Discussion Note

Fitting LYMFASIM to data from SAMOA

- preliminary results -

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1 Summary

LYMFASIM is being developed at the Department of Public Health as a tool for decision making in filariasis control. With the start of the Global Programme to Eliminate Lymphatic Filariasis (GPELF) interest in the use and application of LYMFASIM is increasing. In July we were approached by dr. Biswas from WHO with a concrete question concerning the situation in Samoa. Samoa has a long history of control. After a long period of irregular mass treatment, mass treatment took place regularly using different treatment regimens (single dose DEC, sd DEC+ivermectin or sd DEC+albendazole) from 1993 onwards. Mf prevalence has been reduced considerably and the question is whether treatment should be continued longer.

LYMFASIM until now has only been quantified for Pondicherry, India, and still needs to be validated for this area and other regions. In this first, very explorative exercise, we tried to fit LYMFASIM to data from Samoa. The results are described in this short report.

Although out attempts did not results in a completely quantified version of the LYMFASIM model, the exercise appeared very useful. Firstly, the exercise gives an indication of how the model can be applied to other endemic areas, what type (and quality!) of data are required, and what problems may occur. The exercise also points at parameters that may take different values in the Pondicherry and Samoa quantification of LYMFASIM, which may have important consequences for the effectiveness of mass treatment. Furthermore, failure of the model to reproduce observed data may indicate problems in the structure of the simulation model.

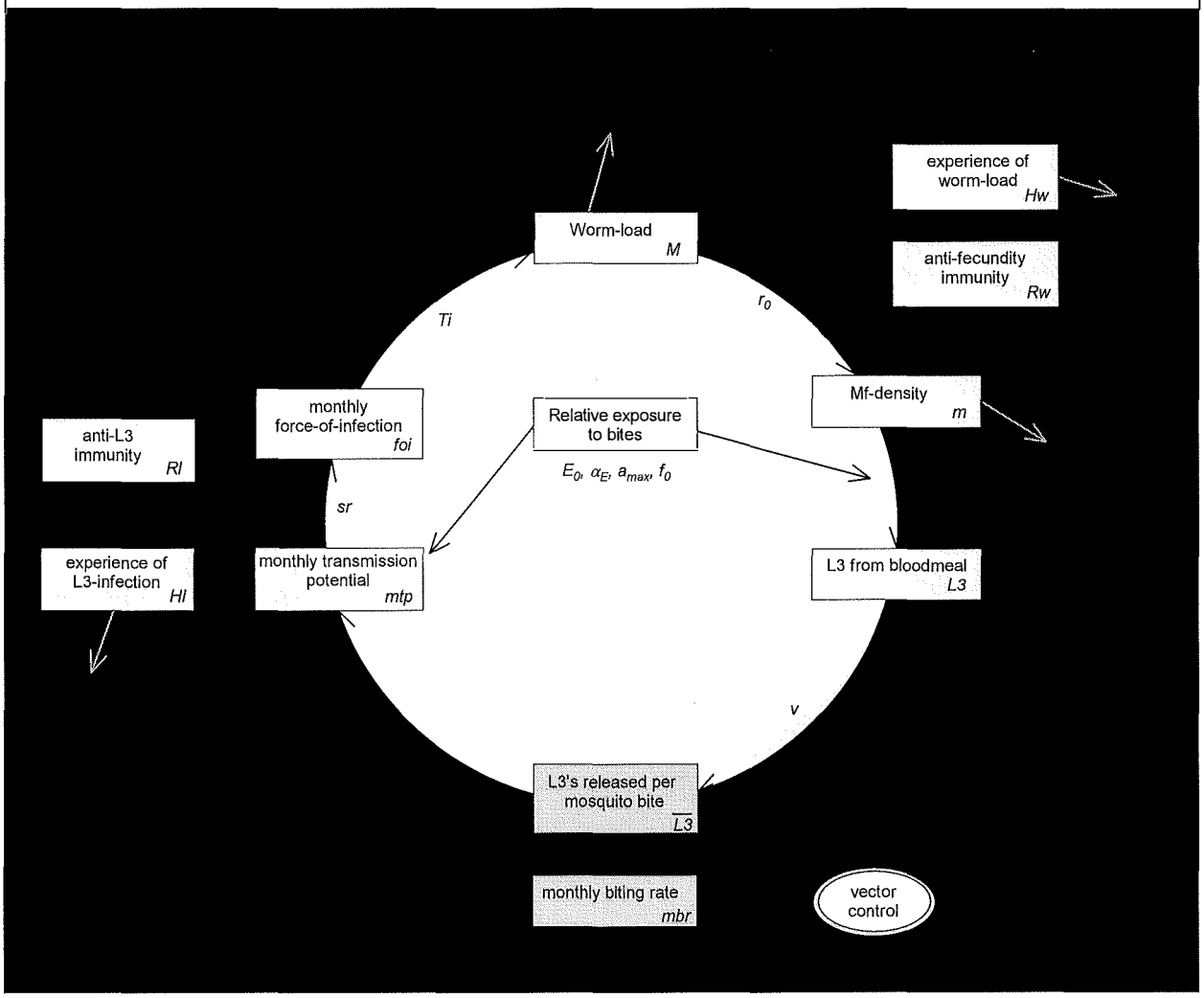
Before LYMFASIM can be used for prediction of the trend in infection prevalence and intensity after mass treatment, the model needs to be tested against independent data from different areas.

