele that persisted for 18 months or longer. Similar findings were observed in Haiti following mass treatment with DEC and albendazole. 89 Hussein and colleagues in Egypt found that 14 of 16 infected men developed detectable fluid in the tunica vaginalis cavity after treatment with DEC and albendazole, of whom three developed chronic hydrocele. 90 It is unclear whether the lifetime risk of acute or chronic hydrocele is increased by DEC treatment, or whether the drug merely synchronizes adult worm death and, therefore, resulting hydrocele.

AFL appears to trigger the onset of lymphoedema less frequently, and persistent lymphoedema is unusual in the absence of other co-factors. 9

3. LYMPHOEDEMA

The literature on lymphoedema in filariasis-endemic areas suffers from a lack of standardization, terminology, and agreed-upon criteria for diagnosis and case definition. Indeed, many authors use the term ‘elephantiasis’ for all forms of lymphoedema. Further, even in non-endemic areas, there is no one system for classifying or staging lymphoedema that is universally accepted. 91 The lack of standardization limits our understanding of the epidemiology, prevalence, and severity of lymphoedema. Further, the prevalence of co-morbidity, especially venous disease, associated with lymphoedema in filariasis-endemic areas is unknown. An urgent need exists for standardization of terms and common case definitions, and for improved knowledge about co-morbidity and its effect on recommended treatment practices. For a matrix of studies published on lymphoedema in filariasis-endemic areas, see table 2.

3.1 Pathogenesis

The pathogenesis of lymphoedema in filariasis-endemic areas has been a matter of intense debate. For many years, it was believed that a shift in antifilarial immunity triggered the onset of lymphoedema, before which time the asymptomatically infected host was ‘in harmony’ with the parasite. 10, 114 Clinical observations and ultrasonographic and lymphoscintigraphic examinations demonstrated that lymphatic vessel dilatation and dysfunction commonly occur in the absence of lymphoedema. The molecules or processes that stimulate lymphatic vessel dilatation, and the mechanisms by which this process is maintained, are unknown. The clinical model proposed by Dreyer emphasizes that lymphoedema in filariasis-endemic areas is a multifactorial process. 4

Alternative models have been proposed. Epidemiologic associations between transmission intensity and the prevalence of lymphoedema have suggested to some investigators that third-stage larvae trigger lymphoedema. 16, 108 This hypothesis is supported by observations of decreases in lymphoedema prevalence and severity following mass treatment with antifilarial drugs. 18 Although such reductions are not always observed, these findings suggest that mass drug administration could have therapeutic benefits on filarial morbidity (see section 4). Longitudinal studies showing that asymptomatic microfilaraemic persons are less likely than uninfected persons to develop lymphoedema suggest an immunologic mechanism. 124

3.2 Epidemiology

Globally, an estimated 15 million persons suffer from lymphoedema in filariasis-endemic areas of the world. 112 Clinically, so-called filarial lymphoedema is often indistinguishable from lymphoedema of other causes, and there is no laboratory marker that proves, at the individual level, that the initial (or only) cause of lymphatic vessel dysfunction was damage associated with adult filarial worms.

The earliest onset of lymphoedema in filariasis-endemic areas is usually observed around the time of puberty, and the prevalence increases with age. 116, 117, 128 In many areas where bancroftian filariasis is endemic, lymphoedema of the leg is more common in women than in men, 97, 105, 109 although this finding is not universal, 117 especially in areas with brugian filariasis. 116 Gyapong and colleagues have reported an association between the prevalence of lymphoedema and that of microfilaraemia. 106
Table 2. Matrix of published studies on lymphoedema in filariasis-endemic areas *

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Little is known about what triggers the onset of clinical lymphoedema in filariasis-endemic areas, or about what factors cause lymphoedema, once triggered, to persist. Once lymphoedema is established, recurrent episodes of ADLA are thought to be the major factor associated with disease progression (see section 2.1.2), although the role of other factors remains largely unexplored. Scarification of the skin, a traditional practice in many filariasis-endemic areas, is considered a risk factor for rapid progression of filarial elephantiasis because of the increased risk of ADLA.68

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* studies on pathogenesis and epidemiology not comprehensively reviewed
### 3.3. Economic and psychosocial impact

#### 3.3.1 Cost

Costs to patients for lymphoedema treatment, reported as both per-visit and per-year costs, vary greatly by study. A study in India reported an average of US$ 0.56 per visit, more than half a day’s wages.\(^{56}\) A Ghanaian study reported costs for treatment of chronic disease (both lymphoedema and hydrocele) of US$ 0.87 per visit, equivalent to almost a day’s wages,\(^{56}\) and greater than costs incurred by controls with other chronic diseases. In India, the annual cost for lymphoedema treatment ranges from US$ 2.17 to US$ 8.70 per person.\(^{60, 119}\) Average treatment costs are often low; many patients who find potential treatment costs prohibitive either self-treat or do not seek treatment.\(^{113, 119}\)

#### 3.3.2 Productivity

Productivity losses from lymphoedema have been captured as lost working hours and as changes in individual output. Lymphoedema patients in India lose 0.55 to 1.61 hours per day in time at work; 11%–31% of workdays are lost annually.\(^{39, 119}\) These findings are similar to those of another study of both lymphoedema and hydrocele patients, which estimated 1.13 hours lost per day, for a total of 19% of workdays lost per year.\(^{93}\) In Ghana, female labour input loss due to lymphoedema was estimated at 1.5% per year, using the average percentage of lymphoedema patients unable to complete certain activities and the local prevalence of lymphoedema.\(^{57}\) In general, many patients report changing to less strenuous occupations or giving up working altogether due to lymphoedema and ADLA.\(^{43, 45, 47}\) A study of male weavers in India with chronic disease, 26% of whom had lymphoedema, found a 27% decrease in output versus controls.\(^{121}\)

#### 3.3.3 Quality of life

A few studies have quantified the impact of lymphoedema on quality of life using standardized measures. McPherson, using a 30-point Dermatology Life Quality Index in Guyana, found a mean baseline score for lymphoedema patients of 10.9 (comparable to patients with psoriasis and atopic eczema in the United Kingdom), with controls scoring 0.5.\(^{70}\) Six months after starting regular hygiene treatment, the scores improved significantly by an average of 6.8 points.\(^{111}\) In Haiti, Kanda compared different ways of measuring quality of life among rural people with lymphoedema.\(^{42}\) Using the EuroQol scale, he found that no respondents had extreme problems in mobility or self-care, but more than half reported pain or discomfort. On a depression scale, the CES-D, these same patients had a mean score of 13.2 (16 and above indicates depression). On the CDC Healthy Days questionnaire, Kanda found that 88% of patients ranked their health as fair or better; however, they also reported an average of 9.9 physically or mentally unhealthy days during the past month. Advanced age, advanced stage of illness, and low educational level were strongly associated with lower quality-of-life measures.\(^{52}\) In India, patients with lymphoedema scored from 9.2 to 12.4 on a 28-point scale of ‘health state severity’ using an extended EuroQol measuring system.\(^{53}\) Severity was associated with stage of lymphoedema; in higher stages, ‘severe or very severe problems’ were reported for the domains of usual activities, pain, anxiety/depression, cognition and social participation.

