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THE APPLICATION OF MODELLING TO CONTROL STRATEGIES IN LYMPHATIC FILARIASIS

Report of a consultative meeting

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INTRODUCTION

An informal meeting was held in Geneva, 14-16 February, 1996 under the sponsorship of Filariasis Operational Research Task Force of the Special Programme for Research and Training in Tropical Diseases (TDR) and the Filariasis Unit of the Division of Control of Tropical Diseases (CTD). The participants included experts in epidemiologic modelling, clinicians, parasitologists, entomologists, epidemiologists, public health planners and members of the WHO secretariat (ANNEX 1).

The meeting was opened by Dr. Kazem Behbehani, Director, CTD/WHO. Dr. Behbehani highlighted the need for applying epidemiologic modelling to lymphatic filariasis control programmes, as has been done for onchocerciasis. With the recent delineation of control strategies for lymphatic filariasis, development and application of epidemiologic models are needed that will lead towards effective control and even elimination of the disease, where feasible. As many potential applications of modelling exist for the control of other tropical diseases, programme managers and researchers are looking forward to examples of success for modelling filariasis.

In his opening remarks, Prof Navaratnam, chairman of the meeting stated that two approaches to modelling are being developed for lymphatic filariasis: "EPIFIL", based on the analytical methods, and "LYMFASIM", based on simulation. These two approaches should be complementary in achieving the goal of filariasis control in endemic countries. The purpose of the current meeting, he said, was to review the current status of modelling for filariasis and to bring forth clear recommendations and work plans for moving forward from research in modelling to its further development and field application in control programmes. He emphasized the need for transferring the modelling techniques, including software, to researchers and programme managers in the field as soon as possible.

Dr. Ramachandran presented an overview of the current global burden of filariasis, population dynamics in lymphatic filariasis, and recent advances in our knowledge in the development of control strategies. He emphasized that modelling is expected to play an important role in translating these strategies into effective control programmes in the field.

Dr. Remme reviewed the importance of modelling for decision making in tropical disease control, citing the example of ONCHOSIM in the Onchocerciasis Control Programme (OCP) and, currently, in the African Programme for Onchocerciasis Control (APOC).

The meeting proceeded with presentations on the current status of the two modelling approaches (EPIFIL by Dr. Chan and LYMFASIM by Dr. Plaisier), followed by discussions as outlined in the schedule of activities (ANNEX II) and described below.

1. RATIONALE

"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. Quantitative models developed from epidemiologic, clinical, and laboratory data can quantify these relationships and thereby provide tools for:

- Steering research, by pointing to the key relationships in the system and identifying areas where additional information is needed to fully understand those relationships;

- Planning control strategies, by assessment of alternative control strategies and identifying their relative cost effectiveness;

- Evaluating control programmes, by providing a framework for data collection and for predicting and monitoring the changes expected during the course of a programme.

Modelling is relevant to filariasis research and control for two important reasons. First, lymphatic filariasis has unusually complex and dynamic relationships which are difficult to comprehend intuitively. Three populations are involved in transmission: human (and animal) host(s); mosquito vectors; and the parasites. Second, control programmes may require many years before their effects are fully realized. Modelling cannot replace field studies, but it can help guide questions of study design, clarify issues that require more refined field data, and provide a basis for predicting outcomes based on local strategies.

In the past few years, several developments have led to increased optimism regarding the possibility for control and elimination of lymphatic filariasis. These developments include the findings that ivermectin or DEC, alone or especially in combination, as well as DEC-fortified salt, can significantly reduce microfilarial density in human blood. In addition, vector control has been shown to be a useful adjunct for reducing or interrupting transmission, particularly in combination with chemotherapy. Development of serologic assays for circulating filarial antigen, which do not require collection of blood at night, and development of PCR assays to detect infection in pools of mosquitoes also represent significant advances towards control. In the last few years our understanding of stages of disease and of the mechanisms of progression of acute and chronic disease has also improved. The possibility that hygiene and antibiotics may reduce episodic adenolymphangitis (ADL) and consequently arrest the progression of lymphoedema has provided new hope in control of morbidity associated with lymphatic filariasis (WHO, 1994; Ottesen and Ramachandran, 1995).

