Effects of Natural Acquired Immunity in an Age-Structured Malaria Model

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Abstract

Malaria, a vector borne disease, is one of the most important major global public health challenges. In this paper we develop a deterministic mathematical model for malaria, which considers the effects on malaria prevalence of the chronological age of human hosts and the role of natural acquired immunity (NAI) of people continuously exposed to the parasite. We identify the basic reproduction number, R_0, and run numerical simulations on a discrete age version of the model. The aim of this study is to determine how different levels of age dependent NAI, which depend on levels of transmissibility (mosquito presence) can affect malaria dynamics. We conclude that the proportion of infectious individuals decrease with increasing levels of transmissibility and that for levels of transmissibility greater than a certain threshold, the number of infectious people in younger age groups is larger than in older ones.

1 Introduction

Malaria is a vector-borne infectious disease caused by *Plasmodium* parasites, which is transmitted to humans by the bites of female *Anopheles* mosquitoes, which exclusively bite at night [1], most commonly from the species *A.gambiae*. Four parasite species are responsible for causing malaria in humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale*. 3.3 billion people live in areas at risk of malaria transmission, which is the 5th leading cause of death from infectious diseases worldwide [4]. Malaria is a major international health problem, with an annual estimate of 216 million documented cases (clinical episodes) and around 1 million deaths [4]. The disease is mostly common in tropical and subtropical regions including much of Sub-Saharan Africa, Asia and the Americas. Most vulnerable to severe malaria when exposed to the parasite are people with little or no immunity to the disease, such as young children, pregnant women, or travelers coming from regions with no malaria transmission or low endemicity (proportion of people tested positive for *P.falciparum* antibodies) [4]. Malaria is a huge economic burden for many countries, with direct costs estimated to be at least US$12 billion per year world wide [4].

P.falciparum is responsible for approximately 1 million deaths and 75% of the malaria cases worldwide [2]. Across Sub-Saharan Africa, where the disease is highly endemic, humans are constantly exposed to the mosquito and hence to the parasite. In these regions, the majority of infected adults do not experience severe clinical manifestations when infected, and continue with their daily routine, despite positive results in diagnostic tests for parasitemia [5]. This ability to suppress parasite growth in the human body after repetitive exposer to *P.falciparum* is called natural acquired immunity (NAI)[25]. NAI can be divided into three types of immunities to malaria: (i) antiparasite immunity, which affects the density of the parasite in the blood; (ii) clinical immunity, which gives protection against clinical symptoms; and (iii) premunition, which gives protection against new infections due to a low-grade parasitemia [25]. If the constant exposure to the parasite is interrupted for a prolonged period of time, the NAI is lost or weakened, which occurs in geographical regions with high seasonality and hence a lower transmissibility of malaria due to a non uniform mosquito presence [6]. For the purpose of realistically studying the risk of malaria infection it is also worth while to consider innate immunity (II), defined by Bruce-Chwatt as: "...an inherent property of the host, a refractory state or an immediate inhibitory response to the introduction of the parasite, not dependent on any previous infection with it..."[11] [25]. II is associated to the immune response of the human host to the infection, and it has been shown to be age dependent [7]. Therefore, people living in areas with high endemicity (high transmissibility of malaria) are constantly exposed to the parasite and therefore acquire natural immunity when aging, whereas people living in lower endemicity areas (low transmissibility of malaria) lose the NAI if previously acquired and are dangerously exposed to new infections.

The first model that outlined the basic features of malaria transmission was developed by Sir Ronald Ross in 1911 [10]. In his model Ross captured the incidence of malaria

in humans related to the number of mosquitoes. He presented a deterministic ordinary differential equations model, with an SIS structure for human hosts and an SI structure for mosquito vectors, where S denotes susceptible and I infected. However, with the availability of more data and knowledge about malaria, this model became not sufficient anymore [3]. That first malaria model was expanded in several ways, for example by introducing the effects of human age [17] [12] [13], acquired immunity to malaria [12] [14] [19] or genetic and spacial heterogeneity of parasite and host [22], among these age and immunity play an important role in endemic malaria regions [5][7][6]. Age structure was included by Anderson and May [17], where they allow the infection to move differentially within different age groups as well as with time, which give rise to a partial differential equation model in time and age. Again it was later noticed that this model did not fit well with real trends in prevalence with age [18] because they had not considered NAI in their model and therefore it was suggested that NAI has to be co-played with age [3]. Immunity has been studied by including an immunity function in existing models [19] or by considering separate immune classes [20][3]. Those models include immunity but do not consider age, ignoring again one of the important factors for risk of malaria infection. Therefore we developed a deterministic partial differential equations malaria model, with non-constant total human population, in which we include NAI of individuals in different compartments and continuously changing with age and time, to study malaria dynamics. Furthermore, in our model we include that NAI varies with age and is related to mosquito presence [8], which to the best of our knowledge has not been previously considered.

Here we use our model to study the role that NAI plays for malaria transmission dynamics. We investigate the possible effects on malaria that weakness and loss of NAI have as a result of changing levels of transmissibility (mosquito presence). It is important for control strategies to determine how people with acquired immunity, which are typically the ones not attending medical facilities, either due to being asymptomatic or having uncomplicated flu like clinical manifestations, affect prevalence of Malaria in African countries and failure to achieve a successful control of the disease.

2 Age-Structured Malaria Model

We construct a compartment malaria model that incorporates the transmission between humans and mosquitoes. The model is a natural epansion of Ross's model [3] that incorporates host's age structure and two classes that account for differences in malaria dynamics considering malaria endemicity of the geographical region and natural acquired immunity (NAI) of humans.

Let $s(t,a)$, $i(t,a)$, $\tilde{i}(t,a)$ and $r(t,a)$ denote the density of susceptible, infectious (with high parasitemia and severe clinical manifestations), infectious (with low parasitemia with a lack or mild disease clinical manifestations) and recovered individuals respectively. We allow the possibility for recovered individuals to have a positive parasitemia count in the blood but at such low levels that are insufficient for transmission to the mosquito. In

addition, we let $S_v(t)$ and $I_v(t)$ denote the number of susceptible and infected mosquitoes respectively at time t.
Some of the host's parameters now depend on age, hence let $d_h(a)$ denote the age dependent natural death rate of humans, while $\delta_h(a)$ and $\tilde{\delta}_h(a)$ denote the age dependent disease induced human death rates. We denote to be $\rho(a)$ the age dependent rate of suppressing the parasite growth in the human body by the II, and $\tilde{\rho}(a)$ the age dependent rate of suppressing the parasite growth by the II and by the antiparasite immunity, a fundamental part of NAI development.
To find the number of new infections for humans define β to be the number of bites of one mosquito to humans per unit of time, $d(a)$ the age dependent probability of transmission of infection from an infected mosquito to a susceptible host given that contact (by biting) between the two occur, and let $N_h(t) := \int_0^\infty (s(t,a) + i(t,a) + \tilde{i}(t,a) + r(t,a))da$, that is the total human population size at time t. Further, let $\tilde{d}(a)$ denote the probability of transmission of infection from an infected mosquito to a recovered host wherever a contact between the two occur. Then, the number of new infections of susceptible [recovered] hosts of age a per unit of time by mosquito bites is given by $d(a)\beta\frac{s(t,a)}{N_h(t)}I_v(t)$, $[\tilde{d}(a)\beta\frac{r(t,a)}{N_h(t)}I_v(t)]$. We assume that the probability of transmission $\tilde{d}(a)$ is different from the probability of transmission $d(a)$, since humans in the recovered class profit from premunition immunity which is part of the NAI, resulting from the repeated exposure to the parasite.
Finally denote $\gamma(a)$ the age dependent rate of recovering from the parasite and becoming completely susceptible, without any NAI protection.
We also include the parameter p that describes the level of transmissibility (chance of getting the disease, i.e. probability of encounter mosquitoes), when defined as proportion of people constantly exposed to mosquitoes in a geographical region; with $p = 1$ representing a high transmissibility area (high mosquito presence $7 - 12$ months a year) and $p = 0$ representing a low transmissibility area (high mosquito presence < 3 months a year).
Finally, the age dependent fertility rates are given by $\lambda_h(a)$ and $\tilde{\lambda}_h(a)$ under the assumption that new born individuals are born susceptible at a constant rate Λ.

