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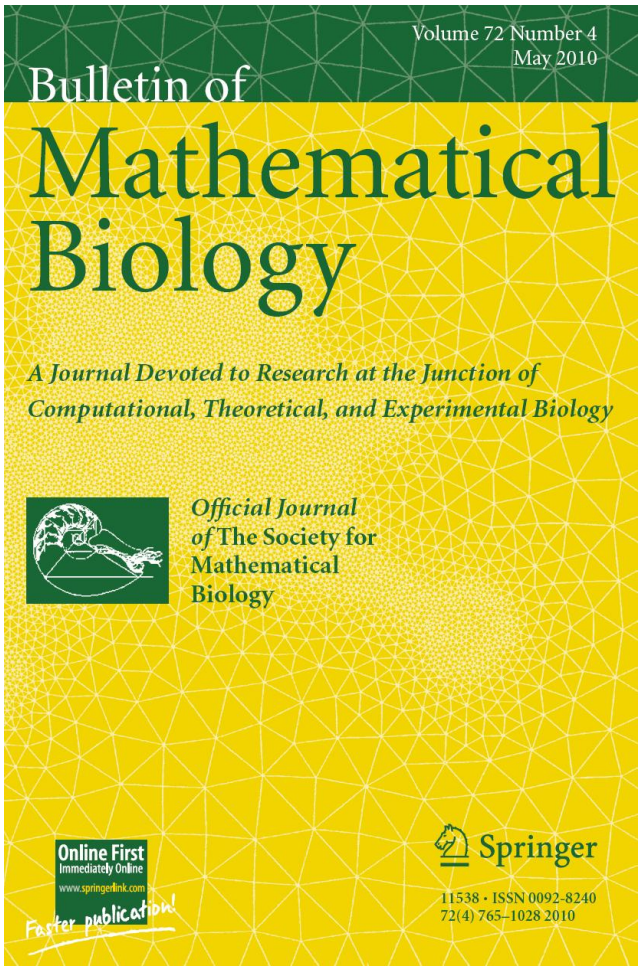

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ORIGINAL ARTICLE

Mathematical Model for Optimal Use of Sulfadoxine-Pyrimethamine as a Temporary Malaria Vaccine

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Abstract In this paper, we introduce a deterministic malaria model for determining the drug administration protocol that leads to the smallest first malaria episodes during the wet season. To explore the effects of administering the malaria drug on different days during the wet season while minimizing the potential harmful effects of drug overdose, we define 40 drug administration protocols. Our results fit well with the clinical studies of Coulibaly et al. at a site in Mali. In addition, we provide protocols that lead to smaller number of first malaria episodes during the wet season than the protocol of Coulibaly et al.

Keywords Drug administration protocol · Dry and wet seasons · Sulfadoxine-pyrimethamine

1. Introduction

According to the 2006 UNICEF report, malaria is one of the most life threatening tropical diseases for which no successful vaccine has been developed. An effective drug for a person infected with malaria is sulfadoxine-pyrimethamine (SP). SP treatment also helps clear the malaria infection in infected individuals. In 2002, Coulibaly et al. conducted experimental trials designed to explore the effectiveness of SP as a temporary malaria vaccine (Coulibaly et al., 2002). Coulibaly et al. chose SP as the drug for initial malaria parasite clearance in their study for the following four reasons: (1) SP has been used in previous vaccine trials; (2) studies have found SP to have greater than 99% efficacy in treating uncomplicated malaria in Mali compared to 85–90% efficacy for chloroquine in

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the area; (3) SP is the approved second-line antimalarial agent in Mali; and (4) SP single-dose regimen ensures compliance when treatment is directly observed.

Along with its desired effects, unwanted common side effects of SP include fever, increased sensitivity of skin to sunlight, irritation or soreness of tongue, and skin rash. Less common SP side effects include abdominal or stomach pains, fast or irregular breathing, puffiness or swelling of the eyelids, pains in joints, and swelling of front part of the neck. Symptoms of SP overdose include bleeding or severe bruising, convulsions, fever and sore throat, irritation or soreness of tongue, loss of appetite, unusual tiredness or weakness, trembling, and severe vomiting.

In their study, Coulibaly et al. considered two groups of people at a site in Bandiagara (Mali), a region of endemic seasonal malaria. At the beginning of the study, the two groups of people did not have the malaria disease. The first group was administered SP at the beginning of the wet season, and the second group was given no drug. The two groups were monitored during the entire season for the first malaria episode. It was found that in the first 4 weeks much fewer first malaria episode cases occurred in the first group, but this was slowly reversed between the fourth and the eighth week. During weeks 8–12, the number of first malaria episodes in the first group became larger than in the second group (see Fig. 1). Figure 1 is reproduced directly from Coulibaly et al. (2002).

