

## Single Patch *Plasmodium falciparum* model

### Mathematical model description

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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:

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

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

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

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

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

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

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

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

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

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

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/>).

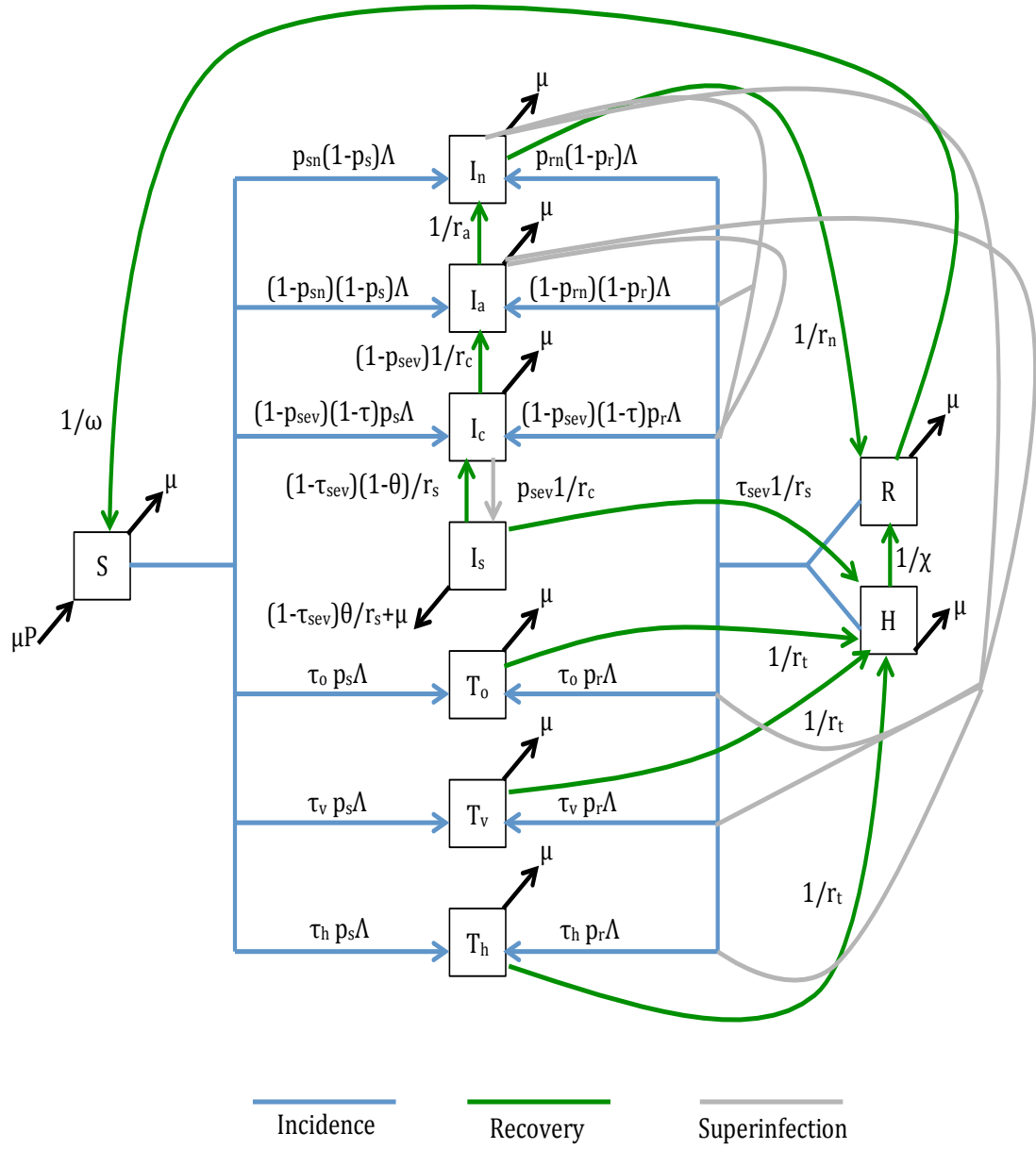


Figure 1 *Plasmodium falciparum* model flow diagram

Table 1 Model Variables

Symbol	Definition
<b><i>Falciparum Variables</i></b>	
<b>S</b>	Uninfected and non-immune population
<b>H</b>	Uninfected and immune population who test positive by RDT
<b>R</b>	Uninfected and immune population
<b>I<sub>N</sub></b>	Infected and asymptomatic malaria population undetectable by microscopy
<b>I<sub>A</sub></b>	Infected and asymptomatic malaria population detectable by microscopy
<b>I<sub>C</sub></b>	Infected and clinical malaria population
<b>I<sub>S</sub></b>	Infected and severe malaria population
<b>T<sub>0</sub></b>	Population under effective treatment by other means (E.g. Private care)
<b>T<sub>V</sub></b>	Population under effective treatment by Village Malaria Worker
<b>T<sub>H</sub></b>	Population under effective treatment through Health Information System

