

Supplementary Information

Substantiating freedom from parasitic infection by combining transmission model predictions
with disease surveys

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Supplementary Table 1. Results from the onchocerciasis PFFI analyses where Se=0.85 and Sp=0.95.

Focus (transmission status)	Village	Year	Probability of null hypothesis, P_0	Probability of alternative hypothesis, P_a	Confidence of freedom	Classification ^a
Mt. Elgon (interrupted)	Bubungi	2005	0.023	0.986	0.977	Y
		2011	0.002	1.000	0.998	Y
	Bunabutiti	2005	0.002	1.000	0.998	Y
		2011	0.009	0.998	0.991	Y
	Bunambatsu	2005	0.035	0.987	0.965	Y
		2011	0.006	0.999	0.994	Y
	Buriri	2005	0.003	0.999	0.997	Y
		2011	0.125	0.961	0.875	insufficient evidence
Madi Mid North (ongoing)	Andra	2004	0.814	0.241	0.186	insufficient evidence
	Madulu	2004	0.167	0.878	0.833	insufficient evidence
		2011	0.052	0.971	0.948	insufficient evidence
	Masaloa	2004	0.317	0.778	0.683	insufficient evidence
	Palaure Pacunaci	2004	0.999	0.001	0.001	N

^a Y= free from infection, N= not free from infection

Supplementary Table 2. Description of model parameters.

Parameter	Definition (units)	Parameter Range		References
		Lymphatic Filariasis Model	Onchocerciasis Model	
λ	Number of bites per vector (per month)	[5, 15]	$= \frac{H_b}{g}$	1, 2, 3, 4, 5
H_b	Human blood index	-	[0.3, 0.99]	6, 7, 8, 9, 10
g	Period of gonotrophic cycle (months)	-	[0.067, 0.13]	8, 9, 11, 12
V/H	Ratio of number of vectors to hosts	MBR^1 / λ	MBR^1 / λ	data
H_{Lin}^2	Threshold value used in $h(a)$ to adjust the age-dependent exposure rate (months)	[240, 360]	[12, 240]	1, 3, 13
A^2	Coefficient describing population age distribution in $\pi(a)$	data	data	data
B^2	Coefficient describing population age distribution in $\pi(a)$	data	data	data
ψ_1	Proportion of L3 leaving vector per bite	[0.1, 0.8]	[0.12, 0.7]	8, 9, 10, 11, 14, 15
ψ_2	Larval establishment rate ³	[0.00003, 0.00364]	[0.02, 0.0854]	1, 2, 3, 8, 9, 10, 11, 16
c	Strength of acquired immunity	[0.015, 0.025]	[0.0001, 0.001]	1, 2, 3, 17, 18
I_C	Strength of immunosuppression ⁴	[0.5, 5.5]	[0.5, 5.5]	1, 2, 3, 17, 18
S_C	Slope of immunosuppression function ⁵ (per worm/month)	[0.01, 0.20]	[0.1, 0.75]	1, 2, 3, 17, 18
δ	Immunity waning rate (per month)	[0.001, 0.01]	[0.00001, 0.0001]	1, 2, 3, 17, 18
μ_w	Worm mortality rate (per month)	[0.008, 0.018]	[0.0083, 0.0104]	1, 2, 3, 8, 9, 10, 11, 15, 19, 20, 21, 22
τ	Pre-patency period (months)	[1, 9]	[9, 26]	11, 15, 23, 24
k_0	Basic location parameter of negative binomial distribution used in k	[0.000036, 0.000775]	[0.00036, 0.0044]	1, 2, 3, 25, 26
k_{Lin}	Linear rate of increase in k	[0.00000024, 0.282]	[0.00000024, 0.282]	1, 2, 3, 25, 26
s	Proportion of female worms	0.5	0.5	-
α	Production rate of microfilariae per worm (per month)	[0.25, 1.5]	[0.25, 1.5]	1, 2, 3, 8, 9, 10, 11, 14, 15
γ	Microfilariae mortality rate (per month)	[0.08, 0.12]	[0.08, 0.12]	1, 3, 8, 9, 10, 11, 14, 15, 21
b	Proportion of vectors which pick up infection when biting an infected host	[0.251, 0.485]	[0.259, 0.481]	1, 3, 8, 9, 10, 11, 27
κ	Maximum level of L3 given Mf density	[3, 5]	[1.16, 2.00]	1, 3, 28, 29
r	Gradient of Mf uptake ⁶	[0.04, 0.25]	[0.01, 0.0495]	1, 3, 28, 29
σ	Vector mortality rate (per month)	[1.5, 8.5]	[1.5, 8.5]	1, 3, 8, 9, 10, 11, 26
σ_e	Excess vector mortality due to mf infection (per month)	-	[0.75, 4.25]	30
σ_L	Larval mortality rate	-	[0.33, 1.16]	8, 9, 10, 11

¹Note MBR (monthly biting rate) serves as an input to initialize the model, measured as 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.

