Single Patch *Plasmodium falciparum* model

Mathematical model description

Sheetal Silal[1,2] & Lisa White[2]

[1] Modelling and Simulation Hub, Africa (MASHA), Department of Statistical Sciences, University of Cape Town, University of Cape Town, Rondebosch, Cape Town 7700, South Africa
[2] Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK

This document provides a description of the methodology, equations and parameters underlying the mathematical model for *P. falciparum* malaria transmission.

Plasmodium falciparum sub-model
We use a compartmental model for the transmission of *P. falciparum* malaria. It's structure is similar to previously published models [1-6]. There are four infection classes in this model representing infections that are: severe; clinical; asymptomatic and detectable by microscopy; asymptomatic and undetectable by microscopy. Each infection class has a distribution of parasitaemia associated with it that is used to estimate the sensitivity of various diagnostic tests. Each infection class also has an infectiousness associated with it based on infectivity data. The probability of individuals entering each class of infection is dependent on their immunity status. We assume that untreated individuals will transition from higher to lower severity infection classes as they recover and that they can be boosted to higher severity classes on superinfection. We assume that treated individuals test positive for HRP2 after clearance of asexual parasitaemia for different durations depending on the detection limit of the test used.

The system is depicted in Figure 1 and described by the following set of ordinary differential equations with compartment descriptions in Table 1:

$$\frac{dS}{dt} = \mu P(t) - \mu S - \Lambda(t)S + \omega R$$

$$\frac{dI_n}{dt} = -\mu I_n + p_{sn}(1-p_s)\Lambda(t)S - r_n I_n + r_a I_a - (1-p_{rn})(1-p_r)\Lambda(t)I_n - p_r\Lambda(t)I_n + p_{rn}(1-p_r)\Lambda(t)(R+H)$$

$$\frac{dI_a}{dt} = -\mu I_a + (1-p_{sn})(1-p_s)\Lambda(t)S + (1-p_{sev})r_c I_c - r_a I_a + (1-p_{rn})(1-p_r)\Lambda(t)I_n - p_r\Lambda(t)I_a + (1-p_{rn})(1-p_r)\Lambda(t)(R+H) + ptf(1-ptfc)r_t(T_o+T_v+T_h)$$

$$\frac{dI_c}{dt} = -\mu I_c + (1-\tau)p_s\Lambda(t)S + (1-\tau_{sev})(1-\theta_1)r_s I_s - (1-p_{sev})r_c I_c - p_{sev}r_c I_c + p_r(1-\tau)\Lambda(t)(I_n+I_a+R+H) + ptf(ptfc)(1-ptftr)r_t(T_o+T_v+T_h)$$

$$\frac{dI_s}{dt} = -\mu I_s - (1-\tau_{sev})r_s I_s - \tau_{sev}r_Q I_s + p_{sev}r_c I_c$$

$$\frac{dT_o}{dt} = -\mu T_o + \tau_o p_s\Lambda(t)S - (1-ptf)r_t T_o + p_r\tau_o\Lambda(t)(I_n+I_a+R+H)$$

$$\frac{dT_v}{dt} = -\mu T_v + \tau_v p_s\Lambda(t)S - (1-ptf)r_t T_v + p_r\tau_v\Lambda(t)(I_n+I_a+R+H)$$

$$\frac{dT_h}{dt} = -\mu T_h + \tau_h p_s\Lambda(t)S - (1-ptf)r_t T_h + p_r\tau_h\Lambda(t)(I_n+I_a+R+H) + ptf(ptfc)(ptftr)r_t(T_o+T_v+T_h)$$

$$\frac{dR}{dt} = -\mu R + r_n I_n - \Lambda(t)R - \omega R + \chi H$$

$$\frac{dH}{dt} = -\mu H + (1-ptf)r_t(T_o+T_v+T_h) + \tau_{sev}(1-\theta_2)r_Q I_s - \Lambda(t)H - \chi H$$

where

$$P = S + I_n + I_a + I_c + I_s + T_o + T_v + T_h + R + H$$

$$\Lambda(t) = (1/\lambda(t) + 1/\gamma_h + 1/\gamma_m)^{-1}$$

$$\lambda(t) = seas(t)\frac{b^2\epsilon_h\epsilon_m\frac{M}{P(t)}I(t)}{(b\epsilon_h\frac{M}{P(t)} + \delta_m)(\frac{\gamma_m}{\gamma_m+\delta_m})}$$

$$I(t) = \frac{\zeta_n I_n(t) + \zeta_a I_a(t) + I_c(t) + I_s(t)}{P(t)}$$

$$seas(t) = 1 + eln * a * \ cos(2\pi(t-\phi))$$

$$\tau = \tau_o + \tau_v + \tau_h$$

where eln is the Bivariate ENSO (El Niño southern oscillation) index time series standardised between 0 and 1 and smoothed with a running median to estimate effect size. (Accessible at: http://www.esrl.noaa.gov/psd/data/climateindices/).