2 Methods for quantification of LYMFASIM

2.1 The model LYMFASIM

LYMFASIM is being developed at the Department of Public Health as a tool for decision making in filariasis control. A detailed description of the LYMFASIM simulation program is given elsewhere [1]. LYMFASIM simulates the transmission of *Wuchereria bancrofti* infection in a dynamic population over time and can be used to predict the short- and long-term effects of vector control or (mass) treatment. To do so, the model mimics each step in the lifecycle of the parasite (see figure 1).

Figure 1. Schematic representation of the lifecycle of the parasite



Using microsimulation, it is possible to simulate the dynamics of parasite development and transmission in detail [2]. It's a flexible method that allows for easy adaptation or extension of the model. However, it also leaves the user with a large number of parameters that needs to be quantified. Only some of these parameters have been displayed in figure 1, namely the parameters concerning parasite development in human host and vector. Other parameters in

LYMFASIM concern for instance the demography of the human population or the effects of mass treatment on Mf and adult worms.

2.2 Methods of quantification

Several sources of information can be used to quantify the parameters in LYMFASIM.

- available statistics: statistics on fertility, mortality and migration are usually available at the country or district level and can be used to directly quantify the demographic component of the model
- (meta-analysis of) published data: e.g. Mf lifespan, immature period, efficacy of treatment
- local observations: e.g. monthly biting rates
- experiments for quantification of a specific parameter: factors related to development of parasites in the vector

When there are no data available, remaining parameters can be quantified by:

- expert opinion
- fitting model to local data: age-specific exposure, variation in exposure, strength of immune response, lifespan of adult worms, etc.

2.3 Pondicherry quantification

For a description of the fitting of LYMFASIM to data from Pondicherry, see Subramanian et al. [3].

As many parameters as possible in the model has been quantified using available data. The remaining parameters were quantified by fitting the model to longitudinal epidemiological data from the evaluation of an integrated vector management programme in Pondicherry that ran from 1981-1986. This VCRC-database is unique in that it combines entomological and epidemiological observations and that it includes a very large sample of the population of Pondicherry (almost 25000 observations in 1981). Furthermore, the infection status of humans has been measured at 4 time points (1981, 1986, 1989, and 1992), which enables the study of longitudinal cohorts. The entomological data could be used directly for quantification of mosquito biting rate.

LYMFASIM was fitted to data from a cohort of 5071 individuals, whose Mf density was measured both in 1981 and 1986, i.e. before and after the integrated vector management programme in Pondicherry. In an automatic fit-procedure, parameter values are estimated so that the results of the simulation best fit to the observations.

Fitting the model to data can serve several aims:

- hypothesis testing: by comparing different conceptual models and assessing which model best explains the data, hypotheses can be tested. Models with and without immunity were compared. A model without immunity, however, did not explain the observations.
- provide insight into the dynamics of infection: not only the testing of different hypotheses, but also the quantification of a parameters gives insight into the dynamics.

By fitting LYMFASIM to data, we estimated the parasite lifespan at 10 years on average. This estimate is higher than previous estimates.
- it renders a quantified model that can be used for evaluation and prediction: based on the Pondicherry-data, we quantified 2 alternative models, both including different types of acquired immunity. Both models could explain the data.

2.4 Validation of the model

The next step in the development of LYMFASIM would be to assess whether the simulation model gives an accurate representation of the transmission of lymphatic filariasis, i.e. whether the model is valid. There may be other explanations for the observations in Pondicherry that have not been considered, and there may be (identified or unidentified) peculiarities in the data that could lead to wrong conclusions.

Conclusions on the role of acquired immunity, for instance, critically depend on age-patterns of infection intensity or prevalence. The prevalence of infection in Pondicherry shows a monotonous increase up to the age of 20 and a decline in older agegroups. Such a convex pattern can be explained by acquired immunity, but there may also be other explanations that have not been considered in our analysis.