²The parameters A , B , and H_{Lin} are estimated from national human demographic data or from the age-prevalence data.

³The proportion of L3-stage larvae infecting human hosts that survive to develop into adult worms ².

⁴The facilitated establishment rate of adult worms due to parasite-induced immunosuppression in a heavily infected human host.

⁵The initial rate of increase by which the strength of immunosuppression is achieved as W increases from 0 ¹⁸.

⁶The gradient of Mf uptake r is a measure of the initial increase in the infective L3 larvae uptake by vector as M increases from 0 ^{2, 13}.

Supplementary Table 3. Description of model functions and functional forms.

Function	Functional form
$h(a)$: age-dependent exposure rate	$= \begin{cases} \frac{a}{H_{Lin}} & \text{for } a < H_{Lin} \\ 1 & \text{for } a \geq H_{Lin} \end{cases}$
k : parasite aggregation	$= k_0 + k_{Lin} \overline{M(a,t)}$
ζ : rate of pre-patent worm maturation	$= e^{-\mu\tau}$
$\phi[W(a,t), k]$: worm mating probability	$= 1 - \left(1 + \frac{W}{2k}\right)^{-(1+k)}$
$\pi(a)$: population age distribution	$= Ae^{(-Ba)}$
$f[M(a,t), k]$: Vector Mf uptake response	$= \begin{cases} \frac{2}{\left[1 + \frac{M(a,t)}{k} \left(1 - e^{-\frac{r}{\kappa}}\right)\right]^k} - \frac{1}{\left[1 + \frac{M(a,t)}{k} \left(1 - e^{-\frac{2r}{\kappa}}\right)\right]^k} & \text{for vectors with cibarial armature (i.e. Culex mosquitoes)} \\ \left[1 + \frac{M(a,t)}{k} \left(1 - e^{-\frac{r}{\kappa}}\right)\right]^{-k} & \text{for vectors without cibarial armature (i.e. Anopheles mosquitoes, Simulium damnosum/Simulium neavei blackflies)} \end{cases}$
Φ : larval establishment rate	$= \lambda \frac{V}{H} h(a) \psi_1 \psi_2$
F_1 : human immunity to larval establishment	$= \frac{1}{1 + cI(a,t)}$
F_2 : human immunosuppression	$= \frac{1 + I_C S_C W_T(a,t)}{1 + S_C W_T(a,t)}$
F_3 : Mf production in the human host	$= \alpha s \phi[W(a,t), k] W(a,t)$
F_4 : L3 stage larval density in the vector	$= \begin{cases} \frac{\lambda \kappa b \int \pi(a) (1 - f[M(a,t), k]) da}{\sigma + \lambda \psi_1} & \text{for lymphatic filariasis model} \\ \frac{\lambda \kappa b \int \pi(a) (1 - f[M(a,t), k]) da}{\sigma_L + \sigma + \lambda \psi_1 + \sigma_e \int \pi(a) h(a) M(a,t)} & \text{for onchocerciasis model} \end{cases}$