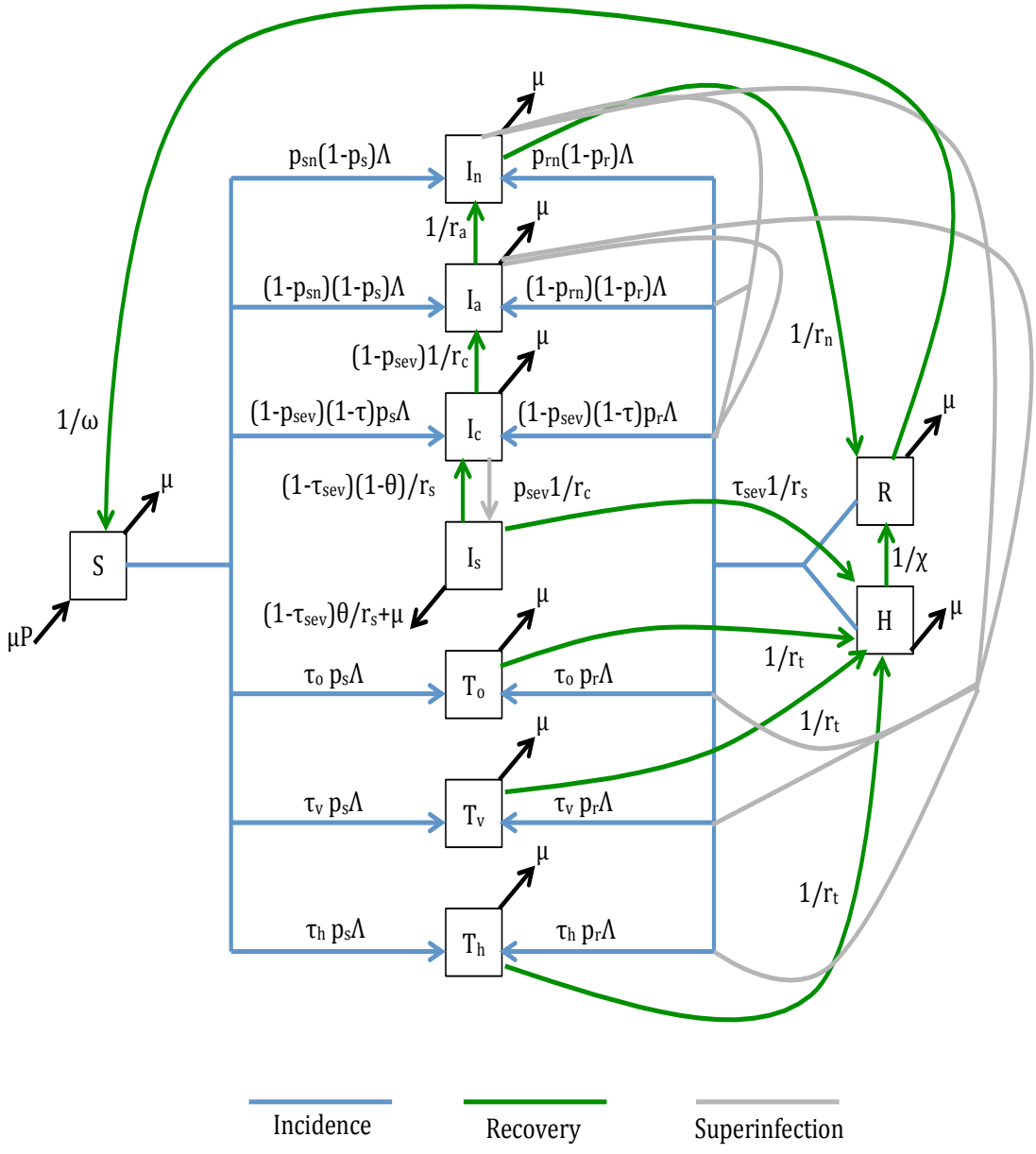

Figure 1 *Plasmodium falciparum* model flow diagram

Table 1 Model Variables

Symbol	Definition
	***Falciparum* Variables**
S	Uninfected and non-immune population
H	Uninfected and immune population who test positive by RDT
R	Uninfected and immune population
$\mathbf{I_N}$	Infected and asymptomatic malaria population undetectable by microscopy
$\mathbf{I_A}$	Infected and asymptomatic malaria population detectable by microscopy
$\mathbf{I_C}$	Infected and clinical malaria population
$\mathbf{I_S}$	Infected and severe malaria population
$\mathbf{T_0}$	Population under effective treatment by other means (E.g. Private care)
$\mathbf{T_V}$	Population under effective treatment by Village Malaria Worker
$\mathbf{T_H}$	Population under effective treatment through Health Information System

Table 2 Model Parameters (Ghana-specific parameters *italicised*)

Symbol	Definition	Value	Units	Sim Range	Source
	Parameters				
	Transmission scale parameter	*(58-600)*	*num*		*estimated from zonal data*
ϕ	*Month of peak transmission*	*(7-10)*	*month*		*estimated from zonal data*
a	*Amplitude of seasonal variation*	*0.7-1*	*na*	*(0,1)*	*estimated from zonal data*
δ_m	Average life expectancy of mosquito	14	days	(10,20)	[7, 8]
b	Number of mosquito bites per human per day	1/3	day^{-1}	(0.1,0.5)	[9, 10]
ε_m	Probability that a bite from an infectious mosquito will result in infection	50	%	(20,50)	[10-12]
$1/\gamma_M$	Duration of latent period in mosquitoes	10	days	(5, 15)	[7, 13-17]
eff_{IRS}	*Effectiveness of indoor residual spraying*	*30*	*%*	*(25, 35)*	*[18]*
eff_{ITN}	*Effectiveness of bednets*	*41.7*	*%*	*(38, 45)*	*[18, 51]*
hl_{NET}	Half-life of bednets	1.5	year	(1, 2)	[19]
eff_{HIS}	*Pr(treatment seeking)*Pr(Diagnosis)*Pr(receive treatment)*		*%*		*estimated from data*
	Proportion of infections seeking treatment	*73.5*	*%*	*(70.7, 80.8)*	*data*
	Proportion of cases receiving diagnosis	*91.0*	*%*	*(90.5, 91.2)*	*data*
	Proportion of diagnosed cases receiving treatment	*100*	*%*		*data*
τ_v	*Treatment seeking with a Community/ Village health worker*	*n/a*			
p_rdt	*Proportion of cases detected with RDT*	*73*	*%*		*[52]*

rdt_pos	*RDT positivity rate*	*58*	*%*		*[52]*