The large increase of the number of first malaria episodes in group 1 was due to the fact that most of the people in that group became vulnerable to the disease because the drug SP is mainly effective during a period of 4 weeks. In contrast, in group 2, most of the people were already infected during weeks 4 and 8. Therefore, group 2 was not comparable to group 1 during weeks 8–12 as more than half of the people in group 2 were already removed from the list of candidates to first malaria episode. After 12 weeks, both groups have approximately the same (but very small) number of malaria episodes (see Fig. 1). Over the entire wet season (April–September in Mali), there was no observed significant advantage to the group that received SP.

In this paper, we focus on using a deterministic mathematical model to determine whether administering different doses of a "generic" malaria drug at a different schedule

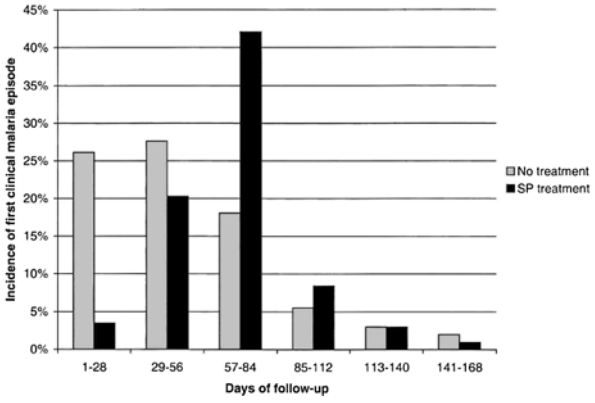

Fig. 1 Coulibaly et al. (2002): Incidence of first clinical malaria episodes over the course of the malaria season among subjects who received curative pyrimethane (SP) treatment or no treatment at the start of the season.

would lead to fewer episodes of malaria in the population. Using a deterministic mathematical malaria model described in the Appendix, we deduce the density of infected mosquitoes during the wet season. We use this information to derive a much simpler deterministic model which is applicable to the two groups, one receiving no drugs (Policy 0) and the other receiving a generic drug on specific days during the wet season (Policy 1). To explore the effects of administering the drug on different days during the wet season while minimizing the potential harmful effects of drug overdose, we define 40 drug administration protocols under Policy 1. These consist of Protocol 1–5 for taking a full dose of the drug once, Protocol 6–20 for taking a half dose of the drug twice and Protocols 21–40 for taking a one-third dose of the drug three times. To make the generic drug prophylactic while keeping the model protocols simple, we assume that a full dose gives 20 days of protection, which fits well with the clinical data of Coulibaly et al. Under Protocol 6–40, individuals are given the drug 2 or 3 times instead of once. To further keep the model framework simple, we neglect the associated extra cost of drug distributions. Our choice of specific days in the wet season for administering the drug is based on the time schedules adopted in Coulibaly et al. (2002). The relative short period of protection given by the drug means there is no significant advantage in administering the drug in the dry season. The observed data of Coulibaly et al. correspond to one protocol of drug treatment. Based on these data, we develop a model that can test the effectiveness of SP in many other protocols. A key observation in our approach is the fact that the total population of the two groups in Bandiagara was much smaller than the total population in Bandiagara, and thus the number of infected mosquitoes in this town is essentially unaffected by any of the protocols. The methods of the present paper can be applied to other malaria models, such as Bailey (1957), Bekessey et al. (1976), Carnevale et al. (2004), Dembele et al. (2009), Dietz (1970, 1988), Gideon and Shu (1999), Grassly and Fraser (2006), Kermack and McKendrick (1927), Lokta (1923), Macdonald (1950), Martini (1921), McKenzie and Bossert (2005), National Institute of Allergy and Infectious Diseases (2002), Norman and Baley (1982), Ross (1911).

The paper is organized as follows: In Section 2, we introduce the simplified malaria model. In Section 3, we define protocols for which a full dose of the drug is administered. Protocols for which half dose and one-third dose are administered are introduced in Sections 4 and 5, respectively. We summarize our results in Section 6. In the Appendix, we use the malaria model of Dembele et al. (2009) to derive the density of infected mosquitoes which is then used in the simplified model throughout the paper.

2. Malaria model with drug administration

In Dembele et al. (2009), we considered a malaria model which includes variables shown in Table 1.

