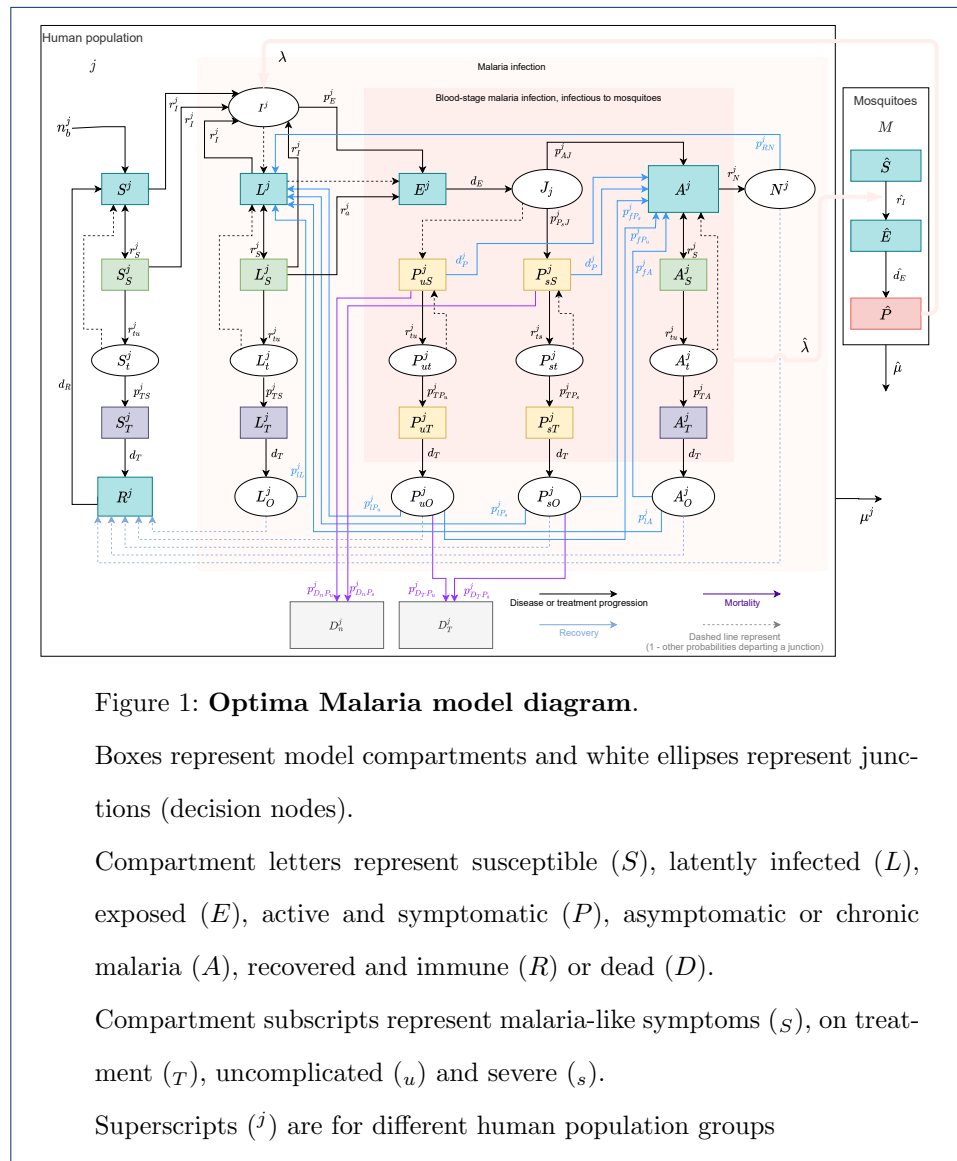Supplemental appendix: Assessing a primaquine intervention in Cambodia to control vivax malaria by the target date of 2025

Model structure

Figure 1: **Optima Malaria model diagram**.

Boxes represent model compartments and white ellipses represent junctions (decision nodes).

Compartment letters represent susceptible (S), latently infected (L), exposed (E), active and symptomatic (P), asymptomatic or chronic malaria (A), recovered and immune (R) or dead (D).

Compartment subscripts represent malaria-like symptoms $(_S)$, on treatment $(_T)$, uncomplicated $(_u)$ and severe $(_s)$.

Superscripts $(^j)$ are for different human population groups

This appendix provides a mathematical description of the model used for the analysis. The epidemiological model at the core of the Optima Malaria model is represented in Figure 1, with compartments and key parameters described below. The code is open source and open access. The epidemiological model was implemented using the Atomica framework (https://github.com/atomicateam/atomica). The calibrated project databooks for this analysis including each

individual input parameter are available in https://github.com/rihickson/vivax-primaquine-Cambodia.