To describe the mosquito dynamics we assume that mosquitoes do not recover from infection due to their short life span, and hence disease vector dynamics are captured by an SI model structure. If we let d_v be the natural death rate and λ_v be the birth rate of mosquitoes, c and $\tilde{c}(a)$ be the probability of transmission of infection to a susceptible mosquito from an infected host $i(t,a)$ and $\tilde{i}(t,a)$ respectively of age a, given that contact between the two occur, then the number of new infections of mosquitoes per unit of time by biting infectious hosts is given by $\beta\frac{I_h(t)}{N_h(t)}S_v(t) + \beta\frac{\tilde{I}_h(t)}{N_h(t)}S_v(t)$ where $I_h(t) := \int_0^\infty ci(t,a)da$ and $\tilde{I}_h(t) := \int_0^\infty \tilde{c}(a)\tilde{i}(t,a)da$. It is important to point out that the age dependency of $\tilde{c}(a)$ can be understood by realizing that subjects in class $\tilde{i}$ have a partially or fully developed antiparasite immunity, that in turn is age dependent and directly affects the transmission of the parasite to mosquitoes. On the other hand, we choose c to be constant since humans in class i are considered to have an equally high parasite load due to first infection if $p = 1$ and first like infection if $p \neq 1$, independent of age. For a diagram of the model see Figure

1.

The disease dynamics in this setting can be described by the following set of coupled ordinary differential equations (1) (for mosquitoes) and partial differential equations (2)(for humans):

$$\begin{cases} \dfrac{dS_v}{dt} = \lambda_v - \beta \dfrac{I_h(t)}{N_h(t)} S_v(t) - \beta \dfrac{\tilde{I}_h(t)}{N_h(t)} S_v(t) - d_v S_v(t) \\ \dfrac{dI_v}{dt} = \beta \dfrac{I_h(t)}{N_h(t)} S_v(t) + \beta \dfrac{\tilde{I}_h(t)}{N_h(t)} S_v(t) - d_v I_v(t) \end{cases} \tag{1}$$

$$\begin{cases} \dfrac{\partial s}{\partial t} + \dfrac{\partial s}{\partial a} = (1-p)\gamma(a)\tilde{i}(t,a) - d(a)\beta \dfrac{s(t,a)}{N_h(t)} I_v(t) - d_h(a) s(t,a) \\ \dfrac{\partial i}{\partial t} + \dfrac{\partial i}{\partial a} = d(a)\beta \dfrac{s(t,a)}{N_h(t)} I_v(t) - \rho(a) i(t,a) - (d_h(a) + \delta_h(a)) i(t,a) \\ \dfrac{\partial \tilde{i}}{\partial t} + \dfrac{\partial \tilde{i}}{\partial a} = \rho(a) i(t,a) + \tilde{d}(a)\beta \dfrac{r(t,a)}{N_h(t)} I_v(t) - p\tilde{\rho}(a)\tilde{i}(t,a) \\ \qquad\qquad - (d_h(a) + \tilde{\rho}_h(a))\tilde{i}(t,a) - (1-p)\gamma(a)\tilde{i}(t,a) \\ \dfrac{\partial r}{\partial t} + \dfrac{\partial r}{\partial a} = p\tilde{\rho}(a)\tilde{i}(t,a) - \tilde{d}(a)\beta \dfrac{r(t,a)}{N_h(t)} I_v(t) - d_h(a) r(t,a) \end{cases} \tag{2}$$

with boundary conditions (B.C.):

$$\begin{cases} s(t,0) = \displaystyle\int_0^\infty (\lambda_h(a)[s(t,a) + r(t,a)] + \tilde{\lambda}_h(a)[i(t,a) + \tilde{i}(t,a)])da =: \Lambda \\ i(t,0) = 0 \\ \tilde{i}(t,0) = 0 \\ r(t,0) = 0 \end{cases} \tag{3}$$

and initial conditions (I.C.):

$$\begin{cases} s(0,a) = s_0(a) \\ i(0,a) = i_0(a) \\ \tilde{i}(0,a) = \tilde{i}_0(a) \\ t(0,a) = r_0(a) \end{cases} \tag{4}$$

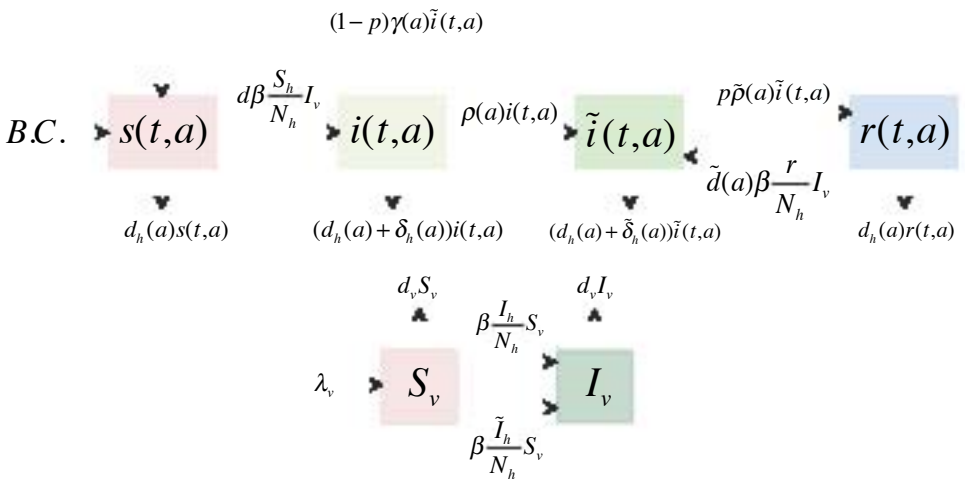

Figure 1: Age-structured Malaria Model

3 Analysis of the age-structure host-vector malaria model

In mathematical models for the spread of infectious diseases there is an important threshold number called the basic reproduction number R_0. If R_0 is greater than one, the disease can invade into the population, whereas if R_0 is less then one the disease dies out. The basic reproduction number is defined in general as the average number of secondary cases produced by one infectious individual, during its total infective period when introduced in a completely susceptible population (a population that is in the disease-free steady state). In this section we find the basic reproduction number by first analyzing the behavior of the population when it is completely susceptible (disease-free) and then by linearizing the system (1) and (2) at the disease free state to find a characteristic equation from where we define R_0. At the end of this section we give an interpretation for the expression for R_0 obtained from our malaria model with age-structure.

3.1 The disease-free state

We analyze how the mosquito and the human population behave in the absence of disease. For this purpose we assume

$$I_v = 0 \qquad \text{and} \qquad i = \tilde{i} = r = 0.$$

We obtain the following linear equation that describes the mosquito population when we enter the above into system (1):

$$\frac{dN_v}{dt} = \lambda_v - d_v N_v(t)$$

where $N_v(t) = S_v(t)$ is the total susceptible mosquito population.
The solution to this equation is given by

$$N_v(t) = \frac{\lambda_v}{d_v} + (N_v(0) - \frac{\lambda_v}{d_v})e^{-d_v t} \to_{t\to\infty} \frac{\lambda_v}{d_v} =: N_\infty$$

Hence, it will be assumed that the vector population has achieved its stable equilibrium defined by N_∞ in the absence of disease. Observe that if we add the two equations for mosquitoes from system (1) we obtain the linear differential equation $\frac{dN_v}{dt} = \lambda_v - d_v N_v(t)$, that is the same linear equation studied above for the disease free case, and so it can be assumed the mosquito population has achieved an equilibrium even in the presence of disease. Thus, because of the short lifespan of mosquitoes (approximately two weeks), we will assume throughout this work, that the mosquito population is at equilibrium N_∞.

