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REVIEW ARTICLE

EVALUATION OF LYMPHATIC FILARIASIS ELIMINATION PROGRAMMES AND PREDICTING ITS IMPACT BY USING A BIOMATHEMATICAL MODEL

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ABSTRACT

Mathematical simulation models for transmission and control of lymphatic filariasis are useful tools for studying the prospects of lymphatic filariasis elimination. Two simulation models are currently being used. The first, EPIFIL, is a population-based, deterministic model that simulates average trends in infection intensity over time. The second, LYMFASIM, is an individual-based, stochastic model that simulates acquisition and loss of infection for each individual in the simulated population, taking account of individual characteristics. Nevertheless, published estimates of the duration of mass treatment required for elimination differed, due to the use of different indicators for elimination (EPIFIL: microfilaraemia prevalence<o.5% after the last treatment; LYMFASIM: reduction of microfilaraemia prevalence to zero, within 40 years after the start of mass treatment). Regions like Puducherry (India), where *Wuchereria bancrofti* infection is transmitted by *Culex quinquefasciatus*, the models give similar predictions of the coverage and number of treatment rounds required to bring microfilaraemis prevalence below a level of 0.5%. The models usefulness could be enhanced by several extensions; inclusion of different diagnostic tests and natural history of disease in the models is of particular relevance. The main challenges for future modeling work are 1) quantification and validation of the models for other regions, for investigation of elimination prospects in situations with other vector-parasite combinations and endemicity levels than in Puducherry; 2) application of the models to address a range of programmatic issues related to the monitoring and evaluation of ongoing control programmes.

INTRODUCTION

Biomathematical models have been used widely in parasitology. They help to understand the complex transmission dynamics of parasitic diseases and are useful tools for planning and evaluating control programmes. The two available models for lymphatic filariasis transmission and control are EPIFIL and LYMFASIM. Both these models have been developed for *Wuchereria bancrofti* transmitted by *Culex quinquefasciatus* (Bryan and Southgate, 1988).

Studies on the transmission dynamics of the *Wuchereria bancrofti–Culex quinquefasciatus* is complex in India and have formed the basis for the development of epidemiologic models such as "EPIFIL" (Chan *et al*., 1998) and (Norman *et al*., 2000) and "LYMFASIM" (Plaisier *et al*., 1998). Biomathematical models can help to clarify these issues and application of such models is considered important for support of Global Programme to Eliminate Lymphatic Filariasis (GPELF) (Michael *et al*., 2006). Models acts as a health policy tool to understand the complex transmission dynamics of parasitic diseases and are useful for planning and evaluation of control programmes especially to eliminate lymphatic filariasis caused by vector *Culex quinquefasciatus* (Goodman, 1994).These models have been quantified using longitudinal data from Puducherry, Southern India (Stolk, 2003; Subramanian *et al*., 2004). Models predict the long-term impact of mass treatment and assess elimination prospects. The present study highlights the recent progress in the modeling of lymphatic filariasis, focusing on EPIFIL and LYMFASIM. The model helps in understanding the transmission and control of lymphatic filariasis. Using data from an integrated vector management control programme carried out in Puducherry, India from 1981 to 1985 was evaluated for its health policy tool in the present study. The basic structure of these models and the parameter quantification are highlighted. Relevant model predictions are compared and differences are discussed.

The main strategy for elimination of lymphatic filariasis goal is interruption of transmission through annual mass treatment with antifilarial drugs, combined with individual management of patients to improve the condition of individuals suffering from chronic disease due to infection (Ottesen *et al.*, 1997). Density dependence and heterogeneity are few variables involved are bio-mathematical models construction. The term heterogeneity points at variation between individuals. Individuals differ for example in genetic background,

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nutritional status and behavior, which may cause differences in exposure to mosquitoes, susceptibility to infection, and survival, maturation and fecundity of parasites (Duerr *et al*., 2003).