The susceptible individuals are those who are not sick but can become infected through bites from infected mosquitoes. The infected individuals are those who were bitten by infected mosquitoes and show symptoms of the disease. The recovered individuals are those who have been treated by a generic drug with a 4-week protective period. Susceptible mosquitoes are those that do not carry any parasite in their salivary glands. The infected mosquitoes are those who carry a multitude of parasites in their salivary glands and are thus able to infect humans.

Table 1 Model variables

$S_h =$ *Number of susceptible humans*
$I_h =$ *Number of infected humans*
$R_h =$ *Number of recovered humans*
$N_h =$ *Total population of humans*
$S_m =$ *Number of susceptible mosquitoes*
$I_m =$ *Number of infected mosquitoes*
$N_m =$ *Total population of mosquitoes*

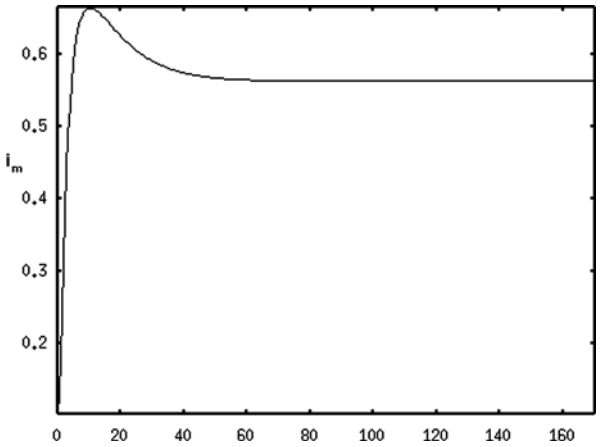

Fig. 2 Profile of $i_m(t)$ for the wet season (168 days).

Set $i_m = \frac{I_m}{N_m}$. As will be deduced in the Appendix, the profile for $i_m = i_m(t)$ is given by Fig. 2.

As already mentioned in Section 1, the number of patients in the study of Coulibaly et al. in Bandiagara was much smaller than the total population in that location; hence the number of infected mosquitoes, I_m, as well as i_m, should not be affected by any of the protocols of drug administration to be considered in the sequel. This observation combined with the given profile of $i_m(t)$ in Fig. 2 (to be derived in the Appendix), will allow us to work with a simplified malaria model. Indeed, let

$$S_h^{(0)}(t) = \text{ Number of susceptible humans in Group 0 (no drug) at time } t,$$

and

$$S_h^{(1)}(t) = \text{ Number of susceptible humans in Group 1 (drug) at time } t.$$

Introducing the variables

$$s_h^{(0)}(t) = \frac{S_h^{(0)}(t)}{S_h^{(0)}(0)} \quad \text{and} \quad s_h^{(1)}(t) = \frac{S_h^{(1)}(t)}{S_h^{(1)}(0)},$$

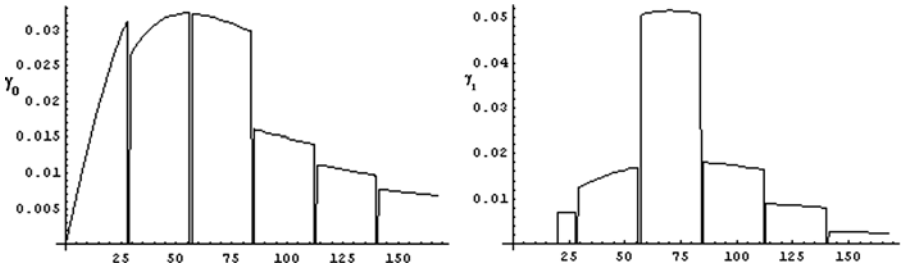

Fig. 3 Profiles of $\gamma_0(t)$ and $\gamma_1(t)$.

we can write

$$\begin{aligned} \frac{ds_h^{(0)}}{dt} &= -\gamma_0 i_m s_h^{(0)}, \\ \frac{ds_h^{(1)}}{dt} &= -\gamma_1 i_m s_h^{(1)}, \end{aligned} \tag{1}$$

where $\gamma_0(t)$, $\gamma_1(t)$ and $i_m(t)$ are functions of t, with $i_m(t)$ as in Fig. 2.

The infection rates $\gamma_0 = \gamma_0(t)$ and $\gamma_1 = \gamma_1(t)$ were derived in Fig. 3 in such a way that upon computing the first episodes of malaria for the two groups we obtained numerical results that agree with the clinical data of Fig. 1.