From the equations involved in system (2), the only process affecting the human population in the disease free case come from vital dynamics. And in this case when substituting 0 for each of the infectious classes the process leads to the following equations, called the McKendrick equation:

$$\frac{\partial s}{\partial t} + \frac{\partial s}{\partial a} = -d_h(a)s(t,a)$$

With B.C. and I.C.:

$$s(t,0) = \int_0^\infty \lambda_h(a)s(t,a)da =: B(t) = \Lambda \qquad s(0,a) = s_0(a)$$

Formal solutions for this equation will evolve along the characteristic lines $a = t + c$, for c constant.
If $a \geq t$, then $s(t,a) = s(0,a-t)e^{-\int_{a-t}^a d_h(\sigma)d\sigma}$, which means that $s(t,a)$ are the individuals who were age $a-t$ at time 0, multiplied by the probability of surviving from age $a-t$ to age a.

If $t > a$, then $s(t,a) = s(t-a,0)e^{-\int_0^a d_h(\sigma)d\sigma}$, which means $s(a,t)$ are the individuals who were newborn ($a = 0$) at time $t-a$, multiplied by the probability of survival through age a.

The density for the total human population is then given by

$$s(t,a) = \begin{cases} s_0(a-t)e^{-\int_{a-t}^a d_h(\sigma)d\sigma}, & \text{if } a \geq t \\ B(t-a)e^{-\int_0^a d_h(\sigma)d\sigma}, & \text{if } t > a. \end{cases}$$

Substituting into the B.C. we find the so called Renewal Equation

$$\begin{aligned} B(t) &= \int_0^\infty \lambda_h(a)s(t,a)da \\ &= \int_0^t \lambda_h(a)B(t-a)e^{-\int_0^a d_h(\sigma)d\sigma}da + \underbrace{\int_t^\infty \lambda_h(a)s_0(a-t)e^{-\int_{a-t}^a d_h(\sigma)d\sigma}da}_{:=f(t)} \end{aligned}$$

where $f(t)$ represents the rate of new offspring generated by individuals in the population present at time $t = 0$.

It can be shown [9] that

$$B(t) = Ce^{\hat{p}t}(1 + \Omega(t))$$

where $C \geq 0$ constant, and $\Omega(t)$ is a function such that $\lim_{t\to\infty} \Omega(t) = 0$ and $\hat{p}$ measures the population dynamics.

So, if $t >>$, then

$$s(t, a) \to Ce^{\hat{p}(t-a)}e^{-\int_0^a d_h(\sigma)d\sigma}$$

Hence, the important solutions to consider are persistent solutions, i.e. exponential solutions with constant population structure:

$$s(t, a) = e^{\hat{p}(t-a)}P(a)$$

where $P(a) = e^{-\int_0^a d_h(\sigma)d\sigma}$ and p solves the characteristic equation

$$1 = \int_0^\infty \lambda_h(a)e^{-\int_0^a d_h(\sigma)d\sigma}e^{-\hat{p}a}da$$

3.2 Basic reproduction number R_0 and local stability

Assume, in the absence of infection, the human population has achieved the stable age-distribution

$$n(t, a) = s(t, a) = s_0P(a) =: P_0(a)$$

where $P(a) = e^{-\int_0^a d_h(\sigma)d\sigma}$.

And the mosquito population reached equilibrium

$$N_\infty = S_v(t) = \frac{\lambda_v}{d_v}$$

To study the local stability of the disease-free state, we need to linearize the equations is systems (1) and (2) at the disease free state:

$$(S_v(t), I_v(t)) = (\frac{\lambda_v}{\mu_v}, 0,),$$

and

$$(s(t, a), i(t, a), \tilde{i}(t, a), r(t, a)) = (P_0(a), 0, 0, 0)$$

by using the transformations

$$x(t, a) = s(t, a) - P_0(a), \qquad X_v(t) = S_v(t) - \frac{\lambda_v}{\mu_v}, \qquad M_h(t) = N_h(t) - \int_0^\infty P_0(a)da.$$

Observe that

$$\frac{1}{N_h(t)} = \frac{1}{\int_0^\infty n_h(t,a)da} = \frac{1}{\int_0^\infty P_0(a)da} - \frac{1}{(\int_0^\infty P_0(a)da)^2}(M_h(t)) + O(M_h^2(t))$$
$$= \frac{1}{\bar{P}} - \frac{1}{(\bar{P})^2}(M_h(t)) + O(M_h^2(t))$$

where we call $\bar{P} := \int_0^\infty P_0(a)da$, and

$$\frac{s(t,a)}{N_h(t)} = (x(t,a) + P_0(a))I_v(t)[\frac{1}{\bar{P}} - \frac{1}{(\bar{P})^2}(M_h(t)) + O(M_h^2(t))] \approx \frac{P_0(a)}{\bar{P}}I_v(t)$$
$$\frac{r(t,a)}{N_h(t)}I_v(t) \approx r(t,a)I_v(t)[\frac{1}{\bar{P}} - \frac{1}{(\bar{P})^2}(M_h(t))]$$

Defining $\tilde{I}_h(t) := \int_0^\infty \tilde{c}(a)\tilde{i}(t,a)da$, the linearized system is as follows:

$$\begin{cases} \frac{dX_v}{dt} = -\beta\frac{N_\infty}{\bar{P}}I_h(t) - \beta\frac{N_\infty}{\bar{P}}\tilde{I}_h(t) - d_vX_v(t) \\ \frac{dI_v}{dt} = -\beta\frac{N_\infty}{\bar{P}}I_h(t) - \beta\frac{N_\infty}{\bar{P}}\tilde{I}_h(t) - d_vI_v(t) \end{cases} \tag{5}$$

$$\begin{cases} \frac{\partial x}{\partial t} + \frac{\partial x}{\partial a} = -d(a)\beta\frac{P_0(a)}{\bar{P}}I_v(t) - d_h(a)x(t,a) + (1-p)\gamma(a)\tilde{i}(t,a) \\ \frac{\partial i}{\partial t} + \frac{\partial i}{\partial a} = d(a)\beta\frac{P_0(a)}{\bar{P}}I_v(t) - (\rho(a) + d_h(a) + \delta_h(a))i(t,a) \\ \frac{\partial \tilde{i}}{\partial t} + \frac{\partial \tilde{i}}{\partial a} = \rho(a)i(t,a) - (p\tilde{\rho}(a) + d_h(a) + \tilde{\delta}_h(a))\tilde{i}(t,a) - (1-p)\gamma(a)\tilde{i}(t,a) \\ \frac{\partial r}{\partial t} + \frac{\partial r}{\partial a} = p\tilde{\rho}(a)\tilde{i}(t,a) - d_h(a)r(t,a) \end{cases} \tag{6}$$

Since, $\int_0^\infty \lambda_h(a)P_0(a)da = \int_0^\infty \lambda_h(a)s_0P(a)da = s_0\int_0^\infty \lambda_h(a)P(a)da = s_01 = s_0$
and $P_0(0) = s_0P(0) = s_0$,
the B.C. and the I.C. are:

$$x(t,0) = \int_0^\infty \{\lambda_h(a)[x(t,a) + r(t,a)] + \tilde{\lambda}_h(a)[i(t,a) + \tilde{i}(t,a)]\}da =: \Lambda$$
$$i(t,0) = 0$$
$$\tilde{i}(t,0) = 0$$
$$r(t,0) = 0$$

$$
\begin{aligned}
X_v(0) &= S_v^0 - \frac{\lambda_v}{d_v} \\
I_v(0) &= I_v^0 \\
x(0,a) &= s_0(a) + P_0(a) \\
i(0,a) &= i_0(a) \\
\tilde{i}(0,a) &= \tilde{i}_0(a) \\
r(0,a) &= r_0(a)
\end{aligned}
$$

When searching for the basic reproduction number, R_0, we want to find a threshold condition that allows us to say how the infected compartments of the model behave. For that, consider persistent solutions of the linearized system, i.e., exponential solutions with constant population structure (exist since the system we are analyzing is homogeneous of degree 1), of the form

$$
X_v(t) = \bar{X}_v e^{\lambda t}, \qquad I_v(t) = \bar{I}_v e^{\lambda t}
$$

$$
x(t,a) = x(a)e^{\lambda t}, \qquad i(t,a) = i(a)e^{\lambda t}, \qquad \tilde{i}(t,a) = \tilde{i}(a)e^{\lambda t}, \qquad r(t,a) = r(a)e^{\lambda t}
$$

Define $C(i) := \int_0^\infty ci(a)$ and $C(\tilde{i}) := \int_0^\infty \tilde{c}(a)\tilde{i}(a)da$.