Globally, the majority of lymphatic filariasis caused by *Wuchereria bancrofti* is transmitted by *Culex quiquefasciatus* lymfila. In India, *Culex quiquefasciatus* is the principal vector of bancroftial filariasis (Das, 2012). *Culex quiquefasciatus* is also the vector of Japanese encephalitis (JE) virus (Sucharit *et al*., 1989). Rapid urbanization and industrialization without proper drainage facilities are responsible for the proliferation of the vector species (Singh, 1967; Mukhopadhyay *et al*., 2007). Transmission of infection through vectors is considered density–dependant. The estimated level of tolerated density of *Culex quinquefasciatus* up to which there is no risk of filariasis transmission is 34 per ten man hour density (Bhatia *et al*., 1958). The density pattern depicted by vector species in any area is influenced by the gross ecology of the terrain and the meteorological variables (Kaul *et al*., 1968).

The present study is aimed to evaluate the Global Programme to Eliminate Lymphatic Filariasis (GPELF) plan for the year 2020 highlighting the need for the establishment of morbidity management programs in endemic area of Puducherry. In particular, the study area Shanmukapuram, South West region of Puducherry need for the development of metrices to monitor the report for the breeding habitats of *Culex quenquifasciatus*. Further, it has been argued that lymphatic filariasis specific tool would allow greater sensitivity in the assessment of outcomes of Global Programme to Eliminate Lymphatic Filariasis (GPELF) interventions, particularly for patients in chronic stages of the disease where the physical impacts are irreversible and quality of life rather than cure becomes the aim of intervention (Zeldenryk *et al*., 2012).

Available Models

The two available models for lymphatic filariasis transmission and control are EPIFIL and LYMFASIM, mainly differ in the amount of detail included. Specific variants of both models have been developed for *Wuchereria bancrofti* transmitted by *Culex quinquefasciatus*, using data from an integrated vector management control programme that was carried out in Puducherry, from 1981 to 1985. These existing Puducherry model variants have been used for the prediction.

EPIFIL

EPIFIL simulates the average course of infection over age and time in a human population. The age–structure of the population is fixed, but its size is unspecified. Limitation in the transmission of infection by culicine mosquitoes is taken into account: the number of infectious L_3 larvae that can develop in mosquitoes saturates at higher mf intensities. Acquired immunity is included as a second limiting mechanism: it is triggered by incoming L_3 larvae and reduces the probability that new larvae develop into adult worms. The model takes account of heterogeneity that is introduced by age–related variation in exposure to mosquitoes. i.e. the exposure increases with age, until a maximum level is reached at the age of 9 years. A predetermined relationship between mf prevalence and intensity is used to translate predicted mf intensity levels into mf prevalence. The model can be used to translate predicted mf intensity levels into mf prevalence. The model can be used to simulate the impact of vector control, assuming that control measures reduce the mosquito biting rate. The effects of mass treatment can be simulated, assuming that a proportion of the population is treated with a drug with pre–specified efficacy; drugs may kill part of the present mf and adult worm and may reduce the mf production rate per adult worm. The design of this population–based model is based on a general differential equation framework describing the dynamics of macro parasitic infections. The model is deterministic, meaning that simulation output is always the same with fixed input specifications.

LYMFASIM

LYMFASIM simulates the acquisition and loss of worms over age and time in a discrete number of human individuals, using stochastic micro-simulation. Individuals interact through biting mosquitoes and together they form a dynamic population, of which the size and age–structure may change over time. Like EPIFIL, LYMFASIM takes account of limitation in the proportion of engorged mf that develops into L_3 larvae inside the mosquito and of acquired immunity in human hosts. Two model variants were developed for Puducherry, which differed with respect to the type of acquired immunity. 'Anti – L_3' immunity is triggered by incoming L_3 larvae and reduces the probability of successful adult worm establishment; 'anti–fecundity' immunity is triggered by the presence of adult worms and reduces the rate of mf production by female worms. By considering individual worms and reduces the rate of mf production by female worms. By considering individual worms in individual hosts, the model inherently takes account of the declining mating probability of female and male worms with lower average infection intensities.