#### 3.3.3.1 Stigma

Many studies mention the stigma surrounding lymphoedema, but they differ in the severity of stigma reported. Diminished marriage prospects and/or threat of divorce due to diminished economic productivity and attractiveness are often cited as problems for persons with lymphoedema, both by the patients themselves and by other community members.\(^{60, 63–67, 96, 102, 107, 122}\) This effect appears to be dependent on age of lymphoedema onset and disease stage.\(^{64}\) In Haiti, patients reported that their children had the most difficulty coping, as they were often teased or embarrassed about the mothers’ lymphoedema.\(^{44}\) Following a series of ‘soap opera’ radio broadcasts in Haiti, which were intended to decrease social stigma associated with lymphoedema, patients reported improved self-efficacy and social support.\(^{129}\)

#### 3.3.3.2 Impact on Activities

A study in Ghana, which did not distinguish between lymphoedema and hydrocele, found that those with chronic filariasis were significantly less likely to be able to perform market and building activities than matched controls.\(^{57}\) Among patients in India who were visited at home during the course of a year, those with chronic filarial disease were found to be totally incapacitated at 22% of visits, compared to 13.4% for controls, a significant difference.\(^{93}\) Another study in India found that lymphoedema patients reported a negative impact on domestic activities (15%–33% of patients), economic activities (65%–83%), and movement (67%–78%).\(^{218}\) Lymphoedema patients in Haiti reported decreased ability to walk, difficulty in finding appropriate footwear, and sometimes inability to sell at the market or do household chores.\(^{44}\) Among those practicing lymphoedema self-care, 25% stated that lymphoedema limited their ability to work.\(^{48}\)
3.3.3.3 EMOTIONAL IMPACT

Among filariasis clinic patients in Sri Lanka, 18% felt they were being shunned by society, although these data were collected after the patients had been enrolled in treatment. In other studies, almost all patients report negative feelings of frustration, isolation, and/or embarrassment resulting from their condition or their inability to find effective treatment. As lymphoedema progresses, the negative emotional and psychological impact often worsens. Patients in an Indian study expressed suicidal thoughts; anecdotal reports from several countries suggest that suicidal ideation and depression are not uncommon among persons with lymphoedema.

3.3.3.4 SOCIAL SUPPORT

A study in Haiti of patients enrolled in a lymphoedema treatment clinic found that the odds of regularly practicing hygiene and skin care were 3.7 times greater among patients who believed that family members supported them than among those who didn’t mention family member support. Participation in patient support groups was shown to decrease the number of ADLA episodes and improve quality of life among lymphoedema patients in Haiti. Studies in India and Ghana show that 46%–100% of persons with lymphoedema sought treatment from health care centres, local healers, or pharmacies during the previous year. Studies in Ghana show that modern medical care is avoided due to lack of interest from health care workers and a belief by patients in spiritual causes of lymphoedema (which require spiritual interventions). Patients consult spiritualists and treat themselves with herbal preparations or analgesics, even though many believe lymphoedema cannot be prevented. In contrast, in areas of India with networks of public healthcare facilities, most patients seek care from medical practitioners, although a minority consult Ayurvedic doctors or use home remedies first. Access to care is not necessarily universal, however; young women in India may not seek treatment because of social constraints, such as the paucity of female doctors. Other barriers to care include distance to a health facility, lack of time, lack of child care, perceived severity of disease, and dissatisfaction with previous treatment. Even when patients seek treatment, health personnel often will prescribe antifilarial or other drugs that are expensive and ineffective. Inadequate knowledge of lymphoedema management by health workers results in suboptimal patient care.

3.3.3.5 Beliefs and traditional practices

Beliefs about the cause of lymphoedema include heredity, supernatural and spiritual causes, and natural causes such as injury, standing in cold water, stepping on insects, and ingesting unhygienic food or drinks. Beliefs about lymphatic filariasis and its transmission can be difficult to alter. Few people in French Polynesia implicated mosquitoes in transmission, although there were ongoing health education programmes. Half of patients who had formerly been involved in a clinical trial in India were unaware of transmission by mosquitoes. Ninety-two percent of women interviewed in an Indian study were unaware that mosquitoes transmitted filariasis, but 50% of the children interviewed knew about filariasis transmission and prevention, which they learned at school or in health camps. Knowledge of transmission and prevention of lymphatic filariasis is associated with younger age, higher educational level and higher socioeconomic status.

In filariasis-endemic areas, people with lymphoedema seek help from traditional healers, herbalists, sorcerers, and pharmacies, or they self-treat. Traditional treatment for lymphoedema includes herbal preparations, burial of the leg, scrubbing the surface of the foot with ants, bloodletting, and scarification, among others. Even in areas with established clinics for lymphoedema management, where patients learn the importance of hygiene, skin care, elevation and proper footwear, many still hope for a permanent cure (B. Person, personal communication).

3.4 Treatment and prevention

Recognition of the importance of secondary bacterial infections (ADLA) in the progression of lymphoedema has led to basic recommendations for the treatment of lymphoedema in filariasis-endemic areas. The cornerstones of this treatment include hygiene, skin care (early detection, treatment, and prevention of entry lesions), exercise, and elevation of the affected limb. In addition to the above measures, appropriate footwear is recommended, and prophylactic antibiotics are recommended for some patients (see section 2.1.4.2).

All of these recommendations are consistent with proper lymphoedema care in developed countries.
where lymphatic filariasis is not endemic.\textsuperscript{132} However, in these areas, additional modalities are also used, including compressive bandages, compressive garments, and manual lymphatic drainage.\textsuperscript{133, 134} These and other measures would no doubt be helpful for individual patients in filariasis-endemic areas,\textsuperscript{76} but may require more training, experience, or resources, and are therefore not included in the public health approach to managing lymphoedema adopted by the GPELF.

3.4.1 \textbf{Effectiveness of treatment on acute dermatolymphangioadenitis}

Relatively few studies have documented the effectiveness or impact of the basic package of lymphoedema management, and most of these have focused on ADLA. The available data indicate that such treatment is associated with a marked reduction in incidence of ADLA.\textsuperscript{29, 31, 51–54, 70} An unpublished study from Haiti reported that risk factors for continued ADLA include more advanced disease, ‘non-compliance’, and illiteracy.\textsuperscript{51}

3.4.2 \textbf{Effectiveness of treatment on leg volume}

A few studies have documented changes in leg volume or circumference in response to basic lymphoedema management. Although an ‘objective’ measurement, leg volume can vary considerably with time of day, exercise, elevation, and other factors. In Orissa, India, Kerketta and colleagues reported significant reductions in leg circumference with all treatment regimens that included basic foot care.\textsuperscript{71} Pani and colleagues reported greater volume reductions in patients with oedema of recent onset than in those with lymphoedema of longer duration.\textsuperscript{75} An unpublished study from Haiti, which initially included compressive bandaging as one of its modalities, reported that 80% of 178 patients had a reduction in leg volume after two years when compared with pre-treatment measurements.\textsuperscript{51}

3.4.3 \textbf{Effectiveness of treatment on entry lesions}

It is commonly observed that, with basic lymphoedema management, the prevalence and severity of entry lesions decrease.\textsuperscript{35}

3.4.4 \textbf{Effectiveness of treatment on odour}

Reduction in offensive odour is commonly observed with regular hygiene. To our knowledge, there have been no studies focusing on reduction in odour as an outcome of lymphoedema treatment in filariasis-endemic areas, although anecdotaly this improvement has an important effect on quality of life.