As plans for control of lymphatic filariasis develop, there will be increasing need for epidemiologic modelling to guide these control efforts. Two different, but complementary approaches to modelling lymphatic filariasis were reviewed in a 1990 WHO/TDR-sponsored informal consultation: (1) analytical models and (2) simulation models (WHO, 1990). These modelling approaches have undergone significant development since 1990, although further refinements are still needed before these models can be used in the field.

2. OBJECTIVES OF THE MEETING

The objectives of the informal consultation were:

1. To review critically the recent advances and current status of these two approaches to epidemiologic modelling for lymphatic filariasis; and

2. To recommend further steps needed to optimize the field use of the epidemiologic models for use in control of lymphatic filariasis in endemic countries.

3. PROGRESS IN MODELLING

Significant advances have been made in lymphatic filariasis modelling since the informal consultation on epidemiologic modelling meeting on filariasis in 1990 (WHO, 1990). WHO/TDR supported the development of a simulation model LYMFASIM (developed at The Centre for Decision Sciences in Tropical Disease Control, Rotterdam, Netherlands with collaboration with Centro de Pesquisas Aggeu Magalhaes, Recife, Brazil). Further advances have been made in this type of modelling, particularly in its validation by using longitudinal cohort data sets (before and after vector control, with data from the Vector Control Research Centre, Pondicherry) (ANNEX 3). Recently a 'suite' of analytical models, EPIFIL, has also been developed at the Centre for the Epidemiology of Infectious Diseases, Department of Zoology, University of Oxford, and these models were presented and discussed in this meeting (ANNEX 4). Both current models have been developed using data related to *Culex*-transmitted bancroftian filariasis. The essential progress in both approaches of modelling is described below.

3.1 Analytic Models

Basic analytical models for filariasis were first developed in the 1960's and have been important in guiding subsequent epidemiologic approaches to filariasis research. Hayashi (1962) first applied a catalytic model, as devised by Muench (1959), to population data on lymphatic filariasis in Japan. Later, Hairston and Jachowski (1968) developed a modification of the catalytic model to relate microfilaraemia to adult worm infection status in patients infected with *Wuchereria bancrofti*. Quantitative models on dynamics of transmission, particularly those relating exposure to infection and human microfilaremia, have also been developed (Hairston and De Meillion, 1968; Gubler and Bhattacharya, 1974). Recently quantitative analytical approaches have been made to study the rates of acquisition and loss of infection in humans (Vanamail et al., 1989), dynamics of infection and disease in humans (Bundy et al., 1991; Srividya et al., 1991; Sabesan et al., 1991), dynamics of infection in vectors (Das et al., 1995), dynamics of vector to human infection (Vanamail et al., 1993), dynamics of exposure and infection, dynamics of exposure and disease (Das et al., 1994), and the dynamics of human to vector infection (Subramanian et al., 1989) all utilizing the extensive data sets available at Vector Control Research Centre, Pondicherry, India.

EPIFIL, a suite of analytical models for the epidemiology and control of lymphatic filariasis (in particular bancroftian filariasis), has been developed with two main objectives: a) to guide research on infection dynamics and filarial immunity and disease, and b) to guide the design of control programs (e.g., selection of drug regimens for chemotherapy). These models have been developed based on age-structured analytical cohort models of human helminth infections (Anderson and May, 1991; Woolhouse, 1992), especially those of schistosomiasis (Chan et al., 1996). This suite of models has primarily focused on alternative descriptions of different disease / immunity mechanisms, and it predicts age-related patterns of infection and disease (particularly the stages of lymphoedema). For this purpose, three different models (and sub-models) have been put forth: a) microbiologically induced development of morbidity with and without acquired immunity to parasites; b) immunopathologically induced development of morbidity and c) morbidity induced by immunopathology with microfilarial immunomodulation. The above models relating to immunopathology consider progression of lymphoedema through different stages. The output of the EPIFIL models include age-specific intensity and prevalence of infection and chronic disease in humans.

