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MATHEMATICAL MODELS FOR OPTIMIZING AND PREDICTING OUTCOMES OF INTERVENTION MEASURES FOR THE CONTROL OF LYMPHATIC FILARIASIS

Lymphatic filariasis is a debilitating disease attaching social stigma to afflicted people living in most of the tropical countries in the world. Globally about 120 million people are affected with the disease of which one-third live in India alone. With the recent advancement in diagnostic and control tools, the hope for the control of filariasis is expanding. However, due to the complex nature of the disease a number of factors are yet to be understood. In the absence of animal models little is known about the mechanisms regulating the parasite population and the development of disease in host populations; knowledge on the efficacy of the currently available drugs on parasite populations and the long-term impact of control programmes are limited. A sound quantitative understanding of the population dynamics of the parasite is important for developing and identifying the most cost-effective and sustainable control strategies. This requires, however, reliable predictions of the long-term impact of alternative control strategies. Mathematical models provide the necessary quantitative framework for investigating the key issues related to parasite population dynamics and for making credible predictions of epidemiological trends and for aiding decisions about control strategies before, during and after cessation of control activities. There are several examples for the successful and practical application of mathematical models for disease control. The best example is the application of a simulation model for the onchocerciasis control programme in the West Africa[1].

The Vector Control Research Centre (VCRC) at Pondicherry has been involved in the development and application of mathematical models for lymphatic filariasis transmission and control since 1989. The epidemiological studies carried out at VCRC have significantly contributed not only for a better understanding of the dynamics of infection and disease in humans and mosquitoes but also for making rational decisions in planning and organization of control programmes both at the national and international levels. This write-up reviews the development of models concerning lymphatic filariasis transmission, infection and disease and their usefulness in prediction and optimisation of control strategies.

What is a Model?

A model is a representation containing the essential structure of some object or event in the real world. The representation may take two major forms *viz.* physical and symbolic. Physical models are miniatures of objects, which can be visualized in future. Model of an airplane or architect's building, *etc*., are examples of physical models.

A single or sets of mathematical equations that represent the relationships of two or more variables are called symbolic or mathematical models. A simple example is the equation, $P_t=P_0+B-D$, describing the population size at time t (Pt) with initial population (P0), births (B) and deaths (D).

Types of Mathematical Models

Most of the mathematical models fall into two broad categories: (i) analytical, and (ii) computer simulation models. Analytical models are usually based on sets of mathematical equations that keep track of few important variables in the system under study. To minimize the mathematical complexity, the number of equations has to be kept low, which consequently leads to oversimplification of reality. Further, the elements of most real-world systems are stochastic in nature; analytical models if developed are too complex to handle mathematically. Simulation models, on the other hand, use a computer to evaluate a model numerically over a time period of interest. Because of the emphasis on realism many parameters are included in this type of model. Simulation models can be either deterministic or stochastic. Further, both types of simulation models can be either static or dynamic. A static simulation model is a representation of a system at a particular time. Whereas a dynamic simulation model is a representation of a system as it evolves over time. A simulation model is said to be deterministic if it contains no random elements (variables) and the model has an unique set of output data for a given set of inputs. A simulation model is stochastic if it contains one or more random variables and the output data are themselves random.

Epidemiological Models

In epidemiology, analytical models are developed to grab the basic characteristics of the disease using simple mathematics. Simulation models provide a comprehensive framework in which the human demography, transmission cycle, the disease process and the impact of control are described. While analytical models are usually designed to clarify concepts and improve the understanding of the transmission process, simulation models by taking advantage of the computer revolution try to fulfil the requirement of realism. Apart from many other applications, the major application of simulation models is to make predictions for operational decisions. However, simulation models can profit greatly from the achievements of analytical models for describing the parts of the epidemiological processes. Both the models have been developed and applied to many infectious diseases to describe their transmission dynamics.

Uses of Epidemiological Models

Models are useful in many ways *viz*. assist in understanding the problem, help manipulating and analyzing a system using computer rather than experimenting with the real system, provide an indication of the information flow and gaps therein, aid in decision making, and help managers to decide what questions to ask themselves. In biology, models are used widely to study complex biological systems, to represent hypotheses, (circulation in physiology), test theories (effect of enzyme concentration on reaction rate), make predictions (pharmacological response to a drug), design outcomes (calculate intake for optimal growth), and analyze data (calculate rate of substrate movement into cells).