It will be useful to introduce the function

$$f(a, b, t) = \frac{at}{b + t^2}, \tag{2}$$

where a and b are positive constants. The definition of the infectious rates in Fig. 3 are then

$$\gamma_0(t) = \begin{cases} f(4.38, 3136, t) & \text{if } 1 \le t \le 28, \\ f(3.63, 3136, t) & \text{if } 29 \le t \le 56, \\ f(3.61, 3136, t) & \text{if } 57 \le t \le 84, \\ f(1.96, 3136, t) & \text{if } 85 \le t \le 112, \\ f(1.57, 3136, t) & \text{if } 113 \le t \le 140, \\ f(1.27, 3136, t) & \text{if } 141 \le t \le 168 \end{cases} \tag{3}$$

and

$$\gamma_1(t) = \begin{cases} 0 & \text{if } 1 \le t \le 19, \\ 0.007 & \text{if } 20 \le t \le 28, \\ f(2.43, 4900, t) & \text{if } 29 \le t \le 56, \\ f(7.22, 4900, t) & \text{if } 57 \le t \le 84, \\ f(2.57, 4900, t) & \text{if } 85 \le t \le 112, \\ f(1.40, 4900, t) & \text{if } 113 \le t \le 140, \\ f(0.47, 4900, t) & \text{if } 141 \le t \le 168. \end{cases} \tag{4}$$

Using Model (1) with the initial conditions $s_h^{(0)}(0) = 1$ and $s_h^{(1)}(0) = 1$ we compute the incidence of first malaria episodes. As in Coulibaly et al., we use a sample size of 180

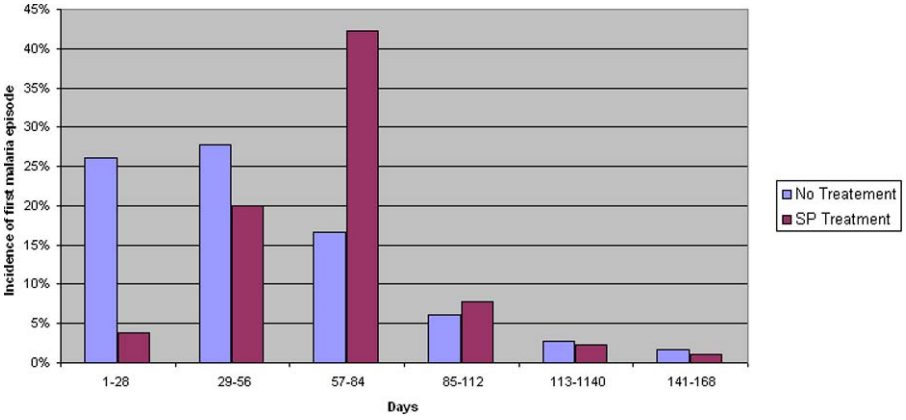

Fig. 4 Simulation of Model (1) under Policy 0 (Group 0) and Policy 1 (Group 1) of the incidence of first malaria episode.

Table 2 Number and % of infected individuals, mean and variance under Policy 1

Days	Number of Infected People
1–28	7
29–56	36
57–84	76
85–112	14
113–140	4
141–168	2
Mean	23.16
Variance	823.36
% of Infected Individuals	77.22%

people for each group. At enrollment, all the 180 people are susceptible to the disease. For the first 4-week period, the number of first malaria episodes is given by $(s_h^{(1)}(0) - s_h^{(1)}(28)) * 180$, for the second 4-week period, the number of first malaria episodes is given by $(s_h^{(1)}(29) - s_h^{(1)}(56)) * 180, \ldots$, etc. Figure 4 shows the simulation of the model for first malaria episode for Groups 0 and 1; the results are in excellent agreement with the clinical results of Coulibaly et al. in Fig. 1. In the sequel, based on (3) and (4), we shall explore the implications of implementing various drug administration protocols on the effectiveness of a generic drug as a temporary vaccine during the course of the wet season.

Table 2 gives the number and percentage of infected individuals under Policy 1 (drug), when the full dose of drug is given at the beginning of the wet season. In the next section, we consider also policies when the full dose is given at other times during the wet season instead of at the beginning of the wet season.

3. Full dose drug administration therapy

In this section, we consider single full dose of drug administration protocols. For Protocol $k \in \{1, 2, \ldots, 5\}$, the single dose is given on day x_k during the wet season. In their

Table 3 Single dose protocols

Protocol k	Dose	Day of Drug x_k
1	Full (one time)	$x_1 = 1$
2	Full (one time)	$x_2 = 28$
3	Full (one time)	$x_3 = 56$
4	Full (one time)	$x_4 = 84$
5	Full (one time)	$x_5 = 112$

work, Coulibaly et al. administered a full dose of SP on Day 1 of the wet season. This is Protocol 1 in our case. The percentage of infected individuals in this case is 77.22% (as compared to 81% when no drug is given). Our single dose protocols and x_k are defined in Table 3.

