Modeling for pandemic preparedness and response (MPPR)

Excursion into Malaria Modeling

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Background

- Professor of Biostatistics, University of Abomey-Calavi
- Coordinator, Master and PhD Programmes in Biostatistics
- Coordinator, Humboldt Research Hub on Socio-ecological modeling of COVID-19 (https://hrh.semca-uac.org/en)
- Group lead, Malaria modeling at the Vaccine Impact modeling Consortium

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VIMC is an international community of modellers providing high-quality estimates of the public health impact of vaccination, to inform and improve decision making.

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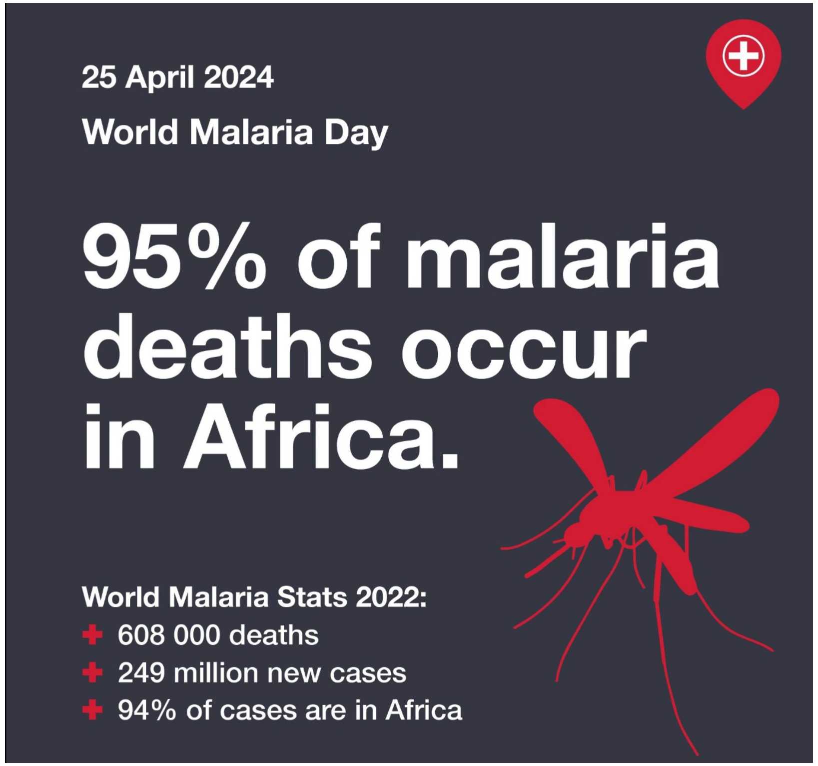
BILL & MELINDA GATES foundation

Gavi
The Vaccine Alliance

wellcome

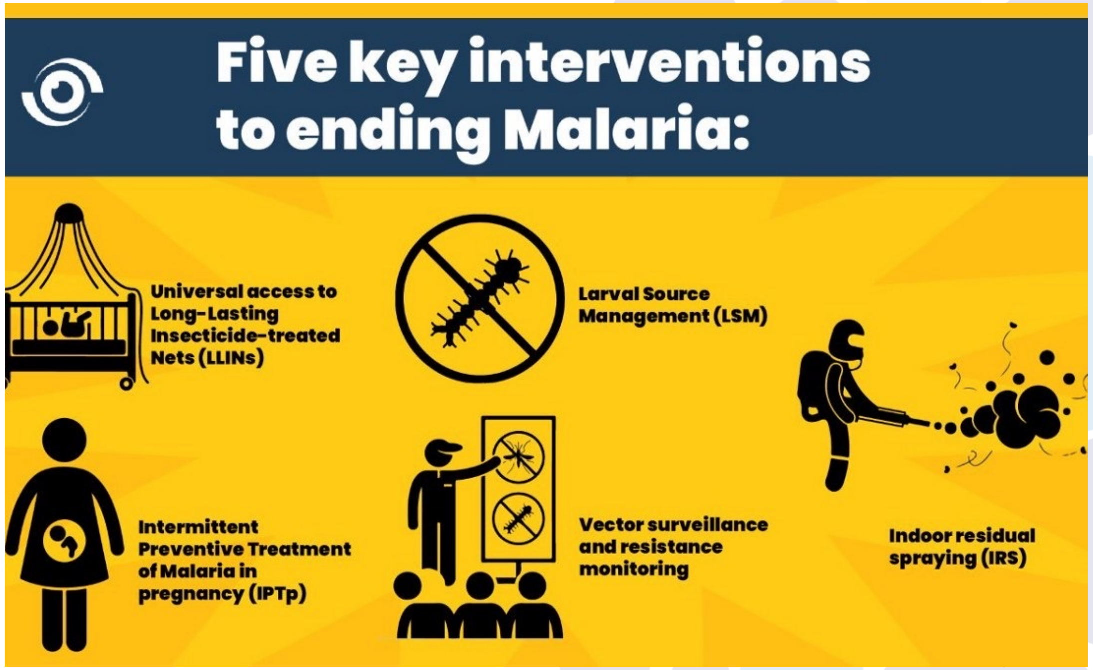
Background

Malaria: vector-borne disease causing devastating health and economic burden



Source: Response-Med

Interventions



https://allafrica.com/

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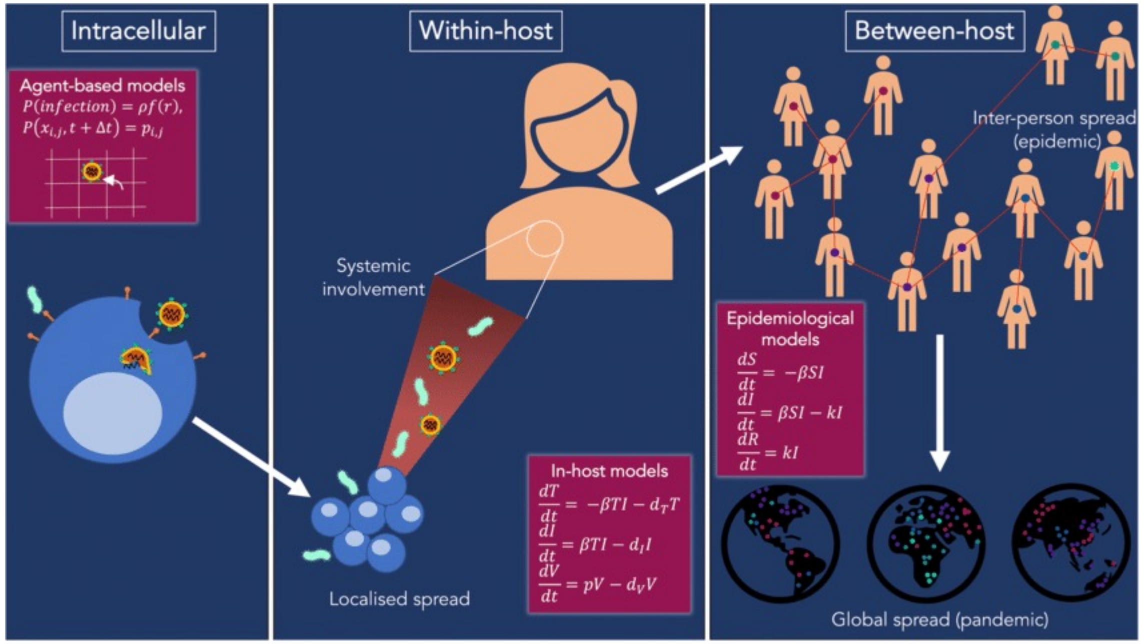
Background

Vaccination

Source: https://lanatayaise.com/

Source: https://www.shutterstock.com/

Background



Source: https://writeoddly.com/

Malaria life cycle

Number of bites per unit time

Probability of infection

Number of infected mosquitoes

$$\lambda_{mh} = \frac{P_{mh} * \beta * I_m}{N_h}$$

Force of infection by mosquitoes

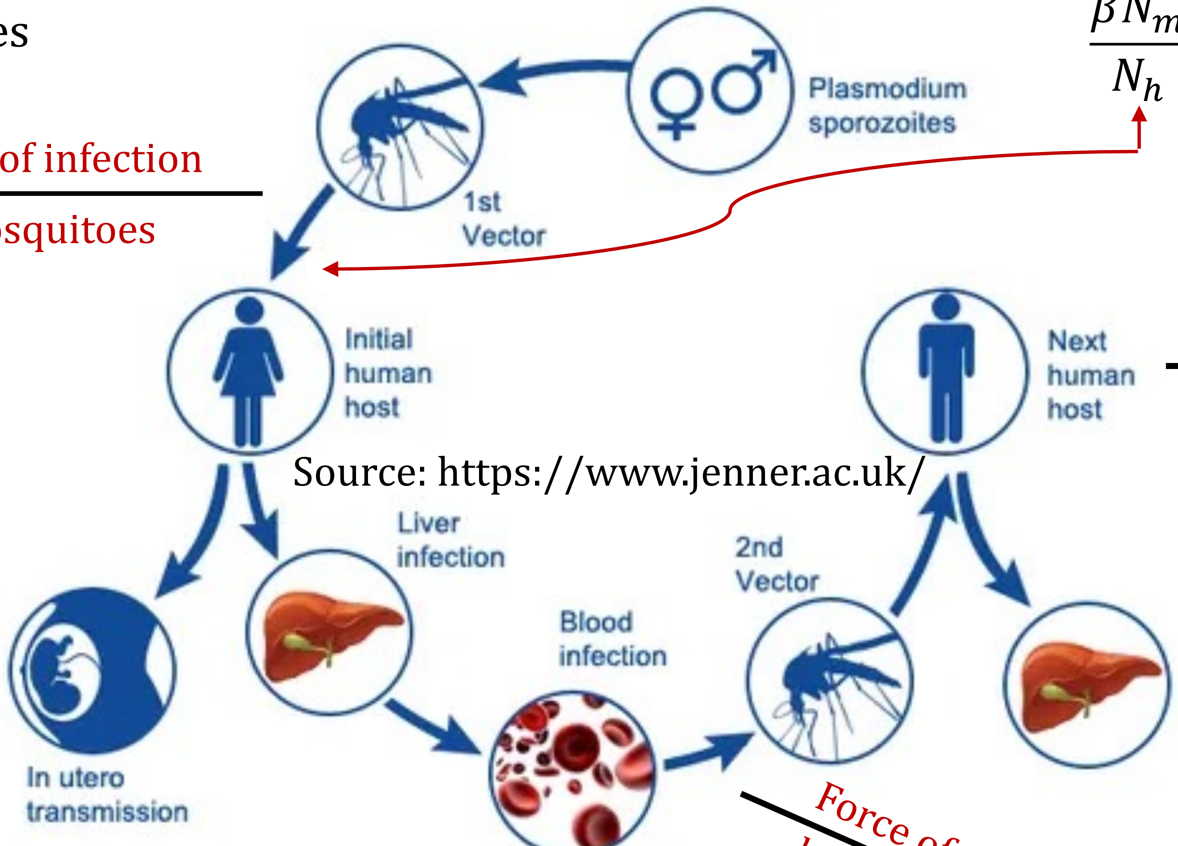
$$N_m = n_0 N_h$$

$(n_0 > 1)$

$$\lambda_{mh} = P_{mh} * \beta * n_0 * \frac{I_m}{N_m}$$

$$\lambda_{mh} = P_{mh} * EIR$$

Entomological Inoculation rate



Source: https://www.jenner.ac.uk/

Number of bites/unit time

Prop. of infected mosquitoes

Probability of infection

$$\frac{\beta N_m}{N_h} * \frac{I_m}{N_m} * P_{mh}$$

Asymptomatic (I_{ah})