slide_pos	*Slide positivity rate*	*45*	*%*		*[52]*
$1/\mu$	*Average life expectancy of the population*	*63*	*year*	*(68,75)*	*[20]*
p_S	Proportion of non-immune individuals expected to develop clinical malaria after infection	90	%	(80,100)	[15, 21]
p_R	Proportion of immune individuals expected to develop clinical malaria after infection	10	%	(0,77)	[22]
p_{SN}	Proportion of non-immune individuals expected to develop sub-patent infection upon challenge	10	%	(0,20)	assumption
p_{RN}	Proportion of immune individuals expected to develop sub-patent infection upon challenge	50	%	(30,70)	assumption
$1/r_S$	Duration of symptoms in an untreated severe infection	10	day	(5,15)	[23, 24]
$1/r_C$	Duration of symptoms in an untreated clinical infection	10	days	(5,15)	[23, 24]
$1/r_A$	Duration of symptoms in an untreated asymptomatic infection	130	days	(60, 200)	[25-27]
τ_{SEV}	Proportion of severe malaria that is treated	80	%	(0, 100)	assumption
p_{sev}	Proportion of clinical infections that become severe	3	%	(5,25)	[28, 29]
ζ_A	Relative infectiousness of asymptomatic infection compared to clinical infection	12.6/27	na	(0,0.50)	[30]
ζ_N	Relative infectiousness of sub-patent infection compared to clinical infection	3.9/27	na	(0., 0.25)	[31]
$1/\omega$	Duration of immunity in an individual without challenge	5	year	(0.5,10)	[26]
θ_1	Probability that untreated severe malaria progresses to death	70	%	(50,80)	[29]
θ_2	Probability that treated severe malaria progresses to death	2	%	(1,20)	estimated from data
ε_h	Probability that a bite from an infectious human will result in infection	50	%	(7,64)	[14, 32]
$1/\gamma_H$	Incubation period and time to gametocytemia in humans	21	days	(14,24)	[14-17, 33]
$1/\chi$	Period of HRP2 detectability by RDT	28	days	(21,37)	[34-36]
$1/r_T$	Time taken to clear asexual parasites after treatment	3	day	(3,7)	[37]
$1/r_Q$	Recovery time with quinine for severe infections	6	days	(4,8)	[38]
ptf	Baseline probability of treatment failure on ACT	5	%	(1,10)	assumption
ptfc	Probability of being clinical after treatment failure	0.75	%	(0.5, 0.9)	assumption
ptftr	Probability of seeking trt if clinical, after treatment failure	0.27	%	(0.1, 0.4)	assumption