Why Model for Lymphatic Filariasis?

Gaps in knowledge

Modelling is essential for filariasis research and control. The epidemiology of the disease is very complex as it depends on the dynamic interaction of three populations, *ie.*, the parasites, the human hosts and the vectors. Although the transmission dynamics of the parasite between humans and mosquitoes is clearly understood, knowledge of the dynamics of infection and development of disease in humans is poor. For example it is not known whether the pathology in the lymphatic system is caused by adult worms or by a combination of adult worms and microfilariae (mf). Since the only feasible measure of infection in humans is the examination of microfilariae in the blood, it is simply not possible to define the relationship between number of adult worms and mf. As a result it may take many years before the effects of control programmes are realized.

Operational issues

Considering the magnitude of the filarial disease problem both in India and around the world, WHO has committed to eliminate filariasis infection from the world [2]. The main strategy towards elimination of this disease is interruption of transmission through annual mass drug administration supplemented by vector control measures and morbidity management by alleviating the suffering of the affected individuals. Though elimination appears to be an achievable goal, a number of operational questions are still open to debate. How long are the costly control programmes to be carried out? What would be the level of coverage to be achieved for a time bound programme? Can a time

bound programme be successful in preventing recrudescence or new infection in the long run? None of these questions have direct answers because they largely depend on the population dynamics of the parasite, drug efficacy, characteristics of the control programme, and the level of endemicity. Mathematical models are useful tools for making decisions in selecting an appropriate control strategy and for assessing the impact of community targeted control programmes which can only be done after many years of cessation of control.

Models for Lymphatic Filariasis

The development and application of mathematical models to filariasis was started in 1960. Hayashi[3] , following the work of Muench[4], was the first to apply catalytic models (originally developed for describing chemical reactions between molecules of a substance and a catalytic substance) for describing the epidemiological changes in susceptible and infected population. Subsequently, Hairston and Jachowski[5] applied the reversible catalytic models for estimating the rates of loss and gain of infections from cross sectional data. These studies formed the basis for subsequent development and application of models to lymphatic filariasis. Section 1 of the write-up reviews the development and application of analytical models for studying certain components of the transmission dynamics of the parasite, whereas section 2 reviews the development and application of comprehensive dynamic models.

Static models

Modelling the dynamics of infection in human

The main purpose of modelling the dynamics of infection in humans is to estimate parameters such as the rate at which persons gain or lose infection. The loss of infection will provide an estimate of the life span of the parasite, which is essential for deciding the duration of the control programme. The gain of infection will indicate the role of immune mechanism in regulating the infection in humans. In this regard a two-stage reversible (*ie*., person turning from positive to negative and vice versa) catalytic model was further applied to estimate the age-specific rates of gain and loss of infection from a cohort data. Application of the model provided an estimate of the fecund life span (patent period) of the adult worm (5.4 years)[6]. Further, an increase in gain of infection in the younger age class and a decline in older age class provided evidence for the role of immune mechanisms in regulating infection.

The estimated rates of gain and loss of infection were used for establishing the relationship between infection and disease. Assuming that people who had been once microfilaraemic and subsequently become amicrofilaraemic tend to develop filarial disease, the cumulative proportion of persons who lost infection in each age class was estimated using the reversible catalytic model. This estimate was found to correlate with the observed disease prevalence in males in different age classes. This finding points to the possible role of the immune system in combating the infection and at the same time provoking disease symptom[7]. This significant contribution was first of its kind in understanding the relation between dynamics of infection and disease.

Modelling dynamics of infection in the vector

In order to have a better understanding of the dynamics of infection in the vector, analyses were done to examine the role of density-dependence in regulating the parasite numbers in the vector and its implications to control programmes. Analysis of the frequency distribution of larval counts of the parasite and the age distribution of infection in mosquitoes demonstrated evidence for the operation of parasite induced vector mortality[8,9]. Further, data from the experimental transmission study were used to quantify the relationships of uptake and development of mf by the vector mosquitoes with human mf-density[10]. This quantification (Fig.1) became the backbone for the later development of a simulation model for this disease. Further, this experimental study confirmed the existence of limitation phenomenon in this vector-parasite complex. The implication of this result is that even if control programmes bring down the mf reservoir to a very low level in the community, in areas where the *Culex quinquefasciatus* is a vector, the mosquitoes can pick up mf, develop L3 and safely transmit the infection to humans. Such a possibility is further confirmed from field