Using the field data of Pondicherry, these models reproduce observed data quite well. EPIFIL

models have also been utilized to predict consequences of different chemotherapy options with drugs of varying efficacy (in terms of percentage microfilaricidal or macrofilaricidal effect), single or multiple treatment regimens, and targeting of different age groups. Outputs have been compared in terms of effect on transmission and on disease. The details of assumptions, parameter values, and the equations used for the models have been referred to in the more detailed document
(ANNEX 4).

3.2 Simulation Model

LYMFASIM is a computer simulation package for modelling lymphatic filariasis. Originally the model package was developed using epidemiological data collected in Greater Recife, before and during mass DEC therapy. It has been prepared using the example of ONCHOSIM, which has been and is still being used extensively in decision making in the Onchocerciasis Control Program (OCP) (Plaisier et al., 1990; Remme et al., 1990; Remme et al., 1995). Like ONCHOSIM, LYMFASIM uses the tool of "microsimulation", which involves the simulation of individual life histories of human hosts. LYMFASIM has been developed with a number of objectives: analysis of field data, quantitative investigation of hypotheses about processes involved in transmission, prediction of future trends of prevalence and intensity of infection and morbidity, and comparison of the control policies. LYMFASIM considers simulation of different components including human demography, dynamics of uninfected mosquito populations, dynamics of human to vector transmission, dynamics of infection in the vector, dynamics of vector to human transmission, dynamics of infection in humans, dynamics of disease (considering different possible mechanisms) and effects of interventions. The model is flexible to allow the continuous modification (for details see
ANNEX 3).

The current model, developed using the Recife data, is being validated using the age structured cohort dataset on microfilaria prevalence and intensity, before and after integrated vector control, collected at VCRC, Pondicherry. Recently, some changes in the structure of the model have also been introduced, particularly relating to development of immune regulated chronic disease. In the original LYMFASIM the anti- adult worm and anti-microfilaria immune responses were related to certain critical level of worm load (tolerance threshold), below which persons were tolerant but above which, they clear their parasites. As an alternative, in the current model an immune response to adult worms and microfilariae is considered as a continuous function of the "experience of infection" (accumulated worm load with time) as proposed for schistosome infections (Woolhouse, 1994). The anti-worm, anti-microfilaria response is considered as an anti-fecundity response. Further, the natural history of lymphoedema and hydrocele are considered separately, instead of together as "chronic disease" in the earlier model. The details of the recent developments are given in ANNEX 3.

4. OPTIMIZING MODELS FOR FIELD APPLICATIONS

4.1 Expected applications of modelling for control

The needs for epidemiologic models in filariasis control programs and the expected applications of these models include:

- Comparing various control strategies with different levels of effectiveness in areas with

different epidemiologic features and mosquito vectors (*Culicine* transmitted versus *Anopheline* transmitted);

- Determining optimum doses and intervals of chemotherapy in different epidemiological situations;

- Using the results of modelling in cost-effectiveness analyses in order to use available public health resources most effectively and efficiently;

- Predicting outcomes of control programs, including reduction of transmission and of infection in humans and vectors, and reduction of short- and long-term acute and chronic morbidity;

- Evaluating and monitoring ongoing interventions and control programs.

Current control strategies, particularly chemotherapy, are directed primarily at interrupting transmission, and considerable data exist to support development of theoretical models of transmission. Interventions are less well-defined for control of acute morbidity, and little is known about the mechanisms of chronic disease progression or the effects of filariasis control programs on the incidence and prevalence of chronic filarial morbidity. Therefore, while highest priority should be given to developing models of transmission, models of morbidity and chronic disease should be developed subsequently.

4.2 Modelling transmission

Models of transmission should be optimized and readied for use in the field in order to evaluate and predict outcomes of interventions on transmission. Independent variables to be included in these models focus on factors of the parasite, host, and vector that influence transmission and the force of infection (see WHO/TDR, 1990). Outcome variables should include age-specific microfilaraemia prevalence and intensity. Based on presentations at this meeting, ample field data currently exist to support the development and validation of simple models. Modelling of cost-effectiveness of various interventions should be included in these models as early as possible to assist in decision making processes.