In Table 3, our choice of days on which the drug is administered in each of the protocols is motivated by the time schedules adopted in Coulibaly et al. (2002). Under this schedule, the percentage of first malaria episodes are measured every 4 weeks. As in the experimental study of Coulibaly et al., we assume that none of the subjects is infected with the malaria disease at the beginning of the wet season. In the clinical study of Coulibaly et al., SP treatment provided near complete protection from malaria episodes for about 1 month and partial protection for 10 weeks. After this period of protection, the group treated with SP showed a peak of incidence of clinical malaria episodes midway through the transmission season.

We now use the following deterministic equations to compute the percentage of first malaria cases under each Protocols $k \in \{2, 3, 4, 5\}$:

$$\frac{ds_h^{(k)}}{dt} = -\gamma_k i_m s_h^{(k)} \tag{5}$$

where γ_k are the mosquito infection rate under Protocol $k \in \{2, 3, 4, 5\}$.

Each $\gamma_k(t)$ is constructed using $\gamma_0(t)$ and $\gamma_1(t)$: When the drug is administered on day x_k, where x_k is defined in Table 3 for $k \in \{2, 3, 4, 5\}$, we take

$$\gamma_k(t) = \begin{cases} \gamma_0(t) & \text{if } 1 \le t \le x_k, \\ \gamma_1(t - x_k) & \text{if } x_k + 1 \le t \le 168. \end{cases} \tag{6}$$

Figure 5 gives the total percentage, mean and variance over time of infected people when implementing Policy 2 under Protocol $k \in \{1, 2, 3, 4, 5\}$. The disease is considered to be better controllable when the percentage of infected people, the mean and the variance are relatively small.

From Fig. 5, we see that the percentage and mean of infected individuals under Protocol 1 are respectively, 77.22% and 23.17; it is the smallest compared to that of Protocol 2–5 (percentage, mean, and variance of infected individuals for Protocol 2–5 are respectively (81.11%, 24.33, 477.06), (85%, 25.5, 414.30), (87.22%, 26.17, 397.36) and (81.11%, 24.33, 453.46)). The results of Protocol 1 are consistent with the results of Coulibaly et al. However, Protocol 1 has the largest variance of 823.36 compared to those of Protocol 2–5. In the next section, we explore the effects of administering half-doses of SP twice in the wet season.

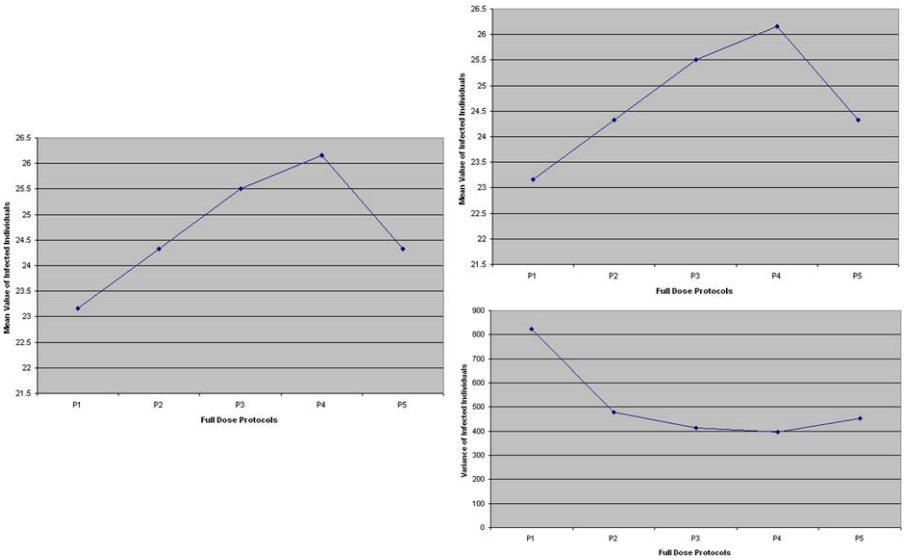

Fig. 5 Protocols 1–5: Percentage, mean, and variance of infected persons during the wet season.

4. Half dose drug administration therapy

In this section, we define half dose of drug administration protocols. In these protocols, the half dosage is given twice at different times during the wet season. For Protocol $k \in \{6, 7, \ldots, 20\}$, the first and second half doses are given on days x_k and y_k, respectively. The half dosage protocols and (x_k, y_k) are defined in Table 4.