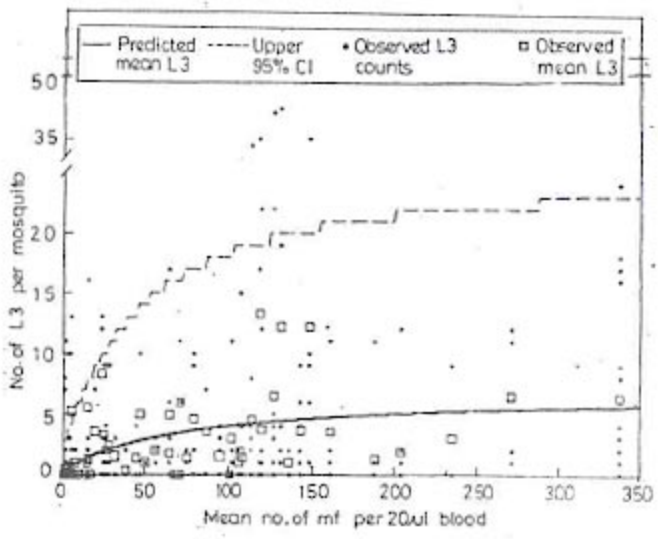

Fig.1. Relation between no. of L3 per mosquito and human mf-density per 20 µl of blood.

collected *C.quinquefasciatus* mosquitoes (VCRC unpublished data).

Dynamic models

Simple models have been applied to understand certain processes involved in the dynamics of infection both in humans and mosquitoes. However, such models have limited value due to a number of issues related to the population biology of the parasite. Therefore the need was felt for an integrated transmission model (linking man, vector and parasite) that can aid in the making of a rational decision for selecting the optimal control strategies and in assessing the impact of the control programme. Two different approaches were made for developing comprehensive models: (i) a stochastic micro-simulation model based on difference equations (LYMFASIM);and (ii) a deterministic macro-simulation model based on differential equations (EPIFIL). The former was the result of a collaborative work between VCRC and the Department of Public Health, Erasmus University, Rotterdam, while the latter resulted from collaboration between VCRC and the Department of Parasite Epidemiology, Oxford University, Oxford.

LYMFASIM simulates the life histories of individual persons, parasites, dynamics of the vector population and the impact of interventions based on vector control, chemotherapy or a combination of both (Fig 2). A typical endemic situation can be characterized by giving details regarding the demography of the population (life-table, fertility figures), the vector involved and its density. The micro-simulation technique allows LYMFASIM to take account of the variation between persons and parasites on a number of characteristics *viz*. age, sex, exposure to mosquito, ability to develop immune responses, inclination to get treatment, *etc*. Similarly adult parasites can differ in their life span, the production of mf, *etc*. Details of treatment (coverage, frequency and duration of treatment), and surveillance (time of survey, complete/ random/cohort survey, and the volume of blood smear) can be specified. Similarly for vector control the duration and effect of vector control in terms of the reduction in man-vector contact can be specified[11].

Depending on the need, a user can get output from the model in two ways *viz*. summary output; and detailed output