3.4.5 \textbf{Effectiveness of treatment on stage of lymphoedema}

Few studies have attempted to address the degree to which basic lymphoedema management results in regression of lymphoedema stage or grade. In part, this is because most staging systems have not been developed for this purpose. Thus, considerable improvement in skin condition or even volume reduction is possible without regression in stage per se.

3.4.6 \textbf{Effectiveness of treatment on limb flexibility and range of motion}

Improved flexibility and a feeling of ‘lightness’ are commonly reported by patients, but few, if any, studies have documented the effectiveness of basic lymphoedema management on limb flexibility.

3.4.7 \textbf{Effectiveness of treatment on quality of life}

Several studies are currently under way that address the extent to which basic lymphoedema management in filariasis-endemic areas improves quality of life. One study, by McPherson and colleagues in Guyana, documented highly significant improvement in quality of life as measured by the Dermatology Quality of Life Index.\textsuperscript{70} Similar work in non-endemic areas has shown substantial gains in quality of life with lymphoedema treatment. Patients who incorporate regular lymphoedema management into their daily routines have reported satisfaction with the results.\textsuperscript{48, 127}

3.4.8 \textbf{Effectiveness of treatment on chronic inflammation}

A study in Haiti collected skin punch biopsy specimens from the lymphoedematous legs of 27 patients before and about 12 months after they initiated basic lymphoedema management.\textsuperscript{136} Follow-up biopsies showed significant reductions in perivascular mononuclear infiltrate in the superficial dermis (41% decrease in prevalence), in perivascular fibrosis in the deep dermis (58% decrease), and in periadnexal mononuclear infiltrate (53% decrease).

3.4.9 \textbf{Optimization of treatment protocols}

Although there is general agreement as to the basic elements of lymphoedema management within the GPELF, considerable regional variation exists in the availability of supplies, including soap, water, and topical skin preparations (e.g. antiseptics, antifungal and antibacterial agents). These differences contribute to variation in approaches used in different regions. For example, in some countries, macerated interdigital lesions are treated with Whitfield
ointment, an inexpensive antifungal agent, on the presumption that dermatophytes are the primary pathogen. In Guyana, McPherson attempted to culture fungi from these lesions and concluded that bacteria probably play a more important role. McPherson’s observations are consistent with studies of intertriginous lesions in non-endemic areas.

Controlled studies of how best to optimize the effectiveness of treatment, particularly for skin care, have not been published. Some investigators have argued for more widespread adoption of breathing exercises to mobilize lymph fluid, and for emollients to protect and rebuild the skin barrier function. These are issues that are amenable to basic, inexpensive clinical trials.

3.4.10 Programmatic challenges

Although there remains some debate about the optimal package of interventions for basic lymphoedema management in filariasis-endemic areas, the benefits of such treatment are generally recognized, and foci of activity in several countries have demonstrated success. However, relatively few persons with lymphoedema living in filariasis-endemic areas currently have access to treatment. Thus, the key programmatic issue is how best to ‘scale up’ basic lymphoedema management to state and national levels. The challenges can be considered in four major categories:

• Finding patients and bringing them to treatment (many are reluctant to seek care as discussed above).
• Education of patients and family members on the principles and practice of lymphoedema self-care.
• Encouragement and support to sustain daily self-care (this support may include improved access to supplies such as clean water, soap, antiseptics, topical antibacterial and antifungal agents, and oral antibiotics).
• Referral networks for management of ADLA and for patients with advanced lymphoedema or lymphoedema complicated by other diseases.

There is general agreement that most patients can manage their lymphoedema routinely at home, and that this is preferable and less costly than clinic-based care. WHO has developed training packages for ‘informal caregivers’ to instruct patients on home-based care, and this approach has been adopted by most programmes. However, numerous key programmatic and operational research questions remain unanswered for each of the four major programme components. For example: 1) the ability of untrained workers to recognize or diagnose lymphoedema is unknown; 2) the frequency and intensity of education required for patients to become competent in lymphoedema self-care has not been evaluated; and 3) basic requirements for referral care, provider training, and clinical competency have not been determined. The costs of treatment need to be better understood, as well as the benefits. These are areas in urgent need of investigation if the benefits of lymphoedema management are to reach those who most need it.

3.4.11 Prevention

Considerable anecdotal evidence suggests that the onset of chronic lymphoedema is triggered by the first or second episode of ADLA. Data from a filariasis-endemic area of Haiti indicate that skin lesions between the toes, which could provide portals of entry for bacteria, are common in children, and are significantly more common in those who test positive for circulating filarial antigenaemia. Similar findings have been observed in northeast Brazil (G. Dreyer, personal communication). The degree to which initial ADLA episodes, and therefore lymphoedema, can be prevented through school-based education programmes focused on hygiene, skin care, and recognition and treatment of entry lesions is unknown.

4. HYDROCELE

Despite the greater public health burden of male urogenital disease in lymphatic filariasis, much more attention has been focused to date on management of lymphoedema of the leg. This is beginning to change, as surgery programmes have been launched in several centres. However, many questions remain about diagnosis, optimal management, and cost and benefits of intervention. For a matrix of studies published on hydrocele, see table 3.
**Table 3. Matrix of published studies on hydrocele in filariasis-endemic areas***

<table>
<thead>
<tr>
<th>Study or publication</th>
<th>Pathogenesis</th>
<th>Epidemiology</th>
<th>Socio-economic impact</th>
<th>Impact of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Economic impact</td>
<td>Quality of life</td>
</tr>
<tr>
<td>Acton 1930</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addiss 2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ahorlu 1999</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ahorlu 2001</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Amuyunzu 1997</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Babu 2002</td>
<td></td>
<td>X</td>
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<tr>
<td>Babu 2004</td>
<td></td>
<td>X</td>
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<tr>
<td>Bernhard 2001</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bockarie 2002</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Das 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dreyer 1997</td>
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<td>Dreyer 2002</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eberhard 1996</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Evans 1993</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fanasa 1983</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Gigliolo 1960</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gyapong 1996</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Gyapong 1996</td>
<td></td>
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<td>Gyapong 1996</td>
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<tr>
<td>Gyapong 2004</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hunter 1992</td>
<td></td>
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<tr>
<td>Hussein 2004</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Kessel 1957</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kumari 2005</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lu 1988</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Michael 1996</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muhondwa 1983</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Mwobobia 2000</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Nanda 2003</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Noroes 2003</td>
<td></td>
<td>X</td>
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<td></td>
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<tr>
<td>Partono 1981</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Ramaiah 1996</td>
<td></td>
<td>X</td>
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<td>Ramaiah 1997</td>
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<td>Ramaiah 2000</td>
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</tbody>
</table>