To validate our conclusions on the role of acquired immunity, the model should be tested in different situations. If this model also explains data from other areas, we can be more confident that acquired immunity indeed plays a role. However, a yet unpublished literature review carried out by VCRC / EUR shows that the convex pattern of Mf prevalence by age that was found in Pondicherry is not representative for other areas. There is much variation in the patterns of infection by age, although overall the prevalence seems to increase with age until a more or less constant level is reached among adults.

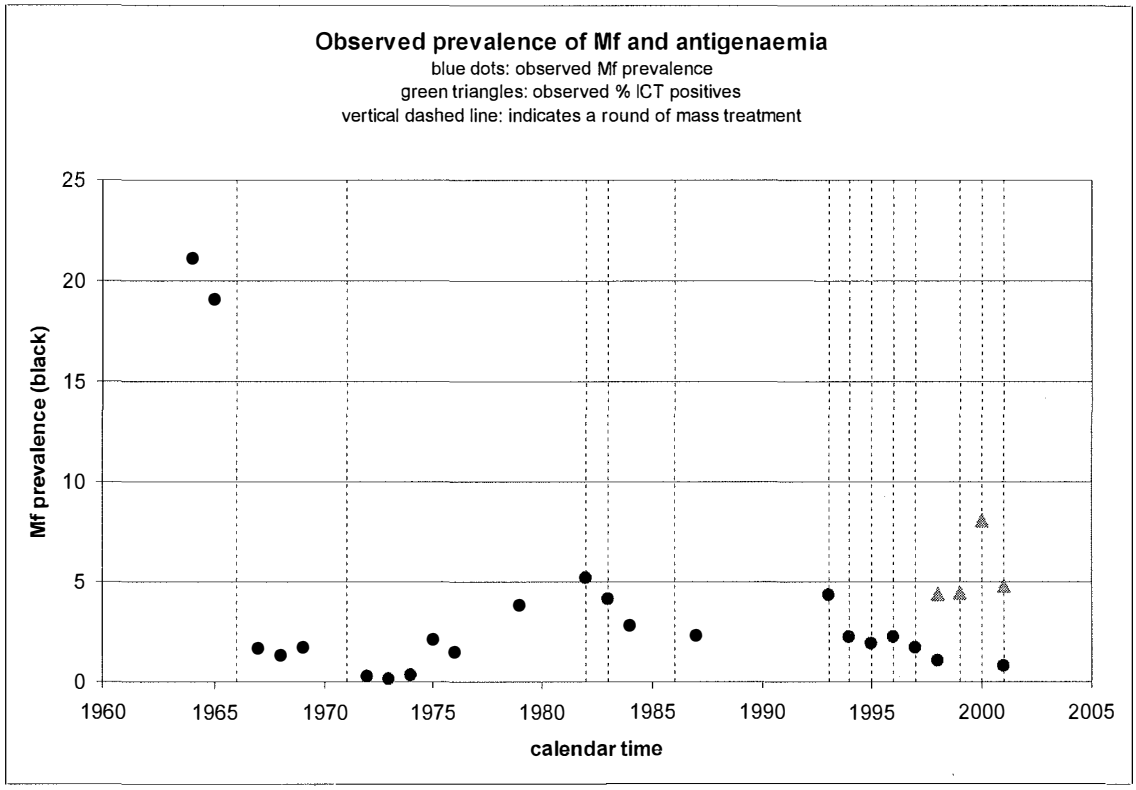
3 Exploratively fitting LYMFASIM to data from Samoa

Samoa has a long history of control. After a long period of irregular mass treatment, mass treatment took place regularly with a single dose of DEC, DEC+ivermectin or DEC+albendazole from 1993 onwards. Mf prevalence has been reduced considerably since then and the question is whether treatment should be continued longer.

3.1 Data available for Samoa

For this explorative fit-exercise we used data on the trend in Mf prevalence from 1964 – 2001. In this period 13 rounds of mass treatment took place. See figure 2 and appendix I.

Figure 1. Observed trend in Mf prevalence in Samoa



NB.
In simulating the effects of mass treatment: be aware that different diagnostic tests have been used.
- Surveys in 1964 and 1966, 1967: Mf counts in 20 µl blood
- other surveys: Mf counts in 60 µl blood

In the current version of LYMFASIM it is not possible to simulate surveys with different diagnostic tests. This means that in assessing the precontrol situation, we need to simulate surveys based on 20 µl blood smears; in that case the Mf prevalence from 1963 may be slightly underestimated. In assessing the trend over time, we need to simulate surveys with 60 µl blood smears; in that case the Mf prevalence until 1967 may be slightly overestimated!

Striking features in the trend in Mf prevalence:
- 1st and 2nd round of multiple dose mass drug treatment were extremely effective
- in spite of extremely effective mass treatment recrudescence occurs within 10 years after the 2nd round of mass treatment
- impact of single dose treatment (from 1982 onwards) is lower than impact of multiple dose mass treatment (1966 and 1971)
- high antigen prevalence in 2000 ➔ based on a selection of villages with highest levels of antigen prevalence in 1999!