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

Symbol	Definition	Value	Units	Sim Range	Source
<b>Parameters</b>					
	<i>Transmission scale parameter</i>	<i>(58-600)</i>	<i>num</i>		<i>estimated from zonal data</i>
$\phi$	<i>Month of peak transmission</i>	<i>(7-10)</i>	<i>month</i>		<i>estimated from zonal data</i>
$a$	<i>Amplitude of seasonal variation</i>	<i>0.7-1</i>	<i>na</i>	<i>(0,1)</i>	<i>estimated from zonal data</i>
$\delta_m$	Average life expectancy of mosquito	14	days	(10,20)	[7, 8]
$b$	Number of mosquito bites per human per day	1/3	day <sup>-1</sup>	(0.1,0.5)	[9, 10]
$\varepsilon_m$	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]
$eff_{IRS}$	<i>Effectiveness of indoor residual spraying</i>	<i>30</i>	<i>%</i>	<i>(25, 35)</i>	<i>[18]</i>
$eff_{ITN}$	<i>Effectiveness of bednets</i>	<i>41.7</i>	<i>%</i>	<i>(38, 45)</i>	<i>[18, 51]</i>
$hl_{NET}$	Half-life of bednets	1.5	year	(1, 2)	[19]
$eff_{HIS}$	<i>Pr(treatment seeking)*Pr(Diagnosis)*Pr(receive treatment)</i>		<i>%</i>		<i>estimated from data</i>
	<i>Proportion of infections seeking treatment</i>	<i>73.5</i>	<i>%</i>	<i>(70.7, 80.8)</i>	<i>data</i>
	<i>Proportion of cases receiving diagnosis</i>	<i>91.0</i>	<i>%</i>	<i>(90.5, 91.2)</i>	<i>data</i>
	<i>Proportion of diagnosed cases receiving treatment</i>	<i>100</i>	<i>%</i>		<i>data</i>
$\tau_v$	<i>Treatment seeking with a Community/Village health worker</i>	<i>n/a</i>			
$p_{rdt}$	<i>Proportion of cases detected with RDT</i>	<i>73</i>	<i>%</i>		<i>[52]</i>

$rdt\_pos$	<i>RDT positivity rate</i>	58	%		[52]
$slide\_pos$	<i>Slide positivity rate</i>	45	%		[52]
$1/\mu$	<i>Average life expectancy of the population</i>	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]
$\tau_{SEV}$	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]
$\zeta_A$	Relative infectiousness of asymptomatic infection compared to clinical infection	12.6/27	na	(0,0.50)	[30]
$\zeta_N$	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]
$\theta_1$	Probability that untreated severe malaria progresses to death	70	%	(50,80)	[29]
$\theta_2$	Probability that treated severe malaria progresses to death	2	%	(1,20)	estimated from data
$\varepsilon_h$	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  $\mu\text{l}$ ) 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 ( $mn_N$ )	$\mu\text{l}^{-1}$	5	[41]	5	[41, 42]
Geometric mean parasitaemia for asymptomatic infections ( $mn_A$ )	$\mu\text{l}^{-1}$	5158	[41]	750	
Geometric mean parasitaemia for clinical infections ( $mn_C$ )	$\mu\text{l}^{-1}$	25000	[40, 43]	5000	[44]
Geometric mean parasitaemia for severe infections ( $mn_S$ )	$\mu\text{l}^{-1}$	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	$\mu\text{l}^{-1}$	200	[47]
Detection limit for microscopy	$\mu\text{l}^{-1}$	100	[47]
Detection limit for proposed RDT	$\mu\text{l}^{-1}$	5	[48, 49]
Detection limit for conventional qPCR	$\mu\text{l}^{-1}$	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:

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

Where  $\mu_i$  and  $\sigma_i$  are the log-mean and the log-standard deviation of the log-normal distribution of parasitaemia for disease class  $i \in \{\text{sub-patent, asymptomatic, clinical, severe}\}$ .

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,  $\delta_N$ , can be extrapolated from the duration of infection of asymptomatic infection,  $\delta_A$ , 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  $\mu_N$  is the log-mean of the log-normal distribution of parasitaemia for sub-patent infection,  $\mu_A$  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,  $\lambda$  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.