Supplementary Methods

Modeling the effects of mass drug administration

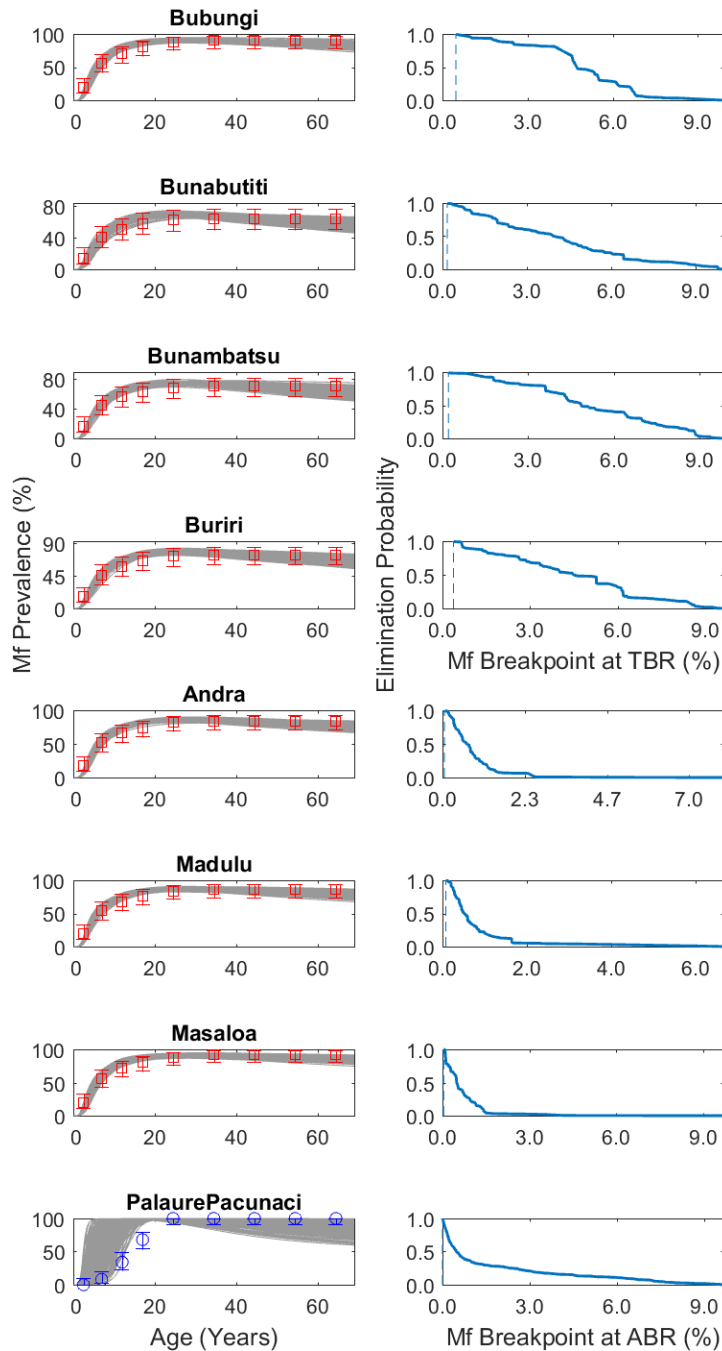
For the Nigerian lymphatic filariasis (LF) endemic sites without baseline microfilariae (mf) prevalence data, baseline model estimates were hindcasted by defining plausible ranges of initial mf and annual biting rate conditions, simulating the observed rounds of mass drug administration (MDA), and fitting the LF model to post-intervention mf data (see Methods in main text). MDA type and coverage data were retrieved from Richards et al. ³¹. The impact of annual mass drug treatment was modelled by assuming that anti-filarial treatment with various drug regimens acts by killing certain fractions of the populations of pre-patent (P) and patent (W) adult worms and mf (M) instantly after drug administration. We denote these fractions as ω for adult worms, and ε for mf, the values of which vary according to the drug that is administered and the targeted parasite ³². The population sizes of worms and microfilariae after drug treatment are calculated by modifying the populations of each parasite stage obtained immediately prior to the treatment:

$$\left. \begin{aligned} P(a, t + dt) &= (1 - \omega C)P(a, t) \\ W(a, t + dt) &= (1 - \omega C)W(a, t) \\ M(a, t + dt) &= (1 - \varepsilon C)M(a, t) \end{aligned} \right\} \text{at time } t = T_{MDAi} \quad (1)$$