Uncomplicated malaria (I_{uh})

Severe malaria (I_{sh})

Force of infection by humans

$$\lambda_{hm} = \frac{\beta * (P_{hma} I_{ah} + P_{hmu} I_{uh} + P_{hms} I_{sh})}{N_h}$$

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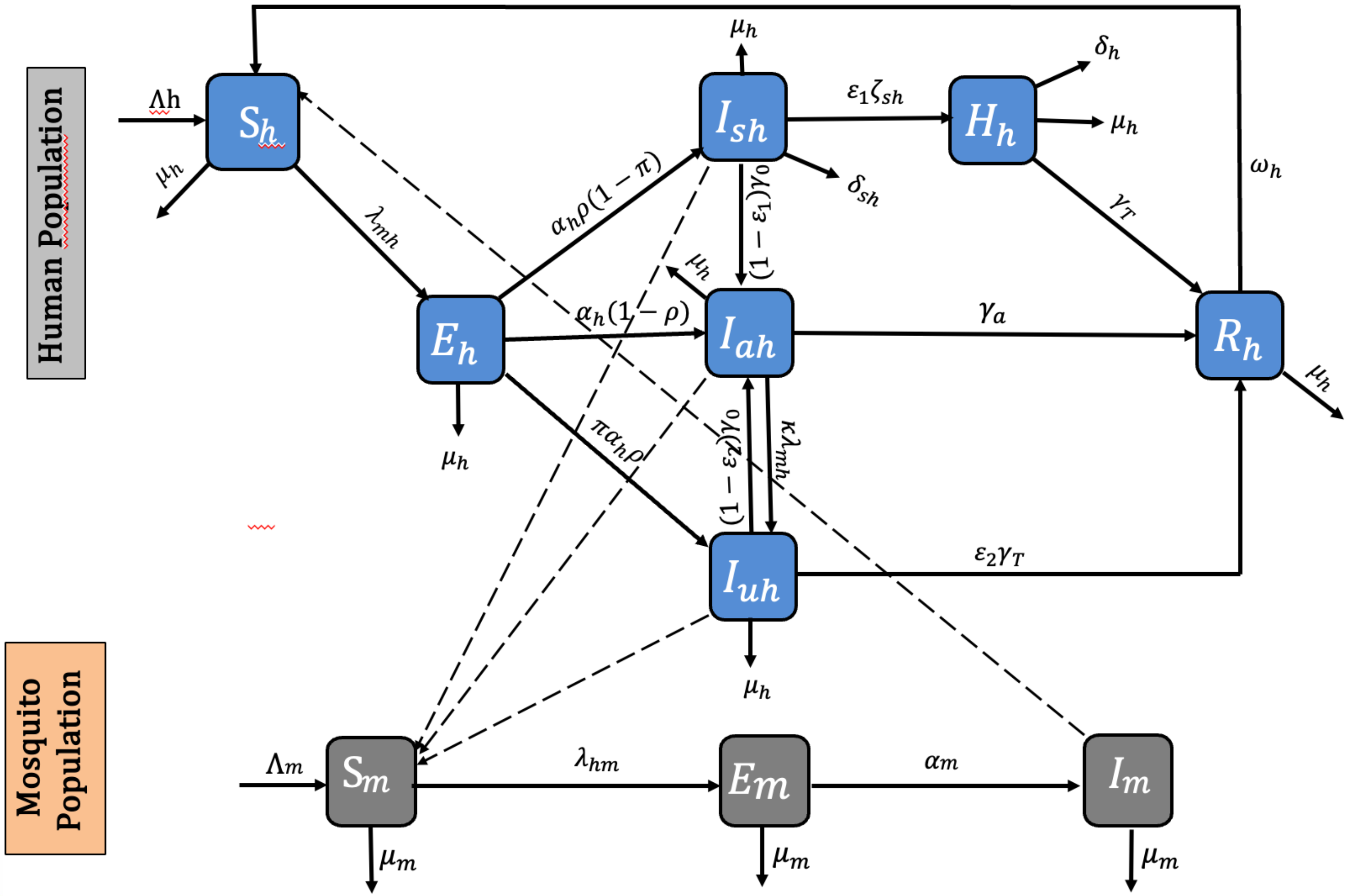
Flowchart of Malaria dynamics



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Set of ODEs

Set of ODEs linked to the model

$$
\begin{aligned}
\dot{S}_h &= \Lambda + \omega_h R_h - \Big(\lambda_{mh} + \mu_h\Big) S_h, && \text{(1a)}\\
\dot{E}_h &= \lambda_{mh} S_h - (\alpha_h + \mu_h) E_h, && \text{(1b)}\\
\dot{I}_{sh} &= \alpha_h \rho (1-\pi) E_h - \Big(\varepsilon_1 \zeta_{sh} + (1-\varepsilon_1)\gamma_0 + \mu_h + \delta_{sh}\Big) I_{sh} - I_{sh}, && \text{(1c)}\\
\dot{I}_{ah} &= \alpha_h (1-\rho) E_h + (1-\varepsilon_1)\gamma_0 I_{sh} + (1-\varepsilon_2)\gamma_0 I_{uh} - a_0 I_{ah}, && \text{(1d)}\\
\dot{I}_{uh} &= \alpha_h \rho \pi E_h + \kappa \lambda_{mh} I_{ah} - \Big(\varepsilon_2 \gamma + (1-\varepsilon_2)\gamma_0 + \mu_h\Big) I_{uh}, && \text{(1e)}\\
\dot{H}_h &= \varepsilon_1 \zeta_{sh} I_{sh} - \Big(\delta_h + \gamma + \mu_h\Big) H_h - H_h, && \text{(1f)}\\
\dot{R}_h &= \gamma_a I_{ah} + \gamma_t H_h + \varepsilon_2 \gamma_t I_{uh} - (\omega_h + \mu_h) R_h, && \text{(1g)}\\
\dot{S}_m &= \Lambda_m N_m - (\lambda_{hm} + \mu_m) S_m, && \text{(1h)}\\
\dot{E}_m &= \lambda_{hm} S_m - (\alpha_m + \mu_m) E_m, && \text{(1i)}\\
\dot{I}_m &= \alpha_m E_m - \mu_m I_m, && \text{(1j)}
\end{aligned}
$$

where, $a_0 = \gamma_a + \kappa \lambda_{mh} + \mu_h$, $a_1 = \gamma_a + \kappa(1-\tau_{v1})\lambda_{mh} + \mu_h$,
$a_2 = \gamma_a + \kappa(1-\tau_{v2})\lambda_{mh} + \mu_h$, $a_3 = \varepsilon_2 \gamma + (1-\varepsilon_2)\gamma_0 + \mu_h$.

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Modeling LLINs

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Quantifying the impact of decay in bed-net efficacy on malaria transmission

Calistus N. Ngonghala [a,b,*], Sara Y. Del Valle [c], Ruijun Zhao [d], Jemal Mohammed-Awel [e]

Long Lasting Insecticide nets (LLINs)

Protect from mosquito bites (reduction in the biting rate)

Kill mosquitoes (increase in the mosquito mortality rate)

Effect on the biting rate

$$\begin{aligned}
\beta(\varepsilon_{\beta(t)}) &= \beta_{max} - (\beta_{max} - \beta_{min})\varepsilon_{\beta}(t),\\
\varepsilon_{\beta(t)} &= p + \left(\frac{2^n+1}{2(n+1)}\right)\left(\frac{2^n-1}{2^n+1} + \frac{1}{1+\left(\frac{t \bmod T}{\frac{T}{2}}\right)^n}\right)\varepsilon_0,
\end{aligned}$$

Effect on the mosquito mortality rate

$$\begin{aligned}
\mu_m(\varepsilon_{\mu_m}(t)) &= \mu_{m0} + \bar{\mu}_m(t) = \mu_{m0} + \mu_{m1}\varepsilon_{\mu_m}(t),\\
\varepsilon_{\mu_m}(t)) &= p + \left(1 + \frac{1}{2^n}\right)\left(\frac{-1}{2^n+1} + \frac{1}{1+\left(\frac{t \bmod T}{\frac{T}{2}}\right)^n}\right)\varepsilon_0,
\end{aligned}$$

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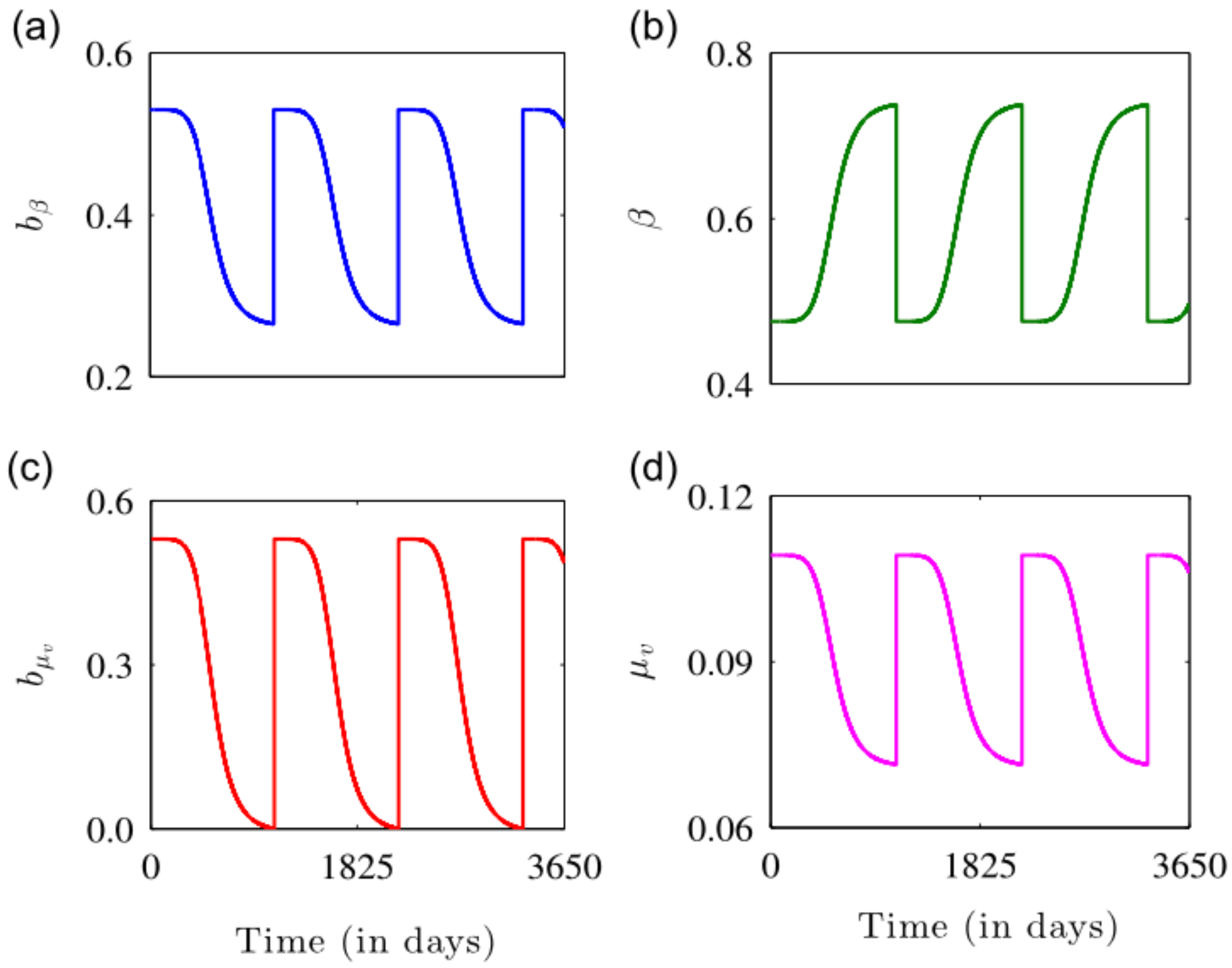
Modeling LLINs



Ngonghala et al. (2014)

Graphical representation of the effects of LLINs.

