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A MALARIA MODEL WITH PARTIAL IMMUNITY IN HUMANS

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Abstract. In this paper, we formulate a mathematical model for malaria transmission that includes incubation periods for both infected human hosts and mosquitoes. We assume humans gain partial immunity after infection and divide the infected human population into subgroups based on their infection history. We derive an explicit formula for the reproductive number of infection, R_0, to determine threshold conditions whether the disease spreads or dies out. We show that there exists an endemic equilibrium if $R_0 > 1$. Using an numerical example, we demonstrate that models having the same reproductive number but different numbers of progression stages can exhibit different transient transmission dynamics.

1. **Introduction.** Malaria is by far the world's most important tropical parasitic disease, and it kills more people than any other communicable disease except tuberculosis. Malaria is a public health problem today in more than 90 countries inhabited by some 2,400 million people - 40 percent of the world's population. Each year 350-500 million cases of malaria occur worldwide, and over one million people die, most of them young children in sub-Saharan Africa. In areas of Africa with high malaria transmission, an estimated 990,000 people died of malaria in 1995 - over 2,700 deaths per day, or 2 deaths per minute. Meanwhile, Asia, Latin America, the Middle East, and parts of Europe have also been affected. In 2002, malaria was the fourth cause of death in children in developing countries. Malaria caused 10.7% of all children's deaths in developing countries. In Malawi in 2001, malaria accounted for 22% of all hospital admissions, 26% of all outpatient visits, and 28% of all hospital deaths. Not all people go to hospitals when sick or having a baby, and many die at home. Thus the true numbers of death and disease caused by malaria are likely much higher [5, 23].

Malaria is not transmitted directly from human to human but through mosquito vectors. Malaria in humans is due to infection by one of four *Plasmodium* species. The infection in humans begins when sporozoites are injected into the blood of a

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human host by an infected female mosquito of the genus *Anopheles*. The sporozoites migrate to the liver where they enter liver cells and develop into schizonts, which give rise, via asexual reproduction, to the form which invades the blood cells, the merozoites. In the blood, some merozoites differentiate into sexual erythrocytic stages (gametocytes), and the gametocytes are ingested by a mosquito when it ingests human blood. Within the mosquito the gametocytes develop into microgametes and macrogametes (the male and female gametes) that fuse to form a zygote. This becomes a motile ookinete form which bores through the gut wall of the vector and forms an oocyst from which large numbers of sporozoites are released. These sporozoites then invade the salivary glands of the mosquito from which they are injected into human hosts when the vector feeds. Such a life-cycle of the *Plasmodium* species causes the transmission of malaria between infected humans and mosquitoes [17, 22].

There is acquired immunity in humans although the mechanisms of immunity to malaria are not fully understood. The acquired immunity appears to depend on both the duration and the intensity of past exposure to infection. Recovery from a primary infection with malaria does not imply fully protective immunity against reinfection. Immunity against malaria evidently influences the production of gametocytes. Frequency and intensity of gametocytemia decrease with increasing age until they reach a minimum among adults [22].

Mathematical models for the transmission dynamics of infectious diseases have proven useful for the purpose of providing a logical structure within which to incorporate knowledge and test assumptions about the complex epidemics, in a way that could not be done by simple thought processes. Mathematical models for malaria have played an important role in helping researchers understand this epidemic, anticipate and plan for the future, and design and analyze control strategies. The earliest malaria mathematical model can be traced to the model formulated by Ross in 1911 [19]. MacDonald extended the Ross model in 1957 [12]. Since then, many other modeling attempts have been made to describe and to predict the transmission dynamics of malaria in the literature. (See e.g., [1, 2, 6, 7, 13]).

The sophistication of the epidemiological modeling efforts has grown steadily. A container-inhabiting mosquito simulation model was developed in [8]. Compartmental SEIR (susceptible-exposed-infected-recovered) differential equations models including asymptomatic immune humans were studied more recently in [14–16]. SEIR differential equations models with different levels of acquired immunity and the loss of immunity among human host populations were formulated in [24,25], and the effects of social and economic conditions and temperature on the transmission were investigated by using numerical simulations in some of these studies. However, it seems that gradual partial immunity induced by infections and hence multiple reinfections have not been considered.

In this paper, we introduce and study a simple compartmental malaria model where the host human population consists of infection-progression stages with repeated infection until the frequency and intensity of gametocytemia reach a minimum. We provide fundamental analysis for the model, including the derivation of an explicit formula for the reproductive number and the investigation of the existence of an endemic equilibrium. The model is derived in Section 2 and analyzed in Sections 3 and 4. The results are discussed in Section 5.