Substituting the persistent solutions into equations (5) and (6) and canceling $e^{\lambda t}$ in each equation, we get the following system of equalities and ODE's, for mosquitoes and humans respectively

$$
\begin{aligned}
\lambda \bar{X}_v &= -\beta \frac{N_\infty}{\bar{P}} C(i) - \beta \frac{N_\infty}{\bar{P}} C(\tilde{i}) - d_v \bar{X}_v \\
\lambda \bar{I}_v &= \beta \frac{N_\infty}{\bar{P}} C(i) + \beta \frac{N_\infty}{\bar{P}} C(\tilde{i}) - d_v \bar{I}_v \\
\frac{dx(a)}{da} &= -d(a)\beta \frac{P_0(a)}{\bar{P}} \bar{I}_v - (d_h(a) + \lambda)x(a) + (1-p)\gamma(a)\tilde{i}(a) \\
\frac{di(a)}{da} &= d(a)\beta \frac{P_0(a)}{\bar{P}} \bar{I}_v - (\rho(a) + d_h(a) + \delta(a) + \lambda)i(a) \\
\frac{d\tilde{i}(a)}{da} &= \rho(a)i(a) - (p\tilde{\rho}(a) + d_h(a) + \tilde{\delta}(a) + \lambda)\tilde{i}(a) - (1-p)\gamma(a)\tilde{i}(a) \\
\frac{dr(a)}{da} &= p\tilde{\rho}(a)\tilde{i}(a) - (d_h(a) + \lambda)r(a)
\end{aligned}
\tag{7}
$$

and I.C.

$$
\begin{aligned}
x(0) &= \int_0^\infty \{\lambda_h(a)[x(a)+r(a)] + \tilde{\lambda}_h[i(a)+\tilde{i}(a)]\}da := \Lambda \\
i(0) &= 0 \\
\tilde{i}(0) &= 0 \\
r(0) &= 0
\end{aligned}
$$

To find the threshold condition we are interested in the equations of $\bar{I}_v$, $i(a)$ and $\tilde{i}(a)$, the infected age structures.
We will solve the linear ODEs in (7) for $i(a)$ and for $\tilde{i}(a)$, then integrate $i(a)$ and $\tilde{i}(a)$ to obtain $C(i)$ and $C(\tilde{i})$, which will be substituted into the equation for for $\bar{I}_v$ in (7):

$$
\begin{aligned}
i(a) &= e^{-\int_0^a(\rho(\sigma)+d_h(\sigma)+\delta_h(\sigma)+\lambda)d\sigma}\left[\int_0^a d(\sigma)\beta\frac{P_0(\sigma)}{\bar{P}}\bar{I}_v e^{\int_0^\sigma(\rho(\xi)+d_h(\xi)+\delta_h(\xi)+\lambda)d\xi}d\sigma\right] \\
&= \bar{I}_v\int_0^a d(\sigma)\beta\frac{P_0(\sigma)}{\bar{P}}e^{-\int_\sigma^a(\rho(\xi)+d_h(\xi)+\delta_h(\xi)+\lambda)d\xi}d\sigma \\
&= \bar{I}_v e^{-\lambda a}\int_0^a d(\sigma)\beta\frac{P_0(\sigma)}{\bar{P}}e^{-\int_\sigma^a(\rho(\xi)+d_h(\xi)+\delta_h(\xi))d\xi}e^{\lambda\sigma}d\sigma \\
&= \bar{I}_v e^{\lambda a}F(a,\lambda)
\end{aligned}
$$

where we define

$$
F(a,\lambda) := \int_0^a d(\sigma)\beta\frac{P_0(\sigma)}{\bar{P}}e^{-\int_\sigma^a(\rho(\xi)+d_h(\xi)+\delta_h(\xi))d\xi}e^{\lambda\sigma}d\sigma.
$$

Similarly we find

$$
\tilde{i}(a) = \bar{I}_v e^{-\lambda a}G(a,\lambda)da
$$

where

$$
G(a,\lambda) = \int_0^a \rho(\sigma)F(\sigma,\lambda)e^{-\int_\sigma^a(p\tilde{\rho}(\xi)+d_h(\xi)+\tilde{\delta}_h(\xi)+(1-p)\gamma(\xi))d\xi}d\sigma.
$$

Integrating over all ages a we obtain

$$
\begin{aligned}
C(i) &= \bar{I}_v\int_0^\infty e^{-\lambda a}cF(a,\lambda)da \\
C(\tilde{i}) &= \bar{I}_v\int_0^\infty e^{-\lambda a}\tilde{c}(a)G(a,\lambda)da.
\end{aligned}
$$

Substituting into the equation for $\bar{I}_v$ in (7) we obtain

$$\bar{I}_v = \beta \frac{N_\infty}{\bar{P}(\lambda + d_v)} \left[\bar{I}_v \int_0^\infty e^{-\lambda a} c F(a,\lambda) da + \bar{I}_v \int_0^\infty e^{-\lambda a} \tilde{c}(a) G(a,\lambda) da \right],$$

and dividing by $\bar{I}_v$ ($\bar{I}_v \neq 0$) we get a characteristic equation for λ

$$1 = \underbrace{\beta \frac{N_\infty}{\bar{P}(\lambda + d_v)} \left[\int_0^\infty e^{-\lambda a} c F(a,\lambda) da + \int_0^\infty e^{-\lambda a} \tilde{c}(a) G(a,\lambda) da \right]}_{=:K(\lambda)}$$

Definition 1. $R_0 := K(0)$.

Theorem 1. *The disease-free steady state is locally asymptotically stable if* $R_0 < 1$ ($\lambda_0 < 0$) *and unstable if* $R_0 > 1$ ($\lambda_0 > 0$).

Proof. Since $\lim_{\lambda\to\infty} e^{-\lambda a} F(a,\lambda) = 0$ and $\lim_{\lambda\to\infty} e^{-\lambda a} G(a,\lambda) = 0$ it is easy to see that

$$\lim_{\lambda\to\infty} K(\lambda) = 0.$$

Similarly, it can also be shown easily that

$$\lim_{\lambda\to-\infty} K(\lambda) = \infty.$$

Observe that

$$\begin{aligned}
\frac{\partial}{\partial\lambda} e^{-\lambda a} F(a,\lambda) &= -a e^{-\lambda a} F(a,\lambda) + e^{-\lambda a} \frac{\partial F}{\partial \lambda} \\
&= -a e^{-\lambda a} F(a,\lambda) + e^{-\lambda a} \int_0^a d(\sigma) \beta \frac{P_0(\sigma)}{\bar{P}} e^{-\int_\sigma^a (\rho + d_h + \delta_h) d\xi} e^{\lambda\sigma} \sigma d\sigma \\
&= e^{-\lambda a} \int_0^a d(\sigma) \beta \frac{P_0(\sigma)}{\bar{P}} e^{-\int_\sigma^a (\rho + d_h + \delta_h) d\xi} e^{\lambda\sigma} \underbrace{(\sigma - a)}_{<0} d\sigma \\
&< 0
\end{aligned}$$

and

$$\begin{aligned}
\frac{\partial}{\partial\lambda}e^{-\lambda a}G(a,\lambda) &= -ae^{-\lambda a}G(a,\lambda) + e^{-\lambda a}\frac{\partial G}{\partial\lambda} \\
&= -ae^{-\lambda a}G(a,\lambda) + e^{-\lambda a}\int_0^a \rho(\sigma)\frac{\partial F}{\partial\lambda}e^{-\int_\sigma^a(\tilde{\rho}+d_h+\tilde{\delta}_h)d\xi}d\sigma \\
&= -ae^{-\lambda a}\int_0^a \rho(\sigma)F(\sigma,\lambda)e^{-\int_\sigma^a(\tilde{\rho}+d_h+\tilde{\delta}_h)d\xi}d\sigma + e^{-\lambda a}\int_0^a \rho(\sigma)\frac{\partial F}{\partial\lambda}e^{-\int_\sigma^a(\tilde{\rho}+d_h+\tilde{\delta}_h)d\xi}d\sigma \\
&= \int_0^a \rho e^{-\int_\sigma^a(\tilde{\rho}+d_h+\tilde{\delta}_h)d\xi}\underbrace{\{-ae^{-\lambda a}F(\sigma,\lambda) + e^{-\lambda a}\frac{\partial F}{\partial\lambda}\}}_{<0}d\sigma \\
&< 0
\end{aligned}$$