Although many of the factors affecting transmission are well-understood, considerable uncertainty exists regarding the role of immunity on transmission. Acquired immunity is thought to affect efficiency of transmission. However, much remains unknown, including the rate at which immunity is acquired, the importance of in-utero transfer of immune experience on subsequent development of tolerance in children, and whether immunologic shifts following treatment with antifilarial drugs affect rates of reinfection. Thus, although immunity is thought to play a potentially important role in transmission, the relationships are not well-defined. Therefore, immunity should be included in transmission models of lymphatic filariasis, but sensitivity analyses should be performed (i.e., immunologic parameter estimates should be varied in the model). Further, because the origins and targets of immunity (e.g.., L3, the adult worm, and microfilariae) are not well-understood, the role of immunity in simple models of transmission should probably focus initially on microfilariae, since microfilaremia is directly related to transmission. Duration of immunity, particularly following treatment, is unknown but may be important in predicting risk of recrudescence of infection when control programs are halted. Therefore, simple models of transmission should include sensitivity analyses of duration

of immunity (e.g. ranging from 2 to 20 years).

4.3 Modelling morbidity

Our understanding of factors responsible for initiation and progression of filarial disease is still in the formative stage, and considerable research is currently focussed on these issues. Efforts to model filarial disease should, at present, focus on the major clinical syndromes associated with lymphatic filariasis: adenolymphangitis (ADL), hydrocoele, and lymphoedema. If necessary or desired, modelling the less common filaria-associated clinical syndromes, such as tropical pulmonary eosinophilia (TPE) or renal disease (e.g., proteinuria or hematuria) can be done in the future.

In cases of successful filarial infection, adult worms live in the lymphatic vessels of infected individuals. These worms produce lymphatic damage, which can be detected in most asymptomatic microfilaraemic persons by lymphoscintigraphy (Freedman et al., 1994) or ultrasound (Noroes et al., 1996). The intervals between the development of early-stage lymphatic pathology that may be reversible, asymptomatic later-stage disease, and clinical manifestations of lymphoedema appear to vary and have not been well-documented. Thus, estimates of these intervals in models of filarial morbidity are imprecise. Several studies now suggest that the progression of lymphoedema and hydrocoele follow different pathways. Hydrocoele is the accumulation of fluid between the layers of the tunica vaginalis. It is thought to be associated with progression of lymphatic disease in the scrotal area, but seems not to be associated with episodes of bacterial adenolymphangitis, and evidence for an immune-mediated pathogenesis is uncertain. Clinical observations from a number of investigators suggest that early-stage hydrocoeles frequently resolve spontaneously; however, adequate quantitative data are lacking.

In contrast, the pathogenesis of lymphoedema appears to have an inflammatory (sometimes immune-mediated) involvement. Progression of lymphoedema and elephantiasis also appears to be associated with episodes of acute adenolymphangitis (ADL). The current data suggest that the frequency of ADL is associated with progression of chronic pathology, particularly for lymphoedema and elephantiasis of the lower extremities. The incidence of ADL in apparently healthy infected individuals is low (unpublished information, WHO/TDR/SER studies); in persons with lymphoedema, the incidence of ADL appears to increase directly with the stage of lymphoedema (Pani et al, 1990; Pani et al., 1995).

4.3.1 Modelling acute morbidity (ADL)

Recent studies have demonstrated the importance of secondary bacterial infections in development of acute adenolymphangitis (ADL), particularly in patients with lymphoedema. Increasing evidence suggests that *Beta*-haemolytic *Streptococci* may be especially important pathogens. These finding have suggested the possibility of controlling morbidity through prevention and control of secondary infection. Therefore, reduction of acute morbidity may be an important component of community control programs for lymphatic filariasis. Modelling of acute morbidity may be useful, for example, in estimating the required duration of these interventions and in predicting the long term consequences of these interventions on the incidence and prevalence of chronic disease, particularly lymphoedema.