2. **Model formulation.** We consider that malaria is transmitted between populations of humans and mosquitoes. We divide the human population into groups of susceptible, incubating, infective, and recovered individuals, and the mosquito population into groups of susceptible, incubating, and infective individuals. Using index h for the human host, we let S_0^h denote the number of susceptible people who have never been infected, S_k^h, $k = 1, \cdots, n$, the number of people who at time t are susceptible and have been infected k times prior to time t, E_k^h the number of incubating people, who are infected but not yet infectious at t, and have been infected k times prior to time t, and I_k^h the number of infectious people at time t, who have also been infected k times prior to t. Then, the model for the humans can be illustrated as in Figure 1, and the model equations for the humans are given by

$$\begin{aligned}
\frac{dS_0^h}{dt} &= \Lambda^h - \left(d^h + \sigma_0 \lambda^h\right) S_0^h, \\
\frac{dS_k^h}{dt} &= \eta_{k-1}^h I_{k-1}^h - \left(d^h + \delta_{k-1}^h + \sigma_k \lambda^h\right) S_k^h, \ k = 1, \cdots, n-1, \\
\frac{dE_k^h}{dt} &= \sigma_k \lambda^h S_k^h - \left(d^h + \delta_k^h + \gamma_k^h\right) E_k^h, \ k = 0, \cdots, n-1, \\
\frac{dI_k^h}{dt} &= \gamma_k^h E_k^h - \left(d^h + \delta_k^h + \eta_k^h\right) I_k^h, \ k = 0, \cdots, n-1, \\
\frac{dS_n^h}{dt} &= \eta_{n-1}^h I_{n-1}^h - \left(d^h + \delta_{n-1}^h\right) S_n^h,
\end{aligned} \tag{2.1}$$

where Λ^h is the input flow of the susceptible people due to births or immigration, d^h is the natural death rate, δ_k^h is the disease-induced death rate for people having been infected k times, γ_k^h is the rate incubating people become infectious such that $1/\gamma_k^h$ is the incubation period of incubating people with disease history k, η_k^h is the recovery rate for infectious people with disease history k, λ^h is the infection rate, or the incidence of infection, from an infectious mosquito to a human who is currently susceptible, and σ_k is the rate measuring the reduction of infection or the immunological memory for people who have been infected before, such that $0 \le \sigma_k \le 1$ and $\sigma_{k+1} < \sigma_k$, for $k = 1, \cdots, n-1$. For notation convenience, we also include σ_0 with $\sigma_0 = 1$. Notice that if there is no infection, the human population has an asymptotically stable steady state, or equilibrium, such that $\lim_{t\to\infty} S_0^h(t) = \Lambda^h/d^h$.

The transmission of malaria is through mosquitoes. Let $N^h = \sum_{k=0}^n S_k^h + \sum_{k=1}^n \left(E_k^h + I_k^h\right)$ be the total human population size, and N^v be the total mosquito population size. Then the average number of mosquitoes per human host is N^v/N^h. Let r be the number of bites on a human by a female mosquito per unit of time. Then, the proportion of infected bites on a human that produce an infection can be approximated by rI^v/N^v. Suppose that the transmission probability to humans per infected bite is β^v. Then, the infection rate, or the incidence of infection, to a human host, λ^h, is determined by

$$\lambda^h = \beta^v r \frac{I^v}{N^v} \frac{N^v}{N^h} = \beta^v r \frac{I^v}{N^h}. \tag{2.2}$$

To account for the transmission dynamics between the mosquito and human populations, we divide the mosquito population into groups of susceptible, incubating, and infective individuals, illustrated as in Figure 2. Using the index v for the

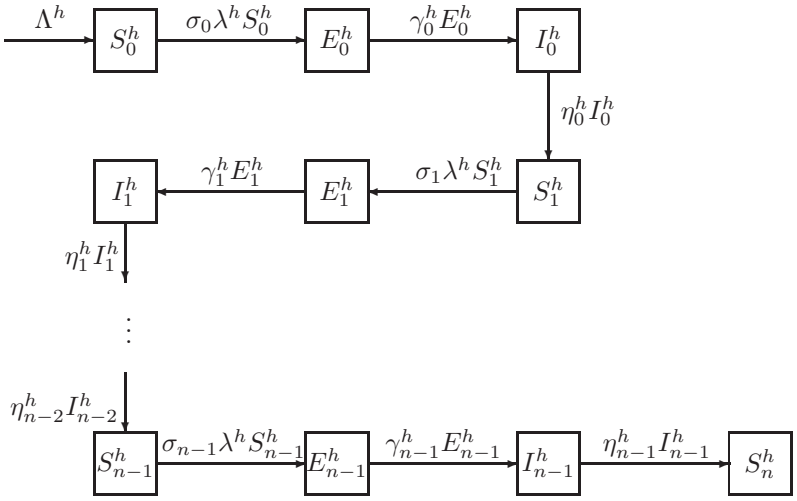

FIGURE 1. In this epidemic model for human, as a susceptible person is first infected this person enters the incubating group E_0^h, and then becomes infectious after an incubating period, entering group I_0^h. After recovering, the person becomes susceptible again with partial immunity, entering group S_1^h. When the person is recovered from the second infection, he/she becomes susceptible again but with more immunity and reduced susceptibility. Gradually, this person moves to the final group S_n^h with complete immunity.