So,

$$\begin{aligned}
K'(\lambda) = &\underbrace{-\frac{\beta N_\infty}{\bar{P}(\lambda+d_v)^2}}_{<0}\underbrace{\{c\int_0^\infty e^{-\lambda a}F(a,\lambda)da + \int_0^\infty e^{-\lambda a}\tilde{c}(a)G(a,\lambda)da\}}_{>0} \\
&+ \frac{\beta N_\infty}{\bar{P}(\lambda+d_v)}\underbrace{\{c\int_0^\infty \frac{\partial}{\partial\lambda}e^{-\lambda a}F(a,\lambda)da + \int_0^\infty \tilde{c}(a)\frac{\partial}{\partial\lambda}e^{-\lambda a}G(a,\lambda)da\}}_{<0} \\
&< 0
\end{aligned}$$

Then, since $K(\lambda)$ is a continuous decreasing function function of λ, there exist a unique real root,λ_0, of the characteristic equation $K(\lambda) = 1$.

If $z \in \mathbb{C}$ is a root, i.e. $K(z) = 1$, then

$$\begin{aligned}
K(\lambda_0) = 1 = |K(z)| &= |\frac{\beta N_\infty}{\bar{P}(\lambda+d_v)}\int_0^\infty e^{-\lambda a}[cF(a,\lambda) + \tilde{c}(a)G(a,\lambda)]da| \\
&\leq \frac{\beta N_\infty}{\bar{P}(\lambda+d_v)}\int_0^\infty e^{-Re\{z\}a}[cF(a,Re\{z\}) + \tilde{c}(a)G(a,Re\{z\})]da \\
&= K(Re\{z\})
\end{aligned}$$

Since $K(\lambda)$ is an decreasing function, this implies that

$$Re\{z\} \leq \lambda_0,$$

i.e. λ_0 is the leading root.
It follows that the disease free state is asymptotically stable if $\lambda_0 < 0$, which happens if $R_0 = K(0) < 1$ and unstable if $\lambda_0 > 0$, which happens if $R_0 = K(0) > 1$. This completes the proof. □

3.3 Interpretation of R_0

For vector-born diseases R_0 is defined to be an infection process including two cycles when introducing an infected vector into a completely susceptible population of humans and vectors. The first cycle will give the average number of infected humans that one infected mosquito introduced into a completely susceptible population can produce during its infectious period. The second cycle is the average number of infected mosquitoes that the humans infected during the first cycle produce during their infectious period. The formal definition for R_0 for vector-born diseases is then the following: R_0 is the average number of new infected mosquitoes that one infected mosquito introduced into a completely susceptible population (of mosquitoes and humans) produces, during its total infective period.

From the previous section we derived the expression for R_0 which is:

$$R_0 = \frac{1}{d_v}\beta N_\infty \frac{1}{\bar{P}}\left[\int_0^\infty cF(a,0)da + \int_0^\infty \tilde{c}(a)G(a,0)da\right]$$

where

$$F(a,0) = \int_0^a d(\sigma)\beta\frac{P_0(\sigma)}{\bar{P}}e^{-\int_\sigma^a(\rho(\xi)+d_h(\xi)+\delta_h(\xi))d\xi}d\sigma$$

and

$$G(a,0) = \int_0^a \rho(\sigma)F(\sigma,0)e^{-\int_\sigma^a(\tilde{\rho}(\xi)+d_h(\xi)+\tilde{\delta}_h(\xi))d\xi}d\sigma$$

To explain how the expression for R_0 can be interpreted to regain the formal definition, we will analyze the right hand side of the definition of R_0 by separating it into parts: First of all suppose an infected mosquito is introduced into a completely susceptible human population (of size $\bar{P}$) and mosquito population (of size N_∞).

We will first analyze the expression to interpret the first cycle described in the R_0 definition: Since $e^{-\int_\sigma^a(\rho(\xi)+d_h(\xi)+\delta_h(\xi))d\xi}$ is the probability of being alive at age a and still in the infected class i given that one entered the i class at age σ, we conclude that $d(\sigma)\beta\frac{P_0(\sigma)}{\bar{P}}e^{-\int_\sigma^a(\rho(\xi)+d_h(\xi)+\delta_h(\xi))d\xi}$ is the number of people that are now of age a, still alive and still in the infected class i, that got bitten at age σ, by the one infectious mosquito that got introduced into the completely susceptible human population.

Therefore one can interpret $F(a,0)$ to be the number of humans that are now of age a, that are still alive and still in the infected class i, that got bitten, sometime in their life, by the one infectious mosquito that got introduced into the completely susceptible human population.

And so, $\int_0^\infty cF(a,0)da$ is the total number of human, that are still alive and still in the infected class i, that got bitten, sometime in their life, by the one infectious mosquito that got introduced into the completely susceptible human population, and that are capable of transmitting the disease to a mosquito if bitten.

Hence, $\rho(\sigma)F(\sigma,0)e^{-\int_\sigma^a(\tilde{\rho}(\xi)+d_h(\xi)+\tilde{\delta}_h(\xi))d\xi}$ is the number of human that are now of age a, still alive and still in the infected class $\tilde{i}$, that reached the infected class $\tilde{i}$ at age σ.

And therefore, $G(a,0)$ is the number of human that are now of age a, still alive and still in the infected class $\tilde{i}$, that reached the infected class $\tilde{i}$ sometime in their life.

Concluding that then $\int_0^\infty \tilde{c}(a)G(a,0)da$ is the total number of human, still alive and still in the infected class $\tilde{i}$, that reached the infected class $\tilde{i}$ sometime in their life, and that are capable of transmitting the disease to a mosquito if bitten.

Now the second cycle has to be interpreted from the equation for R_0, i.e. determine how the infectious humans from the first cycle infect mosquitoes:

The expression $c\beta\frac{\int_0^\infty F(a,0)da}{\bar{P}}N_\infty$ is the total number of new infected mosquitoes (that were among the N_∞ completely susceptible), infected by infectious humans belonging to the class i, per unit of time.

$\beta\frac{\int_0^\infty \tilde{c}(a)G(a,0)da}{\bar{P}}N_\infty$ is the total number of new infected mosquitoes (that were among the N_∞ completely susceptible), infected by infectious humans belonging to the class $\tilde{i}$, per unit of time, and $\frac{1}{d_v}$ is the lifespan of a mosquito.

Therefore, we can conclude that R_0 is the average number of new infected mosquitoes that one infected mosquito introduced into a completely susceptible population (of mosquitoes and humans) produces, during its total infective period, as was required to verify.