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Parameter estimation

Some Fixed Parameters

$\kappa = 0.5.$ %Reduction factor of the force of infection from I_{ah} to $I_{uh.}$ (Assumed)
$Prop = 0.5.$ %Proportion of uncomplicated malaria (Assumed)
$\gamma_0 = 2.02778$ %Progression rate of I_{uh} to I_{ah} (year^{-1}) (Chitnis et al. 2008)
$\gamma_T = 14.6$ %Recovery rate of treated individuals (year^{-1}) (Chitnis et al. 2008)
$\alpha_m = 36.5$ % Progress rate of Exposed mosquito to the Infectious mosquito class (year^{-1}) (Chitnis et al. 2008)
α_h=24 % Progress rate of Exposed humans to the Infectious human class (year^{-1}) (Chitnis et al. 2008)
$P_{mh0} = 0.1$ % Disease transmission probability from infectious mosquitoes to susceptible humans (Chitnis et al. 2008)
$n_s > 1$ % Dimensionless shape constant in the LLIN modeling (Ngonghala et al., 2014)
$\mu_{m0} = 20.27$ % baseline value of mosquito mortality rate (year^{-1}) (Ngonghala et al., 2014)
$\Lambda_m = 45.47$ % baseline value of the mosquito birth rate (Ngonghala et al., 2014)
$T = 3\ years$ % useful life or duration of LLIN efficacy (Ngonghala et al., 2014)

Estimation techniques

- Maximum Likelihood Estimation
- Bayesian Inference
- Least Squares Fitting
- Etc.

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Some key features in malaria modeling

Advanced concepts

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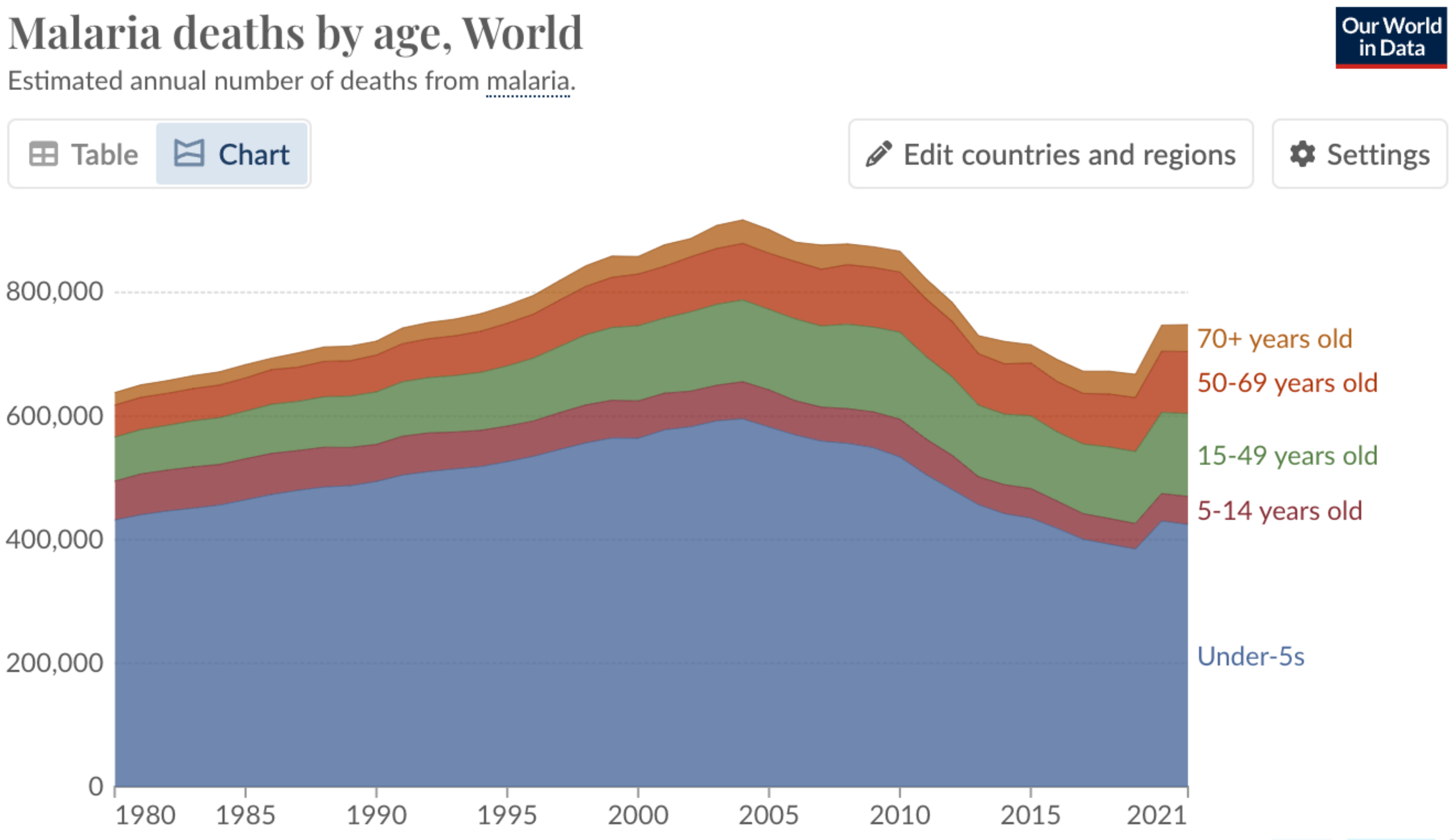
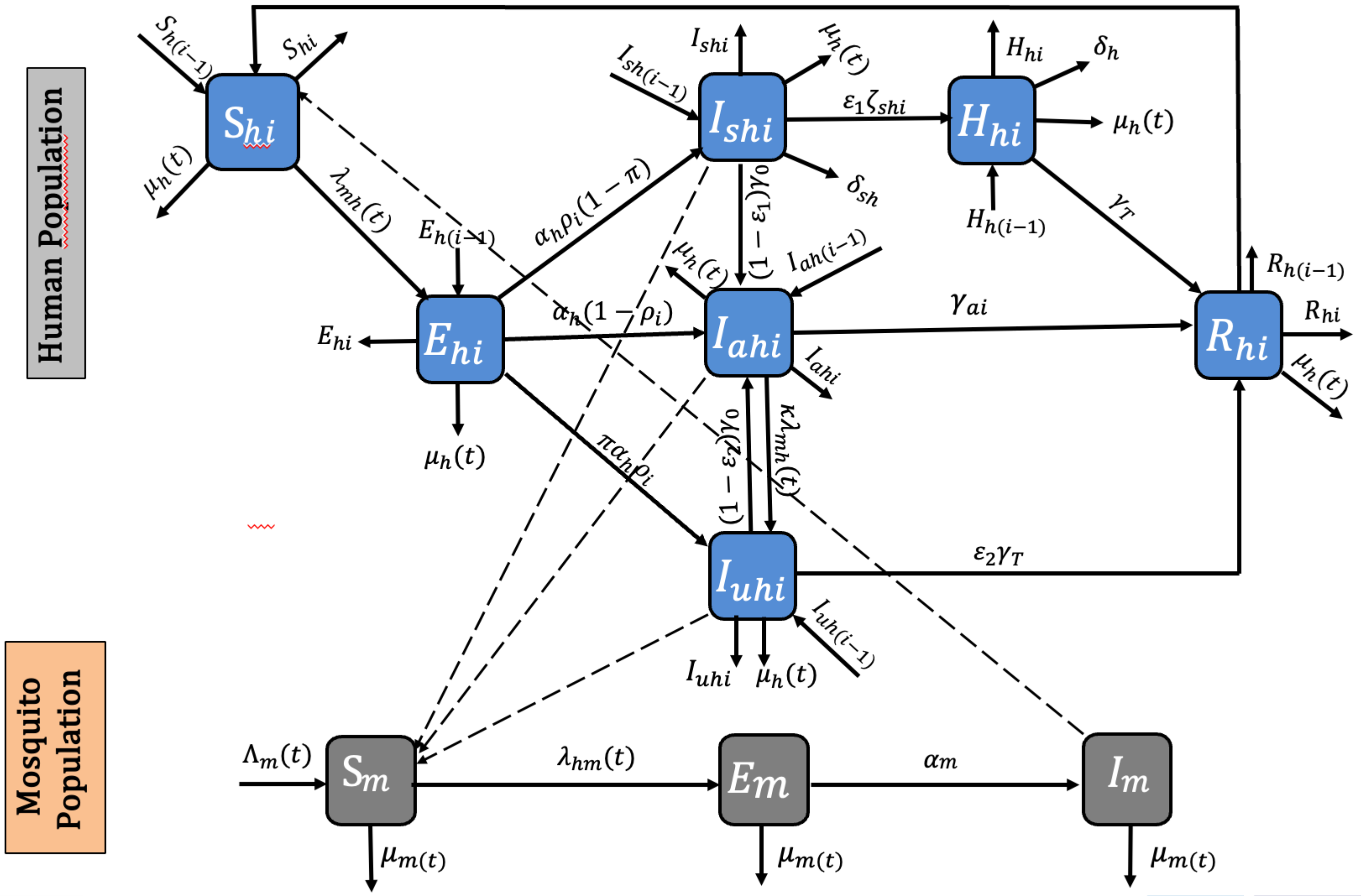
Malaria deaths by age



Data source: IHME, Global Burden of Disease (2024)
OurWorldinData.org/malaria | CC BY

Malaria dynamic parameters are age-dependent

Age structure malaria model



$$\lambda_{hm} = \frac{\beta(t) * \left(P_{hma}\sum_{i=1}^{C} I_{ahi} + P_{hmu}\sum_{i=1}^{C} I_{uhi} + P_{hms}\sum_{i=1}^{C} I_{shi}\right)}{N_h}$$

Age structure malaria model: ODEs

Set of ODEs linked to the model

$$
\begin{aligned}
\dot{S}_{hi} &= S_{h(i-1)} + \omega_{hi} R_{hi} - (\lambda_{mhi} + \mu_{hi})\, S_{hi} - S_{hi}, & \text{(1a)}\\
\dot{E}_{hi} &= E_{h(i-1)} + \lambda_{mhi} S_{hi} - (\alpha_h + \mu_{hi})\, E_{hi} - E_{hi}, & \text{(1b)}\\
\dot{I}_{shi} &= I_{sh(i-1)} + \alpha_h \rho_i (1-\pi) E_{hi} - (\varepsilon_1 \zeta_{sh} + (1-\varepsilon_1)\gamma_0 + \mu_{hi} + \delta_{sh})\, I_{shi} - I_{shi}, & \text{(1c)}\\
\dot{I}_{ahi} &= I_{ah(i-1)} + \alpha_h (1-\rho) E_{hi} + (1-\varepsilon_1)\gamma_0 I_{shi} + (1-\varepsilon_2)\gamma_0 I_{uhi} - a_0 I_{ahi} - I_{ahi}, & \text{(1d)}\\
\dot{I}_{uhi} &= I_{uh(i-1)} + \alpha_h \rho \pi E_{hi} + \kappa \lambda_{mh} I_{ahi} - (\varepsilon_2 \gamma + (1-\varepsilon_2)\gamma_0 + \mu_{hi})\, I_{uhi} - I_{uhi}, & \text{(1e)}\\
\dot{H}_{hi} &= H_{h(i-1)} + \varepsilon_1 \zeta_{sh} I_{shi} - (\delta_h + \gamma + \mu_{hi})\, H_{hi}, & \text{(1f)}\\
\dot{R}_{hi} &= R_{h(i-1)} + \gamma_a I_{ahi} + \gamma_t H_{hi} + \varepsilon_2 \gamma_t I_{uhi} - (\omega_{hi} + \mu_{hi})\, R_{hi} - R_{hi}, & \text{(1g)}\\
\dot{S}_m &= \Lambda_m N_m - (\lambda_{hm} + \mu_m)\, S_m, & \text{(1h)}\\
\dot{E}_m &= \lambda_{hm} S_m - (\alpha_m + \mu_m)\, E_m, & \text{(1i)}\\
\dot{I}_m &= \alpha_m E_m - \mu_m I_m, & \text{(1j)}
\end{aligned}
$$