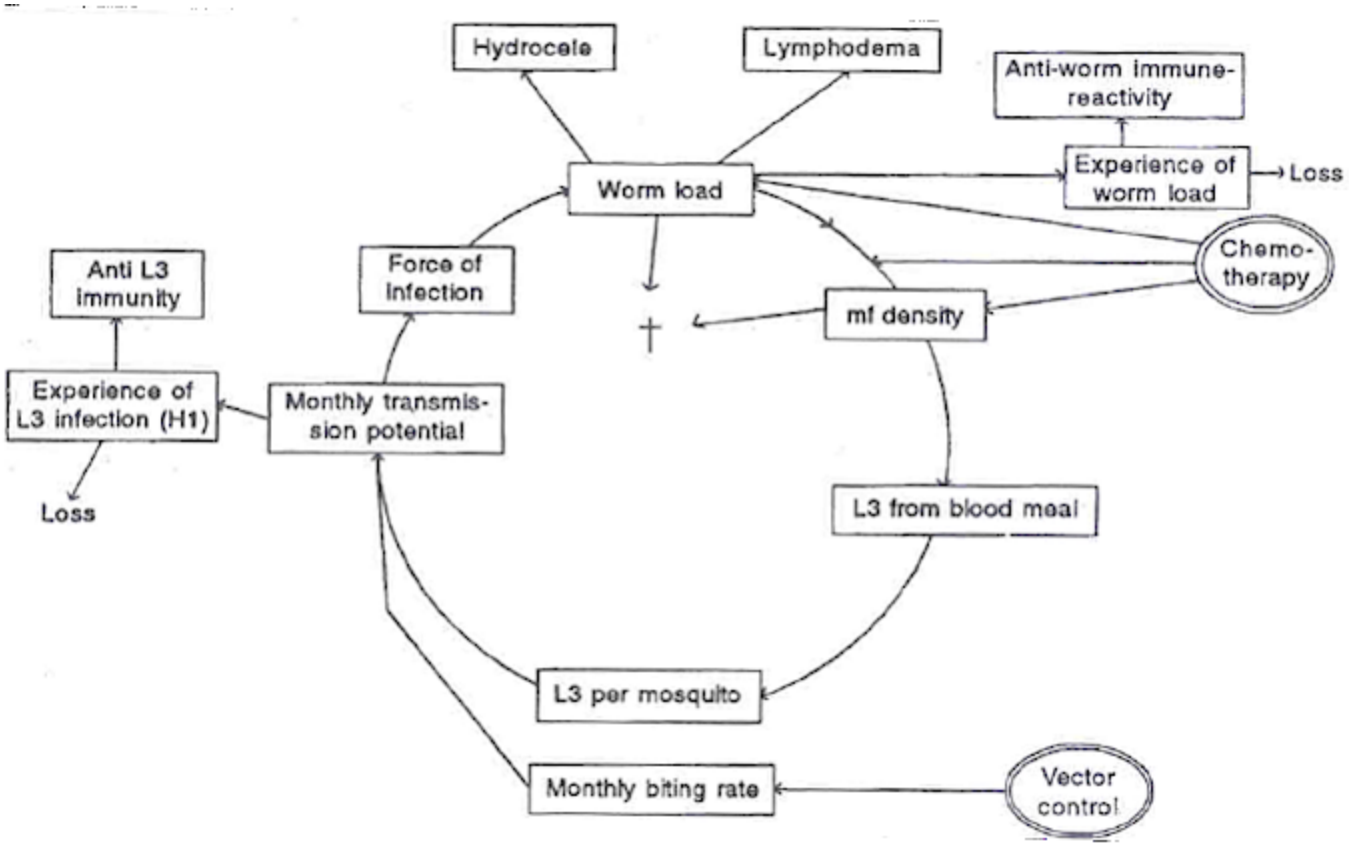

Fig.2. Lymphatic filariasis transmisson cycle implemented in LYMFASIM model.

for each individual person. The summary output includes year-wise details of the prevalence and intensity of mf and adult worms, level of antigenaemia, and the prevalence of hydrocele and lymphoedema. In the detailed output for each person, age, sex, number of mf and adult worms, number of L3 (infective larva) received, antigenaemia level, and disease status are available. The output of the model can be later imported to any spreadsheet programme (*eg*. Microsoft Excel) for further processing and presentations. LYMFASIM has been developed with a number of objectives such as testing hypotheses, forecasting trends, prediction and optimization of control strategies, cost-effectiveness analysis, *etc*.

LYMFASIM for testing hypotheses

The model parameters were quantified using detailed data sets on frequency distribution of mf counts, age-prevalence /intensity of mf in a cohort of individuals followed between two time points (1981 and 1986) in Pondicherry. While fitting the model special emphasis was made to test hypotheses related to the immune mechanisms regulating the density of mf. The good fit of the model to the data suggested that immune mechanism should be an essential component in describing the observed epidemiological patterns in Pondicherry.