*Continues on next page*
4.1 Pathogenesis

In many research papers written during the 1980s and 1990s on the epidemiology or immunology of lymphatic filariasis, all genital swelling in men was labelled as ‘hydrocele’. This was in contrast to detailed, even elegant, clinical descriptions of male urogenital disease by investigators in earlier decades.\(^ {137, 142, 154, 155}\) Dreyer and colleagues recently emphasized the distinction between lymphoedema of the scrotal and penile skin, which has the same pathogenesis as lymphoedema of the limbs, and swelling due to increased fluid inside the tunica vaginalis.\(^ {35}\) This fluid, which is usually considered to be ‘hydrocele’, actually is comprised of several distinct entities including true hydrocele and lymphocele (including chylocele and hematochylocele). The term ‘filaricele’ has been suggested recently to include all of these manifestations.\(^ {156}\)

Norões and colleagues have shown that true filarial hydrocele is triggered by death of the adult worm, which produces an inflammatory nodule that occludes the lymphatic vessel. In this study, the incidence of acute hydrocele following a single ‘scrotal nodule event’, whether spontaneous or induced by DEC, was 22%.\(^ {88}\) Of these, 24% persist to become chronic. These data are similar to those of ultrasonographic and clinical studies from Egypt.\(^ {90}\)

Rupture of lymphatic vessels inside the scrotal cavity can lead to the presence of straw-coloured (lymphocele) or milky (chylocele) fluid, sometimes with red blood cells. The implications for surgical management and for risk of compromised testicular function for these conditions differ from those for hydrocele (Norões, personal communication). Little is known about the relative frequency of these conditions in different filariasis-endemic areas, and techniques and markers to discriminate among them preoperatively are currently inadequate.

4.2 Epidemiology

An estimated 25 million men suffer from fluid accumulation in the tunica vaginalis (filaricele) in areas endemic for bancroftian filariasis.\(^ {112}\) The prevalence of filaricele appears to be strongly associated with intensity of parasite transmission. Gyapong has documented a robust association at the community level between hydrocele prevalence and microfilaraemia prevalence in Ghana,\(^ {143, 144}\) and this association has been observed elsewhere. The prevalence of hydrocele increases with age.

Little is known about the natural history of hydrocele in filariasis-endemic areas, although increasing (but as yet largely unpublished) evidence seems to suggest that it is much more “fluid” (forgive the pun) than previously realized. Recent observations from Brazil, Egypt, and Haiti demonstrate that many acute hydroceles resolve spontaneously.\(^ {88–90}\)

The epidemiology of the various forms of filaricele is unexplored.

4.3 Economic and psychosocial Impact

4.3.1 Costs for non-surgical treatment

Patient expenditures for hydrocele treatment are generally low, as treatment other than surgery is found to be ineffective and most patients cannot afford to pay for surgery. Hydrocele patients in India paid from US$ 1.38 to US$ 4.29 per year for treatment;
daily wages in the areas studied averaged less than US$ 1. 55 A Ghanian study found an average of US$ 0.87 a year (almost one day’s wages) spent for treatment of chronic filariasis, which included both hydrocele and lymphoedema – significantly more than was spent by patients with other chronic diseases. 57 In general, treatment costs are difficult to collect accurately as much of treatment is paid in-kind or provided by traditional healers who are members of the extended family.

4.3.2 Costs for hydrocele surgery

Published costs to patients for hydrocele surgery range from US$ 5 to US$ 60, depending on the country and source of care. The types of surgery performed and the parameters of costing are not known for all studies. Ramaiah reported costs of US$ 5–14 in government hospitals and US$ 14–57 in private hospitals in India, 119 while Babu reported costs of US$ 44 in another Indian study. 93 In Ghana, Gyapong reported surgery costs of US$ 30–35 at local hospitals 67, 54 and Ahorlu reported surgery costs of US$ 30–60 for surgery sponsored by non-governmental organizations (NGOs). 138 Interestingly, the patients in Ahorlu’s study estimated that surgery would have cost US$ 75–125 at local hospitals before the NGO programme was put in place. Ahorlu also reported other costs associated with surgery, including transport to hospital and food, estimated by patients at US$ 20–30, with an average hospital stay of 4–12 days.

4.3.3 Productivity

Early studies on hydrocele differed in their conclusion about the impact on productivity, and reductions in productivity were not quantified. 60, 102, 104, 152 In recent studies, the effect of hydrocele on productivity has been quantified in three different ways:

- Individual working hours. Studies in India have shown that hydrocele patients work approximately one hour less per day than matched controls. 39, 93, 119 Lu et al. in the Philippines found that 30% of 22 males interviewed lost time from work due to hydrocele. 146
- Individual output. A study of weavers with chronic filarial disease in India, 69% of whom had hydrocele, showed that those with disease produced 27% less cloth than matched controls. 121
- National output. In India, 8% of potential male labour input was estimated lost due to hydrocele and lymphoedema 119 and this loss was valued at US$ 704 million per year. 61 In Ghana this figure was similar, more than 7% of potential labour lost. 57

There is almost no evidence on the degree to which hydrocelectomy improves productivity, with only one study reporting qualitative data. 138

4.3.4 Quality of life

Early studies described the socially unacceptable nature of hydrocele, but they were vague about the degree of associated stigma, its consistency across communities and cultures, and the psychosocial burden of hydrocele on those affected. 50, 92, 102, 147 To date, research has not been carried out on quality of life in men with hydrocele in filariasis-endemic areas that would allow for comparison with other diseases, or with men who do not have hydrocele.