Sub-patent infection and diagnostics

We assume that parasitaemia (parasites per μl) within each infection class (sub-patent, asymptomatic and clinical) is log-normally distributed as described in [39]. We also use a mixture model approach to obtain the distribution for severe infection using the data from [40].

The following table summarises the model parameters and their sources:

Description	Unit	Pf Value	Ref	Pv Value	Ref
Geometric mean parasitaemia for sub-patent infections (mn_N)	μl^{-1}	5	[41]	5	[41, 42]
Geometric mean parasitaemia for asymptomatic infections(mn_A)	μl^{-1}	5158	[41]	750	
Geometric mean parasitaemia for clinical infections(mn_C)	μl^{-1}	25000	[40, 43]	5000	[44]
Geometric mean parasitaemia for severe infections(mn_S)	μl^{-1}	350000	[40]	20000	[45]
Log standard deviation of log-normal parasite distribution for sub-patent infections	-	0.75		0.75	
Log standard deviation of log-normal parasite distribution for asymptomatic infections	-	1.5	[43, 46]	1.5	[40, 43]
Log standard deviation of log-normal parasite distribution for clinical infections	-	1.3	[40, 43]	1.3	[8, 40]
Log standard deviation of log-normal parasite distribution for severe infections	-	0.26	[40]	4	[8]

The following table describes the detection limits also described in [39]:

Description	Units	Pf Value	Ref
Detection limit for conventional RDT	μl^{-1}	200	[47]
Detection limit for microscopy	μl^{-1}	100	[47]
Detection limit for proposed RDT	μl^{-1}	5	[48, 49]
Detection limit for conventional qPCR	μl^{-1}	0.2	[50]

Test sensitivity:

The parameters above are used to compute diagnostic sensitivity. For each disease class, i, the sensitivity of a test, x, with detection limit, d_T, is given by the formula:

$$sens_{i,x} = 1 - \frac{1}{2}\left[1 + erf\left(\frac{d_T - \mu_i}{\sigma_i \sqrt[2]{2}}\right)\right]$$

Where μ_i and σ_i are the log-mean and the log-standard deviation of the log-normal distribution of parasitaemia for disease class i ε {sub-patent, asymptomatic, clinical, severe).

Test specificity:
It has been shown that treated individuals remain positive by conventional RDT for approximately 28 days after successful clearance of asexual parasites [34-36]. An H compartment (individuals recently recovered who are not infected but test positive by RDT) has therefore been included in the model in order to simulate this. The duration of time spent in the H compartment is dependent on the sensitivity of the RDT to detect HRP2 which is assumed to be linearly correlated with its asexual parasite detection limit.

Duration in each infection class:
For severe, clinical and asymptomatic infection the duration of infection is well documented. For sub-patent infection, we assume that the duration of sub-patent infection, δ_N, can be extrapolated from the duration of infection of asymptomatic infection, δ_A, and an assumption of log-linear decline in parasitaemia using the following formula:

$$\delta_N = \delta_A \frac{\mu_N - d_0}{\mu_A - \mu_N}$$

Where μ_N is the log-mean of the log-normal distribution of parasitaemia for sub-patent infection, μ_A is the log-mean of the log-normal distribution of parasitaemia for asymptomatic infection and d_0 is the detection limit of the most sensitive test (qPCR).
Using the parameters above, we would expect sub-patent infection to be detectable by qPCR for 75 days.

