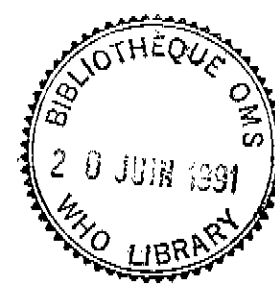




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UNDP/WORLD BANK/WHO SPECIAL PROGRAMME FOR
 RESEARCH AND TRAINING IN TROPICAL DISEASES

Geneva, 21-23 May, 1990



INFORMAL CONSULTATION ON
 EPIDEMIOLOGICAL MODELLING FOR
 RESEARCH AND CONTROL OF LYMPHATIC FILARIASIS

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1. PURPOSE OF INFORMAL CONSULTATION

An informal meeting was held in Geneva on 21-23 May 1990 under the joint sponsorship of the Epidemiology and Filariasis components of the Special Programme for Tropical Disease Research. The participants included parasitologists, epidemiologists, entomologists, clinicians, and public health planners, in addition to members of the TDR Secretariat.

This report contains the collective views of an international group of experts convened by the UNDP/WORLD BANK/WHO SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES (TDR). It does not necessarily reflect the views of TDR/WHO. In the interests of rapid communication it has been submitted to only minimal editorial revision. Moreover, any geographical designations used in the report do not imply the expression of any opinion whatsoever on the part of TDR or WHO concerning the legal status of any country, territory, city or area or of its authorities concerning the delimitation of its frontiers or boundaries.

Ce rapport exprime les vues collectives d'un groupe international d'experts réuni par le PROGRAMME SPECIAL PNUD/BANQUE MONDIALE/OMS DE RECHERCHE ET DE FORMATION CONCERNANT LES MALADIES TROPICALES (TDR). Il ne représente pas nécessairement les vues du TDR/OMS et, en vue d'une diffusion accélérée, il n'a pas été l'objet d'une mise en forme particulièrement soignée. En outre, les noms géographiques utilisés dans le présent rapport n'impliquent, de la part du TDR ou de l'OMS, aucune prise de position quant au statut juridique de tel ou tel pays, territoire, ville ou zone, ou de ses autorités, ni quant au tracé de ses frontières.

The objectives of the Informal Consultation were:

1. To review the current knowledge and understanding of the quantitative aspects of filariasis transmission, disease and control;
2. To determine the potential value of epidemiological modelling for steering research and for planning and evaluating filariasis control programmes.
3. To make appropriate recommendations for further research.

2. INTRODUCTION

'Modelling' is a way of organizing information so that interrelationships of the components can be readily appreciated, and so that the information lacking for complete understanding of the problem can be identified easily. Quantitative models developed from epidemiological data put numbers on these relationships and give the research investigator/epidemiologist tools for:

- Steering research, by pointing to the key relationships in the system and identifying the additional information needed to fully understand those relationships;
- Planning control strategies, by prospective assessment of alternative strategies for control by working out the most effective approaches;
- Evaluating control programmes, by providing a framework for data collection and for gauging the changes to be expected during the course of a programme.

Epidemiological modelling has proven to be a useful tool in both understanding disease transmission and formulating control strategies for diseases other than lymphatic filariasis. The process also has potential pitfalls (e.g., oversimplification, excessive use of cumbersome mathematics and programming, and literal and uncritical interpretation of 'predictions') which must be recognized and avoided.

Modelling is of particular relevance to filariasis research and control for two main reasons. First, lymphatic filariasis has unusually complex and dynamic relationships which are difficult to comprehend intuitively. This complexity occurs because three populations - the human and animal hosts, the vectors and the parasites - are involved, and because host infection levels, vector infectivity and disease expression change in a non-linear fashion with time. Second, control programmes may require many years before their effects are fully realized. Modelling cannot take the place of field studies, but it can help guide study design questions, clarify issues that require more refined field data and provide some basis for predicting outcomes.