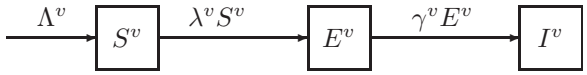

FIGURE 2. The mosquito population is divided into groups of susceptible, incubating, and infective individuals. The lifespan of mosquitoes is shorter than their infective period. Hence, it is assumed that there is no immune nor recovered group of mosquitoes.

mosquitoes, we let S^v, E^v, and I^v denote the number of susceptible, incubating, and infective mosquitoes, respectively. Since the lifespan of mosquitoes is shorter than their infective period, we assume there is no immune nor recovered group of mosquitoes. Then the model equations for the mosquitoes are given by

$$\begin{aligned}\frac{dS^v}{dt} &= \Lambda^v - d^v S^v - \lambda^v S^v,\\ \frac{dE^v}{dt} &= \lambda^v S^v - (d^v + \gamma^v)E^v,\\ \frac{dI^v}{dt} &= \gamma^v E^v - d^v I^v,\end{aligned} \tag{2.3}$$

where Λ^v is the input flow due to births or immigration, d^v is the natural death rate, and γ^v is the rate of incubating individuals becoming infectious for mosquitoes. If there is no infection, the mosquito population has an asymptotically stable steady state Λ^v/d^v.

The infection rate for mosquitoes can be determined in a similar way as for the human host such that

$$\lambda^v = r\frac{\sum_{k=0}^{n-1}\beta_k^h I_k^h}{N^h}, \tag{2.4}$$

where β_k^h is the transmission probability per bite to a mosquito from an infectious human host in group I_k^h.

3. **The reproductive number.** It follows from systems (2.1) and (2.3) that if $I^v = 0$ and hence $\lambda^h = 0$, then $E_k^h = 0$, $k = 0, 1, \cdots, n-1$, and $I_k^h = 0$, $k = 0, 1, \cdots, n-1$. If $I_k^h = 0$, $k = 0, 1, \cdots, n-1$, then $\lambda^v = 0$, which leads to $E^v = 0$ and $I^v = 0$. Therefore, there exists an infection-free equilibrium with $S_0^h = \Lambda^h/d^h$, $S_k^h = 0$, $k = 1, \cdots, n-1$, $E_k^h = 0$, $I_k^h = 0$, $k = 0, 1, \cdots, n-1$, $S_0^v = \Lambda^v/d^v$, $E_v = 0$, and $I^v = 0$.

The local stability of the infection-free equilibrium determines whether the disease spreads if the infection is first introduced into the susceptible human and mosquito populations. Such thresholds are characterized by the reproductive number, R_0, such that if $R_0 < 1$, the disease dies out, and if $R_0 > 1$, the disease spreads. The local stability of the infection-free equilibrium can be determined by using the next-generation operator method [20], or by locating the eigenvalues of the Jacobian matrix of system (2.1) and (2.3) at the infection-free equilibrium. We derive an explicit formula for the reproductive number R_0 by investigating the eigenvalues of the Jacobian matrix at the infection-free equilibrium as follows.

We first linearize system (2.1) and (2.3) at the infection-free equilibrium $E_0 := (S_0^h, S_1^h, \cdots, S_n^h, E_1^h, \cdots, E_{n-1}^h, I_1^h, \cdots, I_{n-1}^h, I^v, E^v, S^v) = \left(\Lambda^h/d^h, 0, \cdots, 0, \Lambda^v/d^v\right)$, and obtain the following Jacobian matrix, at E_0,

$$\begin{pmatrix} J_{11} & \cdot & 0 \\ 0 & J_{22} & 0 \\ 0 & \cdot & -d^v \end{pmatrix}, \tag{3.1}$$

where $J_{11} = \operatorname{diag}\left(-d^h, -c_0, \cdots, -c_{n-1}\right)$, with $c_k = d^h + \delta_k^h$, $k = 0, \cdots, n-1$, and

$$J_{22} = \begin{pmatrix} D_{11} & 0 & D_{13} \\ D_{21} & D_{22} & 0 \\ 0 & D_{32} & D_{33} \end{pmatrix},$$

with

$$\begin{aligned} D_{11} =& \operatorname{diag}\left(-(c_0 + \gamma_0^h), \cdots, -(c_{n-1} + \gamma_{n-1}^h)\right), \\ D_{21} =& \operatorname{diag}\left(\gamma_0^h, \cdots, \gamma_{n-1}^h\right), \\ D_{22} =& \operatorname{diag}\left(-(c_0 + \eta_0^h), \cdots, -(c_{n-1} + \eta_{n-1}^h)\right), \end{aligned}$$

and

$$D_{13} = \begin{pmatrix} r\beta^v & 0 \\ 0 & 0 \\ \vdots & \vdots \\ 0 & 0 \end{pmatrix}, D_{32} = \begin{pmatrix} 0 & \cdots & 0 \\ r\beta_0^h \dfrac{S^v}{S^h} & \cdots & r\beta_{n-1}^h \dfrac{S^v}{S^h} \end{pmatrix}, D_{33} = \begin{pmatrix} -d^v & \gamma^v \\ 0 & -(d^v + \gamma^v) \end{pmatrix}.$$

Here $S^h = \Lambda^h/d^h$ and $S^v = \Lambda^v/d^v$.