Force of infection and Seasonality

The force of infection on humans, λ is derived by assuming that mosquito dynamics of an SEI model are at a steady state resulting in the following:

$$\Lambda(t) = (1/\lambda(t) + 1/\gamma_h + 1/\gamma_m)^{-1}$$

$$\lambda(t) = seas(t)\frac{b^2\epsilon_h\epsilon_m\frac{M}{P(t)}I(t)}{(b\epsilon_h\frac{M}{P(t)} + \delta_m)(\frac{\gamma_m}{\gamma_m+\delta_m})}$$

$$I(t) = \frac{\zeta_n I_n(t) + \zeta_a I_a(t) + I_c(t) + I_s(t)}{P(t)}$$

$$seas(t) = 1 + eln * a * \ cos(2\pi(t - \phi))$$

where eln is the Bivariate ENSO (El Niño southern oscillation) index time series standardised between 0 and 1 and smoothed with a running median to estimate effect size. (Accessible at: http://www.esrl.noaa.gov/psd/data/climateindices/).

Model Interventions

The table below summarises the impact that each of the interventions modelled has on model parameters/equations.

Intervention	Description	Model Impact
Passive treatment	Treatment probabilities (τ) for different avenues of treatment (v, h, o) dependent on coverage (cov), treatment-seeking and treatment effectiveness (*eff*) and diagnostic sensitivity (*sens*)	See below
$\tau_v = cov_v \times eff_v \times sens_v$ $\tau_h = (1 - cov_v eff_v) \times eff_h \times sens_h$ $\tau_o = (1 - cov_v eff_v - (1 - cov_v eff_v) eff_h) \times eff_o \times sens_o$		
Long Lasting Insecticide-treated Nets	Net distribution as a proportion of the population at risk (*itn*) and the half-life of the net (*hlnet*) are used to compute cumulative coverage (itncov). This, together with usage and ability to prevent transmission (*itneff*) is used to decrease the transmission function λ	See below
$itncov_t = itn_t + 0.5 itncov_{t-1} e^{-\frac{1}{12}/(hlnet)}$ $\lambda_t^* = (1 - itncov_t \times itneff) \times \lambda_t$		
Indoor residual spraying	Number of people protected by IRS as a proportion of the population at risk (*irs*) and the half-life of the insectide (*hlspray*) are used to compute cumulative coverage (irscov). This, together with ability to prevent transmission (*irseff*) is used to decrease the transmission function λ	See below
$irscov_t = irs_t + 0.5 irscov_{t-1} e^{-\frac{1}{12}/(hlspray)}$ $\lambda_t^* = (1 - irscov_t \times irseff) \times \lambda_t$		
Injectable artesunate	Switching from treatment of severe infections with quinine to injectable artesunate	Parameters decreased: $1/r_Q$ – recovery time pmort – probability of death of treated severe infections
Seasonal Malaria Chemoprevention	Active preventative treatment at selected coverage levels for a duration determined by the policy in place tauSMC: rate of deploying SMC nuSMC: rate of recovery from SMC	Parameters affected cov_smc - SMC coverage (data) dur_smc - Duration of SMC (data)
$tauSMC = \frac{(-\log(1 - covSMC))}{1/12}$		

<table>
<tr><td colspan="3">$$nuSMC = 12/durSMC$$</td></tr>
<tr><td>Intermittent Preventative Treatment for Pregnant women (IPTp)</td><td>Active preventative treatment at selected coverage levels for up to 5 doses determined by the policy in place</td><td>Parameters affected:
fert rate – fertility rate (data)
anc_rate - rate of attendance to Antenatal care (data)
iptp_dose_i – coverage of IPTp doses</td></tr>
<tr><td colspan="3">$$covIPTp = fertrate * ancrate * \sum_{i=1}^{n} iptp\_dose\_i$$
$$tauIPTp = \frac{(-\log(1 - covIPTp))}{12/12}$$</td></tr>
</table>

Model calibration and validation

The model was calibrated to monthly zonal data from the Ghana National Malaria Control Programme. Figure 2 shows the 50% uncertainty range along with the observed reported data. The model was calibrated using data from 2012 to 2017 and validated with data from 2017 for a year (after dashed line). The seasonality is captured fairly well in all three zones with the majority of data points lying within the uncertainty range in the validation set.