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Modeling the force of infection as a function of age

Epidemiol. Infect. (2017), **145**, 2545–2562.
doi:10.1017/S0950268817001297

Estimating age-time-dependent malaria force of infection accounting for unobserved heterogeneity

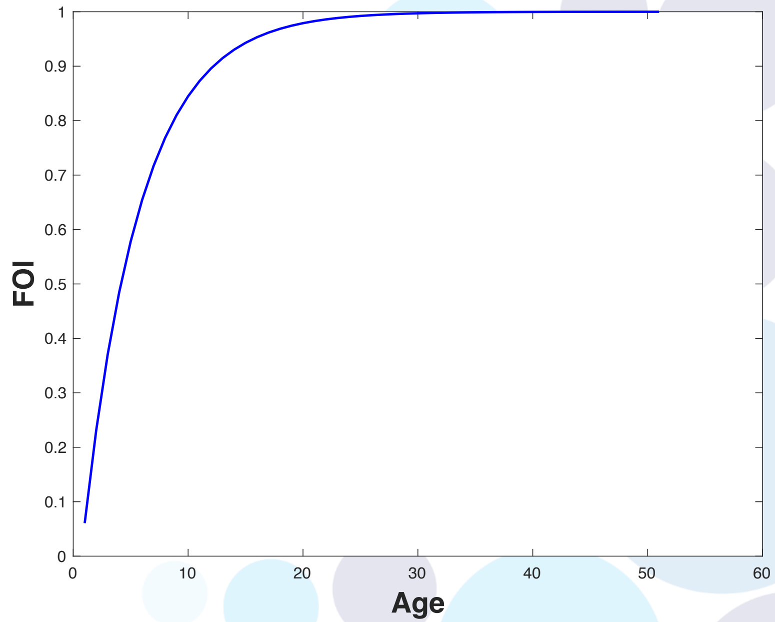
L. MUGENYI[1,2]*, S. ABRAMS[2] AND N. HENS[2,3]

For age=0 : $\lambda_{mh}(0) = \lambda_{mh}(1 - e^{-\frac{age_0}{\alpha_0}})$

For age>0 : $\lambda_{mh}(age) = \lambda_{mh}(1 - e^{-\frac{age}{\alpha_0}})$

α_0: age of half increase in exposure

α_0 and age_0 are estimated by the model.



$\lambda_{mh} = P_{mh} * \beta * n_0 * \frac{I_m}{N_m}$ (FOI)

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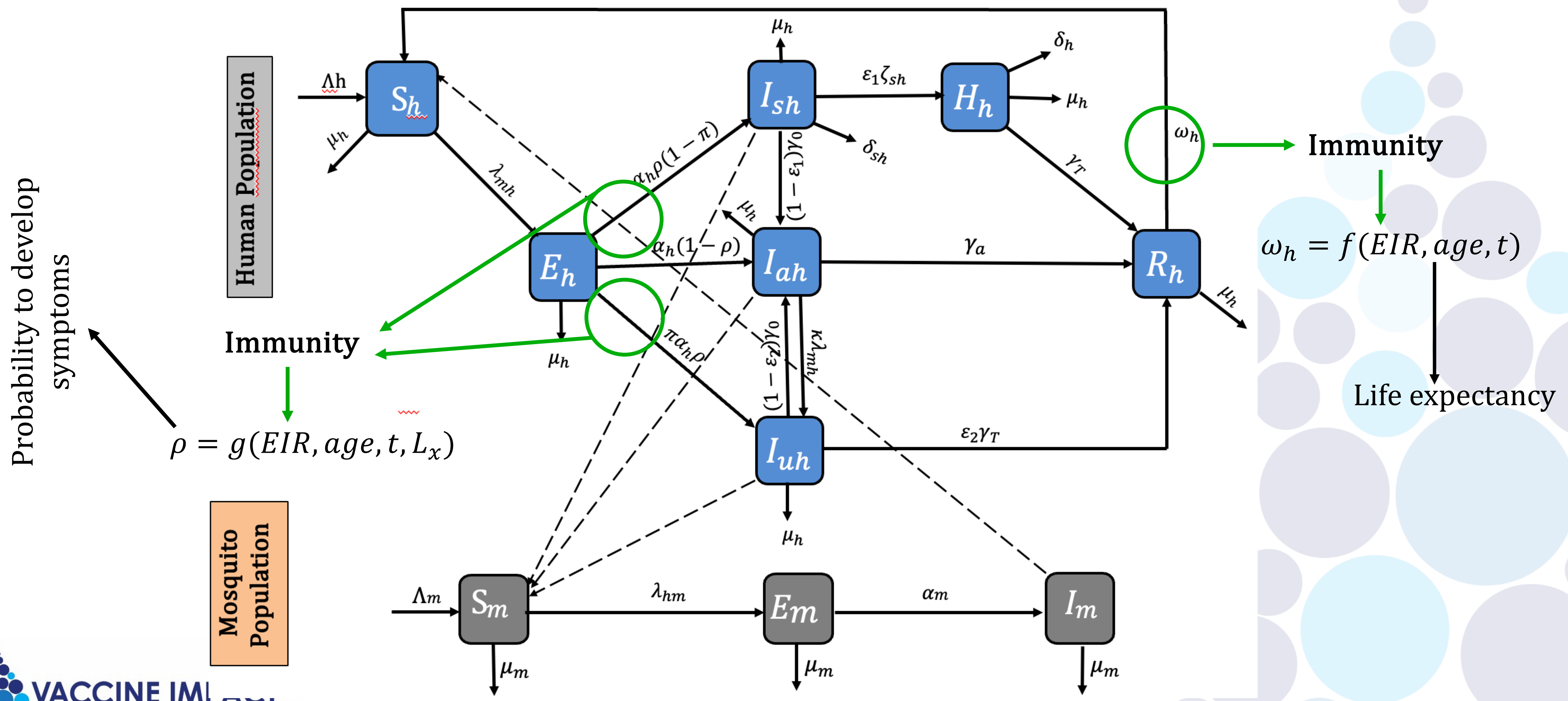
Modeling immunity to Malaria infection



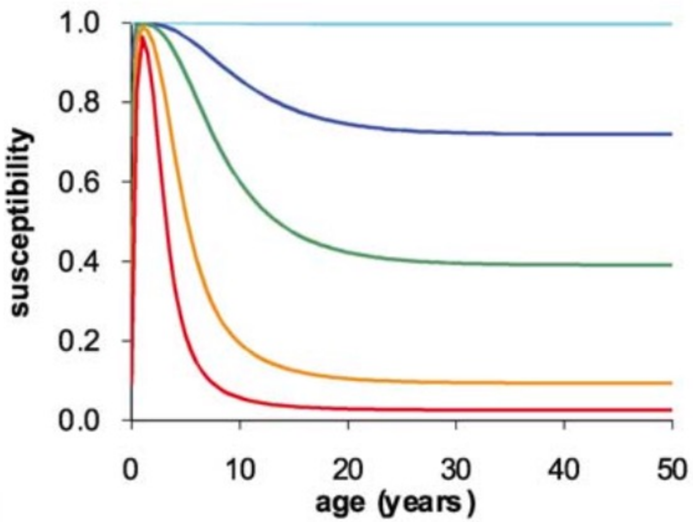
Modeling immunity to Malaria infection in adults

OPEN ACCESS Freely available online

PLoS COMPUTATIONAL BIOLOGY

Determination of the Processes Driving the Acquisition of Immunity to Malaria Using a Mathematical Transmission Model

João A. N. Filipe[1¤a], Eleanor M. Riley[2], Christopher J. Drakeley[2], Colin J. Sutherland[2], Azra C. Ghani[1¤b*]

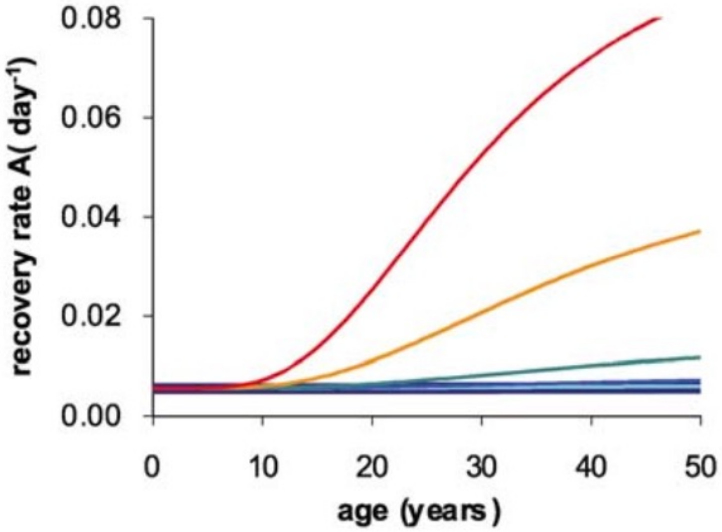


Example of the immunity function

$$\rho(age, EIR, L_x) = \frac{\rho_{max}}{1 + \exp(-\frac{A}{B})}$$

$$A = age - age_0$$

$$B = \theta_0 \frac{L_x}{L - age_0}(1 + c_k EIR)^{ns}$$



$$\omega_h(EIR, age) = 365 * (\omega_0 + \frac{0.038 - \omega_0}{(1 + \frac{age}{1.5})^{1.5}})$$