Since J_{11} is a diagonal matrix with all elements negative, the local stability of the infection-free equilibrium is completely determined by the stability of matrix J_{22}, or more specifically, by the locations of the eigenvalues of J_{22}.

We consider $\rho I_{2(n+1)} - J_{22}$, where $I_{2(n+1)}$ is the $2(n+1) \times 2(n+1)$ identity matrix. Since there is only one nonzero element $r\beta^v$ on the first row of D_{13}, and D_{11} is diagonal, $\rho = -(c_k + \gamma_k^h)$, $k = 1, \cdots, n-1$, are eigenvalues of J_{22}. After we eliminate the second through the nth rows and columns of $\rho I_n - D_{11}$, where I_n is the $n \times n$ identity matrix, and hence those corresponding rows and columns of $\rho I_{2(n+1)} - J_{22}$, the diagonal elements $-(c_k + \eta_k^h)$, $k = 1, \cdots, n-1$, are the only elements on the corresponding rows and columns in $\rho I_{2(n+1)} - J_{22}$. Then, $\rho = -(c_k + \eta_k^h)$, $k = 1, \cdots, n-1$, are also the eigenvalues of J_{22}. Again, we eliminate those rows and columns corresponding to $\rho - (c_k + \eta_k^h)$, $k = 1, \cdots, n-1$. Then, the stability of the infection-free equilibrium is determined by the 4×4 matrix

$$J_4 := \begin{pmatrix} -(d^h + \delta_0^h + \gamma_0^h) & 0 & r\beta^v & 0 \\ \gamma_0^h & -(d^h + \delta_0^h + \eta_0^h) & 0 & 0 \\ 0 & 0 & -d^v & \gamma^v \\ 0 & r\beta_0^h \dfrac{S^v}{S^h} & 0 & -(d^v + \gamma^v) \end{pmatrix}. \tag{3.2}$$

Notice that all off-diagonal elements of matrix J_4 are nonnegative. We consider matrix $-J_4$. The three leading principal minors, up to the 3×3 one, of J_4 are positive. Then, it follows from M-matrix theory [10, 18] that if the 4×4 leading principal minor, that is, the determinant of $-J_4$ is positive, the infection-free equilibrium is locally asymptotically stable. On the other hand, if the determinant of $-J_4$, that is that of J_4, is negative, there exists at least one positive eigenvalue of J_4. Then the infection-free equilibrium is unstable.

Simple algebra shows that the determinant of J_4 is given by

$$\begin{aligned} \det J_4 = {} & d^v \left(d^v + \gamma^v\right) \left(d^h + \delta_0^h + \gamma_0^h\right) \left(d^h + \delta_0^h + \eta_0^h\right) \\ & - r\beta^v \gamma_0^h \gamma^v r\beta_0^h \frac{S^v}{S^h}. \end{aligned}$$

Define

$$R_0 = \sqrt{\frac{r\beta^v \gamma^v}{d^v \left(d^v + \gamma^v\right)} \frac{r\Lambda^v d^h}{\Lambda^h d^v} \frac{\beta_0^h \gamma_0^h}{(d^h + \delta_0^h + \gamma_0^h)(d^h + \delta_0^h + \eta_0^h)}}. \tag{3.3}$$

Then,

$$\det J_4 = d^v \left(d^v + \gamma^v\right) \left(d^h + \delta_0^h + \gamma_0^h\right) \left(d^h + \delta_0^h + \eta_0^h\right) \left(1 - R_0^2\right).$$

Hence, if $R_0 < 1$, the determinant of J_4 is positive, which leads to the local asymptotical stability of the infection-free equilibrium, and if $R_0 > 1$, $\det J_4 < 0$, which implies the instability of the infection-free equilibrium. In summary, we have the following result.

Theorem 3.1. *Define the reproductive number of infection, R_0, as in (3.3). Then, the infection-free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$, and is unstable if $R_0 > 1$.*

Define the reproductive number of infection for the human population by

$$R_0^h = \frac{r\Lambda^v d^h}{\Lambda^h d^v} \beta_0^h \frac{\gamma_0^h}{\left(d^h + \delta_0^h + \gamma_0^h\right) \left(d^h + \delta_0^h + \eta_0^h\right)} \tag{3.4}$$

and the reproductive number of infection for the mosquito population by

$$R_0^v = r\beta^v \frac{\gamma^v}{d^v\left(d^v+\gamma^v\right)}. \tag{3.5}$$

The reproductive number defined in (3.3) is composed of the two reproductive numbers such that

$$R_0 = \sqrt{R_0^h R_0^v}. \tag{3.6}$$

Notice that the definition of R_0 in (3.6) is a geometric mean of the two reproductive numbers R_0^h and R_0^v, and it also agrees with the dimension for a reproductive number.