Several sources of heterogeneity are considered in these models. This includes age– variation in exposure: exposure increases until a maximum is reached at about 20 years of age. Other factors contributing to heterogeneity are between–person variation in exposure [not age–related], and variation in inclination to participate in treatment programmes, the response to treatment, and the ability to develop immune responses. Parasites may vary with respect to their life span (about 10 years on average). Individual mf intensities are translated into the number of mf that would be counted in a 20µl blood smear, taking account of random variability in these counts and reduced sensitivity of diagnostic tests at lower mf densities.

The mf prevalence and mean mf intensity can be directly calculated from the smear counts, using data from all simulated individuals or specific subgroups. Similar to EPIFIL, LYMFASIM can simulate the impact of vector control by assuming that it reduces the mosquito biting rate. The model can simulate mass or selective treatment. In the first case, treatment is given to part of the individuals, irrespective of their infection status; in the latter case, treatment is given only to a proportion of mf positives. Treatment of an individual may kill a proportion of mf and worms and may temporarily or

permanently reduce the fertility of female worms. Treatment effects may vary between individuals.

Processes in lymphatic filariasis transmission and control

Models for the elimination of lymphatic filariasis basically describes the main biological processes involved in transmission of the disease. For prediction of the effects of intervention on the transmission, it is of particular importance to take account of the density dependence in these processes and to consider heterogeneities of the disease. The first major challenge lies in the quantification and validation of model variants for different regions. The discussed models were both quantified for transmission of *Wuchereria bancrofti* by *Culex quinquefasciatus* and tested against data from Puducherry with slight modification following Norman *et al*., (2000) and Subramanian *et al*., (2004).

Density dependence is a biological term, which indicates that the growth rate of a population depends in a non–linear way on its density. The most familiar with negative density–dependent mechanisms that limit the population growth is (i.e. limitation, e.g. reduced survival probabilities due to crowding). Several such limiting mechanisms are known to occur in lymphatic filariasis, particularly in the parasite development of mosquitoes. Density dependence may also–occur in the opposite direction, facilitation transmission or population growth at higher infection intensities (i.e. facilitation). For example, the probability that a female worm mates with a male worm increases with higher worm burdens. Further, in some anopheline mosquito species, the probability that mf develop successfully into L_3 larvae increases mechanisms may eventually get the upper hand again.

Density–dependent mechanisms are important determinants of the elimination prospects. Due to such mechanisms, a reduction of one of the transmission determinants (e.g. mosquito biting rate, mf density in the blood) by control measures does not have a proportional effect on transmission rates and parasite abundance. Hence the present study highlights the role of biomathematical models that concentrates on the transmitted.

Parameter values

Table 1 gives the quantification of key biological model parameters. Both models EPIFIL and LYMFASIM that were quantified for the study area, but several; assumption were different. For example, EPIFIL quantified parameters for the adult worm lifespan, age–variation in exposure and the mf production per worm using information from literature and local data. LYMFASIM estimated these parameters by fitting the model to observed epidemiological data. The quantification of the monthly biting rate was based on local data in both models, but it was much higher in EPIFIL than in LYMFASIM.

EPIFIL'S quantification was based on weekly mosquito catches that had been carried out in several sites in the study area during the first few hours of the night. LYMFASIM'S quantification was based on data from one single site where all night mosquito catches had been carried out. To compensate for the higher biting rate in EPIFIL, a lower value needed to be estimated for the proportion of inoculated L_3 larvae that develops successfully into adult worms.

Both models accurately mimicked epidemiological data from Puducherry even though different assumptions were made. EPIFIL and LYMFASIM predictions of the number of yearly mass treatment rounds that is required to reach a 0.5% micro filaraemia prevalence threshold. Results are shown for mass treatment with a combination diethylcarbamazine plus albendazole, and for various endemicity and coverage levels. The combination treatment is assumed to kill 55% of all adult worms and 95% of the microfilariae, and to interrupt the microfilaria production for 6 months. EPIFIL's predictions were made with a model without acquired immunity. LYMFASIM predictions, from the model with anti–L_3 immunity, were added for comparison for an average pretreatment microfilaraemia prevalence of 10% (Table 2).