These observations should be reproduced by our model and may give an indication of the factors that are different in Pondicherry and Samoa.

Background information can be found in Kimura et al (1992) [6]. In addition, more detailed information is available for the years from 1982 onwards about the treatment coverage and Mf surveys.

3.2 Adapting the Pondicherry quantification to reflect the situation in Samoa

Starting from the Pondicherry quantification for a model with anti-L3 immunity, we aimed to adapt parameters so that the model predictions reasonably fit to the observed trend in Mf prevalence in Samoa. Table 1 lists some differences between the situations in the two areas that should be taken into account.

Table 1. Differences between Pondicherry and Samoa in endemic situation

	Samoa	Pondicherry	source
precontrol Mf prevalence	20%	8.50%	data Samoa
age-prevalence curve	plateau from 30 or 40 years of age	peak in young adults	age-prevalence review, unpublished data VCRC/EUR
parasite species	W. bancrofti (subperiodic, diurnal)	W. bancrofti (nocturnal)	[4]
mosquito-species	Aedes species	Culex quinquesfasciatus	[4]
uptake curve	limitation	some limitation	[5]
efficiency of transmission	(lower in Asia / Oceania than in Africa)		[5]

Adapting the Pondicherry quantification for Samoa is not straightforward, because:
- there remains uncertainty about the model structure (does acquired immunity play a role?);

- both the vector and parasite species in Samoa are different from the vector and parasite in Pondicherry. This leaves us with a large number of parameters that can be varied to obtain a good fit to Pondicherry:
  - variables related to human population and measurement of Mf density
    - demography
    - age-sex specific exposure to mosquitoes
    - variation in exposure
    - k-parameter of binomial distribution
  - variables related to the parasite
    - Mf production by adult worms
    - lifespan of adult worms
    - Mf survival
    - the proportion of inoculated L3-larvae that successfully develops into adult worms
  - entomological variables
    - monthly biting rate
    - relation between Mf density in human blood and number of L3 developing in the mosquito)
    - the proportion of L3 released when a mosquito bites

Furthermore, accurate estimates of the efficacy of the different treatment regimens used in Samoa are not available.

3.3 Results: simulations with the Pondicherry-quantification adapting only input on mass treatment and treatment efficacy

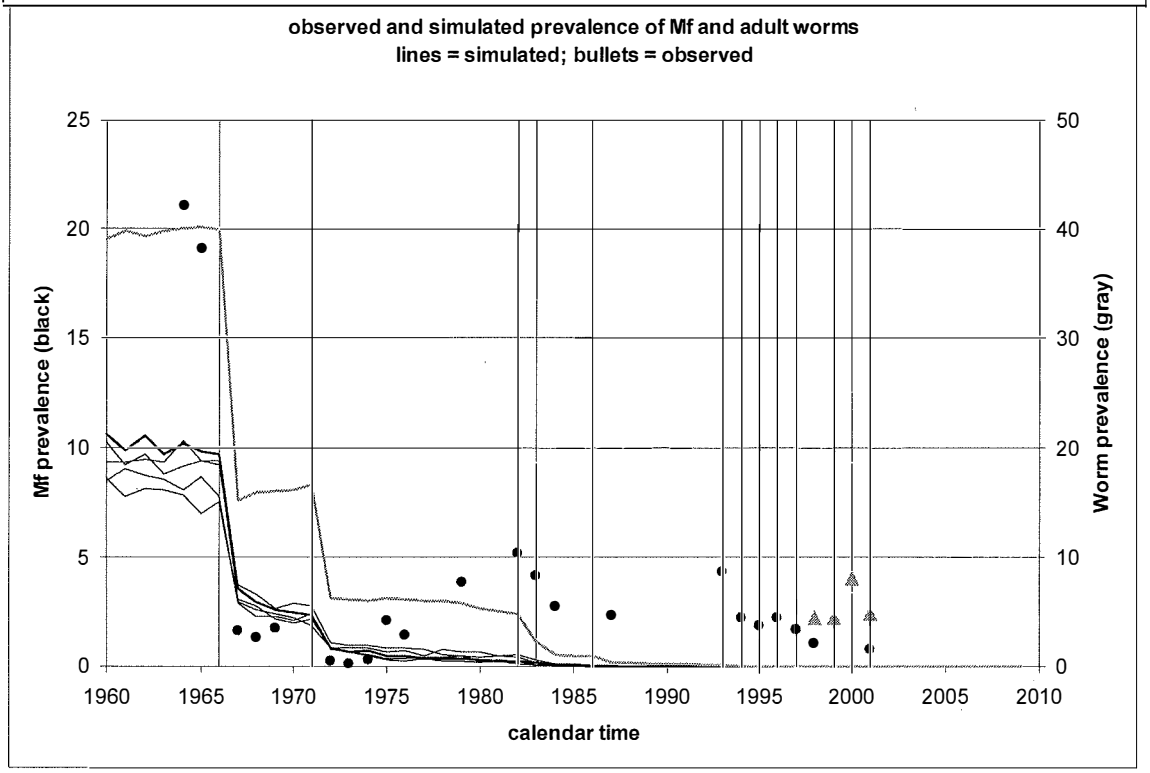
In our first simulations, we used the Pondicherry-quantification for the anti-L3 variant of the LYMFASIM simulation model. We only adapted the input on mass treatment (regimen and coverage) to be the same as in Samoa, but left all other parameters unchanged. Estimates for treatment efficacy for the different treatment regimens applied in Samoa were based on the best available estimates for the efficacy of a standard course of DEC (12 days 6 mg/kg), for a single dose DEC (6 mg / kg), and for a single dose ivermectin (400µg/kg). These estimates have been obtained by model-based analysis of data from Tanzania [Meyrowitsch, 1998 #55] and India [Subramanyam Reddy, 2000 #788] (unpublished data: appendix to TDR report 1998 (project ID 970817); the model was described in [Plaisier, 1999 #690]). Estimates for the combination treatment regimens (DEC + ivermectin, DEC + albendazole) are not yet available for multiple dose DEC treatment, but were obtained by adapting the quantification for the single drug treatment regimens. Appendix II lists the assumptions on efficacy of treatment on adult worms and Mf for the different treatment regimens that have been used in Samoa. Treatment coverage was assumed to be 80% when no information was available.