4.3.4.1 STIGMA

Hydrocele patients report both ‘enacted stigma’ (teasing, problems with marrying and divorce) and ‘felt stigma’ (ashamed to be part of community activities). 57, 138, 147 However, they often develop coping strategies to deal with the stigma. 145 For example, men with hydrocele were less likely to admit that they avoided social events or suffered teasing than were unaffected people to report that they ill-treated men with hydrocele. The severity and visibility of hydrocele, as well as the relationship of patients to community members, seems to correlate with the degree of stigma. 102 Gyapong et al. described general community acceptance of men with hydrocele, but reported that patients with advanced disease often felt ostracized and embarrassed. 66 In Kenya, 36% of men with hydrocele interviewed responded that they were laughed at, while 29%, mostly patients with small hydrocele, reported no reaction from the community. 82 When community members were asked about their reactions to men with hydrocele, those who had family members with hydrocele expressed understanding and sympathy, while others tended to joke about it. In non-endemic villages in Ghana, considerable stigma was associated with hydrocele and lymphoedema, much more than in hyper-endemic villages. 107

4.3.4.2 IMPACT ON ACTIVITIES

In rural India, 8%–10% of men with hydrocele reported a negative impact on domestic work, 53%–55% reported a negative impact on economic activities, and 53%–63% reported decreased motility. 118 A study in Ghana found that 10%–60% of persons with chronic filarial disease, which included both lymphoedema and hydrocele patients, were unable to perform certain daily activities and were less likely to perform market and building activities than matched controls who had other chronic diseases. 57 Of 14 school-aged boys with hydrocele interviewed in India, one had dropped out of school as a
result of being stigmatized and six had high rates of absenteeism, An Indian study measuring the psychosocial and physical burden of hydrocele found that patients’ usual activities and social participation were affected by hydrocele, especially for those with larger hydroceles. In addition, as noted in earlier studies, many men had switched to less demanding occupations as a result of hydrocele.

4.3.4.3 EMOTIONAL IMPACT

Men with hydrocele often describe themselves as frustrated, losing hope and even suicidal. In the Philippines, Lu reported that those in higher socioeconomic classes were less emotionally affected as they were aware of, and had access to, surgery.

4.3.4.4 MALE IDENTITY AND SEXUAL FUNCTION

In Ghana, qualitative research found that men “whose hydrocele interfered with (this) concept of male identity were deeply frustrated”; they felt as if they were a burden to their families because of difficulties in providing for their families. In Brazil, Dreyer and colleagues reported several concerns of men with urogenital disease, including genital elephantiasis, which ranged from lack of intimacy in marriage to thoughts of suicide. Hydrocele patients in India reported that hydrocele adversely affected their sexual functioning and caused ‘moderate problems’ with anxiety/depression, based on an extended EuroQol scale. In Ghana, both community members and men with hydrocele reported that hydrocele impeded sexual intercourse, sometimes leading to divorce. In contrast, Evans summarized the existing literature in 1993 (two studies), which reported little impact on sexual activity or fertility.

4.3.4.4 SOCIAL SUPPORT

While perceived social support is important for psychological well-being, we found no published studies that addressed the impact of hydrocele on patients’ social support networks or the impact of social support networks on recuperation after surgery.

4.3.5 Health care seeking behaviour

A wide range (25%–80%) of hydrocele patients seek treatment. Patients seek treatment from local health centres, traditional healers, and through self-medication. In certain countries, the belief that hydrocele has a supernatural cause leads people to seek out traditional healers or sorcerers instead of modern medical care. While most studies describe treatment sought only during the previous year, patients may have tried various remedies in the past but discontinued seeking care after the treatments were ineffective. Other reasons for not seeking treatment include problems with access, such as cost of surgery or medical treatment, distance from the health centre, inability to take time off work for recovery, and cultural issues such as fear of anaesthesia during surgery and stigma associated with having hydrocele. A study in coastal Kenya found that, in highly endemic districts, hydrocelectomies accounted for 23% of all major operations. Similarly, in Tanzania in 1976, 15% of operations in one district hospital were for hydrocele.

4.3.6 Beliefs and traditional practices

Beliefs about the causes of hydrocele vary by culture and geography, but can be grouped into supernatural causes (including witchcraft and sorcery), heredity, exposure to extreme hot or cold, excessive sexuality, and consumption of certain foods or drinks. Some studies also mention hard work or trauma as the cause of hydrocele. Few mention mosquitoes, even in regions where mass drug administration and health education has begun.

In a study in rural South India believed that filariasis was transmissible. And the link between filarial infection, hydrocele and lymphoedema is often not understood. Only 1%–4% of people interviewed in an Indian study knew that filarial infection was a major cause of hydrocele. In a study in Orissa, India, while less than half of respondents knew that mosquitoes contributed to the spread of hydrocele, about 70% named them as the cause of lymphoedema.

Traditional remedies used to treat hydrocele include herbal preparations, sorcery spells and rites, and draining with hollow reeds. Perceptions of treatment efficacy vary greatly by region, with a majority of people naming surgery as a cure. However, 90% of persons with lymphoedema and/or hydrocele interviewed on the Kenyan coast believed their disease was incurable. This may have been influenced by the experience of two elderly men in the area who had a recurrence of hydrocele after surgery.

4.4 Treatment

Surgery is the recommended intervention for hydrocele, and if done properly, it is regarded as curative. Other techniques, such as aspiration of the fluid and injection of sclerosing substances, are less effective, have unacceptable side effects, and have not been adequately evaluated in filariasis-endemic areas. Recently, Ryan has called for studies of other
Studies using various surgical techniques to experienced significant improvement in self esteem, within three to six months post-surgery, they had Ghana 1.5 years after surgery. Patients reported that Ahorlu et al. interviewed hydrocele patients in

4.4.1 Impact of hydrocele surgery on quality of life

Ahorlu et al. interviewed hydrocele patients in Ghana 1.5 years after surgery. Patients reported that within three to six months post-surgery, they had experienced significant improvement in self esteem, sexual function, and capacity for work, and they participated more in community activities.

5. IMPACT OF ANTIFILARIAL DRUG TREATMENT ON ACUTE AND CHRONIC FILARIAL MORBIDITY

Data on the impact of treatment with antifilarial drugs on filarial morbidity are inconsistent. Several studies have reported reductions in acute attacks, lymphoedema, and/or hydrocele following MDA, but other studies report no such association (table 4). For most of these studies, the primary outcome of interest was microfilaraemia rather than clinical morbidity. Therefore, the studies are often limited by inadequate or non-standardized case definitions, inadequate sample sizes, and intermittent or incomplete follow-up. Many studies have only evaluated the effect of drug treatment in persons with existing morbidity. Such an approach ignores the incidence of new cases, and could lead to an erroneous conclusion regarding the effect of the antifilarial drugs on disease incidence or prevalence.

Clinical studies have also produced inconsistent findings. A detailed case report of a US Peace Corps volunteer demonstrated dramatic clinical improvement in lymphoedema following DEC treatment, but a clinical trial by Das and colleagues in Pondicherry, India, found no change in limb volume or condition. A study using lymphoscintigraphy in Recife, Brazil found no improvement in lymphatic morphology among patients with clinical or subclinical disease following treatment with DEC. A carefully designed placebo-controlled study by Bernhard and colleagues found no effect of DEC treatment (in the context of mass treatment) on hydrocele volume.

As noted above, treatment with DEC can provoke both acute and chronic hydrocele in men with W. bancrofti infection.

Assessing the public health impact of mass treatment with antifilarial drugs is a critically important issue for programme advocacy and for planning morbidity control strategies. Studies on the impact of MDA on the prevalence and incidence of acute inflammatory episodes, lymphoedema, and hydrocele are needed, using rigorous case definitions, close clinical assessment, and control groups. They should be conducted both in areas using DEC/albendazole and in areas using ivermectin/albendazole.