$$\omega_0 = 0.022 * \exp(-0.311 * EIR)$$

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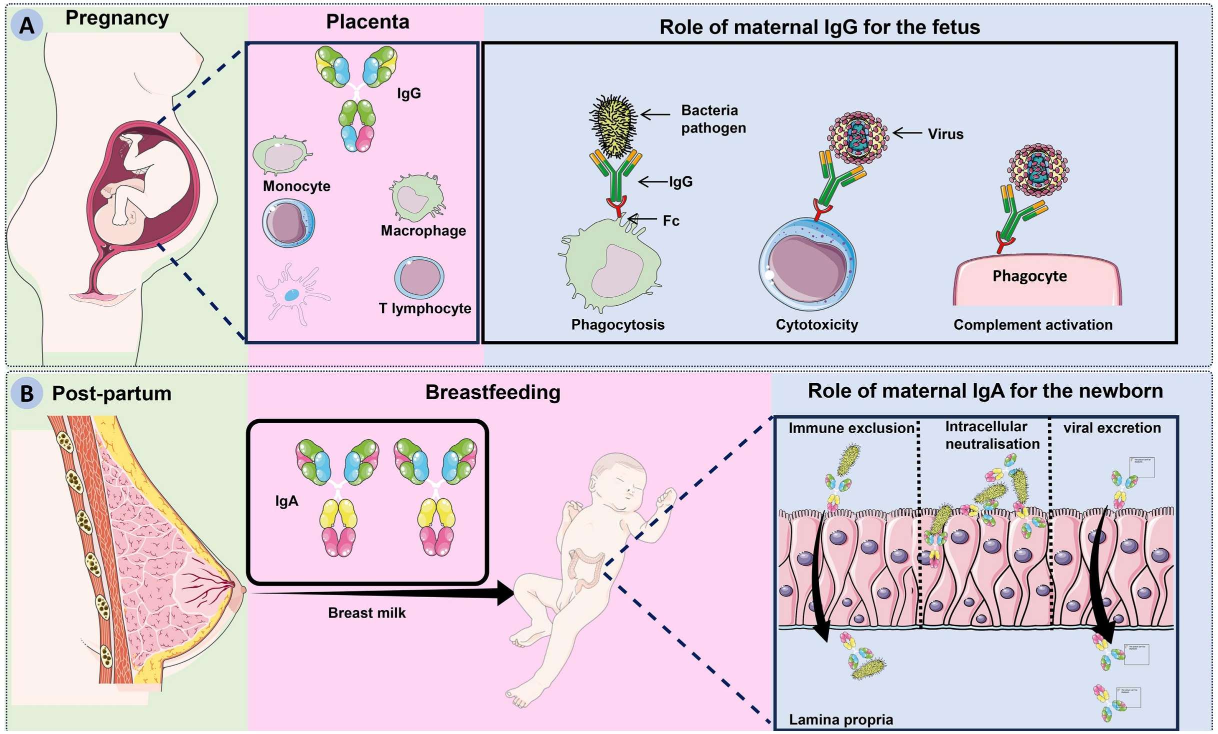
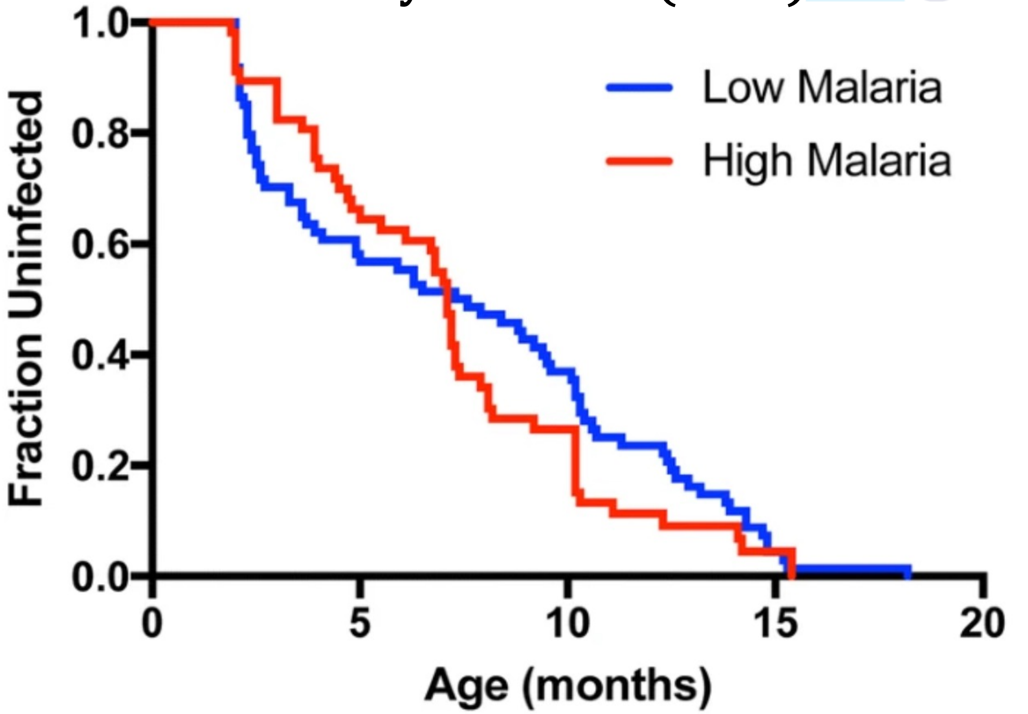
Modeling immunity to Malaria infection

Maternal immunity transferred to newborns



Sereme et al. (2024)

Reynaldi et al. (2019)



$$\rho(age) = \begin{cases} \left(\frac{1}{p}\right) * \rho_{mother} * \exp(-k * age), & age \leq age_0 \\ 0, & age > age_0 \end{cases}$$

Immunity in newborns

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Modeling the effect of seasonality

Emerg Infect Dis. 2023 Apr; 29(4): 801–805. PMCID: PMC10045708
doi: 10.3201/eid2904.220549 PMID: 36958009

Effects of Seasonal Conditions on Abundance of Malaria Vector *Anopheles stephensi* Mosquitoes, Djibouti, 2018–2021

Alia Zayed, Manal Moustafa, Reham Tageldin, and James F. Harwood

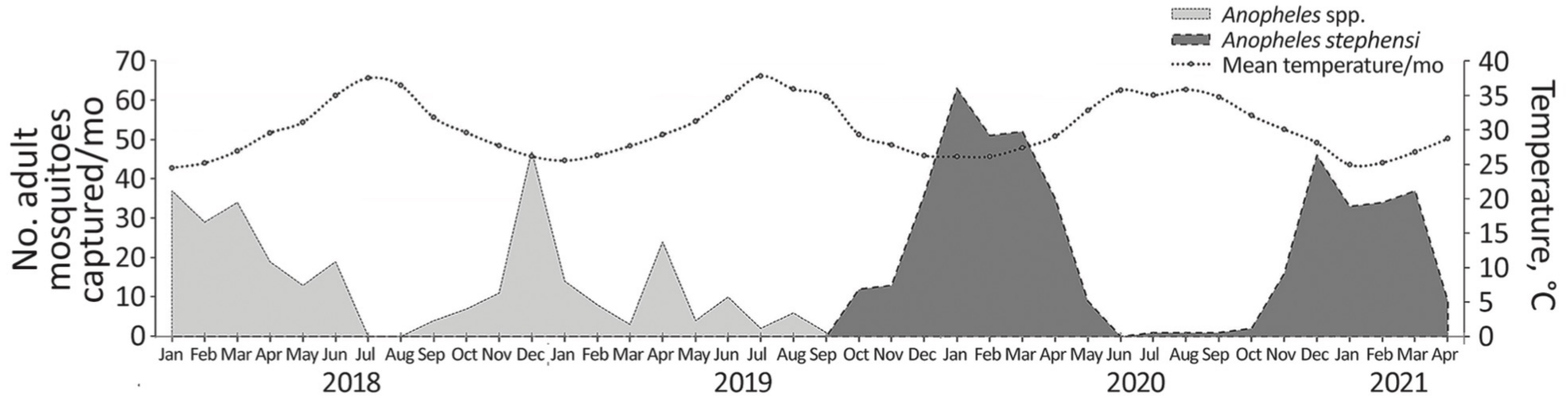
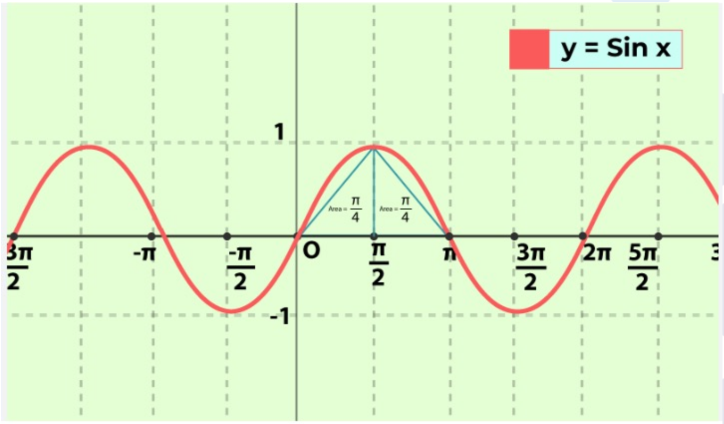


Figure 1. Associations between numbers of adult mosquitoes captured and mean temperature, by month, US military base, Djibouti, September 2019–August 2020. (We began identifying *Anopheles stephensi* mosquitoes specifically in October 2019.)

Seasonality driven by rainfall (or temperature)



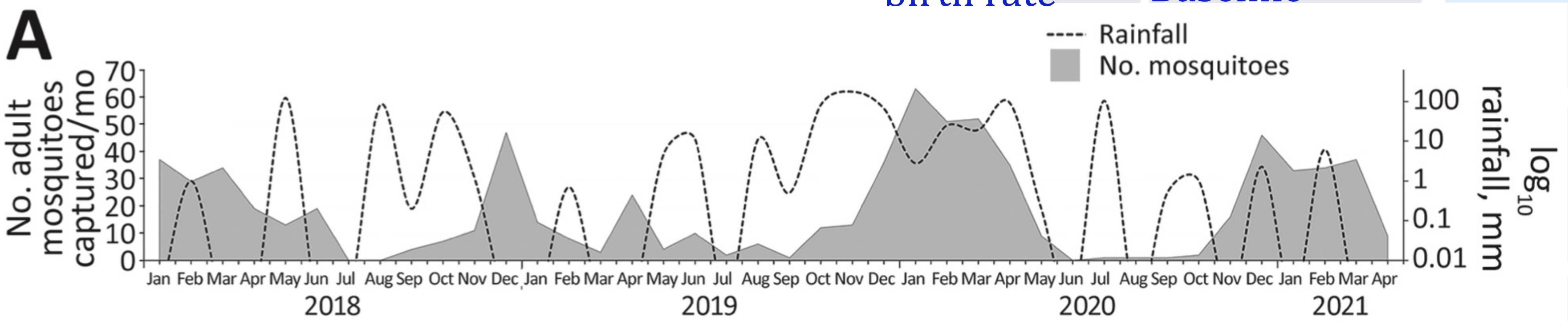
Source: geeksforgeeks

$$\Lambda_m = \Lambda_{m0}\left(1 + a_1 \sin\left(\frac{2\pi}{12}(t+\phi_1)\right)\right)$$

Mosquito birth rate

Baseline

Phase shift



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Modeling the effect of seasonality

Seasonality driven by rainfall (or temperature)

$$\Lambda_m = \Lambda_{m0}\left(1 + a_1 \sin\left(\frac{2\pi}{12}(t + \phi_1)\right)\right)$$

Mosquito birth rate

Baseline

Phase shift

Force of infection

$$\lambda_{mh}(t) = \lambda_{mh0}\left(1 + a_2 \sin\left(\frac{\pi}{6}(t - M'_{Peak} + 3)\right)\right)$$

Force of infection

Baseline

Peak month in rainfall

Linking Peak month and $\boldsymbol{\phi_1}$

$$\sin\left(\frac{2\pi}{12}(t + \phi_1)\right) \text{ is max if } \frac{2\pi}{12}(M_{Peak} + \phi_1) = \frac{\pi}{2} \Longrightarrow \phi_1 = 3 - M_{Peak} \Longrightarrow$$

Mosquito birth rate

$$\boxed{\Lambda_m(t) = \Lambda_{m0}\left(1 + a_1 \sin\left(\frac{\pi}{6}(t - M_{Peak} + 3)\right)\right)}$$

Modeling Seasonal Malaria Chemoprevention

Source: Peoples Gazette

- Administration of drugs to under-five children
- Period: Peak transmission period (3 months)
- Reduction of the force of infection (λ_{mh}^{SMC})