Human compartments for each population group j (e.g. males ages 15 years and older, all other populations) are described in Table 1. Parameters that determine transition rates between model compartments are described in Table 2. A model timestep of 5 days was used for this analysis.

Interventions

Interventions including intermittent presumptive treatment during pregnancy (IPTp), long-lasting insecticide treated nets (LLINs), indoor residual spraying (IRS), seasonal mass chemoprevention in children (SMC), mass drug administration (MDA), larval source management (LSM), and behavioural change communication (BCC) have previously been implemented within this model as previously described and parameterized for *P. falciparum* in the context of Nigeria [1]. In this analysis the impact of standard of care interventions on model parameters relating to malaria transmission, diagnosis, and treatment were captured as part of the status quo calibration and not independently modelled. Changes to other intervention coverage into the future were not considered in this analysis.

Calibration

For this analysis, calibration for each province was completed iteratively using the following inputs

1. **Demographics**

    Data on demographics, annual incidence (2011–2018), testing numbers, test positivity rate, and treatment outcome numbers were used to inform the model parameters $(n_b^j, \mu^j, p_{D_T P_u}^j, p_{D_T P_s}^j)$ for each population stratification (males ages 15 years and older, all other populations) and province.

2. **Malaria incidence**

    The model parameter for relative susceptibility to biting (h_b^j) was calibrated per-population to match estimated malaria incidence, including historical adjustments by year to account for factors such as rainfall that vary year to year and are not otherwise accounted for in the model.

3 **Malaria prevalence**

The initial compartment sizes in the model were calibrated to match prevalence estimates on January 1, 2010 and $d_N^j = 90$ days.

4 **Diagnosis and testing**

Calibrate r_S^j varying by year and province, $r_{tu}^j = 0.03$ implying a 28% chance of being tested for uncomplicated malaria before natural recovery or death (likely encapsulating some asymptomatic malaria), $r_{ts}^j = 0.15$ implying a 94% chance of being tested for severe malaria before natural recovery or death in line with self-reported 96% seeking medical diagnosis for serious fevers in 2020 [2], and ξ_β to reflect the overall number of tests, and the test positivity rate in light of estimated prevalence

5 **Severity and death**

Parameters $p_{P_s J}^j = 0.01$ and $p_{AJ}^j = 0$ were calibrated to match reported mortality rates (zero reported national malaria deaths since 2018 [3]) given reported treatment outcomes by severity.

Human compartments	
S^j	Susceptible
S_S^j	Susceptible to malaria, with non-malarial malaria-like symptoms
S_t^j	Junction to determine the outcome (S^j or S_T^j) if a susceptible human tested due to malaria-like symptoms receives a false positive diagnosis
S_T^j	Susceptible but eligible for malaria treatment due to false positive diagnosis
I^j	Junction to determine the outcome (L^j or E^j) for a human after they are first infected by a mosquito
L^j	Latent *P. vivax* liver-stage infection with no active malaria infection. Not infectious to mosquitoes.
L_S^j	Latent malaria, with non-malarial malaria-like symptoms
L_t^j	Junction to determine the outcome (L^j or L_T^j) if a human with a latent malaria infection tested due to malaria-like symptoms receives a positive diagnosis
L_T^j	Latent infection, diagnosed and eligible for malaria treatment
L_O^j	Junction to determine the outcome (R^j or L^j) for treatment of latent malaria
E^j	Exposed, and will progress to active malaria following an incubation period
J^j	Junction to determine the outcome (P_{uS}^j, P_{sS}^j, or A^j) after the incubation period is complete
P_{uS}^j	Active and symptomatic uncomplicated blood-stage malaria infection.
P_{ut}^j	Junction to determine the outcome (P_{uS}^j or P_{uT}^j) if a human with a an active malaria infection is tested
P_{uT}^j	Diagnosed uncomplicated (clinical) malaria infection eligible for malaria treatment
P_{uO}^j	Junction to determine the outcome (R^j, L^j, A_j, or D_T^j) for treatment of uncomplicated (clinical) malaria
P_{sS}^j	Active and symptomatic severe blood-stage malaria infection.
P_{ut}^j	Junction to determine the outcome (P_{sS}^j or P_{sT}^j) if a human with a an active malaria infection is tested
P_{sT}^j	Diagnosed severe malaria infection eligible for malaria treatment
P_{sO}^j	Junction to determine the outcome (R^j, L^j, A_j, or D_T^j) for treatment of severe malaria
A^j	Asymptomatic or chronic malaria, with natural resistance and both parasites and antibodies present.
A_S^j	Asymptomatic malaria, with non-malarial malaria-like symptoms
A_t^j	Junction to determine the outcome (A^j or A_T^j) if a human with an asymptomatic malaria infection is tested due to malaria-like symptoms
A_T^j	Asymptomatic infection, diagnosed and eligible for malaria treatment
A_O^j	Junction to determine the outcome (R^j, L^j, or A^j) for treatment of asymptomatic malaria
N^j	Junction to determine the outcome (L^j or R^j) after a human with an asymptomatic malaria infection clears the blood-stage infection
R^j	Recovered and immune to further infection, due to recently completing successful treatment or fully clearing malaria parasites naturally, and having antibodies present
D_n^j	Death due to untreated malaria infection
D_T^j	Death due to malaria infection during treatment
Mosquito compartments	
$\hat{S}$	Susceptible
$\hat{E}$	Exposed but not yet infectious
$\hat{P}$	Malaria parasites present and infectious to humans