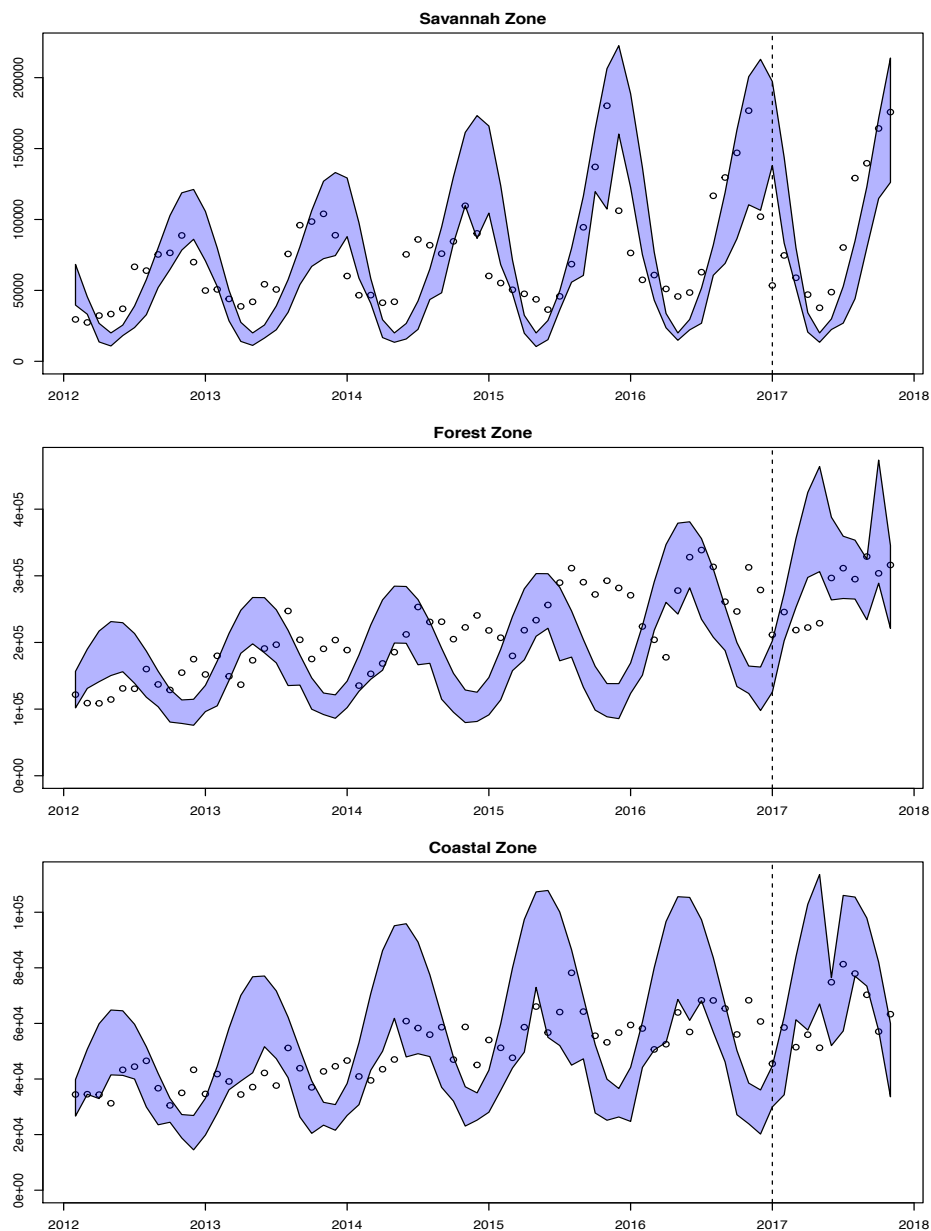
Intervention	Description	Model Impact
Passive treatment	Treatment probabilities ( $\tau$ ) for different avenues of treatment (v, h, o) dependent on coverage (cov), treatment-seeking and treatment effectiveness (eff) and diagnostic sensitivity (sens)	See below
$\tau_v = cov_v \times eff_v \times sens_v$ $\tau_h = (1 - cov_v \times eff_v) \times eff_h \times sens_h$ $\tau_o = (1 - cov_v \times eff_v - (1 - cov_v \times eff_v) \times eff_h) \times eff_o \times sens_o$		
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 $\lambda$	See below
$itncov_t = itn_t + 0.5itncov_{t-1}e^{-\frac{1}{12}/(hlnet)}$ $\lambda_t^* = (1 - itncov_t \times itneff) \times \lambda_t$		
Indoor residual spraying	Number of people protected by IRS as a proportion of the population at risk (irs) and the half-life of the insecticide (hlspray) are used to compute cumulative coverage (irscov). This, together with ability to prevent transmission (irseff) is used to decrease the transmission function $\lambda$	See below
$irscov_t = irs_t + 0.5irscov_{t-1}e^{-\frac{1}{12}/(hlspray)}$ $\lambda_t^* = (1 - irscov_t \times irseff) \times \lambda_t$		
Injectable artesunate	Switching from treatment of severe infections with quinine to injectable artesunate	Parameters decreased: 1/r <sub>Q</sub> – 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)
$tauSMC = \frac{(-\log(1 - covSMC))}{1/12}$		



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

### ***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).

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