Table 2 highlights EPIFIL predictions are made on the impact of mass treatment, vector control and their combination on trends in microfilaraemia prevalence. Predictions were made with the EPIFIL simulation model as quantified for Puducherry (but ignoring acquired immunity), assuming a pre control microfilaraemia prevalence of 10%.

Table 3 reveals the LYMFASIM predictions of the coverage and number of yearly mass treatment rounds with invermectin that are required for lymphatic filariasis elimination in Puducherry, India. Precontrol microfilaraemia prevalence was assumed to be 8.5%. Elimination was said to occur if zero microfilaraemia prevalence is reached 40 years after the start of treatment, with 99% probability. A single treatment with invermectin (200 µg/kg) was assumed to sterilize 77% of female worms permanently and to kill all microfilariae (Table 3).

EPIFIL Vs. LYMFASIM: Predictions

EPIFIL and LYMFASIM have been used to predict the impact of control measures and assess prospects for elimination by mass treatment (Stolk *et al.,* 2005). In the present study the model focuses on the predictions of the coverage and duration of annual mass treatment programmes required for elimination of lymphatic filariasis. LYMFASIM's predictions were based on the models with anti–L_3 or anti–fecundity immunity, with a population size of about 3000-4500 individuals. From the predictions of both models it can be concluded that it is possible to eliminate lymphatic filariasis by yearly mass treatment, but the number of treatment round largely depends on coverage, pre-control of mf prevalence and the microfilaricidal effects of drugs. The results are well substantiated by the findings of Subramanian *et al*. (2004).

The predictions for Puducherry like situations indicate that elimination can be achieved within a reasonable timeframe. In fact, the required time period is shorter than the mean adult worm lifespan. This is possible, because the antifilarial drugs are thought to have strong macrofilaricidal or sterilizing effect (Anderson and May, 1985). The quantitative predictions should be interpreted with some care. Achieving elimination for example will be more difficult, if the macrofilaricidal effects of treatment are lower, if the adult worms live longer, if there is

Table 1: Quantification of several key biological parameters in the EPIFIL and LYMFASIM model variants for Puducherry, where *Wuchereria bancrofti* is transmitted by *Culex quinquefasciatus*

Parameter	EPIFIL	LYMFASIM	
		Anti-L_3 immunity	Anti-fecundity immunity
Parasite lifecycle	8[a]	10.2[b]	11.8[b]
Average adult worm lifespan in years (type of distribution)			
Average mf lifespan in months (type of distribution)	10[a]	10[c]	10[c]
Premature period in months	-	8	8
Exposure variation by age	0	0.26	0.40
Exposure at age zero as fraction of maximum exposure			
Age in years at which maximum exposure is achieved	9	19.1	21.3
Density dependence in mosquitoes	6[d]	6.6[e]	6.6[e]
Maximum number of L_3 larvae that can develop in mosquitoes at high mf intensities			
Acquired immunity	lifelong	9.6[f]	11.2[f]
Duration of acquired immunity in years			
Other parameters	5760	2200	2200
Monthly biting rate			
Proportion of L_3 larvae in mosquitoes that enter the human host when a mosquito bites	O,414x0.32=0.13	0.1	0.1
Proportion of inoculated L_3 larvae that develop successfully into adult worms ($X10^{-3}$)	0.113	1.03[g]	0.42
Mf production per worm	2	0.61[h]	4.03[h,i]

-Not considered in the model: mf, microfilaria

(a) Assuming an Exponential distribution (b) Assuming a Weibull distribution with shape parameter α=2. (c) Assuming an exponential distribution, approximated with discrete time steps. (d) Exponential saturation function with initial increase from zero = 0.047. (e) Hyperbolic saturating function with initial increase from zero = 0.09 (f) Period in which the strength of the immune response is halved in the absence of boosting (g) In the absence of anti – L^3 immunity (h) In the presence of at least 1 male worm, scaled to the number of mf per 20µl peripheral blood. (i) In the absence of anti-fecundity immunity.