Notice that $1/\left(d^h+\delta_0^h+\gamma_0^h\right)$ is the average incubation period of first infected humans who survive to the first infectious stage I_0^h, or the death-adjusted expected incubation period in stage 0 [9,11]; $1/\gamma_0^h$ is the waiting time in the first incubating stage (i.e., the mean time that an incubating human who progresses to the first infectious stage spends in the stage); then $\gamma_0^h/\left(d^h+\delta_0^h+\gamma_0^h\right)$ is the probability that an incubating human survives to the first infectious stage. Likewise, $1/\left(d^h+\delta_0^h+\eta_0^h\right)$ is the death-adjusted infectious period. Hence, the mean duration of first infection within the human population is

$$\tau^h := \frac{\gamma_0^h}{\left(d^h+\delta_0^h+\gamma_0^h\right)\left(d^h+\delta_0^h+\eta_0^h\right)}.$$

Since Λ^h/d^h and Λ^v/d^v are the steady states of the human and mosquito populations, the mean number of bites per human from a mosquito is

$$r^h = r\frac{\Lambda^v d^h}{\Lambda^h d^v}.$$

Therefore, the reproductive number of infection for the human population can be expressed as

$$R_0^h = r^h\beta_0^h\tau^h.$$

Similarly, we can define the mean duration of infection within the mosquito population by

$$\tau^v = \frac{\gamma^v}{d^v\left(d^v+\gamma^v\right)},$$

and denote $r^v := r$. Then, the reproductive number of infection for the mosquito population can be expressed as

$$R_0^v = r^v\beta^v\tau^v.$$

Notice that the transmission of malaria is through the cycle of the infection of susceptible human hosts due to the bites of infected female mosquitos and the infection of susceptible mosquitoes by biting on infected humans. Hence, the reproductive number of infection for the malaria transmission in the human and mosquito populations is the square root of the product of the reproductive number of infection in the humans and the reproductive number of infection in the mosquitoes, as in (3.6). Even if the reproductive number of infection in the humans is less than one, it is possible that the disease will spread if the reproductive number of infection in the mosquitoes is large enough such that the product becomes greater than one.

4. **The endemic equilibrium.** The positive components of an endemic equilibrium satisfy the equations for the humans

$$\Lambda^h = \left(d^h + \sigma_0\lambda^h\right) S_0^h, \tag{4.1a}$$
$$\eta_{k-1}^h I_{k-1}^h = \left(d^h + \delta_{k-1}^h + \sigma_k\lambda^h\right) S_k^h,\ k = 1, \cdots, n-1, \tag{4.1b}$$
$$\sigma_k\lambda^h S_k^h = \left(d^h + \delta_k^h + \gamma_k^h\right) E_k^h,\ k = 0, \cdots, n-1, \tag{4.1c}$$
$$\gamma_k^h E_k^h = \left(d^h + \delta_k^h + \eta_k^h\right) I_k^h,\ k = 0, \cdots, n-1, \tag{4.1d}$$
$$\eta_{n-1}^h I_{n-1}^h = \left(d^h + \delta_{n-1}^h\right) S_n^h, \tag{4.1e}$$

and the equations for the mosquitos

$$\begin{aligned} \Lambda^v =& d^v S^v + \lambda^v S^v, \\ \lambda^v S^v =& (d^v + \gamma^v) E^v, \\ \gamma^v E^v =& d^v I^v. \end{aligned} \tag{4.2}$$

It follows from (4.1b) and (4.1c) that

$$\begin{aligned} S_k^h =& \frac{\eta_{k-1}^h}{c_{k-1} + \sigma_k\lambda^h} I_{k-1}^h, \quad k = 1, \cdots, n-1, \\ E_k^h =& \frac{\sigma_k\lambda^h}{c_k + \gamma_k^h} S_k^h = \frac{\eta_{k-1}^h \sigma_k\lambda^h}{(c_k + \gamma_k^h)(c_{k-1} + \sigma_k\lambda^h)} I_{k-1}^h, \quad k = 1, \cdots, n-1, \end{aligned} \tag{4.3}$$

where we use the same notations as in Section 3. Then it follows from (4.1d) that

$$I_k^h = \frac{\gamma_k}{c_k + \eta_k^h} E_k^h = \frac{\eta_{k-1}^h \gamma_k^h \sigma_k\lambda^h}{(c_k + \gamma_k^h)(c_k + \eta_k^h)(c_{k-1} + \sigma_k\lambda^h)} I_{k-1}^h, \quad k = 1, \cdots, n-1,$$

and hence

$$I_k^h = \prod_{i=1}^{k} \frac{\eta_{i-1}^h \gamma_i^h \sigma_i}{(c_i + \gamma_i^h)(c_i + \eta_i^h)(c_{i-1} + \sigma_i\lambda^h)} (\lambda^h)^k I_0^h, \quad k = 1, \cdots, n-1. \tag{4.4}$$

Substituting (4.4) into (4.3), we have

$$N_k^h := S_k^h + E_k^h + I_k^h = \frac{\eta_{k-1}^h \left((c_k + \gamma_k^h)(c_k + \eta_k^h) + (c_k + \gamma_k^h + \eta_k^h)\sigma_k\lambda^h\right)}{(c_k + \gamma_k^h)(c_k + \eta_k^h)(c_{k-1} + \sigma_k\lambda^h)} I_{k-1}^h. \tag{4.5}$$