The results of simulations with the Pondicherry quantification are shown in figure 3. Clearly, the Pondicherry quantification does not correctly reproduce the data from Samoa:

1. the simulated precontrol prevalence is far too low
2. although the prevalence levels after treatment are actually higher than observed, the simulations do not reproduce the observed recrudescence in infection transmission some years after the 1st, 2nd and 5th rounds of mass treatment.
3. the simulated effectiveness of treatment in the 1st and 2nd round is too low; the observations show a much steeper decrease in Mf prevalence than the simulation results.

4. In our simulations infection was already eliminated in 1985, while the observations show continued transmission up to 2001.

Figure 2. Observed and simulated trends in mf prevalence - Pondicherry quantification



3.4 Results: adapting the Pondicherry quantification

First of all, the model quantification should be adapted so that the precontrol prevalence is about 20%. For this purpose we varied:

- monthly biting rate (mbr):

By varying the mbr a prevalence level of 20% was not achieved: even with a five fold increase in mbr from 2200 → 10000, the precontrol prevalence does not reach a higher level than 15%. However, with this higher mbr the recrudescence after mass treatment does occur in our simulations. From 1995 onwards, the simulated Mf prevalence is lower than observed, and the simulations seems to result in elimination, while the observed Mf prevalence was about 1%. (See figure 4a).
Conclusion: probably the immune regulating of infection intensity in the human hosts is too strong, thus limiting the overall prevalence of infection.

- duration of immune response:

Since the role of acquired immunity already is questionable, this is the second parameter that we tried to adapt. The mbr was set at its "Pondicherry"-value of 2200 bites/ adult person/ month. When the duration of immunity is reduced from 9.6 years to 4.0, the precontrol prevalence increased to about 16%. Recrudescence after cessation of mass treatment

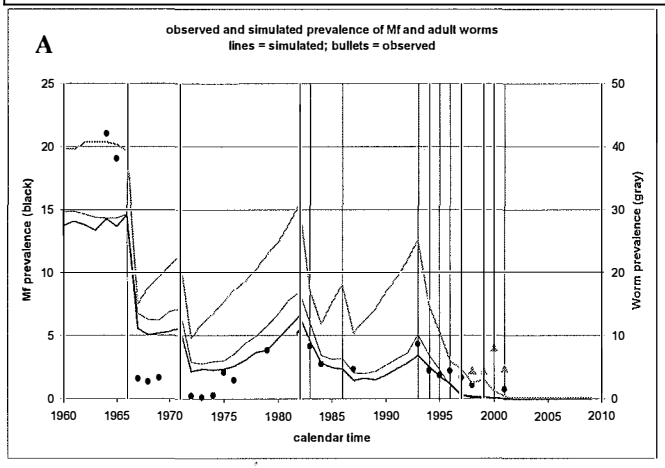
occurred, but less pronounced than observed. With a further reduction in the duration of immunity to 3 years, the precontrol prevalence was increased to about 20%. However, little recrudescence occurs and the predictions from 1995 onwards are too optimistic. See figure 4b.