4.3.2 Modelling chronic morbidity

Factors related to the pathogenesis, development and progression of chronic disease, including the effects on chronic disease of interrupting transmission or treating infection, are poorly understood. Animal experiments have suggested the existence of both immune- and parasite-mediated pathology, and have shown that loss of immune tolerance to the parasite is associated temporally with disappearance of microfilaraemia and development of clinically apparent disease. Data from some, but not all epidemiologic studies has shown that tolerance to infection in children is associated with the infection status of the mother at the time of birth. Further, when exposed to infection, persons with no previous exposure to the parasite develop more vigorous immune responses to the parasite and more exuberant acute disease than do persons born and raised in endemic areas (Ottesen, 1989; Ottesen, 1994). The factors associated with stage specific immunity to L3, the adult worm, and microfilariae, and the importance of each of these to development and progression of disease are poorly understood. Further, cumulative exposure to infective bites may be an important determinant of clinical manifestations of filarial disease. A few reports describe long-term changes of prevalence of disease in endemic communities without interventions; such changes do not usually occur within short intervals (Rajagopalan et al., 1989; Subramanian et al., 1989; Surendran et al., 1996).

Quantitative data on rates of transition of clinical disease (rates of progression or regression) are scanty (Pani et al., 1989). Therefore, currently available data are inadequate to provide accurate parameter values for comprehensive conceptual models of pathogenesis, progression and dynamics of chronic disease, so that, application of modelling to these issues is limited. Modelling can, however, help steer research and can be useful in assessing the validity and epidemiologic

significance of different hypotheses regarding chronic disease. Models of chronic morbidity should focus on lymphoedema and hydrocoele, the most prominent chronic manifestations of lymphatic filariasis.

4.4 Optimizing parameters

The meeting participants agreed on the use of the following parameter estimates in models of transmission and acute ADL, regardless of which modeling approach is used (i.e., EPIFIL or LYMFASIM). Many of these estimates derive from unpublished clinical work by Dr. Gerusa Dreyer in Recife, Brazil, who has used ultrasound to locate the adult worms in the scrotal area of infected men and has recovered these worms surgically (Noroes et al., 1996).

Parameter	**Estimate**
Adult worm:	
Mean life span	5-10 years
No. worms per nest	1-18 (mean, 3-4)
female:male ratio	10:1
Number of worms needed to cause lymphatic damage	1
location in men	90% in scrotal area
location in women	40% in crural area
Microfilariae	
mean life span	10-12 months

In addition, estimates for the following parameters are thought to be available from existing data, which need to be reviewed and summarized (e.g., through meta-analysis):

- *Exposure to infective larvae.* In current models, exposure in a given population is considered to be uniform. However, exposure is likely to be clustered, such as through preferential mosquito feeding by age and sex of the host, or by household. These effects are likely to be related to the species of the vector, and parameters should be established specifically for each vector;

- *Microfilarial density.* Variability of microfilarial density may be caused by day-to-day variation, seasonal factors, the time of day or night the blood is collected, the volume of blood collected, and the method used to process and examine the blood for microfilariae;

- Relationship between microfilarial density and infectivity of vectors at the levels of the individual, family and community.

- Meta-analyses of data on the efficacy of various levels of interventions, including chemotherapy (DEC, ivermectin, and combined DEC/ivermectin) and vector control, on microfilarial density and levels of transmission.

In some cases, new data may have to be generated either directly or indirectly, or parameters will have to be estimated using available data sets (on age profiles of infection and disease) from different endemic areas, e.g.,

- The percentage of infecting third stage larvae that successfully enter the lymphatic vessels and their rate of development to adult worms of both sexes;

- Life span of adult male worms;

- Mating probability between adult worms; and

- Rate of microfilaria production by adult females.

5. WORK PLAN

The immediate goal of modelling should be to develop, validate and transfer the basic model of transmission to the field for its application in control programs. Three main courses of action were identified for development and refinement of the basic transmission and acute morbidity models:

1. Modify the existing models to reflect currently available data and to include parameter estimates agreed upon at this meeting;

2. Validate the revised models by testing them against data from the field. Intensive testing at a few sites should be attempted to model the effect of alternative control strategies on transmission;

3. Apply the revised and validated models to other field sites and refine the models based on this new information.

From the above viewpoint, LYMFASIM model, which includes a transmission component, will require minor modifications and should be ready for field validation within 6 months. The EPIFIL analytic transmission will also be modified within 6 months and can then be tested in field settings.