4 Age-structured model, discrete-age continuous-time

With the aim of running numerical simulations using the ode solvers of MATLAB, we derived from the PDE age-structured model a discrete in age, continuous in time coupled ODE model. We followed a method developed by H. Hethcote [15] which consists of the following:

For simplicity we will assume from now on that $\lambda_h(a) = \tilde{\lambda}_h(a)$. We divide our population into n age groups defined by the n disjoint age intervals, $[a_0, a_1), [a_1, a_2), \ldots, [a_{n-1}, a_n = \infty)$, so that rates are all constant in each interval, i.e., for $a \in [a_{k-1}, a_k]$, $k = 1, \ldots, n$: $d(a) = d_k$, $d_n(a) = d_{n_k}$, $\tilde{\rho}(a) = \tilde{\rho}_k$ $\lambda_h(a) = \lambda_{h_k}$, $\rho(a) = \rho_k$, $\tilde{\delta}_h(a) = \tilde{\delta}_{h_k}$ $\tilde{\lambda}_h(a) = \tilde{\lambda}_{h_k}$,

$\delta_h(a) = \delta_{h_k}$, $\tilde{c}(a) = \tilde{c}_k$

We define,
$N_h(t) = \sum_{k=1}^{n} \underbrace{\int_{a_{k-1}}^{a_k} n(t,a)da}_{:=N_k(t)} = \sum_{k=1}^{n} N_k(t)$, where N_k is the number of humans in age group k at time t.
$I_h(t) = \sum_{k=1}^{n} \int_{a_{k-1}}^{a_k} i(t,a)da =: \sum_{k=1}^{n} I_k(t)$,
$\tilde{I}_h(t) = \sum_{k=1}^{n} \int_{a_{k-1}}^{a_k} \tilde{i}(t,a)da =: \sum_{k=1}^{n} \tilde{I}_k(t)$,
$R_h(t) = \sum_{k=1}^{n} \int_{a_{k-1}}^{a_k} r(t,a)da =: \sum_{k=1}^{n} R_k(t)$,
$S_h(t) = \sum_{k=1}^{n} \int_{a_{k-1}}^{a_k} s(t,a)da =: \sum_{k=1}^{n} S_k(t)$, Integrating system (2) for each age interval: $k = 0, \ldots, n$, we obtain the following for the susceptible class:

$$\frac{d}{dt}\int_{a_{k-1}}^{a_k} s(t,a)da + \int_{a_{k-1}}^{a_k} \frac{\partial s(t,a)}{\partial a}da = -d_k\beta\frac{I_v(t)}{N_n(t)}\int_{a_{k-1}}^{a_k} s(t,a)da - d_{n_k}\int_{a_{k-1}}^{a_k} s(t,a)da$$

$$\frac{d}{dt}S_k(t) + s(t,a_k) - s(t,a_{k-1}) = -d_k\beta\frac{I_v(t)}{N_n(t)}S_k(t) - d_{n_k}S_k(t)$$

Define constants that represent the aging rate from one group to the other by e_k such that $n(t,a_k) = e_k \underbrace{\int_{a_{k-1}}^{a_k} n(t,a)da}_{N_k(t)}$, for $k = 1, ..., n-1$ and $e_n = 0$:

For $\underline{k = 1}$
$\frac{d}{dt}S_1(t) + \underbrace{s(t,a_1)}_{=e_1S_1(t)} - s(t,0) = -d_1\beta\frac{I_v(t)}{N_n(t)}S_1(t) - d_{n_1}S_1(t)$

where

$$\begin{aligned} s(t,0) &= \sum_{k=1}^{n}\int_{a_{k-1}}^{a_k} \lambda_{n_k}[s(t,a) + r(t,a)] + \tilde{\lambda}_{n_k}[i(t,a) + \tilde{i}(t,a)]da \\ &= \sum_{k=1}^{n} \lambda_{n_k}[S_k(t) + R_k(t)] + \tilde{\lambda}_{n_k}[I_k(t) + \tilde{I}_k(t)] \\ &= \sum_{k=1}^{n} \lambda_{n_k}N_k(t) =: \Lambda \text{ (assume } \lambda_{n_k} = \tilde{\lambda}_{n_k}) \end{aligned}$$

For $\underline{k \geq 2}$
$\frac{d}{dt}S_k(t) + e_kS_k(t) - e_{k-1}S_{k-1}(t) = -\left(d_k\beta\frac{I_v(t)}{N_n(t)} + d_{n_k}\right)S_k(t)$

Integrating the same way for the other equations in system (2) we end up with the following ODE system:

For mosquitoes:

$$\begin{cases} \frac{dS_v}{dt} = \lambda_v - \left\{ \frac{\beta}{N_h(t)} \sum_{k=1}^{n} [cI_k(t) + \tilde{c}_k \tilde{I}_k(t)] \right\} \underbrace{S_v(t)}_{=\frac{\lambda_v}{d_v} - I_v} - d_v S_v(t) \\ \frac{dI_v}{dt} = \left\{ \frac{\beta}{N_h(t)} \sum_{k=1}^{n} [cI_k(t) + \tilde{c}_k \tilde{I}_k(t)] \right\} \underbrace{S_v(t)}_{=\frac{\lambda_v}{d_v} - I_v} - d_v I_v(t) \end{cases} \tag{8}$$

For humans:

$$\begin{cases} \frac{d}{dt} S_1(t) = -\left(d_1 \beta \frac{I_v(t)}{N_h(t)} + d_{h_1} + e_1 \right) S_1(t) + (1-p)\gamma_1 \tilde{I}_1(t) + \underbrace{\sum_{k=1}^{n} \lambda_{h_k} N_k(t)}_{=\Lambda} \\ \frac{d}{dt} S_k(t) = -\left(d_k \beta \frac{I_v(t)}{N_h(t)} + d_{h_k} + e_k \right) S_k(t) + (1-p)\gamma_k \tilde{I}_k(t) + e_{k-1} S_{k-1}, \text{ for } k = 2, \ldots, n-1 \\ \frac{d}{dt} S_n(t) = -\left(d_n \beta \frac{I_v(t)}{N_h(t)} + d_{h_n} \right) S_n(t) + (1-p)\gamma_n \tilde{I}_n(t) + e_{n-1} S_{n-1} \end{cases} \tag{9}$$

$$\begin{cases} \frac{d}{dt} I_1(t) = d_1 \beta \frac{I_v(t)}{N_h(t)} S_1(t) - (\rho_1 + d_{h_1} + \delta_{h_1} + e_1) I_1(t) \\ \frac{d}{dt} I_k(t) = d_k \beta \frac{I_v(t)}{N_h(t)} S_k(t) - (\rho_k + d_{h_k} + \delta_{h_k} + e_k) I_k(t) + e_{k-1} I_{k-1}(t), \text{ for } k = 2, \ldots, n-1 \\ \frac{d}{dt} I_n(t) = d_n \beta \frac{I_v(t)}{N_h(t)} S_n(t) - (\rho_n + d_{h_n} + \delta_{h_n}) I_n(t) + e_{n-1} I_{n-1}(t) \end{cases} \tag{10}$$

$$\begin{cases} \frac{d}{dt} \tilde{I}_1(t) = \rho_1 I_1(t) + \tilde{d}_1 \beta \frac{I_(t)}{N_h(t)} R_1(t) - (p\tilde{\rho}_1 + d_{h_1} + \tilde{\delta}_{h_1} + (1-p)\gamma_1 + e_1) \tilde{I}_1(t) \\ \frac{d}{dt} \tilde{I}_k(t) = \rho_k I_k(t) + \tilde{d}_k \beta \frac{I_(t)}{N_h(t)} R_k(t) - (p\tilde{\rho}_k + d_{h_k} + \tilde{\delta}_{h_k} + (1-p)\gamma_k + e_k) \tilde{I}_k(t) + e_{k-1} \tilde{I}_{k-1}(t), \text{ for } k = 2, \ldots, n \\ \frac{d}{dt} \tilde{I}_n(t) = \rho_n I_n(t) + \tilde{d}_n \beta \frac{I_(t)}{N_h(t)} R_n(t) - (p\tilde{\rho}_n + d_{h_n} + \tilde{\delta}_{h_n} + (1-p)\gamma_n) \tilde{I}_n(t) + e_{n-1} \tilde{I}_{n-1}(t) \end{cases} \tag{11}$$

$$\begin{cases} \frac{d}{dt} R_1(t) = p\tilde{\rho}_1 \tilde{I}_1(t) - (\tilde{d}_1 \beta \frac{I_v(t)}{N_h(t)} + d_{h_1} + e_1) R_1(t) \\ \frac{d}{dt} R_k(t) = p\tilde{\rho}_k \tilde{I}_k(t) - (\tilde{d}_k \beta \frac{I_v(t)}{N_h(t)} + d_{h_k} + e_k) R_k(t) + e_{k-1} R_{k-1}(t), \text{ for } k = 2, \ldots, n-1 \\ \frac{d}{dt} R_n(t) = p\tilde{\rho}_n \tilde{I}_n(t) - (\tilde{d}_n \beta \frac{I_v(t)}{N_h(t)} + d_{h_n}) R_n(t) + e_{n-1} R_{n-1}(t) \end{cases} \tag{12}$$