Write $A_k := (c_k + \gamma_k^h)(c_k + \eta_k^h)$, and $B_k := c_k + \gamma_k^h + \eta_k^h$, $k = 0, \cdots, n-1$. Then

$$\begin{aligned} N_k^h =& \frac{\left(A_k + B_k\sigma_k\lambda^h\right)\eta_{k-1}^h (\lambda^h)^{k-1} I_0^h}{(c_k + \gamma_k^h)(c_k + \eta_k^h)(c_{k-1} + \sigma_k\lambda^h)} \prod_{i=1}^{k-1} \frac{\eta_{i-1}^h \gamma_i^h \sigma_i}{(c_i + \gamma_i^h)(c_i + \eta_i^h)(c_{i-1} + \sigma_i\lambda^h)} \\ =& \left(\prod_{i=1}^{k} \frac{\eta_{i-1}^h \gamma_{i-1}^h \sigma_{i-1}}{(c_i + \gamma_i^h)(c_i + \eta_i^h)}\right) \frac{(A_k + B_k\sigma_k\lambda^h)(\lambda^h)^{k-1}}{\prod_{i=1}^{k}(c_{i-1} + \sigma_i\lambda^h)} \frac{I_0^h}{\gamma_0^h \sigma_0}, \end{aligned} \tag{4.6}$$

for $k = 1, \cdots, n-1$.

It follows from (4.1a) that

$$S_0^h = \frac{\Lambda^h}{d^h + \sigma_0\lambda^h},$$

and then

$$E_0^h = \frac{\Lambda^h}{c_0 + \gamma_0^h} \frac{\sigma_0\lambda^h}{d^h + \sigma_0\lambda^h}, \quad I_0^h = \frac{\Lambda^h \gamma_0^h}{(c_0 + \eta_0^h)(c_0 + \gamma_0^h)} \frac{\sigma_0\lambda^h}{d^h + \sigma_0\lambda^h}. \tag{4.7}$$

Hence

$$N_0^h = \frac{\Lambda^h}{d^h + \sigma_0 \lambda^h} \frac{A_0 + B_0 \sigma_0 \lambda^h}{(c_1 + \eta_0^h)(c_1 + \gamma_0^h)}. \tag{4.8}$$

Moreover, it follows from (4.1e) that

$$S_n^h = \frac{\eta_{n-1}^h}{c_{n-1}} I_{n-1}^h = \left(\prod_{i=1}^{n} \frac{\eta_{i-1}^h \gamma_{i-1}^h \sigma_{i-1}}{(c_i + \gamma_i^h)(c_i + \eta_i^h)} \right) \frac{(A_n + B_n \sigma_n \lambda^h)(\lambda^h)^{n-1}}{\prod_{i=1}^{n} (c_{i-1} + \sigma_i \lambda^h)} \frac{I_0^h}{\gamma_0^h \sigma_0} = N_n^h, \tag{4.9}$$

where we let $\gamma_n^h = \eta_n^h = \sigma_n = 0$ and $c_n = 1$ such that $A_n = 1 = B_n$.

Substituting (4.7) into (4.4), (4.6), and (4.9), respectively, and then summing up N_k^h over $k = 0, 1, \cdots, n$, we have

$$\begin{aligned} I_k^h &= \gamma_k^h \sigma_k Q_k \frac{(\lambda^h)^{k+1}}{\prod_{i=0}^{k} (c_{i-1} + \sigma_i \lambda^h)}, \quad k = 0, 1, \cdots, n-1, \\ N^h &= \sum_{k=0}^{n} Q_k \frac{(A_k + B_k \sigma_k \lambda^h)(\lambda^h)^k}{\prod_{i=0}^{k} (c_{i-1} + \sigma_i \lambda^h)}, \end{aligned} \tag{4.10}$$

where $Q_k := \dfrac{\Lambda^h \prod_{i=0}^{k-1} \eta_i^h \gamma_i^h \sigma_i}{\prod_{i=0}^{k} (c_i + \gamma_i^h)(c_i + \eta_i^h)}$, $c_{-1} := d^h$, and $\prod_{i=0}^{-1} \eta_i^h \gamma_i^h \sigma_i = 1$ by convention.

Solving (4.2) for I^v and using (2.2), we obtain

$$I^v = \frac{\Lambda^v \gamma^v \lambda^v}{d^v (d^v + \gamma^v)(d^v + \lambda^v)} = \frac{N^h \lambda^h}{\beta^v r}. \tag{4.11}$$

Then solving (4.11) for λ^v yields

$$\lambda^v = \frac{(d^v)^2 (d^v + \gamma^v) N^h \lambda^h}{\beta^v r \Lambda^v \gamma^v - d^v (d^v + \gamma^v) N^h \lambda^h}. \tag{4.12}$$