In Table 4, our choice of days on which the half doses are administered in each of the protocols follows the time schedules adopted in Coulibaly et al. (2002). As in the full dose protocols, the percentage of first malaria episodes are measured every 4 weeks. To capture the prophylactic effect of the generic drug, we assume that an individual who is given the half dose at day x_k and half dose at later day y_k has infection rate $\gamma_k(t)$, where (x_k, y_k) is defined in Table 4 for $k \in \{6, 7, \ldots, 20\}$. For $k = 6, 7, \ldots, 10$ we take

$$\gamma_k(t) = \begin{cases} 0 & \text{if } 1 \le t \le 10 - x_k, \\ \frac{1}{2}\gamma_0(t) + \frac{1}{2}\gamma_1(t - x_k) & \text{if } 11 - x_k \le t \le y_k, \\ 0 & \text{if } y_k + 1 \le t \le y_k + 10, \\ \frac{1}{2}(\frac{1}{2}\gamma_0(t) + \frac{1}{2}\gamma_1(t - x_k)) + \frac{1}{2}\gamma_1(t - y_k) & \text{if } y_k + 11 \le t \le 168 \end{cases} \tag{7}$$

and for $k = 11, 12, \ldots, 20$ we take

$$\gamma_k(t) = \begin{cases} \gamma_0(t) & \text{if } 1 \le t \le x_k, \\ 0 & \text{if } x_k + 1 \le t \le x_k + 11, \\ \frac{1}{2}\gamma_0(t) + \frac{1}{2}\gamma_1(t - x_k) & \text{if } x_k + 12 \le t \le y_k, \\ 0 & \text{if } y_k + 1 \le t \le y_k + 11, \\ \frac{1}{2}(\frac{1}{2}\gamma_0(t) + \frac{1}{2}\gamma_1(t - x_k)) + \frac{1}{2}\gamma_1(t - y_k) & \text{if } y_k + 12 \le t \le 168. \end{cases} \tag{8}$$

Table 4 Half dose protocols

Protocol k	Dose	Days of Drug (x_k, y_k)
6	Half (two times)	$(x_6, y_6) = (1, 28)$
7	Half (two times)	$(x_7, y_7) = (1, 56)$
8	Half (two times)	$(x_8, y_8) = (1, 84)$
9	Half (two times)	$(x_9, y_9) = (1, 112)$
10	Half (two times)	$(x_{10}, y_{10}) = (1, 140)$
11	Half (two times)	$(x_{11}, y_{11}) = (28, 56)$
12	Half (two times)	$(x_{12}, y_{12}) = (28, 84)$
13	Half (two times)	$(x_{13}, y_{13}) = (28, 112)$
14	Half (two times)	$(x_{14}, y_{14}) = (28, 140)$
15	Half (two times)	$(x_{15}, y_{15}) = (56, 84)$
16	Half (two times)	$(x_{16}, y_{16}) = (56, 112)$
17	Half (two times)	$(x_{17}, y_{17}) = (56, 140)$
18	Half (two times)	$(x_{18}, y_{18}) = (84, 112)$
19	Half (two times)	$(x_{19}, y_{19}) = (84, 140)$
20	Half (two times)	$(x_{20}, y_{20}) = (112, 140)$

We assume that once a half dose is given at day x_k, the individual is protected for 9 days (a little less than half as many days as when a full dose is given). Thereafter, and until day y_k, the protection afforded is half that of a full dose, namely, $\frac{1}{2}\gamma_1(t - x_k)$ while at the same time the level of the initial infection rate $\gamma_0(t)$ is reduced by one half. When another half dose is given at day y_k, again the individual is protected for 9 days, and thereafter the level of the preceding infection rate $\frac{1}{2}\gamma_0(t) + \frac{1}{2}\gamma_1(t - x_k)$ is reduced by one half.

To exert the prophylactic effect of the generic drug, we assume that an individual who is given the half dose is initially immunized for half the time of a person receiving the full dose. The infection rate is assumed to be 0.02 for 10 days and 0.04 for the rest of the days in the 4 weeks. We also assume that once a drug is given, the individual is protected in the same way as a person who took the drug on Day 1. In the above definition, we have ignored the fact that immune system is somewhat weakened by administration of the drug. We now use Model (5) under each Protocol $k \in \{6, 7, \ldots, 20\}$, where $\gamma_k(t)$ is defined by (7) and (8), to compute the percentage of first malaria cases.