Initial Conditions

$$\begin{cases} S_k(0) = \int_{a_{k-1}}^{a_k} s(0,a)da = \int_{a_{k-1}}^{a_k} s_0(a)da \\ I_k(0) = \int_{a_{k-1}}^{a_k} i_0(a)da \\ \tilde{I}_k(0) = \int_{a_{k-1}}^{a_k} \tilde{i}_0(a)da \\ R_k(0) = \int_{a_{k-1}}^{a_k} r_0(a)da \\ k = 1, ..., n. \end{cases} \tag{13}$$

5 Numerical results and discussion

We developed a Matlab computer code for the discrete-age continuous-time version of the model for n non-overlapping age intervals. We run the simulations for 20 years, $p = 1$

(high transmissibility) and choose to work with four age groups: 0 to 4 years, 5 to 20 years, 21 to 40 years and the last age group from 41 years on. The choice of the first age group was made by assuming that young children up to four years are more susceptible to the disease than older children and adults [4], the second age group was chosen in a way that considers woman in fertile age, because they are specially vulnerable to malaria while pregnant due to a slower innate immune system response [4]. The third age group consists of adults with their innate immune system fully functional for their age and the fourth one are older people with a weakened immune system, considering an average lifespan of 50 years for African villages [16].

We start the simulation at initial conditions that follow the age distribution of an African village [16]. For each human compartment, S_h, I_h, $\tilde{I}_h$, R_h, for each age group, and for the infected mosquito compartment I_v, we can find a non-zero equilibria after approximately 20 years or less. We can see that after 20 years the proportion of infected individuals from each age group as shown in the figure 2-2 from Figure 2 as well as the age structure is adequate for a population in Africa, following a decreasing trend with increasing age as seen in field studies [20].

We can observe from Figure 2 that the curves representing infected humans in both infected classes are shaped the same way as the curve representing the infected mosquitoes, and they peak at the same time. This suggests that the number of infected mosquitoes at any given time is proportional to the number of infected humans. Moreover, we can compute from Figure 1-1 in Figure 2 that after the mosquito population reached equilibrium the proportion of infected vectors is approximately 1% of the total mosquito population size. This observation coincides with field data [21].

Figure 3 shows the proportion of all infected individuals $\frac{I_h+\tilde{I}_h}{N_h}$ at equilibrium (for

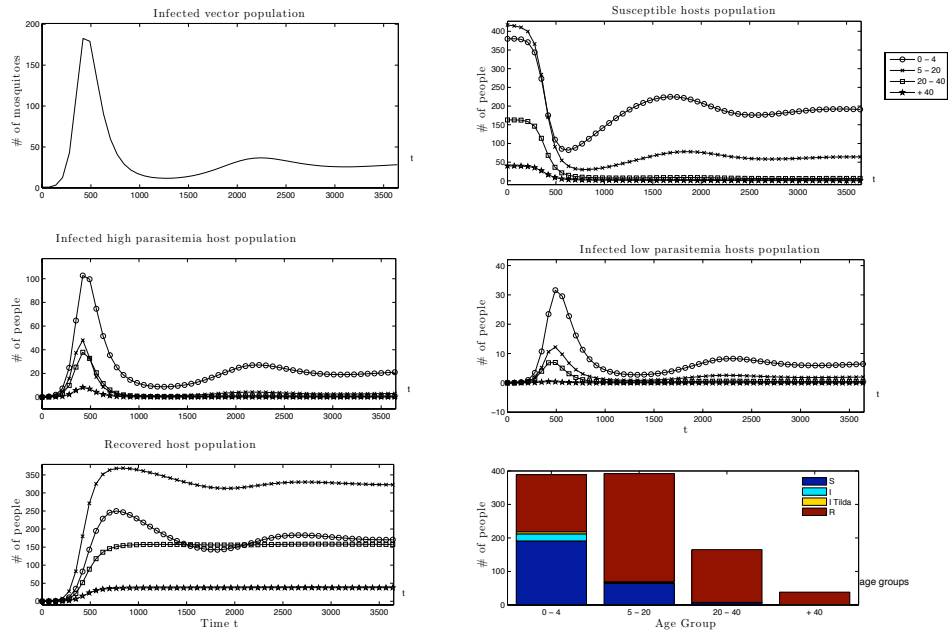

Figure 2: Malaria disease dynamics for p=1. Figures numbered by row and columns (for example the figure in the fist row and second column we call figure 1-2) Figure 1-1 shows the number of infected mosquitoes vs time (0-20 years), Panel 1-2,2-1,2-2,3-1 show the number of people in each compartment for each age-group vs time (0-20 years). Panel 3-2 shows proportion of people per age-group in each compartment and the age distribution of the population.

different p values) relative to proportion of infected people in the infected class of the basic SIS age structured malaria model. The basic SIS malaria model is recovered from our model by choosing $p = 0$ and $\gamma(a) \approx \infty$, i.e. people pass from the susceptible class to the infectious class I, then to the infectious class $\tilde{I}$ and leave that class immediately to return to the susceptible class, such that the $\tilde{I}$ class can be basically ignored. This means that they do not acquire anti-parasite immunity, clinical immunity nor premonitory immunity at any level. The transmissibility level of a region is measured by the parameter p, in the following way: depending on the climate of a geographical region, the presence of mosquitoes behaves seasonal, such that the percentage of people in the population exposed to mosquitoes (depends on human behavior, activities, habits, etc.) vs time (one year) follows a bell shaped curve. When transmissibility of malaria is highest, the percentage of people exposed to mosquitoes is higher, which happens for a certain amount of months a year depending on climate. We define p as the average number of people (in %) constantly exposed to mosquitoes throughout the year, which means that in average p percent of the people in a region would develop NAI. From Figure 3 it can be observed that for all age groups, as p increases, the number of people able to transmit the parasite decreases. For a transmissibility level greater than $p = 0.1$ it is the youngest age group the one having the most number of infectious individuals, followed by the other age groups, in an with age increasing order. For a transmissibility level greater than approximately $p = 0.09$, the proportion of infectious individuals in any of the age-groups relative to infectious individuals with no type of NAI, is less than 1. This means that in a region with transmissibility level greater than $p = 0.09$, the amount of infectious people (of any age) is less than in an area of no transmissibility $p = 0$, where nobody acquired any type of immunity. On the contrary, for levels of $p < 0.09$ the amount of infectious people of younger age groups are overtaken by the older age groups. Also, one can find values for $p < 0.09$ such that the proportion of infectious people of at least one of the age classes is greater than one. This means that for those transmissibility levels the development of NAI of a percentage of the people is increasing the number of infectious people of certain age-groups in the population. Considering this surprising result it can be suggested that endemicity of a region (proportion of people tested positive in ELISA or dot-ELISA *P.falciparum* antibodies test) does not reflect the risk of infection. Since antibodies can be found in both, infectious and recovered individuals, endemicity tests in regions of high transmissibility will usually reflect a high number of people in the recovered class. Assuming that what really reflects the risk of acquiring the parasite is the proportion of infectious people, less endemic regions could have, proportional to the population, more people able to transmit the parasite.

In conclusion, in this paper we did analytical and numerical analysis of an age-structured malaria model that considers different levels of natural acquired immunity (NAI) depending on transmissibility level of the region. In section 3 we computed analytically the basic reproduction number, R_0, and proved the local stability of the disease free state. In section 4 we developed a discrete in age, continuous in time age-structured model and run numerical simulations considering four age groups. We conclude that the

number of infectious individuals is reduced (being highest for young age groups) if the transmissibility level is increased by more than a certain threshold.