3. EXPERIENCE TO DATE IN FILARIASIS MODELLING

There are a number of useful approaches to mathematical modelling and a bewildering variety of terms used to describe them. Two different, but complementary approaches were discussed during this informal consultation: (1) analytical models and (2) epidemiological simulation models.

3.1 Analytical (Conceptual) Models

Basic analytical models for filariasis were first developed in the 1960s and have been important in guiding subsequent epidemiological approaches to

filariasis research. Hayashi (1962) first applied a catalytic model, as devised by Muench (1959), to population data on lymphatic filariasis in Japan. A two-stage catalytic model was used to analyse the incidence of filarial infection and disease by age, using cross-sectional data. Hayashi's basic assumptions were as follows: first, that the entire population is susceptible to what Muench termed the 'force of infection,' which is manifest as microfilaraemia; second, that once a person who was positive for infection converted to negative, that person could not become positive again. Loss of detectable microfilaraemia overtime was assumed to be due to inhibition of reinfection through some immune response (or possibly through another mechanism). Using the model, characteristic patterns of infection and disease, by age grouping, were described for one focus of malayan, and several foci of bancroftian filariasis. He showed remarkable differences between malayan and bancroftian filariasis in the age distributions of microfilaraemia and disease, and in the age-specific microfilaria prevalence curves for bancroftian filariasis at different levels of endemicity.

Attempting to relate microfilaraemia to adult-worm infection status in patients with Wuchereria bancrofti, Hairston and Jachowski (1968) developed a modification of Muench's (1959) catalytic model. An important departure from Hayashi's work was that the model was 'reversible,' meaning that individuals could go back and forth from microfilaraemia negative to positive. People who had lost infection were assumed to be at the same risk for reinfection as those who had never been infected. This change improved the predictiveness of the model considerably over the irreversible model used by Hayashi. In this model, data on microfilaraemia from American Samoa were analyzed to estimate the duration of the microfilaraemia caused by a single fertile female (2½ years), the average adult-worm burden in infected humans (7.7 for women; 11.2 for men), and certain important variables concerning worm fecundity. This analysis provided the first estimates of these variables which even today remain impossible to quantify by direct observation. By providing quantitative insights into the dynamics between adult filarial worms and the human host, the work of Hairston and Jachowski became a landmark in the epidemiology of lymphatic filariasis. The major limitations of the analysis were its reliance on cross-sectional data and the use of indirect estimates (often with unknown errors) of certain critical parameters. These limitations were recognized by the authors.

The third important epidemiological issue in lymphatic filariasis that was subjected to quantitative modelling was the dynamics of transmission from vector to human (Hairston & De Meillon, 1968; Gubler & Bhattacharya, 1974). These analyses concluded that exposure to filarial infection in endemic areas is extremely high (of the order of 10,000 infective bites per annum) and that exposure alone could not explain the observed, often relatively low, levels of detectable infection. In the analyses, however, it was assumed that all members of the population were equally susceptible to infection; more complex analyses, assuming that a proportion of the population becomes resistant to infection, have yet to be undertaken.

In trying to understand onchocerciasis, Dietz (1982) developed a deterministic analytical model to examine the overall epidemiological dynamics of the infection, but there has been no similar attempt for lymphatic filariasis. The quantitative issues generally involved in the epidemiological dynamics of helminth infections have been reviewed by Anderson and May (1985) (particularly with respect to schistosomiasis, intestinal nematode infection and onchocerciasis), but only selected components of the overall dynamics of lymphatic filarial infection have yet been considered.