Table 1: Model compartments

Parameter	Description	Value	Source
Human demographics			
n_b^j	Number of births (begin in S^j)	*	Data
μ^j	Other cause mortality rate	*	Data
r_S^j	Daily rate of developing malaria-like symptoms for those without symptomatic malaria	*	Calibrated
Human malaria transmission and progression			
r_I^j	Daily rate of being exposed to malaria parasites	$\frac{\hat{P}}{M} \cdot \lambda \cdot h_b^j \cdot m_b^j$	
h_b^j	Relative susceptibility to biting	*	Calibrated
λ	Probability of transmission from (infected) mosquito to human per bite	5%	[4]
p_E^j	Proportion of new infections that continue to blood-stage infection	1	Default
d_E	Duration of exposure before progression to active malaria	10 days	[5, 6]
$p_{P_s J}^j$	Proportion of blood-stage infections that will become severe	*	Calibrated
p_{AJ}^j	Proportion of blood-stage infections that will remain asymptomatic	*	Calibrated
d_P^j	Average duration of symptomatic malaria infection before developing clinical immunity	10 days	
$p_{D_n P_u}^j$	Proportion of untreated uncomplicated malaria cases that will result in death before developing clinical immunity	0.00001	Assumption
$p_{D_n P_s}^j$	Proportion of untreated severe malaria cases that will result in death before developing clinical immunity	0.99	Assumption [7]
d_N^j	Average duration in days of asymptomatic or chronic malaria before clearing parasites in the absence of repeated exposure	*	Calibrated
r_N^j	Average daily rate of clearing asymptomatic or chronic malaria	$\frac{(1-r_I^j)}{d_N^j}$	Calibrated
Human testing and treatment			
r_{tu}^j	Daily rate of testing when experiencing malaria-like symptoms	*	Calibrated
r_{ts}^j	Daily rate of testing when experiencing severe malaria-like symptoms	*	Calibrated
p_{TS}^j	Proportion of S or L with no blood-stage infection that are diagnosed with malaria when tested	0.048	1 - RDT specificity

Parameter	Description	Value	Source
$p_{TP_u}^j$	Proportion of P_u that are diagnosed with malaria when tested	0.948	RDT sensitivity
$p_{TP_s}^j$	Proportion of P_s that are diagnosed with malaria when tested	0.99	Assumption
p_{TA}^j	Proportion of A that are diagnosed with malaria when tested, given that this compartment covers the range of recovery and reduction in malaria parasites	$\frac{P_{TS}+P_{TP_u}}{2}$	
d_T	Duration of treatment	10 days	
$p_{D_T P_u}^j$	Proportion of treated uncomplicated malaria cases that will result in death	*	Data
$p_{D_T P_s}^j$	Proportion of treated severe malaria cases that will result in death	*	Data
τ	Proportion of complete treatments (successfully clear malaria parasites)	0.95	Assumption
ψ	Proportion of completed treatments which successfully clear malaria hypnozoites for full recovery in *P. vivax* infections	0.25	[8]
$p_{fP_u}^j$	Proportion of incomplete (failed) treatments from P_u	$(1-\tau)\cdot(1-p_{D_T P_u}^j)$	
$p_{fP_s}^j$	Proportion of incomplete (failed) treatments from P_s	$(1-\tau)\cdot(1-p_{D_T P_s}^j)$	
p_{fA}^j	Proportion of incomplete (failed) treatments from A	$(1-\tau)$	
p_{lL}^j	Proportion of treatments that result in a remaining liver-stage malaria infection from L	$1-(1-\tau)\cdot(1-\psi)$	
$p_{lP_u}^j$	Proportion of treatments that result in a remaining liver-stage malaria infection from P_u	$(1-p_{D_T P_u}^j)\cdot\tau\cdot(1-\psi)$	
$p_{lP_s}^j$	Proportion of treatments that result in a remaining liver-stage malaria infection from P_s	$(1-p_{D_T P_s}^j)\cdot\tau\cdot(1-\psi)$	
p_{lA}^j	Proportion of treatments that result in a remaining liver-stage malaria infection from A	$\tau\cdot(1-\psi)$	
Mosquito			
t	Normalized time parameter, where $t=0.25$ is the peak season for mosquito population size, incubation rate, and human malaria-like symptoms		
$\hat{\mu}$	Life expectancy of mosquitoes	35 days	[9, 10]
β	Daily rate of feeding on humans	0.33	[11]