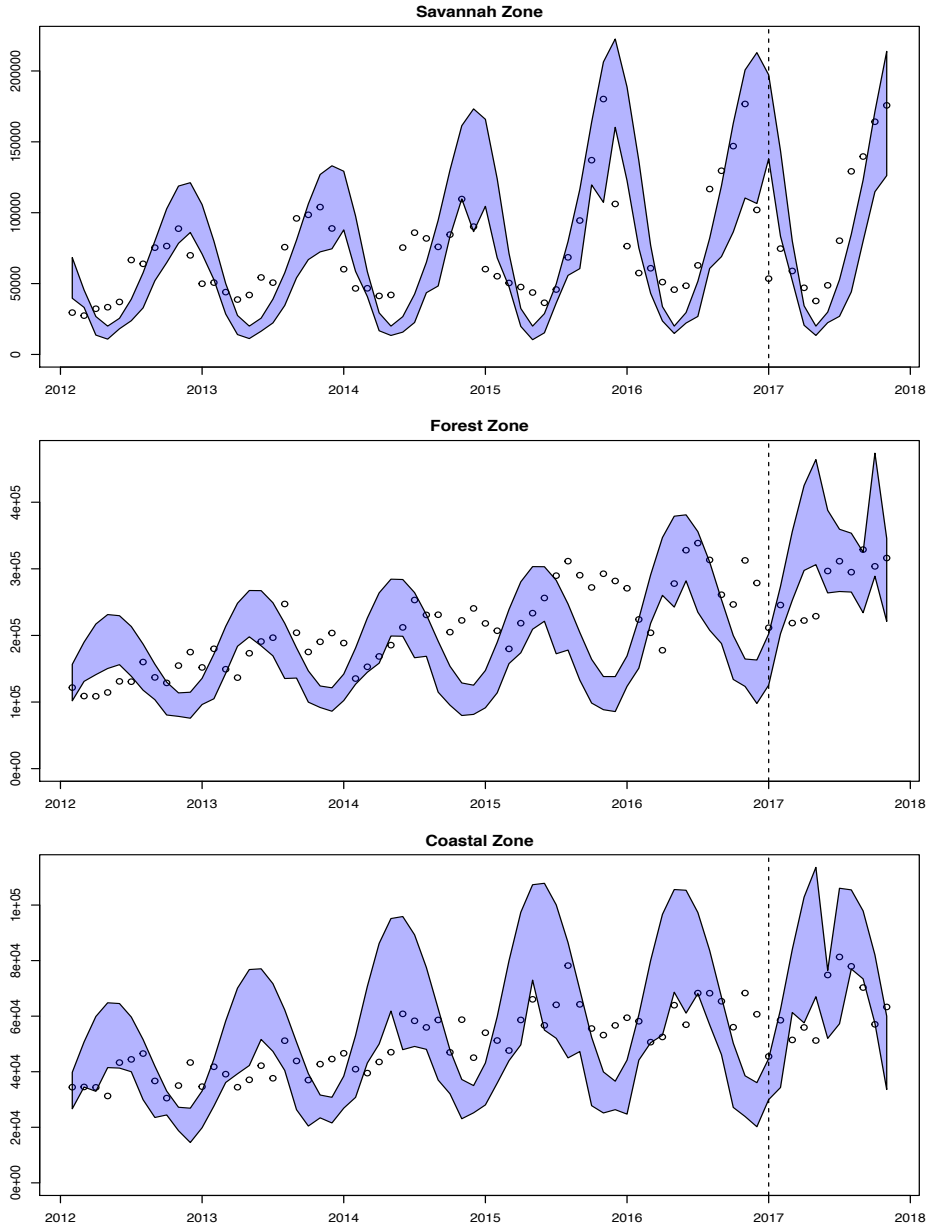

Figure 2 50% projected uncertainty range for reported cases in the three ecological zones in Ghana (blue shaded) with observed reported cases (points). The model was trained with data from 2012 to 2017 and validated with data from 2017 (dashed line).