Most recently, the extensive data set assembled by the Vector Control Research Centre in Pondicherry, India (Rajagopalan & Das, 1989) has been analysed using dynamic methods related to those of Hairston and Jachowski

(1968). The data set comprises the microfilaraemia status of two cohorts of individuals examined twice over a period of 5 years, one in an area of vector control, in which transmission was virtually eliminated after the first survey, and the other in a comparable area in which transmission was not interrupted. This unique data set has permitted direct estimates of the age-specific rates of acquisition and loss of microfilaraemia (a measure of 'fecund infection') (Vanamail et al., 1989), improving on Hairston and colleagues' earlier indirect estimates based on cross-sectional data. The analyses indicate that, in the absence of reinfection, the rate of loss of microfilaraemia is independent of age but dependent upon the duration of microfilaria production by adult worms, estimated to have a mean duration of 5.4 years. The appearance of detectable microfilaria does follow an age-dependent curve, peaking in the 16-20 year age class, then falling and leveling off in the older age classes. This pattern leads to a peak in age-specific prevalence of microfilaraemia in the 21-25 year age class. However, the simple assumption of the reversible catalytic model, that all individuals without fecund infection (defined by detectable microfilaria) were equally susceptible to reinfection, led to considerable disagreement between predicted and observed microfilaraemia prevalence. A correction, embodying the assumption that individuals with clinical signs of disease are amicrofilaraemic and will not again become microfilaraemic, brought the predictions much closer to the observed rates. Such a pattern is compatible with the hypothesis that there is an increase in resistance to infection (or at least 'resistance' to microfilaraemia) resulting from prior experience of infection.

In further analysis of this Pondicherry data set, Srividiya and colleagues (1990) attempted to define the relationship between microfilaraemia and the development of chronic lymphatic obstructive disease in an infected population. Two assumptions were made: first, that the development of infection progresses from microfilaraemia to amicrofilaraemia; and second, that amicrofilaraemic individuals with any lymphatic disease are entirely resistant to subsequent reinfection. This simple model was then used to predict a cumulative age-specific prevalence of the population 'at risk' of developing lymphatic obstructive disease. Examination of data from two different Indian populations (Pondicherry and Calcutta) showed that the predicted age profiles were close approximations to the actual observed age-prevalence of chronic obstructive disease (lymphoedema and hydrocele) among males in both populations (though the fit for the Calcutta data was poorer, particularly in the older age groups). It was also found that the proportion of the population with irreversible lymphoedema (i.e., elephantiasis) was linearly correlated with the proportion of individuals with any form of obstructive pathology; approximately 12% of the diseased individuals in each age class had irreversible lymphoedema, regardless of age.

These analyses of the Pondicherry data do provide predictions consistent with the observed age-specific prevalence of the disease. However, the assumptions about the natural history of lymphatic filarial disease embodied in this model are considered by at least some observers to be oversimplifications that should be brought more closely in line with reality. Further analysis will continue in order to determine whether alternative, more realistic models will also be compatible with direct observations on disease in populations.

3.2 Epidemiological Simulation Models

An epidemiological simulation model can provide a framework for the quantitative description of the dynamics of transmission, infection and disease, and of the impact of control. Though inevitably a simplification of reality, a simulation model may be elaborate enough to give a usefully realistic description of the major events involved. There may be many parameters involved in this type of model, often too many to be tackled by mathematical methods alone. The quantitative manipulation of the model

requires the use of computer simulation techniques which are less dependent on considerations of mathematical tractability. Fortunately, the revolution in microcomputer technology has made these techniques more generally available.

A good example of an epidemiological model in the research and control of filarial diseases was developed by the Onchocerciasis Control Programme in West Africa (OCP). Initially, modelling was introduced in the OCP for the analysis, interpretation and prediction of the epidemiological trends following vector control. This modelling greatly improved the understanding of the parasite dynamics, pointed toward areas requiring more research, and led to predictions of epidemiological trends that were later proven to be correct (Remme et al., 1990). Following the initial success, the modelling activities were expanded and have culminated in ONCHOSIM, a model and computer programme for the simulation of the full transmission cycle and long-term impact of the available methods of control (Plaisier et al., 1990). ONCHOSIM uses the powerful tool of 'microsimulation,' which involves the simulation of individual life histories of human hosts and the filarial parasites. This approach is highly flexible and allows the continuous modification of the model to incorporate the latest research findings. ONCHOSIM runs on identical microcomputers in the Institute of Public Health of the University of Rotterdam, where the computer programme was developed and where detailed sensitivity analyses are undertaken, and in the OCP where the model has now become a routine epidemiological tool for the planning and evaluation of field research and control of onchocerciasis in West Africa.