LYMFASIM in predicting the impact of vector control

As on date the model has been applied to evaluate the impact of the 5 years integrated vector management (IVM) programme in Pondicherry as well as to predict the trend in prevalence beyond the period of vector control (Fig. 3). The predicted trend beyond the period of IVM (1981-85) was based on the assumption that the vector population has returned to the pre-control level. In spite of resurgence of the vector population to the pre-control level, the predicted and the observed trends continue to decline even 7 years after cessation of the IVM programme suggesting the sustained effect of IVM. However, the trend tends to increase to reach the pre-control level at about 50 years after stopping the control activities. Observations during 1999 suggest that the mf prevalence (approx. 4.0%) in Pondicherry remained stable (1992, 4.5%). The long-term predictions may not be in accordance with the observations because the model did not include the factors/ changes that might have occurred during this period. For example, immediately after cessation of the IVM programme intensive selective treatments were given to the affected persons. Further, changes in ecological, environmental and social factors may have an impact on the transmission dynamics of the parasite.

LYMFASIM for optimizing control strategies

In LYMFASIM the impact of transmission control (vector or parasite or both) can be simulated. The effect of vector control can be mimicked by specifying the duration and effect of vector control (in terms of man biting rate of mosquitoes). Using the quantification obtained for the Pondicherry situation, the model has been applied to determine the duration of vector control required for complete elimination of infection. The predicted trends showed that at least 13 years of vector control is required to reach zero prevalence of infection (Fig. 4).

Although, the efficacy and effectiveness of the DEC in reducing mf prevalence and intensity has been proved beyond doubt both in clinical[12-14] and community trials[15-18],

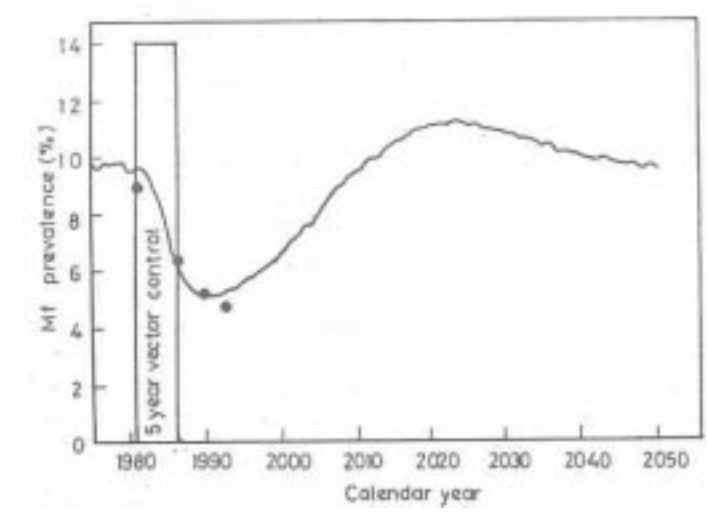

Fig.3. Observed (circle) and predicted (line) trends in prevalence of microfilaraemia in Pondicherry.

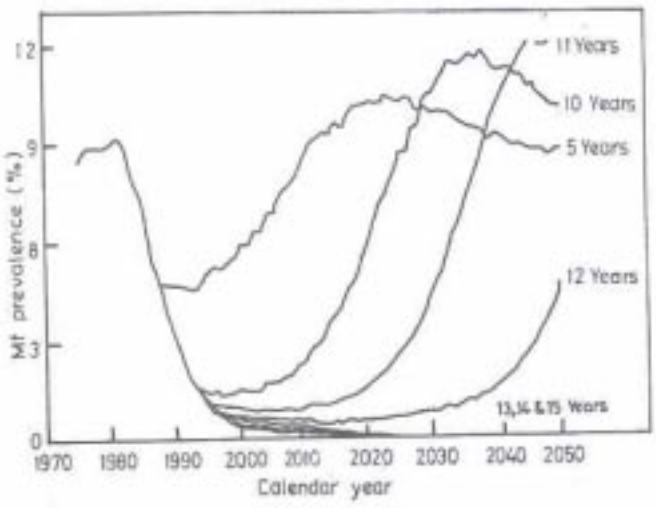

Fig.4. Predicted trends in prevalence of microfilaraemia in relation to duration of vector control.

it is not clear how long the mass treatment programmes are to be continued to prevent recrudescence or new infection after stopping control and the level of mass treatment coverage required to achieve the goal of elimination. Presently the model has been applied to optimize the annual mass DEC treatment programme with respect to coverage and duration of treatment (Fig. 5). Predictions based on preliminary analysis suggest that at least 90 and 60% coverage are required to achieve the goal of elimination with 5 and 11 annual DEC treatments respectively.