Substituting (4.12) into (2.4), we have

$$(N^h)^2 (d^v)^2 (d^v + \gamma^v) \lambda^h = \left(\beta^v r \Lambda^v \gamma^v - d^v (d^v + \gamma^v) N^h \lambda^h \right) r \sum_{k=0}^{n-1} \beta_k^h I_k^h,$$

or equivalently,

$$\lambda^h = \frac{\Lambda^v \gamma^v \beta^v r^2}{d^v (d^v + \gamma^v)} \frac{\sum_{k=0}^{n-1} \beta_k^h I_k^h}{N^h \left(N^h d^v + r \sum_{k=0}^{n-1} \beta_k^h I_k^h \right)}. \tag{4.13}$$

Write $G := \left(\Lambda^v \gamma^v \beta^v r^2 \right) / (d^v (d^v + \gamma^v))$ and define function $F := \left(\sum_{k=0}^{n-1} \beta_k^h I_k^h \right) \cdot \left((N^h)^2 d^v + N^h r \sum_{k=0}^{n-1} \beta_k^h I_k^h \right)^{-1}$. Then substituting (4.10) into this function and

multiplying the numerator and denominator both by $\left(\prod_{i=0}^{n}(c_{i-1}+\sigma_i\lambda^h)\right)^2$ yields

$$F(\lambda)=G\frac{W_1(\lambda)}{W_2(\lambda)+W_3(\lambda)}, \tag{4.14}$$

where

$$\begin{aligned}
W_1(\lambda) :=& \prod_{i=0}^{n}(c_{i-1}+\sigma_i\lambda)\sum_{k=0}^{n-1}\beta_k^h\gamma_k^h\sigma_k Q_k\prod_{i=k+1}^{n}(c_{i-1}+\sigma_i\lambda)\lambda^{k+1},\\
W_2(\lambda) :=& d^v\left(\sum_{k=0}^{n}Q_k\prod_{i=k+1}^{n}(c_{i-1}+\sigma_i\lambda)(A_k+B_k\sigma_k\lambda)\lambda^k\right)^2,\\
W_3(\lambda) :=& r\sum_{k=0}^{n}Q_k\prod_{i=k+1}^{n}(c_{i-1}+\sigma_i\lambda)(A_k+B_k\sigma_k\lambda)\lambda^k\\
&\cdot\sum_{k=0}^{n-1}\beta_k^h\gamma_k^h\sigma_k Q_k\prod_{i=k+1}^{n}(c_{i-1}+\sigma_i\lambda)\lambda^{k+1}.
\end{aligned}$$

Here we write $\lambda^h=\lambda$ for convenience. Then it follows from (4.13) that there exists an endemic equilibrium if and only if there exists a positive solution λ for $F(\lambda)=\lambda$.

Since $W_1(0)=0=W_3(0)$ and $W_2(0)=\left(d^vQ_0\prod_{i=1}^{n}c_{i-1}A_0\right)^2$, we have $F(0)=0$. Notice that $W_i(\lambda)$ are all polynomials of degree $2(n+1)$ in λ. Then

$$\lim_{\lambda\to\infty}F(\lambda)=G\frac{W_1(\infty)}{W_2(\infty)+W_3(\infty)}>0,$$

where

$$\begin{aligned}
W_1(\infty) =& \prod_{i=0}^{n}\sigma_i\sum_{k=0}^{n-1}\beta_k^h\gamma_k^h\sigma_k Q_k\prod_{i=k+1}^{n}\sigma_i,\\
W_2(\infty) =& d^v\left(\sum_{k=0}^{n}Q_k\prod_{i=k+1}^{n}\sigma_i B_k\sigma_k\right)^2,\\
W_3(\infty) =& r\sum_{k=0}^{n}Q_k\prod_{i=k+1}^{n}\sigma_i B_k\sigma_k\sum_{k=0}^{n-1}\beta_k^h\gamma_k^h\sigma_k Q_k\prod_{i=k+1}^{n}\sigma_i,
\end{aligned}$$

are all finite. Hence there exists an endemic equilibrium if $F'(0)>1$.

Again, since $W_1(0)=0=W_3(0)$, $F'(0)=GW_1'(0)/W_2(0)$. Simple calculation gives

$$W_1'(0)=\prod_{i=0}^{n}c_{i-1}\beta_0^h\gamma_0^h\sigma_0Q_0\prod_{i=1}^{n}c_{i-1}.$$

Then

$$F'(0)=G\frac{d^h\beta_0^h\gamma_0^h\sigma_0}{d^vQ_0A_0^2}=\frac{\Lambda^v\gamma^v\beta^vr^2}{d^v(d^v+\gamma^v)}\frac{d^h\beta_0^h\gamma_0^h}{d^v\Lambda^h(c_0+\gamma_0^h)(c_0+\eta_0^h)}=R_0^2.$$

Therefore we have the following result.

Theorem 4.1. *There exists an endemic equilibrium for systems* (2.1) *and* (2.3) *if* $R_0>1$.

5. **Concluding remarks.** Humans acquire partial immunity to malaria after infection, although the mechanisms of immunity are not fully understood. The acquired immunity depends on both the duration and the intensity of past exposure to infection. Recovery from a primary infection with malaria does not imply fully protective immunity against reinfection, which influences the production of gametocytes. Frequency and intensity of gametocytemia decrease with increasing age until they reach a minimum among adults. To better understand how the partial immunity affects the transmission of malaria, we have formulated a compartmental model, based on a system of differential equations in this paper, where we divided the human population into groups of susceptible, incubating, infective, and recovered individuals, with disease progression stages and partial immunities.