References

1. Aguas, R., et al., *Prospects for malaria eradication in sub-Saharan Africa.* PLoS One, 2008. **3**(3): p. e1767.
2. Silal, S.P., et al., *Towards malaria elimination in Mpumalanga, South Africa: a population-level mathematical modelling approach.* Malaria Journal, 2014. **13**(1): p. 297-297.
3. White, L.J., et al., *The role of simple mathematical models in malaria elimination strategy design.* Malar J, 2009. **8**: p. 212.
4. Silal, S.P., et al., *Predicting the impact of border control on malaria transmission: a simulated focal screen and treat campaign.* Malaria Journal, 2015. **14**.
5. Silal, S.P., et al., *Hitting a Moving Target: A Model for Malaria Elimination in the Presence of Population Movement.* PLoS One, 2015. **10**(12): p. e0144990.
6. Slater, H.C., et al., *Assessing the impact of next-generation rapid diagnostic tests on Plasmodium falciparum malaria elimination strategies.* Nature, 2015. **528**(7580): p. S94-101.
7. Anderson, R.M. and R.M. May, *Infectious diseases of humans: dynamics and control London*. 1991, Oxford: Oxford University Press.
8. Wanji, S., et al., *Anopheles species of the mount Cameroon region: biting habits, feeding behaviour and entomological inoculation rates.* Trop Med Int Health, 2003. **8**(7): p. 643-9.
9. Churcher, T.S., J.F. Trape, and A. Cohuet, *Human-to-mosquito transmission efficiency increases as malaria is controlled.* Nat Commun, 2015. **6**: p. 6054.
10. Ross, R., *SOME A PRIORI PATHOMETRIC EQUATIONS.* Br Med J, 1915. **1**(2830): p. 546-7.
11. Robinson, L.J., et al., *Strategies for understanding and reducing the Plasmodium vivax and Plasmodium ovale hypnozoite reservoir in Papua New Guinean children: a randomised placebo-controlled trial and mathematical model.* PLoS Med, 2015. **12**(10): p. e1001891.
12. Smith, D.L., et al., *A quantitative analysis of transmission efficiency versus intensity for malaria.* Nat Commun, 2010. **1**: p. 108.
13. Chamchod, F. and J.C. Beier, *Modeling Plasmodium vivax: relapses, treatment, seasonality, and G6PD deficiency.* J Theor Biol, 2013. **316**: p. 25-34.
14. Chitnis, N., J.M. Hyman, and J.M. Cushing, *Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model.* Bull Math Biol, 2008. **70**(5): p. 1272-96.
15. Collins, W.E. and G.M. Jeffery, *A retrospective examination of sporozoite- and trophozoite-induced infections with Plasmodium falciparum: development of parasitologic and clinical immunity during primary infection.* Am J Trop Med Hyg, 1999. **61**(1 Suppl): p. 4-19.
16. Eyles, D.E. and M.D. Young, *The duration of untreated or inadequately treated Plasmodium falciparum infections in the human host.* J Natl Malar Soc, 1951. **10**(4): p. 327-36.
17. Thompson, D., *A research into the production, life and death of crescents in malignant tertian malaria, in treated and untreated cases, by an enumerative method; the leucocytes in malarial fever: a method of diagnosing malaria long after it is apparently cured*. 1911: University Press.
18. Kesteman, T., M. Randrianarivelojosia, and C. Rogier, *The protective effectiveness of control interventions for malaria prevention: a systematic review of the literature.* F1000Research, 2017. **6**.
19. Center for Disease Control. Accessed: 20 January 2015]; Available from: http://www.cdc.gov/malaria/malaria_worldwide/reduction/itn.html.

20. United Nations Statistics Division, *World Statistics Pocketbook*. 2016, United Nations.
21. Griffin, J.T., N.M. Ferguson, and A.C. Ghani, *Estimates of the changing age-burden of Plasmodium falciparum malaria disease in sub-Saharan Africa.* Nat Commun, 2014. **5**: p. 3136.
22. Collins, W.E. and G.M. Jeffery, *A retrospective examination of secondary sporozoite- and trophozoite-induced infections with Plasmodium falciparum: development of parasitologic and clinical immunity following secondary infection.* Am J Trop Med Hyg, 1999. **61**(1 Suppl): p. 20-35.
23. Griffin, J.T., et al., *Reducing Plasmodium falciparum malaria transmission in Africa: a model-based evaluation of intervention strategies.* PLoS Med, 2010. **7**(8).
24. Miller, M.J., *Observations on the natural history of malaria in the semi-resistant West African.* Trans R Soc Trop Med Hyg, 1958. **52**(2): p. 152-68.
25. Felger, I., et al., *The dynamics of natural Plasmodium falciparum infections.* PLoS One, 2012. **7**(9): p. e45542.
26. Filipe, J.A., et al., *Determination of the processes driving the acquisition of immunity to malaria using a mathematical transmission model.* PLoS Comput Biol, 2007. **3**(12): p. e255.
27. Sama, W., et al., *An immigration-death model to estimate the duration of malaria infection when detectability of the parasite is imperfect.* Stat Med, 2005. **24**(21): p. 3269-88.
28. Griffin, J.T., et al., *Gradual acquisition of immunity to severe malaria with increasing exposure.* Proc Biol Sci, 2015. **282**(1801): p. 20142657.
29. Lubell, Y., et al., *Likely health outcomes for untreated acute febrile illness in the tropics in decision and economic models; a Delphi survey.* PLoS One, 2011. **6**(2): p. e17439.
30. Lindblade, K.A., et al., *The silent threat: asymptomatic parasitemia and malaria transmission.* Expert Rev Anti Infect Ther, 2013. **11**(6): p. 623-39.
31. Okell, L.C., et al., *Factors determining the occurrence of submicroscopic malaria infections and their relevance for control.* Nat Commun, 2012. **3**: p. 1237.
32. Macdonald, G., *The epidemiology and control of malaria*. 1957, London: Oxford University Press.
33. Bousema, T. and C. Drakeley, *Epidemiology and infectivity of Plasmodium falciparum and Plasmodium vivax gametocytes in relation to malaria control and elimination.* Clin Microbiol Rev, 2011. **24**(2): p. 377-410.
34. Aydin-Schmidt, B., et al., *Usefulness of Plasmodium falciparum-specific rapid diagnostic tests for assessment of parasite clearance and detection of recurrent infections after artemisinin-based combination therapy.* Malar J, 2013. **12**: p. 349.
35. Kyabayinze, D.J., et al., *Operational accuracy and comparative persistent antigenicity of HRP2 rapid diagnostic tests for Plasmodium falciparum malaria in a hyperendemic region of Uganda.* Malar J, 2008. **7**: p. 221.
36. Swarthout, T.D., et al., *Paracheck-Pf accuracy and recently treated Plasmodium falciparum infections: is there a risk of over-diagnosis?* Malar J, 2007. **6**: p. 58.
37. Makanga, M. and S. Krudsood, *The clinical efficacy of artemether/lumefantrine (Coartem).* Malar J, 2009. **8 Suppl 1**: p. S5.
38. Pasvol, G., *The treatment of complicated and severe malaria.* Br Med Bull, 2005. **75-76**: p. 29-47.
39. Silal, S.P., et al., *Predicting the impact of border control on malaria transmission: A Simulated Focal Screen and Treat campaign.* In Preparation, 2015.