The experience of the OCP has shown that epidemiological modelling can make important contributions to filariasis research and control. Not only has it encouraged a comprehensive quantitative approach to these problems, but it has facilitated the integrated analysis of parasitological, entomological, clinical, immunological, behavioural and other relevant data, thereby enabling a better synthesis of the available information. The process of developing, quantifying and testing the model has also helped to identify research needs and priorities, while the predictive use of the model is contributing to the planning of appropriate field research. One of the most important potential applications of such modelling is the prediction of the impact of alternative control strategies, which can aid decision making for control in different epidemiological situations. Such modelling can provide a 'yardstick' of predicted satisfactory outcome against which the actual results of an intervention can be compared. If significant differences are found between the predicted and realized outcomes, modelling can be used for analysis of the data to formulate adjustments in control operations. Sensitivity analysis will help define the extent and importance of the uncertainties involved and the key variables needed for planning control operations. Finally, the development and application of epidemiological modelling in the OCP has greatly reinforced interdisciplinary communication and collaboration in research and control.

No such models yet exist for lymphatic filariasis.

4. INFORMATION REQUIRED FOR THE DEVELOPMENT OF QUANTITATIVE MODELS FOR LYMPHATIC FILARIASIS

The construction of quantitative models requires numerical estimates of the various parameters associated with infection, transmission, disease and control of lymphatic filariasis. The availability of such estimates has, however, been limited mainly by the lack of adequate longitudinal data sets and the lack of sensitive diagnostic tests for filariasis infection.

Quantifying the linkage between infection and disease remains a major challenge in filariasis research. In models of other helminth infections, the amount of disease has been assumed to be proportional to the intensity of

infection. In filarial infections the only feasible measure of 'intensity of infection' is counts of microfilariae in the blood or skin, since adult worms are difficult or impossible to detect and not accurately quantifiable. Quantitative modelling has been possible in onchocerciasis since the most important pathology (ocular and dermal) is caused by microfilariae (countable in the skin) and not by the adult worms (poorly quantifiable in subcutaneous or deep locations). For lymphatic filariasis, however, it is unclear whether the pathology in the lymphatics is caused by adult worms only or by a combination of adult worms, developing larvae and microfilariae. What is clear, however, is that there is no way of confidently determining the number of adult worms infecting a patient and that, in the individual, there is no direct relationship between the degree of microfilaraemia at any given time and either the number of adult worms or the presence of lymphatic disease. Indeed, it is usually not the heavily microfilaraemic individual who manifests lymphatic disease; much more commonly, disease is manifest in those with little or no microfilaraemia. Virtually no data are available from longitudinal studies which would provide information as to whether heavy microfilaraemia loads are a prelude to chronic disease manifestation. The discrepancy between intensity of infection (as defined by microfilaraemia) and disease consequence is presumed to result from a host immune response, which has been described in qualitative and semi-quantitative terms (Ottesen, 1989) but which is not yet sufficiently understood or quantified for confident use in epidemiological models.

Recent epidemiological analyses (Srividya et al., 1990) suggest that this lack of understanding is also due in part to a lack of appreciation of the dynamics of the processes involved. Studies to date have attempted to correlate current immune status with current disease and/or infection. Since the exposure to infection, the immunological status, the level of microfilaraemia and the development of disease in an individual all appear to change through time, it is necessary to adopt a dynamic approach to understanding the relationship between infection, immunity and disease.

