# S1 Supporting Information. Lymphatic filariasis model descriptions and Monte Carlo p-values for pre- and post-MDA data.

**EPIFIL model description and methods**

## The mathematical model of LF transmission dynamics

We employed a genus specific mosquito-vectored transmission model of LF to carry out the modelling work in this study 1-7. Briefly, the state variables of this hybrid coupled partial differential and differential equation model vary over age (*a*) and/or time (*t*), representing changes in the pre-patent worm burden per human hostadult worm burden per human hostthe microfilariae (mf) level in the human host modified to reflect infection detection in a 1 mL blood samplethe average number of infective L3 larval stages per mosquito (*L*), and a measure of immunitydeveloped by human hosts against L3 larvae; and intensity of Circulating Filarial Antigen (CFA) (denoted by *A(a, t))*. The state equations comprising this model are:



The above equations involve partial derivatives of four state variables (*P* - pre-patent worm load; *W* - adult worm load; *M* - microfilaria intensity; *I* - immunity to acquiring new infection due to the pre-existing total worm load; *A* - intensity of CFA where *WT = W(a,t) + P(a,t)*). Given the faster time scale of infection dynamics in the vector compared to the human host, the infective L3-stage larval density in mosquito population is modelled by an ordinary differential equation essentially reflecting the significantly faster time-scale of the infection dynamics in the vector hosts. This allows us to make the simplifying assumption that the density of infective stage larvae in the vector population reaches a dynamic equilibrium (denoted by *L\**) rapidly1, 2, 5, 8, 9. This basic coupled immigration-death structure of the model as well as its recent extensions has been extensively discussed previously1-3, 5, 8, 9. The effects of worm patency are captured by considering that at any time *t*, human individuals of age less than or equal to the pre-patency period, *τ*, will have no adult worms or mf, and the rate at which pre-patent worms survive to become adult worms in these individuals at *a > τ* is given by . The term enables us to account for the different establishment and development rates of the incoming L3-stage larvae as adult worms depending on the genus of mosquito vectors as expressed below:

 for mosquitoes of *Anopheline* genus;

for mosquitoes of *Culicine* genus.

In the above,  is the shape parameter of the negative binomial distribution on the mf uptake whereas r and are respectively the rate of initial increase and the maximum level of L3 larvae. See Table 1 for the description of all the model parameters and functions.

**Table 1** - **Description of EPIFIL model parameters and functions.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **Definition (*units*)** | **Range** | **Refs** |
| ***λ*** | Number of bites per mosquito (*per month*) | [5, 15] | 1, 2, 5, 10, 11 |
| ***τ*** | Pre-patency period | [1, 9] | 12 |
| ***s*** | Proportion of female worms | 0.5 | - |
| ***μ*** | The worm mortality rate (*per month*) | [0.008, 0.018] | 1, 2, 5, 13-16 |
| ***α*** | Production rate of microfilariae per worm (*per month*) | [0.25, 1.5] | 1, 2, 5, 17 |
| ***γ*** | The death rate of the microfilariae (*per month*) | [0.08, 0.12] | 1, 5, 15, 17 |
| ***α2*** | Production rate of CFA (*per worm per month*) | [2, 8] | This study |
| ***γ2*** | Decay rate of CFA (*per month*) | [0.4, 0.5] | This study |
| ***g*** | Proportion of mosquitoes which pick up infection when biting an infected host | [0.251, 0.485] | 1, 5, 18 |
| ***κ*** | Maximum level of L3 given Mf density | [3, 5] | 1, 5 |
| ***k0*** | The basic location parameter of negative binomial distribution used in aggregation parameter  () | [0.000036, 0.000775] | 1, 5, 19, 20 |
| ***δ*** | Immunity waning rate (*per month*) | [0.001, 0.01] | 1, 5 |
| ***V/H*** | Ratio of number of vector to hosts |  | data |
| ***kLin*** | The linear rate of increase in the aggregation parameter defined above | [0.00000024, 0.282] | 1, 5, 19, 20 |
| ***σ*** | Death rate of mosquitoes (*per month*) | [1.5, 8.5] | 1, 5, 20 |
| ***ψ1*** | Proportion of L3 leaving mosquito per bite | [0.1, 0.8] | 17 |
| ***ψ2*** | The establishment rate1 | [0.00003, 0.00364] | 1, 2, 5, 21 |
| ***HLin*** | A threshold value used in*h(a)*to adjust the rate at which individuals of age *a* are bitten: linear rise from 0 at age zero to 1 at age *HLin* in years. | [240, 360] months | 1, 5, 9 |
| ***r*** | Gradient of Mf uptake2 | [0.04, 0.25] | 1, 5 |
| ***c*** | Strength of acquired immunity | [0.015, 0.025] | 1, 5 |
| ***IC*** | Strength of immunosuppression3 | [0.5, 5.5] | 1, 5 |
| ***SC*** | Slope of immunosuppression function4  (*per worm/month*) | [0.01, 0.20] | 1, 5 |
| ***Intervention-related parameters*** | | | |
| ***ω*** | Worm killing efficacy of drug (instantaneous) | dependent on drug regimen | 3 |
| ***ε*** | Microfilariae killing efficacy of drug (instantaneous) | dependent on drug regimen | 3 |
| ***δreduc*** | Reduction in the worm’s fecundity over a period of time *p* due to drug | dependent on drug regimen | 3 |
| ***p*** | A time period during which the drug remains efficacious in reducing the fecundity of the surviving adult worms | dependent on drug regimen | 3 |
| ***C*** | Percentage of the population administered the drug | data | data |
| ***MBRVC*** | Vector control (VC) modifies () where  , withfor when VC is implemented, otherwise. | data and estimates | 19, 20 |
| **Description** | **Mathematical expressions of the functions** | **Parameters** |  |
| Probability that an individual is of age *a****π(a)*** |  | Human age *a* in month, *A0*and *B0*estimated from country demographic data | 1, 5, 9 |
| Larvae establishment rate (modified by acquired immunity) ***Ω(a,t)*** |  | - proportion of L3 leaving mosquito per bite; - the establishment rate1 | - |
| Adult worm mating probability ***ϕ(W,k)*** |  | *k* – negative binomial aggregation parameter | 2, 5, 22 |
| Immunity to larval establishment ***g1(I)*** |  | *c* – strength of immunity to larval establishment | 1, 5 |
| Host immunosuppression  ***g2(WT)*** |  | *IC* – strength of immunosuppression;  *SC* – slope of immunosuppression | 1, 5 |