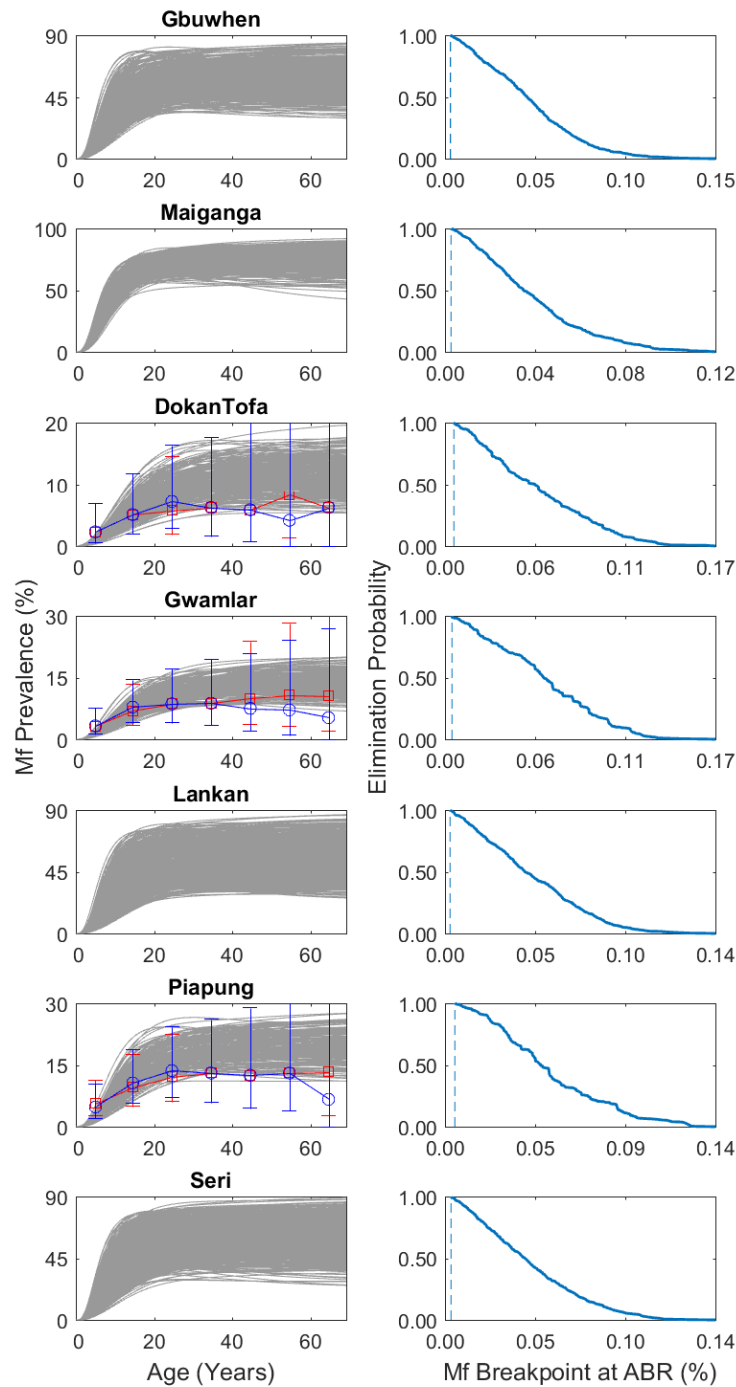
In the above, dt represents a short time-period since the time-point T_{MDAi} when the i^{th} MDA was administered. The parameter C is the population level drug coverage. Apart from instantaneous killing of adult worms and mf, filariasis drug regimens are also thought to reduce the production of mf by worms surviving each MDA. Here we modeled this effect by introducing a new parameter (denoted by δ_{reduc}) as follows:

$$\frac{\partial M}{\partial t} + \frac{\partial M}{\partial a} = (1 - \delta_{reduc} C) s \alpha \phi[W(a, t), k] W(a, t) - \mu_2 M(a, t), \text{ for } T_{MDAi} < t \leq T_{MDAi} + P \quad (2)$$

where $\alpha' = \alpha(1 - \delta_{reduc} C)$ reflects the suppressed fecundity (over a period of T_P months since the i^{th} MDA) of adult worms that survive the administration of drugs at each MDA.



Supplementary Figure 1. Model fits and estimated transmission breakpoints for onchocerciasis endemic sites. The model fits (gray curves) to baseline microfilariae prevalence from eight onchocerciasis endemic sites are shown. Age-stratified Mf prevalence patterns (shown in the figure as red squares for plateau-type and blue circles for convex-type patterns) used for fitting were constructed according to the reported community-level Mf prevalence (Table 1). The error bars represent the 95% binomial confidence intervals. The constructed age pattern which best matched the community-level Mf prevalence based on mean-squared error calculations was used for fitting. The empirical cumulative density functions (right) of the model-calculated Mf breakpoints are shown for each site. The vertical dashed lines in the ECDF plots denotes the Mf breakpoint values corresponding to the 95% elimination probability thresholds applicable in each village. Note that the breakpoints for Bubungi, Bunabutiti, Bunambatsu, and Buriri were calculated at the threshold biting rate because vector control was used in these sites, while the breakpoints for Andra, Madulu, Masalao, and Palaure Pacunaci were calculated at the annual biting rate.