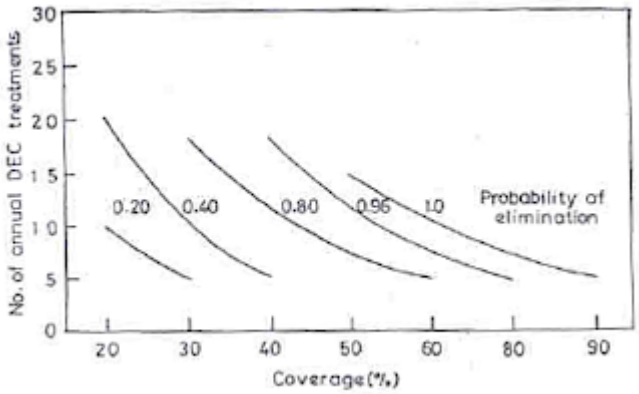

Fig.5. Probability of elimination of infection in relation to coverage and number of annual mass DEC treatments.

EPIFIL, a deterministic simulation model was developed for two specific objectives: (i) developing an epidemiological model that adequately describes the age-dependent patterns of filarial infection, intensity and disease observed in an endemic area; and (ii) developing a model to predict the impact of intervention (vector control and community chemotherapy) on the mean levels of infection and disease in the community. This model was developed based on differential equation framework for describing the dynamics of macroparasitic infections. Based on the current knowledge of lymphatic filariasis, the framework of this model is adopted to explicitly link the dynamics of adult filarial worm populations to the age distribution of infection and chronic disease, specifically lymphodema and hydrocele.

This model was developed with a simpler assumption that adult filarial worms cause damage to the lymphatic system and thus progression to disease (Fig.6). It incorporated differential equations to describe changes by age in worm burden, microfilariae intensity, immunity and prevalence of lymphatic damage, lymphodema and hydrocele. The parameters of the model were estimated using epidemiological data collected in Pondicherry [19]. The number of parameters estimated indirectly by fitting data was kept to a minimum. The good fit of the model shows that both hydrocele and lymphodema are irreversible conditions that develop as consequence of lymphatic damage caused by worms, with the risk of disease being higher for hydrocele than lymphodema. The fit of the model to the data did not support the hypothesis that disease progression is immune mediated. The EPIFIL model has only two parameters related to disease: *ie*. the rate of development of hydrocele and the rate of development of lymphodema. These rates can be interpreted as a risk of developing disease, per worm-year of infection experienced. Further, the use of this model has led to information of biological interest. The presence of acquired protective immunity is suggested by the age-infection data. The model also suggests that protective response leads to only partial protection and that the development of hydrocele be simply related to the past experience of worms. From the model it has been estimated that a single worm will increase the host risk of progressing to hydrocele by about 18%. However, the model suggests that the risk of developing lymphodema is small (2.6% per worm over its lifetime).

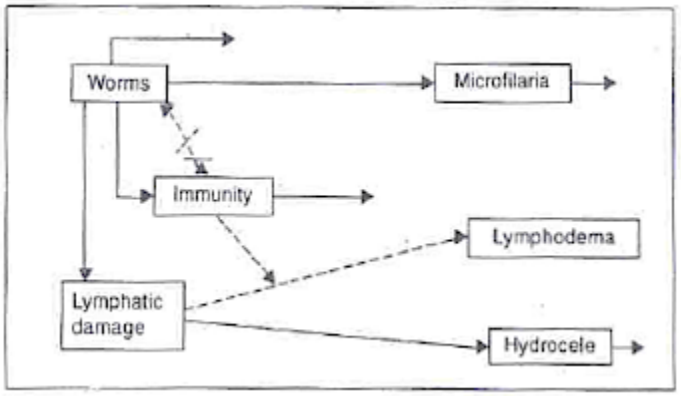

Fig.6. Conceptual frame work of EPIFIL model.

Advancement of EPIFIL model

The EPIFIL model has been extended by incorporating explicitly both host age structure and vector transmission dynamics in order to provide a more realistic framework for assessing the impact of the different intervention options currently available for filariasis control. This model has included age-dependent functions of infection as well as the effects of the demographic age structure of the human community. This model has been developed by assuming that the population parasite distribution is initially at equilibrium, which has been calculated by using the monthly biting rate and community mf load[20].