Normal seasonal force of infection

$$\lambda_{mh}(t) = \lambda_{mh0}\left(1 + a_1 \sin\left(\frac{\pi}{6}(t - M'_{Peak} + 3)\right)\right)$$

$$\lambda_{mh0} = P_{mh} * \beta * n_0 * \frac{I_m}{N_m}$$

SMC Coverage

$M_{Peak} - 1$ $\quad$ $M_{Peak} + 2$

$$\lambda_{mh}^{SMC}(t, age) = \begin{cases} (1 - \varphi_0) * \lambda_{mh} + \left(1 - \varphi_0 \xi_0 e^{-k*(t - t_{SMC})}\right) * \lambda_{mh}, & age \leq 60 \text{ and } start \leq m(t) \leq End \\ \lambda_{mh}, & age > 60 \end{cases}$$

SMC initial efficacy

$$m(t) = (mod(t-1), T) + 1$$

$$\lambda_{hm}^{total}(t) = \sum_{c=1}^{n_c} p_a \lambda_{mh}^{SMC}(t, age)$$

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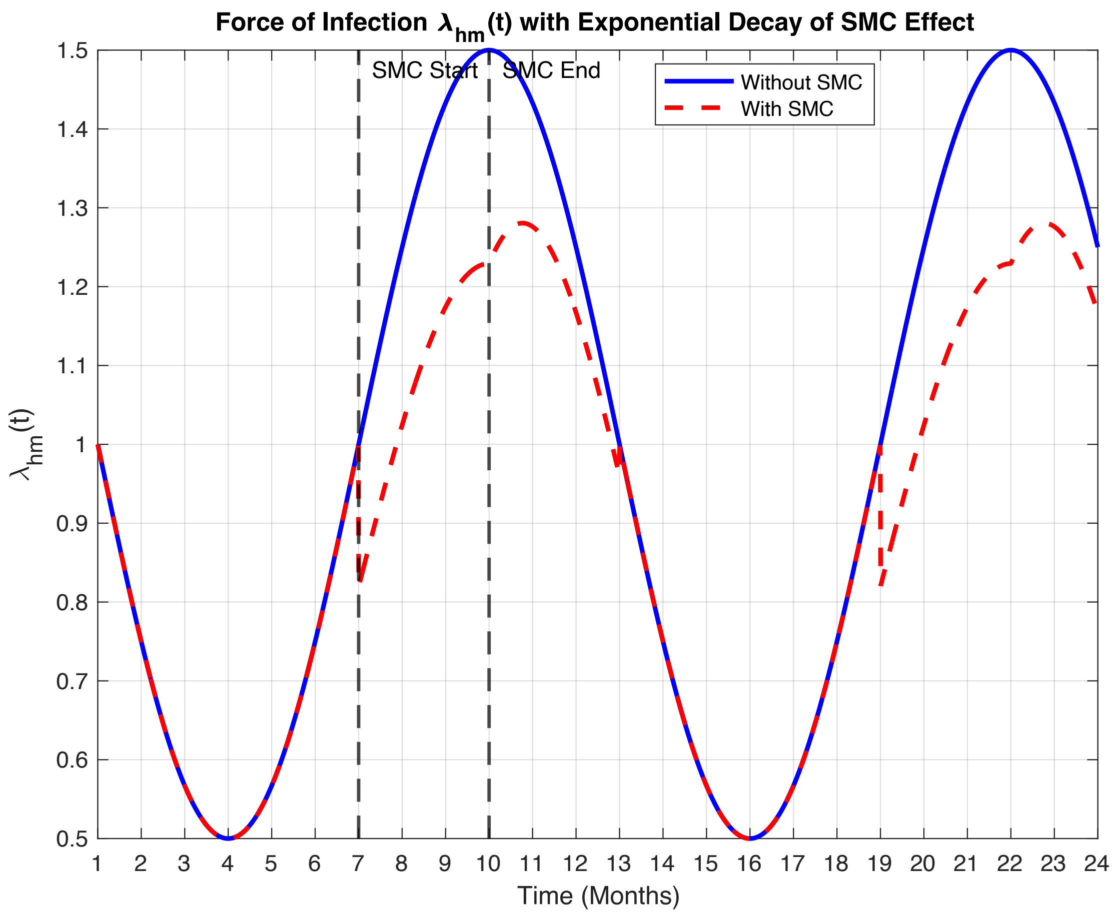
Modeling Seasonal Malaria Chemoprevention

Graphical illustration



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Vaccine impact modeling

Vaccine

Volume 33, Issue 52, 22 December 2015, Pages 7544-7550

Vaccine approaches to malaria control and elimination: Insights from mathematical models ☆

Michael T. White, Robert Verity, Thomas S. Churcher, Azra C. Ghani

Exponential decay functions

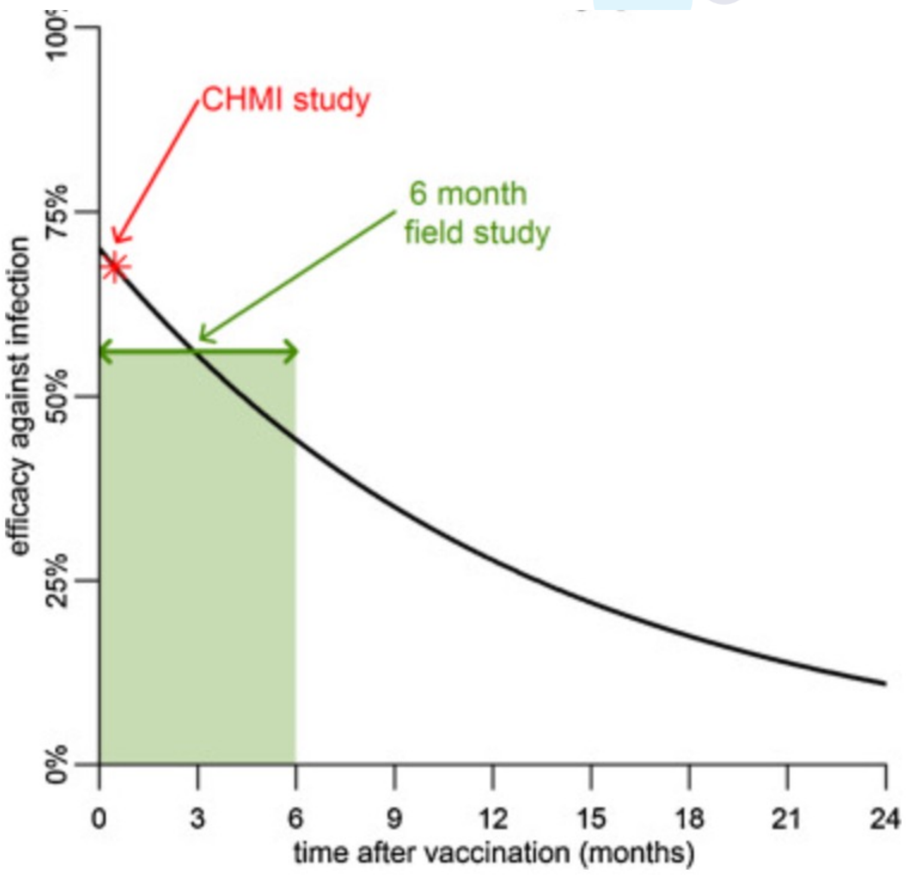
Force of infection

Exponential decay rate

$$\lambda_{mh}(Vaccine) = \lambda_{mh}(1 - VE_0 e^{-\omega_0 * t})$$

$$\lambda_{mh}(Booster) = \lambda_{mh}(1 - VE_{boost} e^{-\omega_{boost} * (t - t_{boost})})$$

Initial vaccine efficacy



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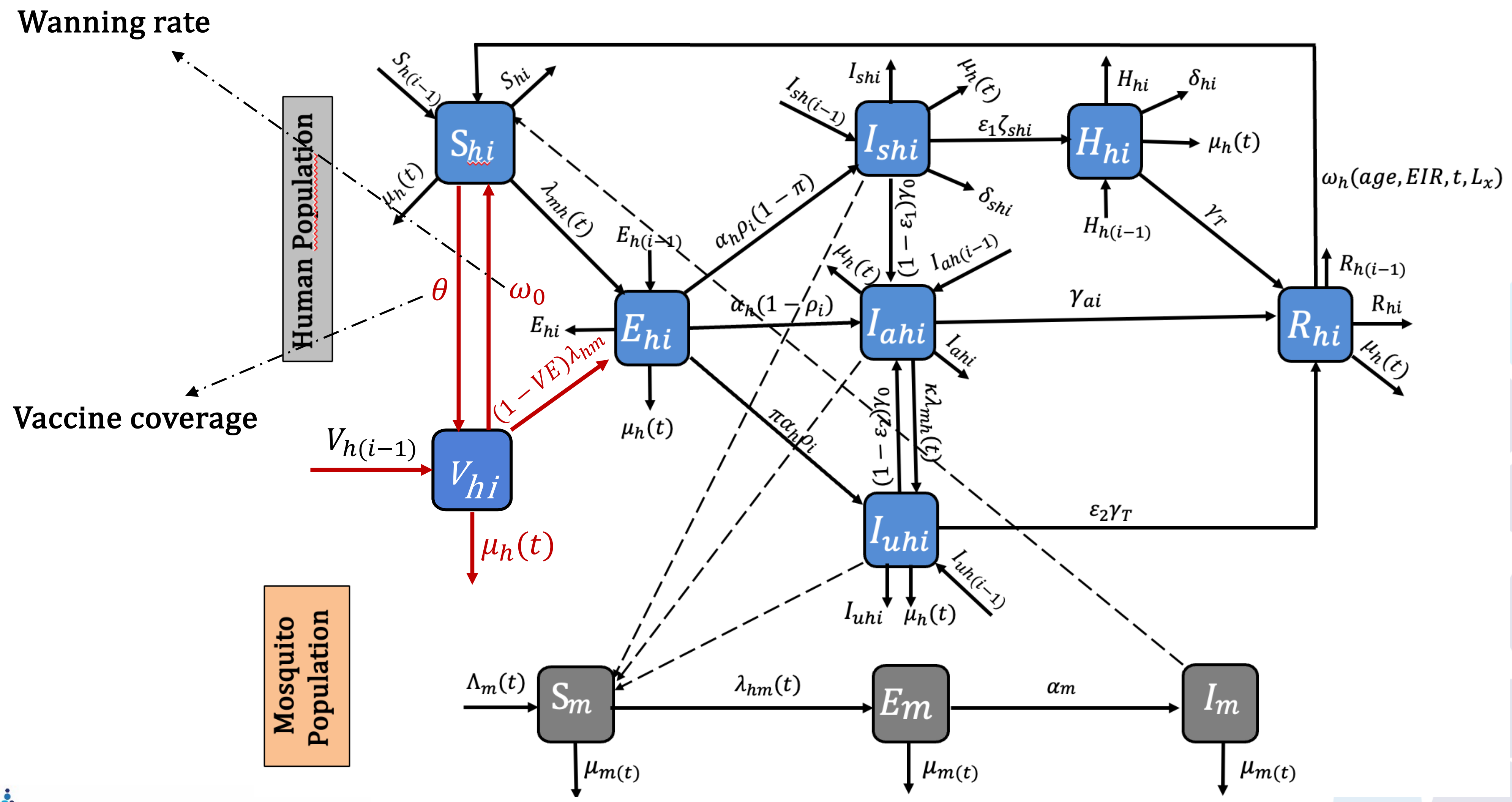
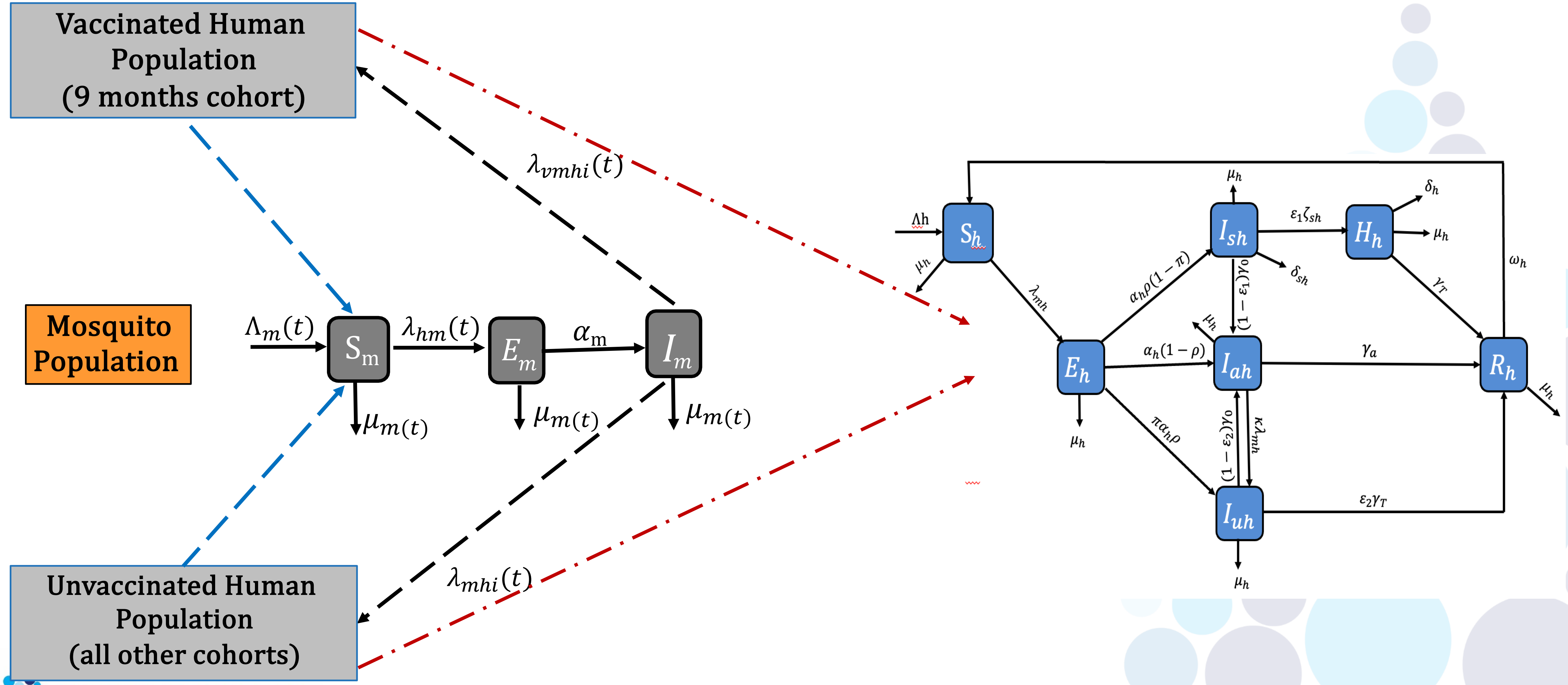
Accounting for vaccination