6. CONCLUSIONS

Morbidity control efforts within the GPELF have focused on: 1) basic lymphoedema management (hygiene, skin care, and simple physical measures)
to reduce the incidence of ADLA and prevent progression of lymphoedema; and 2) surgical repair of hydrocele. Since the GPELF was launched in 1998, considerable research has documented the effectiveness of basic lymphoedema management and provided a stronger scientific base for this intervention. Less work has been done to document the costs and benefits of hydrocele surgery in filariasis-endemic areas. Additional research is needed to support efforts to ‘scale up’ morbidity control and disability alleviation programmes at the national level, and to document the extent to which antifilarial drug treatment influences the course of filariasis-associated disease.

Acknowledgements

The authors thank Dr. Gerusa Dreyer for helpful comments on an early draft of the manuscript and Ms. Tsu-Chin Wu for help in reviewing studies on the effect of antifilarial drug treatment on clinical morbidity.

Table 4. Summary of studies that assessed the effect of antifilarial drug treatment on the clinical manifestations of lymphangitis (acute attacks), hydrocele, and lymphoedema.

<table>
<thead>
<tr>
<th>Source</th>
<th>Acute attacks</th>
<th>Hydrocele</th>
<th>Lymphoedema</th>
<th>Drug</th>
<th>Delivery</th>
<th>Follow-up interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciferri 1969</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>DEC</td>
<td>MDA</td>
<td>2 years</td>
</tr>
<tr>
<td>March 1960</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>DEC</td>
<td>MDA</td>
<td>10 years</td>
</tr>
<tr>
<td>Bernhard 2001</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>DEC</td>
<td>MDA, clinical trial</td>
<td>1 year</td>
</tr>
<tr>
<td>Partono 1989</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>DEC</td>
<td>MDA, selective</td>
<td>11 years</td>
</tr>
<tr>
<td>Beje 1952</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>DEC</td>
<td>MDA, selective</td>
<td>16 months</td>
</tr>
<tr>
<td>Simonsen 1995</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>DEC</td>
<td>Selective</td>
<td>11 years</td>
</tr>
<tr>
<td>Kessel 1957</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>DEC</td>
<td>Selective</td>
<td>1 year</td>
</tr>
<tr>
<td>Fan 1995</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>DEC</td>
<td>Selective</td>
<td>1 year</td>
</tr>
<tr>
<td>Meyrowitch 1996</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>DEC</td>
<td>Salt</td>
<td>2 years</td>
</tr>
<tr>
<td>Meyrowitch 1998</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>DEC</td>
<td>Salt</td>
<td>4 years</td>
</tr>
<tr>
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<td>-</td>
<td>+</td>
<td>-</td>
<td>DEC</td>
<td>MDA, salt</td>
<td>4 years</td>
</tr>
<tr>
<td>Hewitt 1950</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>DEC</td>
<td>Clinical trial</td>
<td>8–14 months</td>
</tr>
<tr>
<td>Das 2003</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>DEC</td>
<td>Clinical trial</td>
<td>1 year</td>
</tr>
<tr>
<td>Kenney 1949</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>DEC</td>
<td>Clinical trial</td>
<td>1 year</td>
</tr>
<tr>
<td>Pani 1989</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>DEC</td>
<td>Clinical trial</td>
<td>&gt;1 year</td>
</tr>
<tr>
<td>Moore 1996</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>DEC</td>
<td>Case report</td>
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<td>-</td>
<td>+</td>
<td>+</td>
<td>DEC, DEC + IV</td>
<td>MDA</td>
<td>5 years</td>
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<tr>
<td>Dunyo 2000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>IV + Alb</td>
<td>MDA</td>
<td>1 year</td>
</tr>
<tr>
<td>Malecela, MacKenzie</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>IV + Alb</td>
<td>MDA</td>
<td>1–2 years</td>
</tr>
</tbody>
</table>

* 2 of 8 hydroceles resolved
† Disease progression also observed
‡ Reductions seen primarily in patients with early-stage disease
†† Included other interventions, but improvement related to number of DEC doses
+ Decrease noted (not necessarily statistically significant)
− No decrease noted (if noted, inconsistent or not considered significant by authors)
‡ Not evaluated or extremely small numbers
DEC, diethylcarbamazine; IV, ivermectin; Alb, albendazole
MDA, Mass drug administration using DEC tablets
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Annex 8

WORKING PAPER:
Social and behavioural issues of mass drug administration and morbidity management in the programme to eliminate lymphatic filariasis
Lymphatic filariasis (LF) is a major tropical disease. Approximately 40 million people in 83 disease-endemic countries have clinical LF, and another 80 million people are infected, while more than 1000 million live in endemic areas and are at risk of becoming infected. Human infection with the parasite leads to damage in the lymphatic vessels and then to a large range of temporary and permanent disabilities.

LF is particularly associated with grossly swollen limbs and genitals. The disease has been identified as an eradicable or potentially eradicable disease by the International Task Force for Disease Eradication. In 1997, the World Health Assembly passed a resolution that called for member states of the World Health Organization (WHO) to support the global elimination of LF as a public health problem. The programme to eliminate LF (PELF) has two principal goals: (i) to interrupt transmission of infection, and (ii) to alleviate and prevent both the suffering and disability caused by the disease.

The most practical and feasible method of controlling LF is to rapidly reduce the microfilarial load in the community by annual mass drug administration (MDA) of a single dose of antifilarial drugs, i.e. of diethylcarbamazine (DEC) or ivermectin with or without albendazole. MDA has been initiated in 36 of 83 endemic countries. Research has shown MDA to be an effective tool for the control of LF; 5–10 rounds of treatment with 75%–80% compliance could possibly eliminate the disease by reducing transmission to very low levels. Therefore the principal challenge before planners, programme managers and researchers is to develop effective and sustained drug delivery strategies to achieve higher treatment compliance, the importance of which has recently been highlighted. Studies on treatment compliance and other socio-behavioural issues of implementation of large-scale MDA and other activities under PELF are necessary for refining and reframing the PELF strategies to achieve desirable results. A few reviews are available on social and behavioural aspects of LF. This paper identifies areas where social and behavioural issues can contribute significantly to the success of PELF.

**COVERAGE WITH MDA, COMPLIANCE, AND ASSOCIATED SOCIO-BEHAVIOURAL FACTORS**

Studies on MDA indicate that compliance is relatively low in the majority of endemic areas. The percentage of population covered by MDA is the most important factor in determining the success of mass control/elimination programmes. If the PELF is to be successful, it is essential that microfilaraemia is cleared, or at least reduced to very low levels, in almost all of those living in at-risk areas for at least five consecutive years. Both MDA coverage (the percentage of population in a targeted district recorded as having ingested antifilarial drugs during MDA) and geographical coverage (the percentage of at-risk communities where MDA is regularly conducted) have to be kept high. Extension of geographical coverage usually depends on the operational feasibility and previously achieved treatment coverage or compliance with MDA. In many endemic countries, coverage and compliance are not at the desired levels. Significant variations occur between reported coverage and actual compliance in many places due to several factors; data from some Indian states and Haiti show that failure of distributors to visit the community for treatment, and absenteeism of the people at the time of the distribution, are reasons for low coverage/compliance. Furthermore, as many as 25% of individuals fail to consume the drug after having received it, mostly due to behavioural reasons, particularly the fear of adverse reactions, forgetting to take the drug, losing the tablets, and feeling it unnecessary to take them.