1The proportion of L3-stage larvae infecting human hosts that survive to develop into adult worms2.

2The gradient of Mf uptake *r* is a measure of the initial increase in the infective L3 larvae uptake by vector as *M* increases from 02, 9.

3 The facilitated establishment rate of adult worms due to parasite-induced immunosuppression in a heavily infected human host

4 The initial rate of increase by which the strength of immunosuppression is achieved as *W* increases from 023.

# Note MBR (monthly biting rate) serves as an input to initialize the model, measured as mosquito bites per person per month, the value of which may be obtained from entomological surveys conducted in study sites. In the absence of the observed MBR value, the model has been adapted to estimate it from the community-level Mf prevalence data.

## Modeling intervention by mass drug administration

Intervention by mass drug administration was modeled based on the assumptions that anti-filarial treatment with a combination drug regimen act by killing certain fractions of the populations of adult worms and microfilariae instantly after the drug administration24. These effects are incorporated into the basic model by calculating the population sizes of worms and microfilariae as follows:



where *dt* is a short time period since the *i*th MDA was administered. During this short time interval, a given proportion of adult worms and microfilariae are instantly removed. The parameters *ω* and *ε* are drug killing efficacy rates for the two life stages of the parasite while the parameter *C* represents the MDA coverage. Apart from instantaneous killing of microfilariae, the drug continues to kill the newly reproduced mf by any surviving adult worms at a rate *δreduc* for a period of time, *p*. We model this effect as follows:



We simulated LF intervention by running the model with fixed values of *ε*, *δreduc*, and *p* (here δreduc=1) for MDA coverage levels given by data. The worm-kill parameter, *ω*, was drawn from a uniform prior distribution such that the post-intervention data could inform this efficacy value. The first MDA round was implemented in the model by affecting the population sizes of worms and microfilariae from the baseline fits, and then the intervention is simulated forward in time for a number of years, with subsequent MDA rounds implemented annually.

## Modeling intervention by Vector Control

In addition to MDA, we also modeled the added effect of long-lasting insecticidal nets (LLINs) as described previously6. The impact of LLINs with three main actions against mosquito biting was modelled: 1) deterrence from entering the home (efficacy ), 2) inhibition of their ability to feed on humans (efficacy ), and 3) killing them (efficacy )25,26. To capture these effects, which decay over time as the larvicide efficacy declines exponentially at rate Λ, we adjust the term V/H to be appropriately modified according to the population coverage for LLINs ():

**Table 2. Monte Carlo p-values for pre- and post-MDA data.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Age-stratified and overall Monte Carlo p-values for baseline data** | | | | | | | | | |
|  | **0-9** | **10-19** | **20-29** | **30-39** | **40-49** | **50-59** | **60-69** | **70-79** | **Overall** |
| **DokanTofa** | 0.012 | 0.988 | 0.396 | 0.882 | 0.966 | 0.677 | 0.535 | 0.111 | 0.135 |
| **Piapung** | 0.026 | 0.055 | 0.031 | 0.315 | 0.315 | 0.002 | 0.48 | 0.125 | 0.011 |
| **Missasso** |  |  |  |  |  |  |  |  | 0.149 |
| **Kirare** |  |  |  |  |  |  |  |  | 0.022 |
| **Peneng** |  |  |  |  |  |  |  |  | 0.878 |
| **Dozanso** |  |  |  |  |  |  |  |  | 0.215 |
|  | ***MDA round wise and overall Monte Carlo p-values for post MDA data*** | | | | | | | | | |
|  | **1st** | **2nd** | **3rd** | **4th** | **5th** | **6th** | **7th** | **8th** | **Overall** |
| **DokanTofa** |  |  | 1.0 | 0.974 | 1.0 | 0.907 | 0.977 |  | 1.0 |
| **Piapung** |  |  | 1.0 | 1.0 | 1.0 |  | 1.0 |  | 1.0 |
| **Missasso** | 0.91 |  |  |  |  |  | 0.884 |  | 0.815 |
| **Kirare** | 0.99 | 0.994 | 1.0 |  | 1.0 | 0.986 | 0.998 |  | 0.972 |
| **Peneng** | 0.761 | 0.938 | 0.249 | 0.122 | 0.508 | 0.273 |  |  | 0.671 |
| **Dozanso** | 0.952 |  |  |  |  |  | 0.878 |  | 0.865 |

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