(Model1)



Accounting for vaccination

(Model2)



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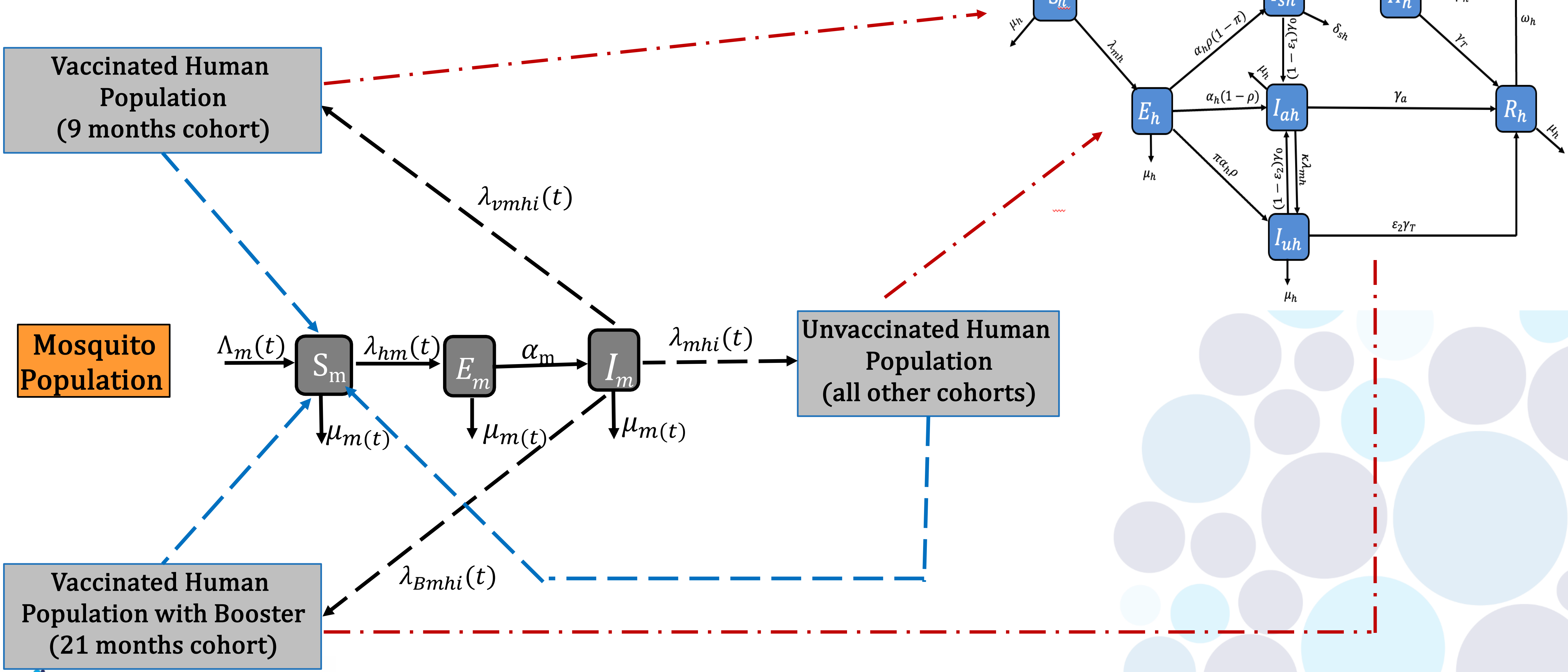
Accounting for a booster dose

(Model3)



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Associated computer code

Model code

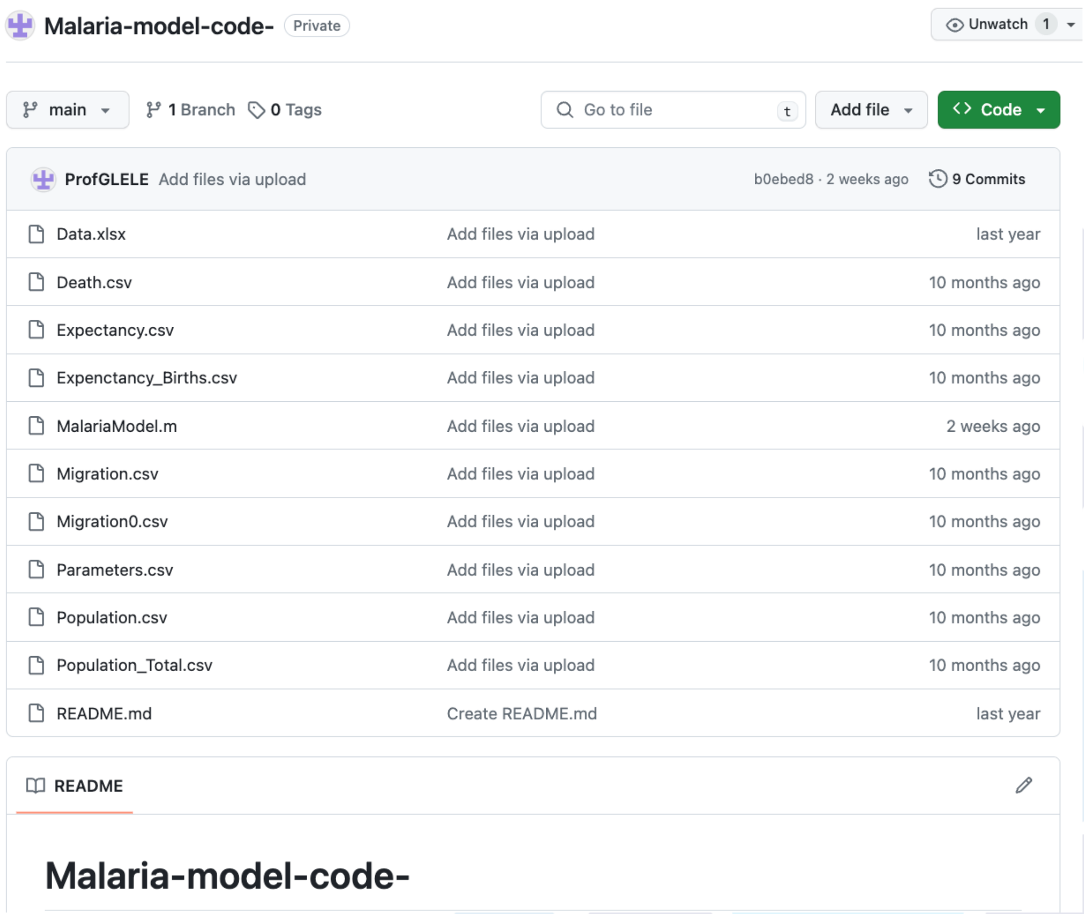
```
function MalariaModel
tstart=cputime;

% This function computes for each age cohort (0 to 100) of a country, the
% number of individuals (CohortSize), the number of severe Malaria cases (Cases),
% the number of DALYs (DALYs) and the number of deaths due to Malaria (Deaths)
% from year 2000 to year 2100 using a mechanistic model.
% The function imports variables from the following .csv files:
% - Total population of the country from 2000 to 2100 ('PopT'; Population_Total.csv)
% - Total births of the country from 2000 to 2100 ('Births'; Population.csv)
% - Size of each cohort from 2000 to 2100 ('Ncohort'; Population.csv)
% - Net migration rate for cohort 0 from 2000 to 2100 ('Migrat'; Migration0.csv)
% - Net migration rate for other cohorts from 2000 to 2100 ('Migrationr'; Migration.csv)
% - Death rate for cohort classes ('Tdeaths'; Death.csv)
% - The Expected remaining years of life for cohort 0 ('Exp0'; Expectancy Births)
% - The Expected remaining years of life for other cohorts ('Exp'; Expectancy.csv)
% We consider:
% - theta1: vaccination coverage for cohort 0 in 2023=0.8
% - theta2: vaccination coverage for cohort 2 in 2025=0.64
% - r: number of stochastic runs of the model; here, we consider r=30.

% Author: Prof Romain GLELE KAKAÏ, Laboratory of Biomathematics and
% Forest estimations, University of Abomey-Calavi; 04BP1525, Cotonou, Benin
% Email: romain.glelekakai@fsa.uac.bj/glele.romain@gmail.com


% Importing the total population of the country from 2000 to 2100
Population = readmatrix('Population_Total');
% Importing death rates from 2000 to 2100
TDeath = readmatrix('Death');
```