Parameter	Description	Value	Source
ξ_β	Seasonal variation in mosquito biting rate for peak season	*	Calibrated
m_β	Seasonal relative propensity to bite	$1 + \max\left(0, \xi_\beta \cdot \sin\left(2\pi(t - 0.5)\right)\right)$	
$\hat{\lambda}$	Probability of transmission from (infected) human to mosquito per bite	47%	[12, 6, 13, 14, 15]
$\hat{r_I^j}$	Daily rate of being exposed to malaria parasites, where prev is the prevalence of malaria parasites in humans	$\text{prev} \cdot \hat{\lambda} \cdot \beta \cdot m_\beta$	
$\hat{d_E}$	Duration of exposure before progression to active malaria	$\frac{(30-7)\sin\left(2\pi t + (30+7)\right)}{2}$	7 – 30 days [10, 16]

Table 2: Model parameters

* Varies by population and province, data available in project files

Author details

References

1. Scott, N., Hussain, S.A., Martin-Hughes, R., Fowkes, F.J.I., Kerr, C.C., Pearson, R., Kedziora, D.J., Killedar, M., Stuart, R.M., Wilson, D.P.: Maximizing the impact of malaria funding through allocative efficiency: using the right interventions in the right locations. Malaria Journal **16**(1) (2017). doi:10.1186/s12936-017-2019-1. Accessed 2018-08-30

2. Kheang, S.T., Por, I., Sovannaroth, S., Dysoley, L., Chea, H., Po, L., AlMossawi, H.J., Al Imran, A., Kak, N.: Cambodia malaria indicator survey 2020: Implications for malaria elimination. MalariaWorld Journal **12** (2021)

3. World Health Organization: World Malaria Report 2021

4. Churcher, T.S., Trape, J.-F., Cohuet, A.: Human-to-mosquito transmission efficiency increases as malaria is controlled. Nature communications **6**(1), 1–8 (2015)

5. Anderson, R.M., May, R.M.: Infectious diseases of humans: dynamics and control. Oxford University Press (1992)

6. Labadin, J., Kon, C., Juan, S.: Deterministic malaria transmission model with acquired immunity. In: Proceedings of the World Congress on Engineering and Computer Science, vol. 2, pp. 20–22 (2009)

7. White, N.J.: The management of severe falciparum malaria. American Thoracic Society (2003)

8. Commons, R.J., Simpson, J.A., Watson, J., White, N.J., Price, R.N.: Estimating the proportion of plasmodium vivax recurrences caused by relapse: a systematic review and meta-analysis. The American journal of tropical medicine and hygiene **103**(3), 1094 (2020)

9. Chitnis, N., Cushing, J.M., Hyman, J.: Bifurcation analysis of a mathematical model for malaria transmission. SIAM Journal on Applied Mathematics **67**(1), 24–45 (2006)

10. Baton, L.A., Ranford-Cartwright, L.C.: Spreading the seeds of million-murdering death: metamorphoses of malaria in the mosquito. Trends in parasitology **21**(12), 573–580 (2005)

11. Killeen, G.F., McKenzie, F.E., Foy, B.D., Schieffelin, C., Billingsley, P.F., Beier, J.C.: A simplified model for predicting malaria entomologic inoculation rates based on entomologic and parasitologic parameters relevant to control. The American journal of tropical medicine and hygiene **62**(5), 535 (2000)

12. Mandal, S., Sarkar, R.R., Sinha, S.: Mathematical models of malaria-a review. Malaria journal **10**(1), 1–19 (2011)

13. Mehlhorn, H.: Encyclopedic reference of parasitology: diseases, treatment, therapy **2** (2001)

14. Dietz, K., Molineaux, L., Thomas, A.: A malaria model tested in the african savannah. Bulletin of the World Health Organization **50**(3-4), 347 (1974)

15. Chitnis, N., Hyman, J.M., Cushing, J.M.: Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model. Bulletin of mathematical biology **70**(5), 1272 (2008)

16. Vaughan, J.A.: Population dynamics of plasmodium sporogony. Trends in parasitology **23**(2), 63–70 (2007)