In addition to these effects of the host immune response on infection, disease and transmission, which remain poorly quantified, there are many other parameters of the vector/host/parasite/environment interaction that also need quantification in order to formulate useful epidemiological models. Figure 1 is a schematic representation of the transmission cycle, disease process and available options for controlling lymphatic filariasis. The important relationships figured there are listed in Table 1, specifying the information needed to formulate quantitative models, and the current availability of that information (as assessed by those attending the informal consultation).

5. ASSESSMENT AND RECOMMENDATIONS

As indicated above, the development of epidemiological models provides a framework for the many disparate facts acquired over years of observation and study. The models become a capsulization of our knowledge about an infection's transmission, associated disease, and susceptibility to interventions. Indeed, the most practical outcome of the development of such models is the ability to pinpoint the deficits in our overall understanding and to identify the threads in the epidemiological web that are most vulnerable to chemotherapeutic or vector control intervention. In view of these considerations, the group participating in the Informal Consultation strongly supported the further development of epidemiological models of lymphatic filariasis.

Table 1 indicates those parameters for which quantitative estimates are necessary in order to create useful epidemiological models; some of the information required to make reasonable estimates for these parameters is already available, and some is not. Therefore, the following are specific recommendations for addressing these issues.

1. For each topic ('modelling parameter') in Table 1 where information is now available, a written, referenced summary of this information should be prepared, with specific quantitative estimates (or ranges) that can be factored directly into the models under development.
2. For each topic ('modelling parameter') in Table 1 where information is not available but where existing data sets probably contain this information, these data sets should be reviewed and a written summary of the quantitative estimates derived from them should be prepared so that they can be factored into the model under development. (This approach should include further analysis of the data from longitudinal studies undertaken by the VCRC group in Pondicherry and of other longitudinal studies undertaken on Wuchereria bancrofti in India, Papua New Guinea, Fiji, Egypt, Cook Island and Tanzania, and on Brugia malayi in Indonesia and Malaysia.)
3. For each topic ('modelling parameter') in Table 1 where information is not available and further research is required, populations should be identified where the relevant information can be acquired, and specific field studies designed to address these questions. There is particular interest in applying the forthcoming tools for detecting circulating parasite antigen to attempt to quantify the dynamics of the adult parasite population. Longitudinal studies which relate the level of parasite antigen, the level of microfilaraemia, the changing immune status, and the progression of disease should be specifically encouraged. Whenever possible, these and other relevant field studies should be incorporated in the planned field trials of ivermectin/DEC and Bacillus sphaericus.
4. For each topic ('modelling parameter') in Table 1 where the information is not available and for which it is not possible to formulate research protocols to define these issues in human populations, acceptable animal or animal-model data that are available or could be acquired should be identified and a written summary of the specific required research should be prepared.
5. Further development, testing and application of epidemiological models for lymphatic filariasis should be encouraged. The current analytical models should be further elaborated and used in the analysis of longitudinal data on infection and disease in order to test alternative hypotheses on the development of lymphatic pathology. Epidemiological simulation models, similar to those for onchocerciasis (e.g., ONCHOSIM), should be developed for lymphatic filariasis. As soon as the information currently available is codified (i.e., Recommendation 1 has been completed), the available estimates should be incorporated into the different models with whatever estimates of the "unknown" parameters can be made, so that at least a crude approximation ('best available estimate') of the epidemiological dynamics of lymphatic filariasis can be made. Such estimates could be of practical value to morbidity or transmission control even now, and they can be progressively refined as better information becomes available (i.e., Recommendations 2-4 are completed). The development and testing of new epidemiological models for lymphatic filariasis should be done collaboratively with ongoing and planned longitudinal epidemiological surveys and intervention studies to ensure that the focus in model development remains on its practical application for disease control. In turn, the field research projects themselves could benefit considerably from the comprehensive approach of epidemiological modelling.
6. The field research subgroup of the Steering Committee on Filariasis, assisted by external expertise when required, should coordinate this Initiative on Lymphatic Filariasis Epidemiology and focus efforts, assign priorities, stimulate relevant specific research projects and provide

momentum to complete the data acquisition required to formulate valid, usable, practical models.