Figure 6 gives the total percentage, mean and variance of infected individuals for implementing Policy 1 under Protocol $k \in \{6, 7, 8, \ldots, 20\}$.

Using Fig. 6, we deduce that the percentage of infected individuals under Protocol 7 is the smallest, namely 73.89%, and the mean and variance are respectively 22.17 and 285.37. Thus, Protocol 7 is the best protocol for controlling malaria whenever the drug is administered twice during the wet season. In the next section, we explore the effects of administering one-third doses of SP three times in the wet season.

5. One-third dose drug administration therapy

In this section, we consider one-third dose of drug administration protocol given three times during the wet season. For Protocol $k \in \{21, 22, \ldots, 40\}$, the one third doses are given on days x_k, y_k and z_k. The one third dosage protocols and (x_k, y_k, z_k) are defined in Table 5.

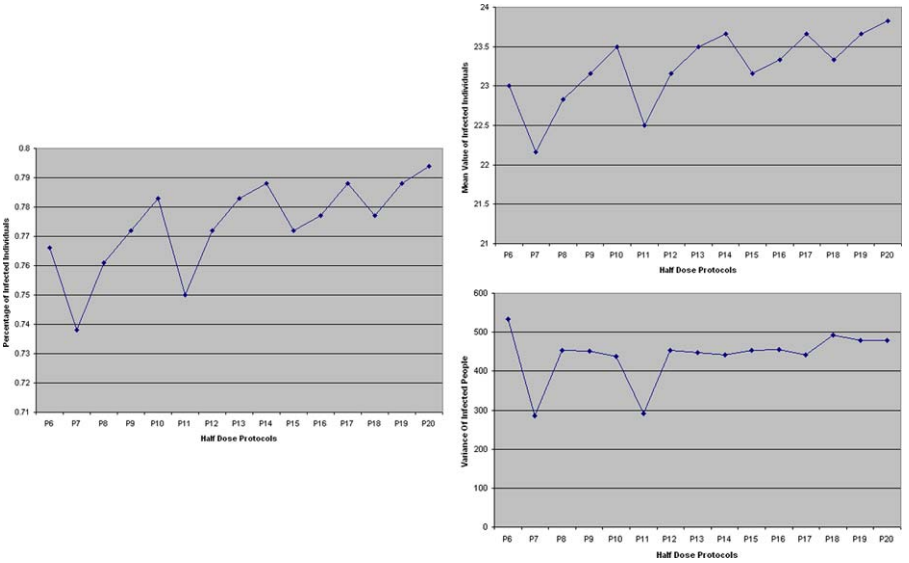

Fig. 6 Protocols 6–20: Percentage, mean and variance of infected persons during the wet season.

Table 5 One-third dose protocols

Protocol k	Dose	Days of Drug (x_k, y_k, z_k)
21	One-third (three times)	$(x_{21}, y_{21}, z_{21}) = (1, 28, 56)$
22	One-third (three times)	$(x_{22}, y_{22}, z_{22}) = (1, 28, 84)$
23	One-third (three times)	$(x_{23}, y_{23}, z_{23}) = (1, 28, 112)$
24	One-third (three times)	$(x_{24}, y_{24}, z_{24}) = (1, 28, 140)$
25	One-third (three times)	$(x_{25}, y_{25}, z_{25}) = (1, 56, 84)$
26	One-third (three times)	$(x_{26}, y_{26}, z_{26}) = (1, 56, 112)$
27	One-third (three times)	$(x_{27}, y_{27}, z_{27}) = (1, 56, 140)$
28	One-third (three times)	$(x_{28}, y_{28}, z_{28}) = (1, 84, 112)$
29	One-third (three times)	$(x_{29}, y_{29}, z_{29}) = (1, 84, 140)$
30	One-third (three times)	$(x_{30}, y_{30}, z_{30}) = (1, 112, 140)$
31	One-third (three times)	$(x_{31}, y_{31}, z_{31}) = (28, 56, 84)$
32	One-third (three times)	$(x_{32}, y_{32}, z_{32}) = (28, 56, 112)$
33	One-third (three times)	$(x_{33}, y_{33}, z_{33}) = (28, 56, 140)$
34	One-third (three times)	$(x_{34}, y_{34}, z_{34}) = (28, 84, 112)$
35	One-third (three times)	$(x_{35}, y_{35}, z_{35}) = (28, 84, 140)$
36	One-third (three times)	$(x_{36}, y_{36}, z_{36}) = (28, 112, 140)$
37	One-third (three times)	$(x_{37}, y_{37}, z_{37}) = (56, 84, 112)$
38	One-third (three times)	$(x_{38}, y_{38}, z_{38}) = (56, 84, 140)$
39	One-third (three times)	$(x_{39}, y_{39}, z_{39}) = (56, 112, 140)$
40	One-third (three times)	$(x_{40}, y_{40}, z_{40}) = (84, 112, 140)$