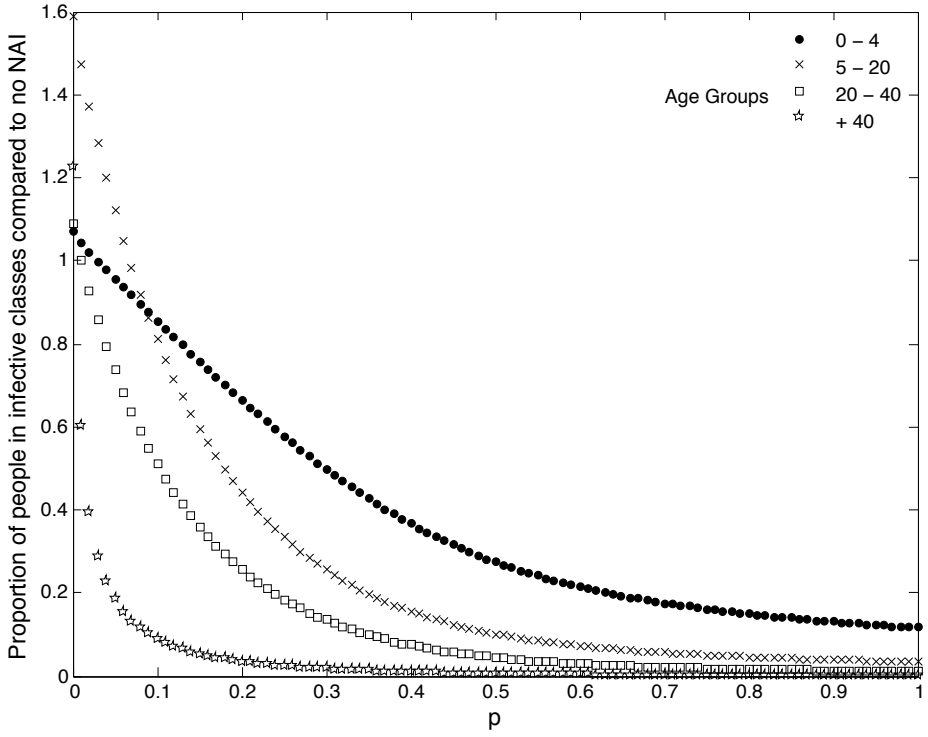

Figure 3: Proportion of individuals in infected classes relative to individuals in the infected class of the basic SIS age structured malaria model.

Table 1. Parameters. Units of all rates $\frac{1}{day}$.

Symbol	Description	Value Age-group			
		$0-4$	$5-20$	$21-40$	$41+$
d_v	Mosquito death rate	0.1			
d	Probability of transmission of infection from I_v to s of age a, given that contact between the two occurs.	0.08			
$d_h(a)$	Natural death rate of humans depending on age	6×10^{-4}	5×10^{-4}	3×10^{-4}	6×10^{-4}
$\delta_h(a)$	Disease induced death rate of humans depending on age	4×10^{-4}	3×10^{-4}	2×10^{-4}	4×10^{-4}
$\tilde{\delta}_h(a)$	Reduced disease induced death rate of humans	4×10^{-5}	3×10^{-5}	2×10^{-5}	4×10^{-5}
$\rho(a)$	Rate of suppressing parasite load by II	1/90	1/30	1/70	1/60
$\tilde{\rho}$	Rate of suppressing parasite load by II and anti-parasite immunity.	1/15	1/3	1/12	1/3
c	Probability of transmission of infection from i to S_v given the contact between the two occurs	0.05			
$\tilde{c}$	Host-age dependent probability of transmission of infection from $\tilde{i}$ to S_v given that contact between the two occurs	0.05	0.5×10^{-2}	0.5×10^{-3}	10^{-4}
e	human aging rate	0.25/365	1/(15×365)	1/(20×365)	0
γ	recovery rate from class $\tilde{i}$ to class s	1/30	1/50	1/25	1/50
$\tilde{d}$	age dependent probability of transmission from I_v to r given that contact between the two occurs	0.07	10^{-1}	10^{-2}	2×10^{-3}
p	proportion of people constantly exposed to mosquitoes in a region	varies			
β	Biting rate of mosquitoes to humans	0.6			
λ_v	Mosquito birth rate	3×10^{-2} overall			

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References

[1] World Health Organization *http://www.who.int/mediacentre/factsheets/fs094/en/index.html*

[2] Nadjm B, Behrens RH *Malaria: an update for physicians*
Infectious Disease Clinics of North America 26 (2): 24359.

[3] S.Mandal, R. Rup Sarkar, S. Sinha *Mathematical models of malaria- a review.* Malaria Journal; 2011.

[4] CDC-(Centers for Disease Control and Prevention) *http://www.cdc.gov/malaria/about/index.html*

[5] J.Kevin Roird et al. *Age-Dependent Acquired Protection against Plasmodium Falciparum in People Having Two Years Exposure to Hyperendemic Malaria*
Am.J.Trop.Med.Hyg. 45(1) 1991 p 65-75

[6] Simone Ladeia-Andrade et.al *Age-Dependent Acquisition of Protective Immunity to Malaria in Riverine Populations of the Amazon Basin of Brazil*
Am J Trop Med Hyg March 2009 80:452-459

[7] S.K. Sharma et al Am J Trop Med Hyg 71(9)2004

[8] Doug Smith and F.Ellis McKenzie Malaria Journal 2004 3:13.

[9] Mimmo Iannelli *Mathematical Theory of Age-Structured Population Dynamics* Giardini Editori E Stampatori in Pisa 1995.

[10] Ross R. *The prevention of malaria*
London:John Murray; 1911.

[11] Bruce-Chwatt, L.J. 1980. Essential malariology, vol. 354. William Heinemann Medical Books Ltd., London, United Kingdom.

[12] Aron Jl, May RM *The population dynamics of malaria*
Population Dynamics of Infectious Disease. London: Chapman and Hall; 1982:139-179.

[13] Dietz K *Mathematical models for transmission and control of malaria*
Principles and Practice of Malariology. Edingburgh: Churchill Livingston; 1988:1091-1133.

[14] Aron JL: *Mathematical modeling of immunity to malaria.*
Math Biosci 1988, 90:385-396.

[15] Herbert W. Hethcote *The Mathematics of Infectious Diseases*
SIAM Review, 42, 4;599-653.

[16] Victoria A. Velkoff and Paul R. Kowal *Population Aging in Sub-Saharan Africa: Demographic Dimensions 2006 International Population Reports*
June 2007.

[17] Anderson RM, May RM *Infectious diseases of humans: dynamics and control*
London: Oxford University Press; 1991.

[18] Boyd MF *Epidemiology of malaria: factors related to the intermediate host.*
Malariology, 1949,551-607.

[19] Filipe et. all *Determination of the processes driving the acquisition of immunity to malaria using a mathematical transmission model.*
PloS Comp Biol, 2007, 3:2569-2579.

[20] Dietz K, Molineaux L, THomas A *A malaria model tested in the African savannah.*
Bull World Healrh Organ, 1974, 50:347-357.

[21] Mohammad Shafiul Alam et. all *Prevalence of anopheline species and their Plasmodium infection status in epidemic-prone border areas of Bangladesh*
Malaria Journal 2010, 9:15.

[22] Hasibeder G, Dey C *Population dynamics of mosquito-borne disease: persistence ina completely heterogenoeous environment.*
Theor Popul Biol 1988, 33:31-53.

[23] MARA/ARMA Project *http://www.mara.org.za/*

[24] T. Bousema and C. Drakeley *Epidemiology and Infectivity of Plasmodium falciparum and Plasmodium vivax Gametocytes in Relation to MalariaControl and Elimination*

[25] Denise L. Doolan, Carlota Doban, and J. Kevin Baird *Aquired Immunity to Malaria*

[26] C.E. Contreras *Detection of specific antibodies to P.falciparum in blood bank donors from malaria-endemic and non-endemic areas of Venezuela*
Am. J. Trop. Med. Hyg., 60(6), 1999, pp. 948953