6. CONCLUSIONS

1. Both epidemiologic modelling packages for lymphatic filariasis (EPIFIL and LYMFASIM) have good potential to contribute to efforts to control lymphatic filariasis in a complementary manner.

2. Models needed most urgently for control programmes are simple models of transmission since the current control interventions (chemotherapy and vector control) influence transmission directly or indirectly. The current models should be revised and validated with a goal towards making them available for use by lymphatic filariasis control programs in countries where such programs exist.

3. Complex models of pathogenesis are also needed, but development of these models will require better estimates of model parameters, particularly for models of chronic disease pathogenesis, progression and regression, with and without interventions to control transmission. These estimates should be obtained by rigorous meta-analyses of existing data, sharing of existing data among investigators, and new studies to generate necessary data. Modelling the disease process should be undertaken as a part of modelling research in lymphatic filariasis.

7. RECOMMENDATIONS

1. Existing transmission models (appropriately modified) should be further developed and validated. TDR should support such validation studies and facilitate collaborative efforts among investigators from field sites where the necessary data are available.

2. Formal and comprehensive meta-analyses should be done for existing treatment studies using ivermectin or DEC. In addition to the traditional measurement of reduction in geometric mean microfilarial density, data should be analyzed in terms of percent reduction in prevalence and absolute numbers of microfilariae.

3. Parameter estimates for the effectiveness of combined ivermectin and DEC in community trials in progress in Polynesia, Papua New Guinea, and Pondicherry should be incorporated into the models as they become available.

4. Training in the use of the models should be made available initially to field researchers in endemic countries and subsequently to control programme managers and other public health officials who plan to use these models to guide control efforts.

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Schedule of Work

Wednesday
14 February 1996

9.00 - 9.15 Introduction, purpose and expected outcome of the meeting

9.15 - 10.00 Overview of the population biology of lymphatic filariasis

- population process in vector-borne diseases
- the modelling approach to understanding the epidemiology and control of infection and disease

10.00 - 11.30 EPIFIL: a suite of analytical models for the epidemiology and control of lymphatic filariasis.

- model specification and technical content
- demonstration
- validation
- predictions

11.30 - 13.00 LYMFASIM: a microsimulation model for the epidemiology and control of lymphatic filariasis.

- model specification and technical content
- demonstration
- validation
- predictions

14.00 - 17.30 Field study sites for collaboration on model quantification and testing: presentation of study sites and field data

- Pondicherry, India
- Ghana
- Haiti
- PNG
- Polynesia
- Recife, Brazil
- Tanzania

Thursday
15 February 1996

9.00 - 11 00 Modelling the immune response and pathogenesis
- overview of filarial immune response
- role of acquired immune response
- disease mechanisms
- current modelling of immune and disease mechanisms in LYMFASIM and EPIFIL

11.00 - 12.30 Modelling of interventions
-chemotherapy
-vector control
-current modelling of interventions in LYMFASIM and EPIFIL

14.00 - 16.00 Data analysis
- quantification of model parameters
- model validation
- field testing of predicted impact of interventions

16.00 - 17.30 Discussion

- validity and operational usefulness of the current versions of LYMFASIM and EPIFIL.
- next steps to ensure the rapid development of LYMFASIM and EPIFIL as tools for operational decision making in filariasis control.
- alternative modelling approaches of relevance for operational decision making in filariasis control.

Friday,
16 February 1996

- Workshop session and planning for follow-up activities and collaborative research.

- Conclusions and Recommendations.