Available on GitHub



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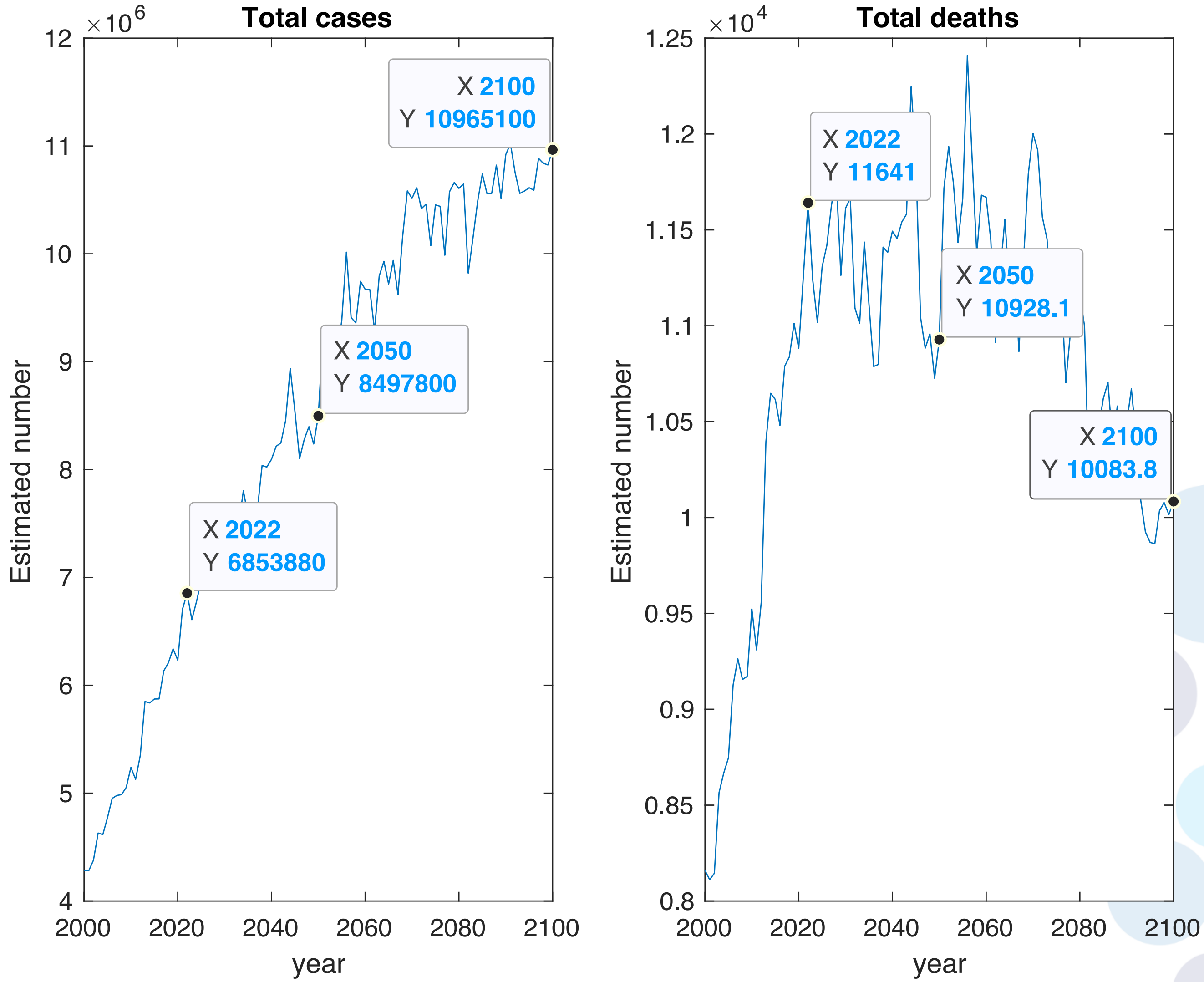
https://github.com/ProfGLELE/Malaria-model-code-.git

Applications

Malaria projection: Ghana

Without vaccination



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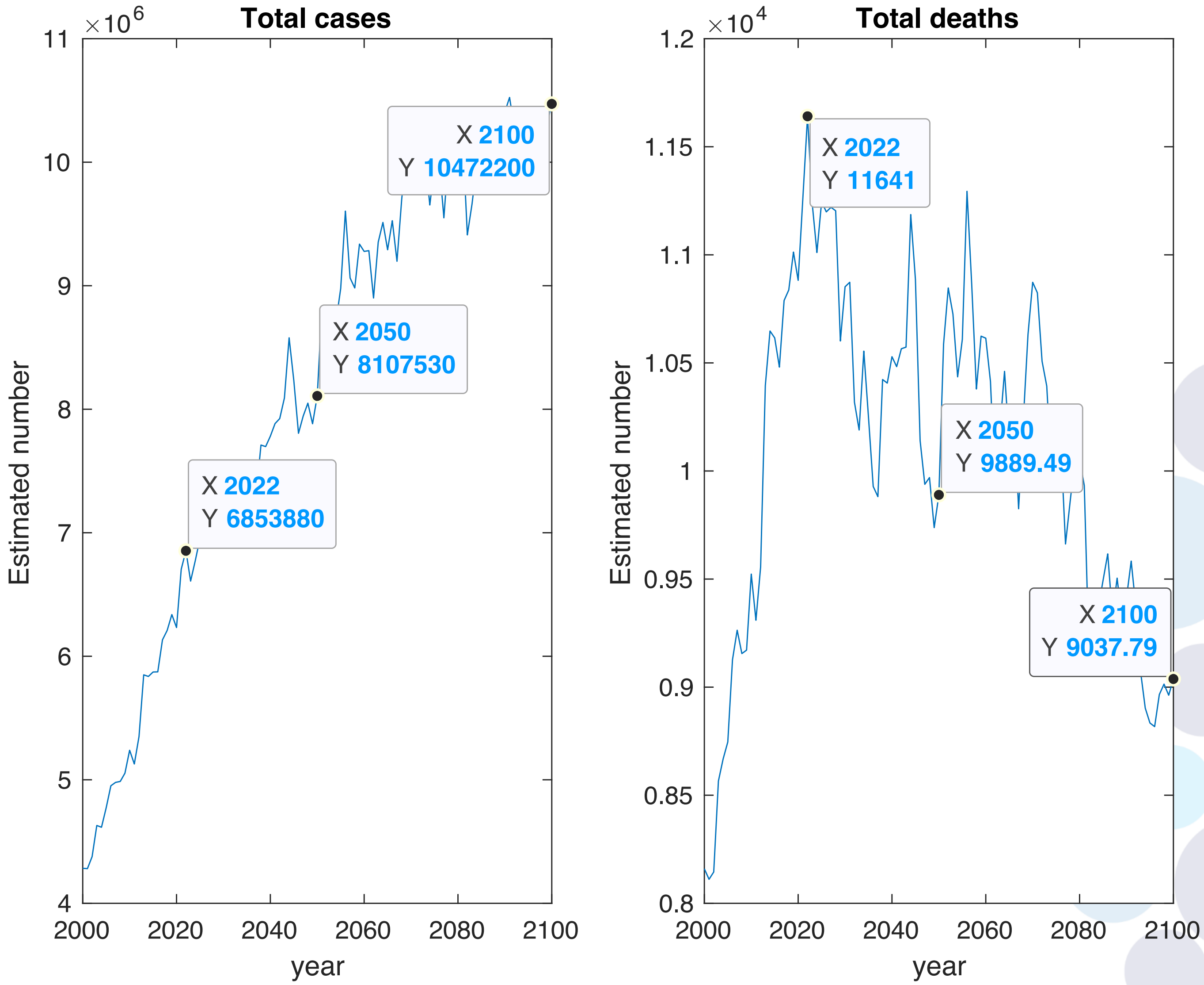
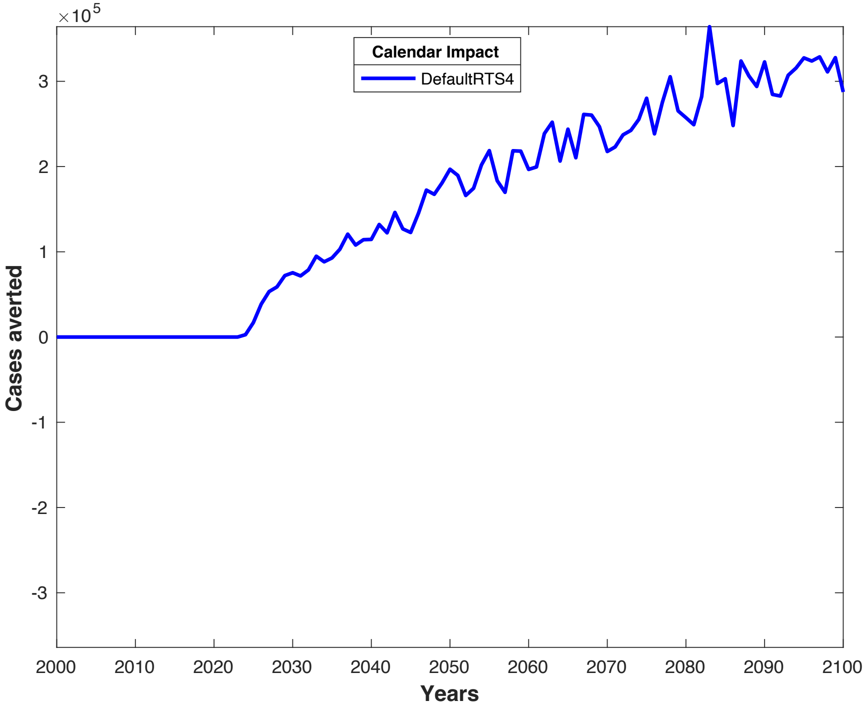
Applications

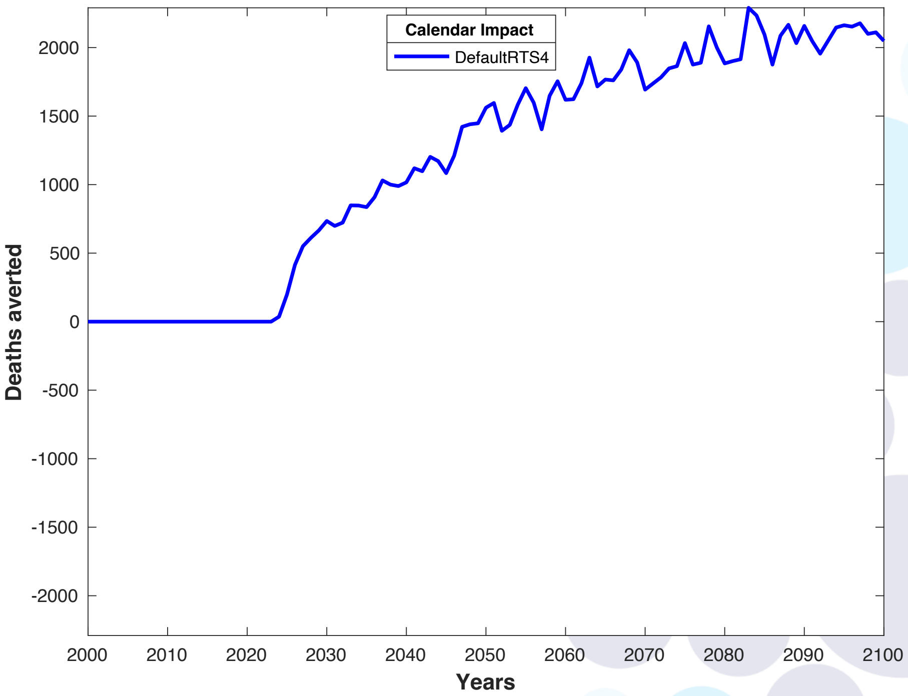
Malaria projection: Ghana

With vaccination (RTS,S with a booster dose)



Applications
Malaria projection: Ghana





VACCINE IMPACT MODELLING CONSORTIUM

Thank you for your attention

VACCINE IMPACT
MODELLING CONSORTIUM