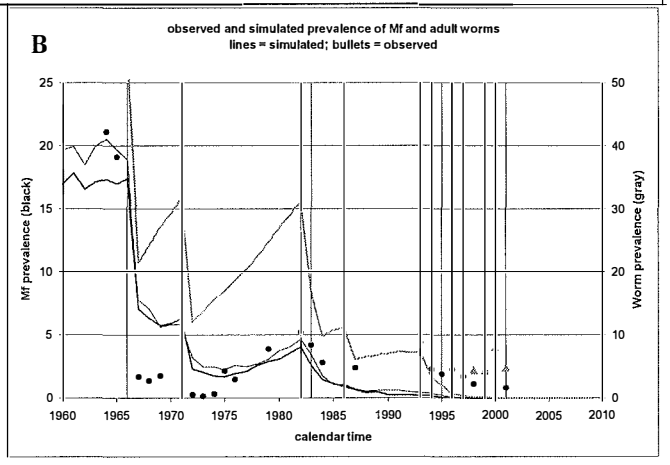
Conclusion: the precontrol Mf prevalence is quite sensitive to changes in the duration of immunological memory. By changing this parameter, the precontrol prevalence was increased to levels of about 25%.

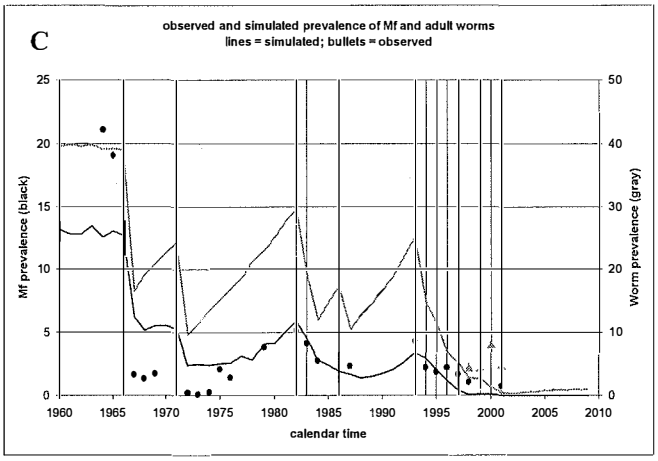
- uptake curve, i.e. relation between Mf density in human blood and number of L3 developing in the mosquito

The uptake curve for Pondicherry was based on experimental data. It is known that mosquito-species vary in efficiency of transmission. And *Aedes*-species, that are responsible for transmission of LF in Samoa, are known to show limitation, meaning that the vector very efficiently transmits infection when Mf density in the blood is low, but becomes less efficient when Mf density is high. The higher efficiency at low Mf densities could explain the recrudescence of transmission after reduction of Mf prevalence to almost 0%. If we change the uptake curve so that "limitation" is stronger (i.e. efficiency at low Mf density higher), indeed, recrudescence occurs in our simulations. The precontrol prevalence in this simulation, though, is far too low. See figure 4c (mbr here was 4000).

Figure 2. Selected simulation results. See text for explanation.







Other ways to get a better fit of the precontrol situation:

- excluding immunity: given the uncertainty around the role of acquired immunity, this would be an interesting option. However, this would require requantification of many other parameters of the biological core of the LYMFASIM simulation model. When we exclude immunity without requantification of other parameters the precontrol prevalence "explodes" and reaches prevalence levels of 80-85%.
- change in parameters on parasite development in vector and human host: e.g. % of L3 larvae released when a mosquito bites, or the proportion of inoculated larvae that successfully develops into adult worms.

All possibly relevant factors should be considered in combination to find the best fitting model quantification. This takes much time and is difficult to do manually.

4 Discussion of preliminary results

We did not yet find a model that correctly reproduces the observed trends in Mf prevalence in Samoa. Below we'll discuss the problems in fitting the model to the precontrol Mf prevalence, in mimicking the effectiveness of mass treatment, and in reproducing the observed trend in Mf prevalence and especially the strong recrudescence that occurred within a few years after a single round of mass treatment.

4.1 Fitting LYMFASIM to the precontrol Mf prevalence level by changing the monthly biting rate

We expect monthly biting rate (mbr) to be an important determinant of variation in endemicity levels in areas with the same vector parasite combination. Our analyses show that the impact of changes in monthly biting rate on endemicity level is very limited. Even with a monthly biting rate of 20000, Mf prevalence levels did not increase above 15%. Probably, the impact of mbr on Mf prevalence is limited by the strong immune response that regulates infection intensity in the human host. This indicates a potential problem in the Pondicherry quantification: with the current model structure and quantification of "biological" parameters it will be difficult to explain high Mf prevalence levels, which may also occur in areas surrounding Pondicherry. This may indicate that the assumed impact of host immunity in LYMFASIM is too strong.
NB. For fitting LYMFASIM to data from Samoa, the monthly biting rate is not the only factor that would have to be adapted. By adapting other parameters in the transmission of LF as well, it will be possible to reproduce the higher Mf prevalence levels.