6. THE NEED FOR COLLABORATION

Development of a successful model will require the collaboration of a large number of investigators, contributing both their study results and ideas. The effort will be under the general direction of the field research subgroup of the Steering Committee on Filariasis.

Of particular interest is information on completed or ongoing work relevant to the data needs outlined in Table 1. This may include both published and unpublished data, and need not necessarily be recent. For investigators considering new research projects, protocols for particular studies critical to the modeling effort may be available from the Epidemiology and Field Research component of the Special Programme for Research and Training in Tropical Diseases (TDR/TDE). These include general protocol outlines for field trials and for investigating the relationship of microfilaria to acute and chronic disease. For other types of study that could meet some of the modeling data needs, or for investigators interested in the modelling process itself, consultation with appropriate individuals from the field research subgroup or from WHO may be arranged.

Investigators with an interest in collaborating are encouraged to contact Dr. J. Remme, TDR/TDE, WHO, 1211 Geneva 27, Switzerland.

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Figure 1

Schematic representation of the transmission cycle, disease process and available options for control of lymphatic filariasis

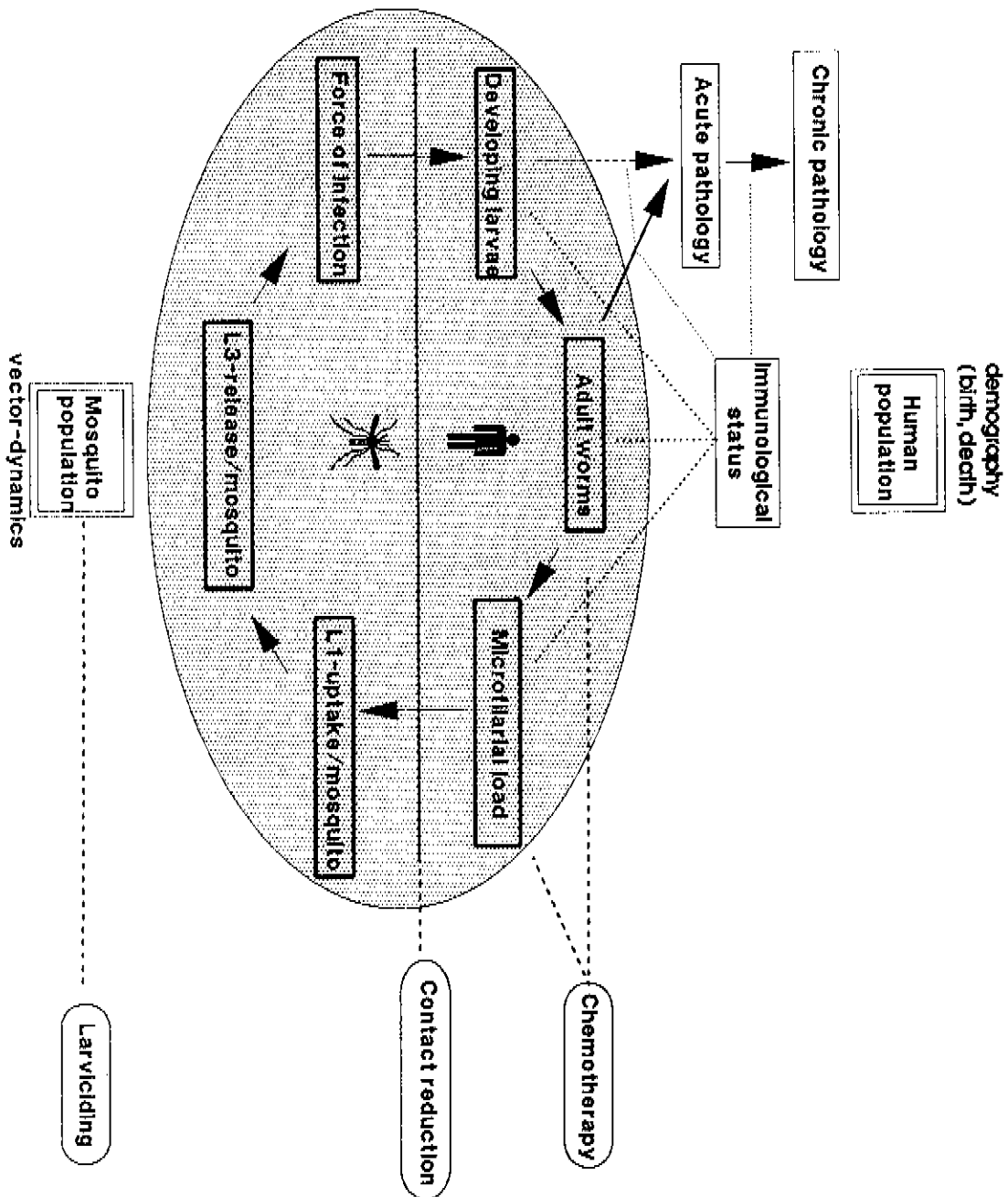


Table 1
INFORMATION NEEDS AND AVAILABILITY

| Modelling Parameter | Information Availability | | |
|---|--------------------------|----------------------|-------------------|
| | Some Available | Existing/ Available? | Research Required |
| Dynamics of Uninfected Mosquito Population | | | |
| Mosquito Reproductive Potential | X | | |
| Longevity/Mortality | X | | |
| Immigration/Emigration | X | | |
| Spatial Dispersion (environmental factors) | | | X |
| Dynamics of Human-to-Vector Transmission | | | |
| Infection Rate of Vector | | | |
| Relation with microfilaria density | X | | |
| Relation with microfilaria frequency distribution in humans | X | | X |
| Relation of human & vector population densities | X | | |