Table 2: Prediction of number of yearly mass treatment rounds required to reach a 0.5% microfilaraemia prevalence threshold, using a combination of diethylcarbamazine plus albendazole in relation to endemicity and coverage.

Pretreatment Mf prevalence	60%	70%	80%	90%
EPIFIL	7	6	5	4
2.5%				
5%	9	7	6	5
10%	10	8	7	6
15%	12	9	8	7
LYMFASIM	10	8	6	5
10% (P^5 – P^{95}: 8.8% - 11.4%)				

The combination treatment is assumed to kill 55% of all adult worms and 95% of the microfilariaem and to interrupt the microfilaria production for 6 months. **EPIFIL'S** predictions were made with a model without acquired immunity**. LYMFASIM** predictions from the model with anti-L_3 immunity, were added for comparison for an average pretreatment microfilaraemia prevalence of 10%. Details of the variability between **LYMFASIM** runs are included in the lower part of the table.

Table 3: LYMFASIM predictions of the number of annual mass drug treatment rounds required to achieve elimination in an area like Puducherry, with 99% probability

Drug(s)	Adult Worms (%)	Microfilariae (%)	65 %	80%
Invermectin + Albendazole	30	100	10	6
Diethylcarbamazine	50	60	6	3
Diethylcarbamazine + Albendazole	70	60	4	2
Doxycyclinine	80	0	2	2

Results are shown for four different drugs or drug combinations and two coverage levels. Predictions are based on the anti-L_3 variant of the model for Pondicherry, with a precontrol microfilaraemia prevalence of 8.5%. Elimination is defined as zero microfilaraemia prevalence 40 years after the start of treatment.

stronger aggregation of worm- burdens, or if density–dependent mechanisms operate that enhance parasite transmission at low infection intensities. Inspite of these uncertainties, the predictions give important on the determinants of elimination (Plaisier *et al.,* 2000) of lymphatic filariasis.

The predictions of EPIFIL and LYMFASIM cannot be compared directly, because the original publications reported results for different treatment regimens, with different assumptions of efficacy of the drugs, and different precontrol mf prevalence levels. Further, different criteria for elimination were used in EPIFIL elimination was assumed to occur if the mf prevalence after treatment was below 0.5% in LYMFASIM elimination was defined as a zero mf prevalence 40 years after the start of control in 99% of the runs (Krishnamoorthy *et al*., 2004). To allow better comparison of the models, a series of additional simulations with LYMFASIM for mass treatment with the combination of diethlycarbamazine plus albendazole, using the same assumptions on drug–efficacy and, the same criterion for elimination of lymphatic filariasis as in published EPIFIL predictions (Norman *et al*., 2000). Current models need to be improved to enable them to make more realistic predictions. This will necessitate validation in different epidemiological settings and incorporation of new knowledge as evidenced by Das and Subramanian, (2002).Presently available simulation models should account for the mode of action of drugs (e.g. direct effects or immune mediated effects), drug resistance, and changes in efficacy after repeated treatment. This necessitates generation of knowledge on the effects of drugs on the adult worms as predicted by Pani and Lall, (1998). Parasite–related factors such as its reproductive biology need to be quantified as they are critical for predictions based on models. Besides parasites, vector habitats and seasonal prevalence are needed as a preliminary data. Models should be fine–tuned to different epidemiological settings to explore the mechanisms regulating infection and disease. Incorporation of knowledge on disease dynamics and progression can help set new targets to reach the goal of lymphatic filariasis elimination as a public health problem, or identify aspects that would need to address to achieve this target (Das, 2002). There is an urgent need to consolidate and bring out user friendly models with the minimum necessary inputs / outputs for application in decision making and evaluation by programme mangers. Models will remain only research tools if their scope of application in Global Programme to Eliminate Lymphatic Filariasis (GPELF) is not broadened.