4.2 Mimicking the effects of mass treatment

The 1st and 2nd round of multiple dose mass drug treatment were extremely effective; in spite of extremely effective mass treatment recrudescence occurs within 10 years after the 2nd round of mass treatment. This is difficult to explain in LYMFASIM.

Our estimates for the efficacy of multiple dose treatment were obtained in a model-based analysis of data from a village in Tanzania were mass treatment with standard course DEC (12 days, 6 mg/ kg DEC) was carried out [Meyrowitsch, 1998 #55]. Furthermore, a coverage level of 80% was assumed, which is very high especially for a multiple dose treatment regimen. With these assumptions, LYMFASIM failed to reproduce the observed strong decline in Mf prevalence. This could indicate that the coverage and/or the efficacy of multiple dose treatment are more effective than assumed. The question is whether a model, which correctly simulates the strong decline in Mf prevalence after treatment, would be able to reproduce the fast recurrence of infection in the subsequent years.

4.3 Problems in reproducing observed trends in Mf prevalence and especially the strong recrudescence that is observed

Of peculiar aspect in the data from Samoa is the strong and rapid recurrence of transmission after a single round of mass treatment. Even when Mf prevalence was reduced to almost 0% recrudescence occurred. LYMFASIM with the Pondicherry failed quantified to reproduce the observed recrudescence in transmission after 1st, 2nd and 5th round is important. There are several possible explanations for this failure:

- there can be problems in the data itself;
- the model quantification may have to be adapted for Samoa because of actual differences between the two areas;
- the model structure may be wrong.

The quality of data should be assessed before fitting the model, because there may be problems with the interpretation of data. When the survey data are not representative for the entire population, then observed trends may be biased and a good model would not be able to reproduce these trends. This can be the case if only few villages from Samoa were included in the survey (which actually happened in the last surveys). Furthermore, trends in Mf prevalence may be biased when the characteristics of diagnostic tests used in the different surveys is not the same, e.g. because better tests have become available. Another pitfall in monitoring of mass treatment appears when Mf surveys are carried in those persons who were treated previously: people who do not get treated, are also not included in the Mf survey. These people may continue to provide a pool of Mf for transmission, while the observed Mf prevalence in the survey was already very low.
The failure of the Pondicherry-quantification of LYMFASIM in reproducing the observed recrudescence could be explained by actual differences in transmission between Pondicherry and Samoa. These differences are such that recrudescence occurs much sooner in Samoa than in Pondicherry. This can be explained by higher monthly biting rates, by more efficient transmission by the vector, by a lower level of immunity in the population, or other factors. A more extensive fit-procedure would be required to simultaneously quantify local parameters and parameters that are specific for the vector-parasite combination. If the model structure is valid, than the model would be able to explain data from Samoa after requantification of these parameters.
Possibly the model still does not explain the data from Samoa, even after requantification of local parameters. This would mean that the model structure does not accurately mimic the transmission of *Wuchereria bancrofti*. If so, predictions based on the quantification for Pondicherry may give wrong results and our predictions of the number of treatment rounds and coverage required for achieving elimination in this area may be incorrect [7].

4.4 Concluding remarks

Based on this explorative analysis no conclusions can be drawn on the model structure and its quantification, but our results clearly raise some important points for discussion. Firstly, the data per se show that achieving elimination in Samoa may be difficult, because recrudescence occurs even after reduction of Mf prevalence to levels below 1%. We should be aware that there could be differences in transmission dynamics between regions, which may have enormous consequences for the risk of recrudescence after cessation of control and the probability of achieving the goal of elimination. The general idea that 4-6 treatment rounds can be sufficient to achieve elimination in any area has to be abandoned.

Our analysis did not result in a model quantification that can be used to reliably predict the effects of mass treatment and to calculate the probability of elimination in Samoa. In all preliminary simulations, the Mf prevalence in our simulations was lower than was observed, which means that long-term predictions would probably be too optimistic.

