2.6 EPIDEMIOLOGY, PARASITE BIOLOGY, MODELING

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Summary of Prioritized Research Needs

1) Define transmission dynamics for the various vector-parasite complexes, including the estimated reproductive life span of the adult worms.
2) Determine end points at which MDA can be stopped with low probability of recrudescence, under different epidemiologic settings and using different diagnostic tests.
3) Develop mathematical models to support decision-making on the duration of local MDA programs in different epidemiologic situations (e.g., initial endemicity, coverage rates, migration patterns, drug combinations, etc.).
4) Define the comparative effectiveness of available tools and indicators for monitoring the progress of LF elimination programs and incorporate such indicators as model outputs to enable models to help decide when to stop MDAs and when to initiate surveillance to detect recrudescence.

2.6.1 Overview

The identification of LF as a potentially eradicable disease by the International Task Force for Disease Eradication was based on the development of new tools and strategies deemed effective for the successful intervention against LF. These strategies and operational criteria for eliminating LF were very much influenced by China’s earlier successful experience in eliminating the infection. Whether this experience can be directly extrapolated to all remaining LF endemic regions, however, is a matter that requires further scrutiny.

Although much work has already been carried out in different geographic areas to define the local epidemiology of LF and the nature of the vector-parasite complexes involved in its transmission, many gaps in our knowledge still remain. Indeed, the exact distribution and transmission dynamics of different LF parasite/vector complexes are still not well documented in many parts of the world, especially Africa. Such knowledge is essential, however, not only to gauge the feasibility of elimination and to design appropriate interventions, but also to parameterize the mathematical models describing the population biology and control of LF. Such epidemiologic models can themselves be important intervention tools, playing a role both in offering insight for decision-making and in helping to understand the processes regulating parasite population abundance and the effects of control interventions on the dynamics of these processes. Furthermore, when the development and calibration of these models go hand-in-hand with the design and implementation of public health programs, they can also be valued tools for monitoring and evaluating these programs.

2.6.2 Research Needs

Transmission dynamics.

Knowledge of the heterogeneity in LF epidemiologic patterns across geographic regions and of the vector-parasite complexes involved in its transmission is crucial to defining the spatial ecology of transmission and understanding the processes regulating population dynamics. Particularly important are the intensity and prevalence of infection, including their age-specific profiles; the vector competence for local parasite species/strains, including issues relating to the periodicity of the parasites and vectors; the vector preferences and biting rates on humans; and the distribution of parasite numbers among different hosts and vectors. In addition, information on the reproductive biology of the adult worms, their sexual systems, sex ratios, and distribution among different individuals are all factors important for the estimation of mating probabilities, transmission breakpoints, and the spread of potential anthelminthic resistance alleles. Estimations of the reproductive life expectancy and the distribution of survival times underpin all epidemiologic projections for control scenarios and the expected durations of intervention. Therefore, comprehensive biological studies are needed

- to document the spatial ecology and transmission dynamics of LF by different vector-parasite complexes, including estimation of the reproductive lifespan of the worm.

Transmission breakpoints—when to stop/when to start an MDA.

In a chemotherapy-based elimination program such as the GPELF, a crucial issue to resolve is the level to which the parasite population density must be reduced to safely stop the MDA, having minimized the risk of recrudescence (i.e., having reached the transmission breakpoint). In ecologic terms, the aim of the program is local (and eventually global) extinction of the parasite population. Clearly, treatment for too short a period or MDAs with inadequate duration, frequency, and coverage will lead to parasite population recovery and occurrence of recrudescence. Treatment for too long a period will be wasteful of resources and inappropriate for those being treated.

Transmission breakpoints are those parasite densities in the host and vector populations that correspond to unstable equilibria; i.e., parasite densities below which the basic reproduction number, $R_0$, of the parasite in that particular environment is less than 1 and, therefore, if driven below this level the parasite may undergo local extinction. Above such parasite densities $R_0$ will be greater than 1, and therefore the parasite population will eventually return to its original (stable) endemic state. The nature and magnitude of these unstable equilibria will vary according to the vector-parasite complex, the type and severity of regulatory processes operating on the parasite population, the reproductive biology of the parasite, and the distribution of parasites within the host populations. Model-based predictions for reaching this transmission breakpoint will require definition and quantification of relevant demographic and environmental variables. Therefore, studies are required to define and quantify those epidemiologic variables necessary

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to determine the end points at which MDA can be stopped with low probability of LF recrudescence, under different epidemiologic settings.

The theoretical equivalent of the LF prevalence threshold for initiating MDA in endemic areas is also the transmission breakpoint (since it is assumed that prevalence below such a cut-off would drive the parasite population to local extinction). Because of the marked overdispersion usually characterizing the distribution of such parasite populations among their hosts and the impact of density-dependent mechanisms regulating parasite abundance,4,8–10 it is likely that these cut-off thresholds will be quite low. The WHO recommendations2 identify a prevalence threshold for initiating an MDA that was based on the LF program experiences in China,3 without provision for possibly different cut-off points under different epidemiologic settings. Furthermore, the relationship between the prevalence of microfilaremia and the prevalence of antigenemia (which are the measures for defining the threshold values) is not yet clear. Since there are definite needs for unambiguously identifying regions that do not need MDA (i.e., where transmission is sporadic or not autochthonous), studies are necessary

• to confirm the validity of the currently recommended LF prevalence threshold for initiating MDA activities,
• to establish the relationship between these thresholds being measured in terms of microfilaremia or antigenemia.

Epidemiologic modeling.

Studies on the transmission dynamics of the W. bancrofti–Culex quinquefasciatus complex in India have formed the basis for the currently available epidemiologic models using either deterministic (EPIFIL)11,12 or stochastic micro-simulation (LYMPFASIM)13 frameworks. These models have been quantified using longitudinal data from Pondicherry10,14, and more recently LYMPHASIM has also been calibrated with published data from French Polynesia.

Such epidemiologic models for the transmission dynamics and control of LF should, if possible, be an integral part of the GPELF. The nature of the model used, in terms of its structural assumptions, parameter estimates, and modeling approach, must be guided by the research questions of interest. These models may need to be geographically specific to address the issues of local parasite population extinction and reintroduction. Also, incorporation of population genetics into population dynamics frameworks will be of value for investigating the potential evolution and spread of resistant parasites and for the design of strategies to minimize the probability of treatment failure. Therefore, it is necessary

• to expand the range of locally relevant models available by quantifying the parameters describing LF population dynamics in areas where different vector-parasite complexes prevail, and in particular those for Africa,
• to use the models available for supporting decision making on the duration of local MDA activities in different epidemiologic circumstances and in relation to
a) initial endemicity (force of infection),
b) coverage levels,
c) compliance patterns (systematic versus random),
d) migration issues (of infected people and vectors; of native populations into endemic areas),
e) different drugs and their combinations (DEC, albendazole, ivermectin) and treatment regimens (MDA versus DEC salt) and frequency (annual versus multiple),
f) emergence and/or spread of resistance,
g) vector control (in isolation or in combination with MDA, and its relationship with anti-vector measures against other infections, such as insecticide-treated nets [ITNs] for malaria control),
h) treatment of different population groups (rural versus urban),
i) MDA in relation to seasonality of transmission,
• to test the models’ predictions through their validation with results from on-going national LF elimination programs.

2.6.3 References