Supplementary Figure 2. Model fits and estimated transmission breakpoints for lymphatic filariasis endemic sites. The model fits (gray curves) to baseline microfilariae prevalence from seven lymphatic filariasis endemic sites are shown. Age-stratified Mf prevalence patterns (shown in the figure as red crosses for plateau-type and blue circles for convex-type patterns) used for fitting were constructed according to the reported community-level Mf prevalence (Table 2). The error bars represent the 95% binomial confidence intervals. Both plateau and convex constructed age patterns were used as an ensemble. In those sites that do not have constructed data shown, the baseline curves were hindcasted from fits to post-intervention data. The empirical cumulative density functions (right) of the model-calculated Mf breakpoints are shown for each site. The vertical dashed lines in the ECDF plots denotes the Mf breakpoint values corresponding to the 95% elimination probability thresholds applicable in each village. Breakpoint values were calculated at the annual biting rate.

Supplementary Note 1: Software

Description

The PFFI function description and code that follows allows the calculation of freedom from infection probabilities in R. PFFI analyzes data from a parasitic infection survey for determining whether a population is free from infection at the design prevalence. The calculations employ the exact hypergeometric distribution as given by Cameron and Baldock 1998, and are based on one-stage sampling, use of an imperfect diagnostic test, and a finite population.

Usage

```
PFFI(p, ...)
```

Arguments

p	the design prevalence given as a proportion
Se	the sensitivity of the diagnostic test
Sp	the specificity of the diagnostic test
N	the population size
n	the number of individuals sampled in the survey
x	the number of sampled individuals who test positive for infection
alpha	the desired rate of Type I error
beta	the desired rate of Type II error

Value

A data frame is returned which contains the probability of the null hypothesis, the probability of the alternative hypothesis, the confidence of freedom, and the survey freedom classification.

References

Cameron and Baldock, (1998) A new probability formula for surveys to substantiate freedom from disease. *Preventative Veterinary Medicine*, 34(1), 1-17.

Examples

```
p = 0.005  
Se = 0.8  
Sp = 0.95  
N = 1500  
n = 200  
x = 1
```



```

alpha = 0.05
beta = 0.05

out = PFFI(p,Se,Sp,N,n,x,alpha,beta)

```

Code

```

PFFI <- function(p,Se,Sp,N,n,x,alpha,beta){

# probability of null hypothesis (prob that prevalence >= design
# prevalence)

  d = floor(p*N) # diseased in population
  P_null = 0
  for (x1 in 0:x){ # summation of P(T+=x)
    c = 0
    for (y in 0:d){ # outer summation of hypergeometric
      a = (choose(d,y)*choose(N-d,n-y))/choose(N,n)
      b = 0
      for (j in 0:min(x1,y)){ # inner summation of hypergeometric
        b = b + choose(y,j)*Se^j*(1-Se)^(y-j)*choose(n-y,x1-j)*(1-
          Sp)^(x1-j)*Sp^(n-x1-y+j)
      }
      c = c + a*b
    }
    P_null = P_null+c
  }

# probability of alternative hypothesis (prob that prevalence < design
# prevalence)
  d=0 # disease free population
  P_alt = 0
  for (x2 in x:n){ # summation of P(T+=x)
    c = 0
    for (y in 0:d){ # outer summation of hypergeometric
      a = (choose(d,y)*choose(N-d,n-y))/choose(N,n)
      b = 0
      for (j in 0:min(x2,y)){ # inner summation of hypergeometric
        b = b + choose(y,j)*Se^j*(1-Se)^(y-j)*choose(n-y,x2-j)*(1-
          Sp)^(x2-j)*Sp^(n-x2-y+j)
      }
      c = c + a*b
    }
    P_alt = P_alt+c
  }

# probability of freedom = 1-P_null
  P_free = (1-P_null)

# draw a conclusion regarding whether the survey indicates the

```

```
# population is free from infection
if (P_null>alpha && P_alt>alpha){
  conc = "insufficient evidence, sample size too small"
}
else if (P_null<alpha && P_alt>(1-beta)){
  conc = "free from infection"
}
else if (P_alt<(1-beta)){
  conc = "not free from infection"
}

# return list of probabilities
vars = c('P_null','P_alt','P_free','Decision')
Prob = c(P_null,P_alt,P_free,conc)
out = data.frame(Prob,row.names = vars)

return (out)
}
```

Supplementary References

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