| Zoophily of vector | X | X | |
| Dynamics of Infection in the Vector | | | |
| Rate of successful development of infection to L3 | X | | |
| Time period for development to L3 | X | | |
| Gonotrophic cycle | X | | |
| Vector mortality | X | | |
| Relation with larval density | X | | |
| Relation with larval stage | X | | |
| Dynamics of Vector-to-Human Transmission | | | |
| Vector biting patterns in relation to host factors | X | X | |
| Vector infection rates | X | | |
| Vector infectivity rates | X | | |
| Vector L3 density | X | | |
| Annual transmission potential | | X | |
| Dynamics of Infection in Humans | | | |
| Relation with human immune status | | | X |
| Period for larval development | | | X |
| Rate of larval development to maturity | | | X |
| Mating probability of adult female worms | | | X |
| Period of fecundity | | | X |
| Lifespan of adult worms | | | X |
| Microfilaria production | | | X |
| Survival of mf | X | | |
| Relationship of microfilaremia to adult worm burden | | | X |
| | | | X |
| Dynamics of Pathogenesis in Humans | | | |
| Morbidity | | | |
| Relation to L3 exposure | | | X |
| Relation to developing larvae | | | X |
| Relation to living/dying adult worm burden | | | X |
| Relation to microfilaremia rate and density | | | X |
| Relation to duration of infection | | | X |
| Relation to age/gender | X | | |
| Relation to host immune response | | | X |
| Mortality | | X | |

Notes:

Subjects are grouped in the table to correspond to components of the model, as currently envisioned. The designations across the top, which are not mutually exclusive, are defined roughly as follows:

Some Available: At least some studies completed and data analyzed in a manner useful to the model.

Available/Existing(?): Some data known to the field epidemiology subgroup, but not necessarily analyzed or readily accessible. To be pursued and value and applicability assessed by the subgroup. At least some additional research will probably be required in these categories.

Research Needed: Existing data known to the subgroup is insufficient to quantify the corresponding model parameters. These categories represent the most urgent research needs.

APPENDIX I

LIST OF PARTICIPANTS

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