References

1. Plaisier, A.P., et al., *The LYMFASIM simulation program for modeling lymphatic filariasis and its control.* Methods of Information in Medicine, 1998. **37**: p. 97-108.
2. Habbema, J.D., et al., *The microsimulation approach to epidemiologic modeling of helminthic infections, with special reference to schistosomiasis.* Am J Trop Med Hyg, 1996. **55**(5 Suppl): p. 165-9.
3. Subramanian, S., et al., *The dynamics of Wuchereria bancrofti infection in the population of Pondicherry, India: a model-based analysis of longitudinal data.* submitted for publication.
4. WHO, *Lymphatic filariasis: the disease and its control. Fifth report of the WHO Expert Committee on Filariasis.* World Health Organ Tech Rep Ser, 1992. **821**: p. 1-71.
5. Southgate, B.A., *Intensity and efficiency of transmission and the development of microfilaraemia and disease: their relationship in lymphatic filariasis.* J Trop Med Hyg, 1992. **95**(1): p. 1-12.
6. Kimura, E., et al., *Long-term efficacy of single-dose mass treatment with diethylcarbamazine citrate against diurnally subperiodic Wuchereria bancrofti: eight years' experience in Samoa.* Bull World Health Organ, 1992. **70**(6): p. 769-76.
7. Stolk, W.A., et al., *Prospects of elimination of bancroftian filariasis by mass drug treatment in Pondicherry, India: a simulation study.* submitted for publication.

Appendix I. Data from Samoa

YEAR	MDA	Treatment	Blood Survey				Coverage
	round		n	Mf %	Mf density	ICT %	%
1928				37			
1964			2,077	21.1	19*		
1965			10,129	19.1	24*		
1966	1	DEC (12-18 doses)					
1967			42,697	1.63	2.7*		
1968			5,371	1.32	4.8		
1969			7,393	1.74	7.6		
1970							
1971	2	DEC (12-18 doses)					
1972			6,361	0.24			
1973			5,145	0.14			
1974			30,272	0.33			
1975			11,499	2.12			
1976			3,649	1.43			
1977							
1978							
1979			8,385	3.83	18.6		
1980							
1981							
1982	3	DEC (6mg/Kg) single dose	10,361	5.21	20.2		
1983	4	DEC (6mg/Kg) single dose	9,627	4.17	9.4		
1984			11,146	2.76	9.8		
1985							
1986	5	DEC (6mg/Kg) single dose					
1987			13,708	2.33	9.2		
1988							
1989							
1990							
1991							
1992							
1993	6	DEC (6mg/Kg) single dose	10,256	4.33	11.8		84.0
1994	7	DEC (6mg/Kg) single dose	10,112	2.23	11.7		67.0
1995	8	?	4,551	1.89	6.8		80.0
1996	9	DEC (6mg/Kg) + Ivermectin (200ug/Kg)	5,997	2.22	11.5		79.0
1997	10	DEC (6mg/Kg) + Ivermectin (200ug/Kg)	8,305	1.7	8.9		85.0
1998			4,054	1.06	5.5	4.4	
1999	11	DEC (6mg/Kg) + Albendazole (400 mg)	7,006			4.5	90.5
2000	12	DEC (6mg/Kg) + Albendazole (400 mg)	404			8.1	93.6
2001	13	DEC (6mg/Kg) + Albendazole (400 mg)	1,392	0.78		4.8	68.4
Volume of blood smear was 60 mm3, but only 20 mm3 if marked (*)							

Appendix II Efficacy estimates used in our simulations

	standard course DEC *	sd DEC *	sd DEC *	6mg/Kg DEC + 200µg/Kg ivermectin **	DEC (6mg/Kg) + Alb (400 mg)_1 ***
% mf killed					
- fraction with no effect	0.00	0.28	0.18	0.00	0.20
- fraction with 100% effect	0.57	0.12	0.25	0.37	0.20
- beta distribution remaining: mean	0.85	0.71	0.51	0.91	0.80
- beta distribution remaining: alpha1	5.34	2.94	1.24	10.00	2.94
% worms killed:					
- fraction with no effect	0.08	0.08	0.06	0.08	0.05
- fraction with 100% effect	0.59	0.32	0.51	0.32	0.40
- beta distribution remaining: mean	0.70	0.56	0.60	0.56	0.65
- beta distribution remaining: alpha1	1.98	0.80	1.39	0.80	0.80
% irreversible fecundity reduction					
- fraction with no effect				0.00	
- fraction with 100% effect				0.56	
- beta distribution remaining: mean				0.70	
- beta distribution remaining: alpha1				1.64	

* Estimates are based on model-based analysis of data from DBL or VCRC; see appendix to TDR report 1998; see appendix to TDR report 1998 (project ID 970817)

** Based on efficacy estimates for single dose with either DEC or ivermectin based on data from VCRC;
- efficacy on Mf is set equal to efficacy of single dose of ivermectin as was estimated based on VCRC data
- efficacy on % adult worms killed is set equal to efficacy of sd DEC as was estimated based on VCRC data
- efficacy on fecundity reduction is set equal to efficacy of sd ivermectin as was estimated based on VCRC data

*** Adaptation of estimate of efficacy of sd DEC.