People’s perception of the MDA programme as a whole is positive as they consider it a welfare programme; however, low level of knowledge about the disease and its treatment and prevention persist in all endemic areas. Poor awareness of the role of mosquitoes in LF transmission is reported in many endemic areas including Thailand, Ghana, Haiti, Malaysia, The Philippines, French Polynesia, and the states of Tamil Nadu, Orissa and Madhya Pradesh in India. In most of these areas, trauma to the testes is perceived to be the cause of hydrocele. In many areas where MDA is implemented, people link the programme
to prevention of elephantiasis but not of hydrocele, though prevalence of the latter is expected to be significantly higher than prevalence of the former. Achieving higher compliance with MDA and involving the community in the programme is possible by strengthening their hands with adequate information.

In countries like India, annual MDA is an economic option\textsuperscript{29} and the existing government health care system is capable of operating the programme,\textsuperscript{10,31} although more inputs are required to achieve the desired levels of compliance. In African countries, community-directed treatment (ComDT), as developed by TDR, is feasible and can achieve the high coverage needed for LF elimination. A multicountry study in India and Africa, undertaken with the support of TDR, compared mass treatment of communities through the public health system alone with mass treatment delivered through a community-directed system but with significant public health services involvement. In the latter system, the communities decided how to implement the treatment and selected their own drug distributors, who distributed the drugs at the convenience of the community, while the health service’s role was to introduce the concept to the community, train the distributors, and help with monitoring and supervision. In Africa, the combined community-directed/health services system resulted in significantly greater treatment coverage than was achieved by the health services alone. ComDT was thus recommended as the drug delivery strategy for LF elimination in Africa.\textsuperscript{27,28} In India on the other hand, drug delivery by the combined health services/community approach achieved less coverage than delivery by the health services alone. However, this study showed that good coverage was associated with strong political and administrative commitment, with motivation and training of health workers, with more effective communication between the health worker and community, and with greater involvement of the community. The most effective strategy in India was drug delivery through the regular health system but with active community involvement.\textsuperscript{29} However, a method to ensure that consumption of the drugs is supervised should be developed to minimize the gap between coverage and consumption.

**ADVOCACY**

Many factors associated with high/low coverage and compliance with MDA have been identified. In spite of the many issues related to the health system or policy which have influenced compliance with MDA, several obstacles have already overcome and MDA receives support at global and national levels. Effective implementation protocols have been developed\textsuperscript{30} and rationalization of programme activities has increased.\textsuperscript{31} The problems at planning level can be solved with proper mobilization of resources and advocacy through highlighting the benefits of the programme in relation to the social and economic costs. Data on the operational costs of MDA, effectiveness of MDA, epidemiology of disease, and economic loss due to the disease, are essential in this endeavour. A recent analysis based on data from South India concluded that elimination of LF through MDA is the most beneficial disease control strategy in the annals of public health history.\textsuperscript{32} Advocating the feasibility and significant benefits of the programme at very low costs could be useful for sensitizing health authorities and donors, and for generating resources and commitment to the PELF.

Ottesen identified three potential benefits of the PELF: direct benefits, i.e. relief from suffering and disability, and prevention of economic loss; ancillary benefits with broad public health importance such as impact on intestinal helminth infection; and consequential benefits such as reinforcement of a new approach to the health problems of the developing world.\textsuperscript{33} In spite of all this, a negative attitude and resultant low priority persist among many programme partners. A recent study in Orissa, India, on the attitudes of different programme partners, including peripheral level programme managers, health workers, private practitioners, key personnel in the community, and non-governmental organizations, indicated an undesirable level of attitude to the PELF.\textsuperscript{34} Some of these partners, particularly private practitioners and non-governmental organizations, do not know the rationale and benefits of MDA. Even some health workers, who are expected to convince the community to consume the drugs, are not clear on the benefits of MDA. Similar information has to be obtained from other endemic areas undergoing MDA, and the rationale and benefits of MDA need to be integrated carefully in advocacy strategies. The PELF involves the committed partnership of many, each bringing different strengths. If all programme partners have a good understanding of the programme and are eager to participate in it, the elimination of LF will be possible.

**SOCIAL MOBILIZATION AND ENHANCEMENT OF COMMUNITY PARTICIPATION**

In many endemic areas, not all community members receive the drugs, while some fail to consume the drug even though they received it. The reasons for this are mostly either operational or behavioural;
they can be corrected to achieve high coverage and compliance through IEC and social mobilization activities. The recently developed strategy of ‘communication for behavioural impact’ (COMBI), which has a sharp focus on expected behavioural results, i.e. on acceptance and swallowing of the tablets, has given good results in achieving the desired levels of MDA compliance. With the implementation of COMBI, MDA coverage in Sri Lanka increased from 65.4% in 2001 to 86% in 2002. In the same year, India covered about 53.5 million people with the backing of COMBI. The heart of this effort was a group of volunteers, mostly community members, who went from door to door, convincing people and delivering the drugs. They were supported by a strong IEC campaign. To elevate the programme to high priority among the community, IEC and community participation should be strengthened, as the best mass treatment strategies rely heavily on active community participation.35,36 The IEC should be culture specific, and should involve endemic communities, particularly political and administrative figures who are respected by the community. The IEC activities should not remain exclusively in the hands of programme people. All types of communication techniques, advocacy tools and media outlets should be exploited, given that the most effective method of IEC depends on the local environment, health system, social structure, culture, population density and method of drug distribution.9

MANAGEMENT OF ADVERSE REACTIONS AS PART OF SOCIAL MOBILIZATION

Another important issue that affects coverage and compliance with MDA is the presence of adverse reactions to treatment. The severity of adverse reactions seen in endemic communities may be due to high levels of microfilariae.38 The problem of adverse reactions may subside as the programme progresses, given the reductions in microfilaria prevalence and adult filarial antigen level seen after each round of MDA with DEC and albendazole.39,40 In Papua New Guinea, adverse reactions were associated with increased rates of compliance in the following year, possibly because the adverse reactions were perceived as indicators of the efficacy of treatment.41 These messages should be carefully incorporated in IEC campaigns. In addition, an active surveillance system for managing adverse reactions during MDA should be developed.