LYMFASIM: Summary of past achievements and recent developments
(A.P. Plaisier, March 1996)

The first version of LYMFASIM has been developed in collaboration with the Centro de Pesquisas Aggeu Magalhaes (CPqAM, Recife, Brazil). The initial quantification was based on pre-control (DEC-treatment) epidemiological surveys held in two areas in Greater Recife (Coque and Mustardinha). A two-step survey was done: first for 5000 persons a thick drop of 45 cmm blood was examined for the presence of Mf; secondly from those who were Mf-positive (400) a blood smear of 60 cmm blood was examined for density of Mf. Although a sample of persons was examined twice, the data set was essentially cross-sectional. This was apparent from the wide range of model-assumptions which were compatible with the data. In the final report[1] we have shown that the data could be described by three models which largely differed in terms of the mechanisms regulating the infection and explaining the heterogeneous nature of the infection ('exposure/innate immunity model', 'acquired immunity model', 'tolerance model').

An important question emerging from these results is: how could the validity of the model be improved and how could the wide range of possible assumptions be narrowed down. We conclude that there might be a number of overlapping approaches. The first is to discuss the model with experts and criticize the model in the light of current knowledge. The development of LYMFASIM had mainly relied on our own interpretation of literature. A systematic discussion of each of the assumptions with experts was lacking. Such a discussion will lead to rejection of unrealistic assumptions. A second important step towards model validation is the inclusion of longitudinal data-sets. This could be the data collected in Recife during (low dose) DEC treatment, but it should preferably also include data from other areas. A start has been made to use LYMFASIM for the analysis of the longitudinal data set collected by VCRC to evaluate the impact of vector control. A third essential pillar under a valid model is availability of experimental data to arrive at *direct* estimates of important model parameters. An example is mosquito feeding experiments which enable estimation of relation between human Mf-density and the number of infectious stages developing in the vector. Finally, simulation models like LYMFASIM tend to become very complicated with many parameters which are not identifiable on the basis of available data. Though this should not lead to a model which is so simplistic that it conflicts with biological evidence, we should continuously be aware of the need for avoiding complications which are not based on sound knowledge and which could be replaced by more simple and interpretable assumptions.

Since the above-mentioned final report, we have concentrated on fitting LYMFASIM (in its original form) to the longitudinal data-set of VCRC, especially a cohort of persons surveyed in 1981 and in 1986. Until now, the conclusion is that, though to a lesser extent than with the Recife data set, still there is a wide range of assumptions which is in agreement with the observations. It is expected that

[1]The LYMFASIM simulation modelling package for lymphatic filariasis and its use in analysis of data from Recife (Brazil); March 10, 1995.

a further restriction will be possible when the full data set (including surveys in 1989 and 1992) is utilized. Further restrictions are anticipated when parasitological data are linked with clinical data (collected in 1986 and 1992).

Apart from applying LYMFASIM to another data set, also the structure of the program has been adapted. The most important changes are in the immunological part of the model and the development of chronic disease. In the original LYMFASIM the anti-worm and anti-Mf immune response was related to a certain critical worm load ('tolerance threshold'): below this threshold persons are tolerant, above the threshold they tend to clear their worms and Mf. As an alternative we have modified this part of the model according to a model proposed by Woolhouse[2] for the immune-regulation of schistosome infections. In this model, an immune-response against worms and / or eggs is some continuous function of the 'experience of the infection' (the accumulation of the worm load over time)[3]. In fact this is very similar to what we already assumed for the anti-L3 immune response ('resistance'). The advantage is that the model becomes better interpretable and that model calculations can be placed more easily in a tradition of mathematical modelling. At present an anti-worm/Mf immune response is interpreted as an anti-fecundity response. The second major change is that in LYMFASIM we now explicitly consider the natural history of lymphoedema and hydrocoele, instead of considering 'chronic disease' as a whole. Lymphoedema is assumed to proceed as a result of a person's worm load in combination with the above mentioned anti-fecundity immune-responsiveness (i.e. without this responsiveness there will be no or only little disease progression, irrespective of the worm load). Hydrocoele is assumed to proceed only as a result of a person's worm load.

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2 Woolhouse, MEJ. Immunoepidemiology of Human Schistosomes: Taking the Theory into the Field. Parasitology Today 10 (1994) pp. 196-202.

3 This function may be a simpler linear function, but may also be a "peaked" function. Such a "peaked" function implies that (immunologically naive) persons start to elicit an anti-worm, anti-Mf immune response but that this decreases as experience of infection increases (induction of tolerance).