We derived an explicit formula in (3.3) for the reproductive number, R_0, by investigating the local stability of the infection-free equilibrium. By defining the reproductive numbers of infection for the humans and mosquitoes, respectively, the reproductive number of infection for the entire modeled human and mosquito populations is the square root of the product of the two reproductive numbers, where the square root takes care of the scalar matching for the model. We also showed that when the reproductive number R_0 is greater than one, there exists an endemic equilibrium. Although having not been able to prove its uniqueness and stability, we believe it is unique and stable, when it exists.

We notice that although there are multiple disease-progression stages for humans, the calculation of the reproductive number R_0^h for humans depends on only the average incubation period of first infected humans who survive to the first infectious stage, the waiting time in the first incubating stage, and the probability that an incubating human survives to the first infectious stage, but not the infection parameters from recovery and reinfection. This is not surprising if we remember that the reproductive number characterizes the epidemic threshold under which the number of infected individuals will either increase or decrease as a small number of infectives introduced into a fully susceptible population. Therefore the reproductive number, in general, only accounts for the initial growth of infection for infectious diseases. However, the other parameters play a role in determining the endemic equilibrium and the transient transmission dynamics. A numerical example provided below illustrates such a phenomenon.

We consider two cases, respectively. In case one, the human population consists of S_0^h, E_0^h, I_0^h, and S_1^h, and in case two, the human population consists of S_0^h, E_0^h, I_0^h, S_1^h, E_1^h, I_1^h, and S_2^h. Parameters for case one are given by

$$\begin{array}{lllllll} \Lambda^h = 100, & d^h = 0.125, & \delta_0 = 0.35, & \gamma_0 = 0.5, & \eta_0 = 0.6, & r = 5, & \beta_1^h = 0.35, \\ \Lambda^v = 400, & d^v = 0.5, & \gamma^v = 0.45, & \beta^v = 0.6, & & & \end{array}$$

and the parameters for case two are given by

$$\begin{array}{lllllll} \Lambda^h = 100, & d^h = 0.125, & \delta_0 = 0.35, & \delta_1 = 0.2, & \gamma_0 = 0.5, & \gamma_1 = 0.4, & \\ \eta_0 = 0.6, & \eta_1 = 0.8, & \sigma_1 = 0.65, & r = 5, & \beta_1^h = 0.35, & \beta_2^h = 0.3, & \\ \Lambda^v = 400, & d^v = 0.5, & \gamma^v = 0.45, & \beta^v = 0.6. & & & \end{array}$$

The reproductive numbers are the same in both cases as $R_0^h = 1.6579$, $R_0^v = 1.4311$, and $R_0 = 1.5403$. Hence the initial infections are the same for the two cases. However, the endemic equilibrium and the transient transmission dynamics are different. We list the sizes for I_0^h and I^v at the endemic equilibria for the two cases in Table 1. The transient transmission dynamics are demonstrated in Figure 3.

TABLE 1. The final sizes at the Endemic Equilibrium.

Number of stages	I_0^h	I^v
1	41.86	108.74
2	44.48	153.59

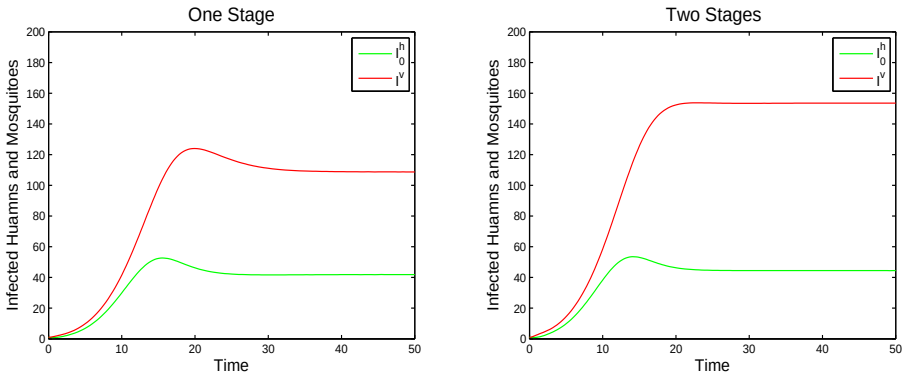

FIGURE 3. Two cases are considered where the human population consists of either one group of incubating and infected individuals, or two groups of incubating and infected individuals, respectively. The reproductive numbers are the same so that the initial infections are the same for the two cases, but their endemic values and transient transmission dynamics are different. Only I_0^h and I^v are plotted for both cases.

While the reproductive number still provides important information for disease prevention and control, in particular, in determining whether the infection takes off initially, the time-dependent running reproduction number, which represents the number of secondary infection caused by a single individual in the population who becomes infective at time t, may provide more appropriate information for disease control [4]. It is worth further investigations based on a running reproduction number in the future.

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