Application of EPIFIL Model

This model can be used to produce trends in mean values (age-specific prevalence and intensity). It does not suffer from stochastic variation and provides a quick indication of the efficacy of certain control measures. It helps to understand the transmission dynamics by showing the implications of certain assumptions (*eg.* about density regulation through the immune system) on the shape of the age-prevalence and intensity curve. Efforts were made to make EPIFIL, a user-oriented model that can be linked to the user's own data set (such as the age-prevalence curve, the life table and operational indices like the desired level of prevalence to be reached by control).

The model has been applied to simulate the effects of four control options (DEC, ivermectin, DEC+ivermectin and vector control) on the mean microfilaria intensity over 10 years (Fig.7). The results suggest that chemotherapy has a larger short-term impact than vector control but that the effects of vector control can last beyond the treatment periods of five years. Among the three drugs (DEC, ivermectin and albendazole), treatment with DEC showed superiority in reducing community microfilarial loads. Under the same compliance and treatment plans, DEC alone or in combination is predicted to decrease mf load much longer than ivermectin alone, over the 10 year time period. The results suggest that although DEC adds considerably to the benefits of ivermectin, there is relatively little benefit in combining ivermectin with DEC.

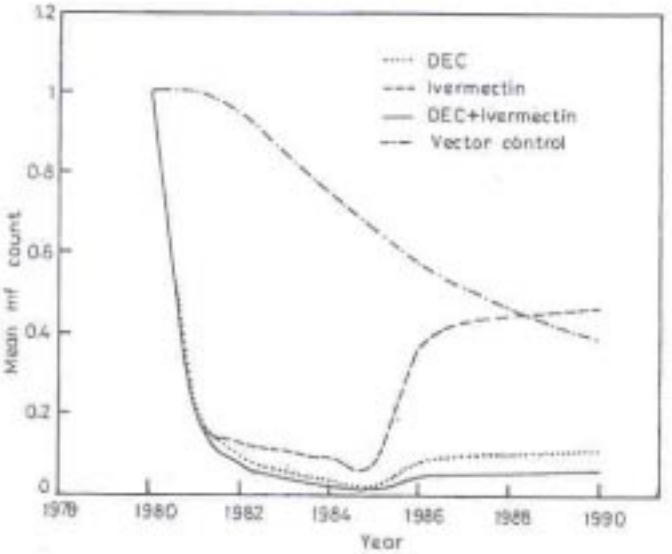

Fig.7. Predicted trends in microfilaria intensity with different control options.

LYMFASIM and EPIFIL

There are similarities but also important differences between the LYMFASIM and EPIFIL models and between the outcomes of the models. The most important similarity is that both models describe the dynamics of the worm and mf. This approach helped in testing assumptions about immune regulation and disease development compared to the classical catalytic models which primarily describe the gain and loss of infections by human [6,7]. Both the models render the conclusion that the force of infection is age dependent and that establishment of worms is immune regulated. The most striking difference is that EPIFIL is a simple deterministic model while LYMFSIM is a comprehensive stochastic model. In LYMFASIM the unit of simulation is each individual human host and parasite (micro-simulation) whereas EPIFIL is population-based (macro-simulation) and so the model outputs are individual- and population-based respectively.

Conclusions

Both LYMFASIM and EPIFIL can be used at any stage of a control programme to predict the prevalence and intensity of infection. Further, the models can also be used to compare the potential effectiveness of the different possible schedules of interventions. During the intervention phase of a programme, these models can be of use to monitor the progress of the programme, to assess whether the programme is achieving its targets and also to adopt intervention schedules while the programme is running.

At present both models are being used by researchers to plan for a more rational approach to allocation of funds and efforts in the control of lymphatic filariasis. The quantification of both LYMFASIM and EPIFIL are based on data from the Pondicherry urban situation. Since application of these models in different endemic situations will improve the robustness and validity of the models, they need to be tested under different epidemiological situations. Therefore, it is planned to validate the models based on data collected through an evaluation of the annual mass DEC/ivermectin treatments on the transmission of bancroftian filariasis. Lastly both the models are also intended for educational use in developing and understanding the concepts of epidemiology and to train public health workers in the use of predictive methods.

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