EPIFIL: A Suite of Analytical Models for the Epidemiology and Control of Lymphatic Filariasis

Centre for the Epidemiology of Infectious Diseases, University of Oxford

Objectives of Current Modelling Work:

1. To guide research on lymphatic filariasis, in particular:
    a. To characterize the patterns and processes of infection
    b. To aid understanding of immunity and disease.

2. To guide the design of control programmes, for example:
    a. To use the models to select chemotherapy programmes based on the model outputs and economic data.
    b. To use models to design future chemotherapy programmes.
    c. To use the models to aid drug design by determination of desirable drug characteristics.

Recent Progress:

A 'suite' of analytical models has been developed to describe the dynamics of infection and disease on lymphatic filariasis. These models are based on models previously developed for other helminth infections (Anderson & May, 1991; Woolhouse, 1992 Chan et al, 1995, 1996). A suite of different models of disease progression has been developed due to the continued uncertainty on the actual mechanisms that operate. Models assuming both microbiologically and immunologically driven mechanisms of disease progression are explored. The advantage of this multiple approach is that the behaviour of the model under different assumptions can be compared and related to field data.

The output of the model in terms of the relationship between infection intensity or disease prevalence and age have been explored. The models reproduce very well the observed patterns of infection and disease in the field. Quantitative comparison between model output and field data has also shown that the model performs well.

Furthermore, the model has been used to examine the consequences of chemotherapy on lifetime infection and disease for the treated individuals. The drug used was initially assumed to have an efficacy of 100% against microfilariae and 50% against adult worms. Benefits accrued from the treatment programme were estimated by the average lifetime reduction in microfilarial density (measure of transmission benefit) and prevalence of lymphoedema (measure of disease benefit).

Analysis of a variety of treatment programmes which vary both the ages treated, number of treatments and intervals of treatment all suggest that to reduce microfilarial density treatment should cover the ages with the highest microfilarial densities whereas to reduce disease, treatment should be targeted at younger ages before serious lymphatic damage occurs.

The model was also used to examine the consequences of increasing the macrofilaricidal efficacy of the drug used. The results indicate that any increase in macrofilaricidal efficacy is likely to result in a detectable increase in both transmission and disease benefit.

Strength of approach:

Analytical models are based on an understanding of the basic biology of the parasite and aim only to include processes fundamental to the behaviour of the model excluding details which do not influence this. This understanding forms the core of the model and largely determines the behaviour of the model and predictions made from the model. The strength of analytical models lies in the fact that it is possible to directly determine the consequences of different assumptions on the behaviour of the model either by mathematical analysis (which is not possible with more complex simulation models) or by a variety of numerical techniques. This means that the overall behaviour of the model can be understood at a level which is not possible for more complex models. It is worth noting that however complex a model (whether analytical or simulation), the behaviour of model will ultimately depend on the biological assumptions and therefore the analysis of the influence of these is of crucial importance.

Since a good analytical model is based on a sound understanding of important biological processes, such models tend to be particularly powerful when used in the context of extrapolation. This includes the transfer of a model between different sites and even to other similar species. Likewise, analytical models are particularly useful for making long term simulations to show the consequences of treatment on lifetime measures of infection or disease.

The running of an analytical model involves the estimation of relatively few parameters. Therefore the validation of analytical model is relatively less laborious than the validation of simulation models. This opens up the possibility of the simultaneous analysis of data from different sites hence greatly increasing the validity, predictive ability and generality the model.

Future Plans:

It should be noted that development of a model and control planning tool is already underway for other helminth models. Therefore, the modelling technique, computer programs and data analysis techniques are already developed (Chan et al., 1995; 1996) and their use in lymphatic filariasis is not expected to present any technical problems. Therefore we are confident that a useful validated version of the filariasis model which could be used by researchers in the field could be produced in the relatively short time frame. The main tasks are:

1. Development of the full transmission model and refinement of the disease and chemotherapy models.
2. Parameterisation of the model with field data and validation of the model.
3. Development of a user-friendly planning tool software.

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