40. Hendriksen, I.C., et al., *Defining falciparum-malaria-attributable severe febrile illness in moderate-to-high transmission settings on the basis of plasma PfHRP2 concentration.* J Infect Dis, 2013. **207**(2): p. 351-61.
41. Imwong, M., et al., *Numerical Distributions of Parasite Densities During Asymptomatic Malaria.* J Infect Dis, 2016. **213**(8): p. 1322-9.
42. Chourasia, M.K., et al., *Burden of asymptomatic malaria among a tribal population in a forested village of central India: a hidden challenge for malaria control in India.* Public Health, 2017. **147**: p. 92-97.
43. Zaloumis, S., et al., *Assessing the utility of an anti-malarial pharmacokinetic-pharmacodynamic model for aiding drug clinical development.* Malar J, 2012. **11**: p. 303.
44. Branch, O., et al., *Clustered local transmission and asymptomatic Plasmodium falciparum and Plasmodium vivax malaria infections in a recently emerged, hypoendemic Peruvian Amazon community.* Malar J, 2005. **4**: p. 27.
45. Kochar, D.K., et al., *Severe Plasmodium vivax malaria: a report on serial cases from Bikaner in northwestern India.* Am J Trop Med Hyg, 2009. **80**(2): p. 194-8.
46. Starzengruber, P., et al., *High prevalence of asymptomatic malaria in south-eastern Bangladesh.* Malar J, 2014. **13**: p. 16.
47. Grueninger, H. and K. Hamed, *Transitioning from malaria control to elimination: the vital role of ACTs.* Trends Parasitol, 2013. **29**(2): p. 60-4.
48. Hopkins, H., et al., *Highly sensitive detection of malaria parasitemia in a malaria-endemic setting: performance of a new loop-mediated isothermal amplification kit in a remote clinic in Uganda.* J Infect Dis, 2013. **208**(4): p. 645-52.
49. Polley, S.D., et al., *Clinical evaluation of a loop-mediated amplification kit for diagnosis of imported malaria.* J Infect Dis, 2013. **208**(4): p. 637-44.
50. Imwong, M., et al., *High-throughput ultrasensitive molecular techniques for quantifying low-density malaria parasitemias.* J Clin Microbiol, 2014. **52**(9): p. 3303-9.
51. Smith, Paintain L, Awini E, Addei S *et al*. *Evaluation of a universal long-lasting insecticidal net (LLIN) distribution campaign in Ghana: cost effectiveness of distribution and hang-up activities*. Malaria Journal 2014 13:71.
52. WHO. 2018. *World Malaria Report*. Available at: https://www.who.int/malaria/publications/world-malaria-report-2018/en/