Criteria for elimination

EPIFIL predictions were based on the assumption that transmission will not continue when the mf prevalence falls below 0.5%. The choice for this threshold is somewhat arbitrary in the absence of evidence from the field. Given its individual-based structure, LYMFASIM is more suitable for examining in how many runs infection is 'truly' eliminated, as indicated by zero mf prevalence 40 years after the start of control (Stolk *et al*., 2003). For example, in the runs with 10% pre-control, prevalence below 0.5% (Table 1). However, only 87% of the runs did this result in zero mf prevalence 40 years after the start of control. It is clear that to be 99% certain of elimination (Table 2 & 3), much longer continuation of mass treatment would be required. This threshold level (or threshold levels) will depend on local transmission dynamics and mosquito biting rates, immigration of parasite carriers or infected mosquitoes, but also on heterogeneities and population size in view of the stochastic processes involved (Stolk *et al*., 2004).

Application of models for other regions

The existing model variants were all quantified for transmission of *Wuchereria bancrofti* by *Culex quinquefasciatus* and tested against data from Puducherry. Biological parameters are not expected to vary much between regions. Most importantly, this concerns the relationship between mf density in the human blood and the number of L3 larvae developing in mosquitoes. Unfortunately, few data are available to quantify this relationship for the different mosquito species involved. Especially for the anopheline mosquito species responsible for trans-mission in needed.

However, our understanding of the biology of infection (in spite of in-depth model based analysis of the Puducherry data) is incomplete and there is uncertainty about the quantification of several key parameters, such as the parasite lifespan or role of acquired immunity (Table 1).

The basic structure of the models is generalized to other areas, but various model parameters may take different values. Other parameters that may need re-quantification relate to the composition of the human population, mosquito biting rates and heterogeneity in exposure, and operational characteristics of intervention (Southgate and Bryan, 1992). Therefore, it is crucial to continue testing the validity of existing and new model variants against epidemiological data. Testing models against age specific data may help to determine the role of acquired immunity of other processes.

Trends during vector control are especially informative about the adult worm lifespan. Trends during mass treatment may give information about the effects of drugs on worm survival and productivity (Snow and Michael, 2002) and trends after cessation of control may help to determine whether density-dependent mechanisms have appropriately been included in the model. Better information on all these aspects should eventually come from field research. Using combinations of available diagnostic tests (mf and antigen detection, ultrasound to visualize adult worms), it may be possible to further increase the validity of our existing models.

The LYMFASIM model has been applied to age-patterns observed in an area of South-East India that has the same vector-parasite combination and presumably the same transmission dynamics as Puducherry. This led to the development of new model variants with less strong or no immunity (Subramanian *et al.*, 2004). Comparison of predictions from the new LYMFASIM model variant and EPIFIL with observed trends during mass treatment in this region indicated that assumptions regarding efficacy of drugs, or possibly coverage and compliance patterns, had to be adapted.

Challenges in the evaluation of current elimination programme

Predictions of the number of treatment rounds required for elimination were only a first step. However, specific programmes also need to be monitored and evaluated. For example, the observed results can be compared with model predictions to see whether progress is as expected. Lf results lag behind, programmes can be adapted. Also, the models could help to determine when mass treatment can be stopped with low risk of recrudescence, taking account of the specific local conditions, local coverage and compliance levels, and the achieved reduction in mf prevalence and intensity.

Analogously, models can help to determine cost-effective surveillance strategies for early detection of recrudescence of infection after cessation of control and measures to be taken to stop this recrudescence. In some situations, focus may shift to reducing the public health problem without explicitly eliminating infection. To address this with the models, more attention is required for the development of disease (Woolhouse, 1992). Simple mechanisms of disease development are included in both models, but this has received little attention in published work until now. To address the discussed issues on monitoring and surveillance the models must be extended to include the results of antigen detection, which is widely used in monitoring and surveillance by ongoing control programmes. Although discussion until now focused on the elimination of transmission, this goal may be difficult to achieve in some areas (Vanamail *et al*., 1996).

Conclusion

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

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