SPECIFIC STRATEGIES FOR URBAN AREAS

Studies from India have shown that coverage is far below the expected level in all Indian states, and is significantly lower in urban than in rural areas.10,12 Comparative 2002 MDA data from urban and rural areas in Orissa, India, showed 45% coverage in urban areas and 76% in rural areas; similarly there was lower compliance in urban than rural areas, of 23% and 49% respectively.12 While a drug delivery strategy, which is under continuous modification for refinement, has been developed for rural areas, no specific strategy exists for drug delivery in urban areas. More importantly, a well functioning peripheral primary health care system as found in rural areas, where a strong network of peripheral level health workers undertakes all preventive activities including LF elimination, is almost non-existent in urban areas. An ongoing TDR-initiated study, based on a partnership and community-participation approach, is an attempt to develop urban area specific strategies for MDA. Early results from the Orissa component of this study suggest that the approach is feasible and sustainable in urban areas of India; the approach succeeded in building partnership and attaining compliance at least similar to that in rural areas. The approach can be scaled up to larger urban areas with necessary modifications through experimentation. More efforts need to be made to raise community-level awareness of: risk of getting the disease, the benefits of the programme, and the perceived health needs. Finally a revised strategy has to be integrated into the national programme.

SOCIAL AND BEHAVIOURAL ISSUES IN THE MANAGEMENT OF FILARIAL MORBIDITY

LF has been ranked as the second leading cause of disability worldwide.42 Chronic forms of LF, such as lymphoedema and hydrocele, have significant impact on the patient’s life.43–46 Acute attacks of lymphangitis are also common, and in fact repeated acute episodes, which lead to progression of the disease from lymphoedema to elephantiasis,47,48 are responsible for greater short-term disability and subsequent economic loss43,47,48 than the chronic manifestations.

The discovery that bacterial infection plays a key role in the occurrence of acute attacks and progression of LF disease is very significant. It has become increasingly evident that regular hygiene practices such as washing of the affected part, including simple exercises etc., may play an important role
in preventing progression of oedema and reducing acute attacks. Shenoy et al. demonstrated how a programme of foot care can significantly decrease the frequency of acute adenolymphangitis (ADL) attacks and help alleviate LF disability.\textsuperscript{31} In such programmes, meticulous hygiene in treating the affected area needs to be incorporated along with the creation of hope and understanding among the patients, their care providers and the community as a whole.\textsuperscript{53} Dreyer et al. recommended washing of the affected limb regularly with soap and clean water to avoid progression of lymphoedema to elephantiasis.\textsuperscript{34} As foot care is the mainstay for morbidity control of LF,\textsuperscript{51,54} attempts should be made to promote foot care among lymphoedema patients. It is essential to assess current practices of foot care in the communities in light of the information from some endemic areas of India\textsuperscript{55-58} and Sri Lanka\textsuperscript{59} that the use of footwear, and foot hygiene, is not extensive. Since little information on foot care is available to patients, foot care measures are little practiced. A home-based morbidity management approach needs to be developed for lymphoedema patients; advocacy to promote foot care practices should be intensive and behaviourally driven.

Appropriate care in the early stages can help prevent or reverse progression of the disease. Hence peripheral level health institutions whose workers have the appropriate knowledge and technical skills to demonstrate foot care methods to patients, and to guide patients in the use of locally available resources, should take the lead in encouraging patients to modify their behaviour and take up foot care practices. This activity should be undertaken during regular visits of health workers to the community as well as during patients’ visits to health institutions.

Hydrocele patients should be encouraged to opt for surgery, and increased access to hydrocele surgery should be provided at peripheral level hospitals. Initially, large-scale surgeries at camps may be useful in endemic areas where there are large numbers of patients with hydrocele, but there is a need for operational research to assess the feasibility and benefits of hydrocele surgery and home-based lymphoedema care, and to explore the possibilities of integrating these activities with other programmes. Studies from Mali and Nigeria indicate that home-based morbidity management is possible and, for all cases, the resource persons are the patients themselves and their families and neighbours.\textsuperscript{60} The pilot studies currently under way in Sri Lanka, Madagascar and Zanzibar, which involve treating lymphoedema patients, appear to show the method is feasible – there are indications of a significant reduction in the occurrence of acute attacks.\textsuperscript{51} Another study has documented the benefits of support groups in teaching affected women the principles of lymphoedema self-care and motivating them to continue.\textsuperscript{62}

Filarial patients visit primary health centres in rural areas as well as urban health centres for treatment of the various forms of LF.\textsuperscript{55,59,63} However, peripheral health workers should promote home-based foot care practices such as regular cleaning of affected parts with soap and water, use of antibiotics/antiseptics, limb elevation, and exercising. Optimal disease prevention at the community level requires the development of simple, reliable and effective strategies to control secondary infections, as these infections are essential cofactors in the development of filarial lymphoedema and the progression of elephantiasis.\textsuperscript{64} Although people living in endemic areas may be aware of elephantiasis, many fail to recognize the early stages of lymphoedema and fail to get treatment.\textsuperscript{24}

A recent study from India revealed that many health workers are not aware of the concept of foot care and its importance in LF morbidity management.\textsuperscript{65} A similar study on physicians in Pondicherry, India, indicated that whereas 75% of physicians prescribed DEC for lymphoedema patients, only 10% gave advice about foot care.\textsuperscript{66} The medical and paramedical staff of these peripheral institutions should therefore be oriented as to recent developments in the clinical management of LF.

An area of research to be explored is the development of a measure or index to assess the severity of morbidity and/or quality of life among LF patients. This measure will be useful for assessing the impact of various interventions, and the results can be used in the up-scaling of activities. A few studies have attempted to utilize the widely used Dermatology Life Quality Index (DLQI) to assess the quality of life of lymphoedema patients.\textsuperscript{56,67} However, it cannot be concluded from the results that DLQI adequately fulfils this need.

**CONCLUSIONS**

This paper identifies areas where social and behavioural issues can contribute significantly to the success of the PELF. Coverage and compliance with MDA in many endemic areas are not at the desired levels; the reasons for this are behavioural, and could be due to poor knowledge of the disease. These are issues that can be redressed by providing communities with correct and adequate information.
In African countries, community-directed treatment is in wide use; the method is feasible and can achieve higher compliance. In India however, where the government health system is capable of operating MDA, care should be taken to minimize the gap between coverage and compliance. The attitudes of programme managers and other partners need to be studied and reoriented through advocacy campaigns. Similarly, community participation has to be promoted through social mobilization; many community level factors for low compliance can be addressed through, for example, communications for behavioural impact (COMBI). Research on developing specific strategies for urban areas needs to be continued given the promising results from the Orissa studies.

The second pillar of PELF, i.e. morbidity management, needs to be strengthened. As foot care is the mainstay in morbidity control, attempts should be made to promote hydrocele surgery and home-based lymphoedema care. Research to understand the current knowledge and practices of patients as well as of healthcare providers is therefore required. behaviourally driven advocacy should be promoted.

Improvement of the DLQI index, to assess the severity and or quality of life among lymphoedema patients, is also called for.

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