We capture the prophylactic effect of the one-third doses by assuming that if these doses are administered at days x_k, y_k, and z_k, then the corresponding infection rate is $\gamma_k(t)$, where (x_k, y_k, z_k) is defined in Table 5. For $k = 21, 22, \ldots, 30$, we take

$$\gamma_k(t) = \begin{cases} 0 & \text{if } 1 \le t \le 8 - x_k, \\ \frac{3}{4}\gamma_0(t) + \frac{1}{4}\gamma_1(t - x_k) & \text{if } 9 - x_k \le t \le y_k, \\ 0 & \text{if } y_k + 1 \le t \le y_k + 7, \\ \frac{3}{4}(\frac{3}{4}\gamma_0(t) + \frac{1}{4}\gamma_1(t - x_k)) + \frac{1}{4}\gamma_1(t - y_k) & \text{if } y_k + 8 \le t \le z_k, \\ 0 & \text{if } z_k + 1 \le t \le z_k + 7, \\ \frac{3}{4}\{\frac{3}{4}(\frac{3}{4}\gamma_0(t) + \frac{1}{4}\gamma_1(t - x_k)) & \\ \quad + \frac{1}{4}\gamma_1(t - y_k)\} + \frac{1}{4}\gamma_1(t - z_k) & \text{if } z_k + 8 \le t \le 168 \end{cases} \tag{9}$$

and for $k = 31, 32, \ldots, 40$ we take

$$\gamma_k(t) = \begin{cases} \gamma_0(t) & \text{if } 1 \le t \le x_k, \\ 0 & \text{if } x_k + 1 \le t \le x_k + 7, \\ \frac{3}{4}\gamma_0(t) + \frac{1}{4}\gamma_1(t - x_k) & \text{if } x_k + 8 \le t \le y_k, \\ 0 & \text{if } y_k + 1 \le t \le y_k + 7, \\ \frac{3}{4}(\frac{3}{4}\gamma_0(t) + \frac{1}{4}\gamma_1(t - x_k)) + \frac{1}{4}\gamma_1(t - y_k) & \text{if } y_k + 8 \le t \le z_k, \\ 0 & \text{if } z_k + 1 \le t \le z_k + 7, \\ \frac{3}{4}\{\frac{3}{4}(\frac{3}{4}\gamma_0(t) + \frac{1}{4}\gamma_1(t - x_k)) & \\ \quad + \frac{1}{4}\gamma_1(t - y_k\} + \frac{1}{4}\gamma_1(t - z_k) & \text{if } z_k + 8 \le t \le 168. \end{cases} \tag{10}$$

Similar to the case of half dose, we assume that when one third dose is first given at day x_k, the individual is protected for 6 days (a little less than one-third of the 19 days of protection afforded by a full dose). Thereafter, the effect of the one-third dose is $\frac{1}{4}\gamma_1(t - x_k)$ while the level of the preceding infection rate $\gamma_0(t)$ is reduced by three-fourths. Similar assumptions are made when one third dose is given on days y_k and z_k. When more data are obtained, this assumption may possibly need to be revisited. Here again, we ignore the fact that the immune system is somewhat weakened by administration of the drug. We thus accordingly define $\gamma_{21}, \gamma_{22}, \ldots, \gamma_{40}$ for the protocols defined in Table 5. We then proceed to solve for the first malaria episode by using (5) with the $\gamma_k(t)$ in (9) and (10).

Figure 7 gives the percentage, mean and variance of infected people for implementing Policy 2 under Protocol $k \in \{21, 22, 23, \ldots, 40\}$.

Using Fig. 7, we see that the percentage of infected individuals under Protocol 21 is the smallest; namely 72.22%. The mean and variance of Protocol 21 are 21.67 and 237.47, respectively. Protocol 21 is the best protocol for controlling malaria whenever the drug is administered three times during the wet season.

Decreasing SP dose significantly increases the probability of selecting mutations in Plasmodium falciparum dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS), and this may cripple the drug. As a result, we do not define protocols in which the dosage is decreased significantly (for example $\frac{1}{4}$-dose, $\frac{1}{5}$-dose, $\frac{1}{6}$-dose, ...). Also, we do not consider multiple full dose protocols in the wet season since a multiple full dose of SP is a drug overdose with potential detrimental effects on the individual.

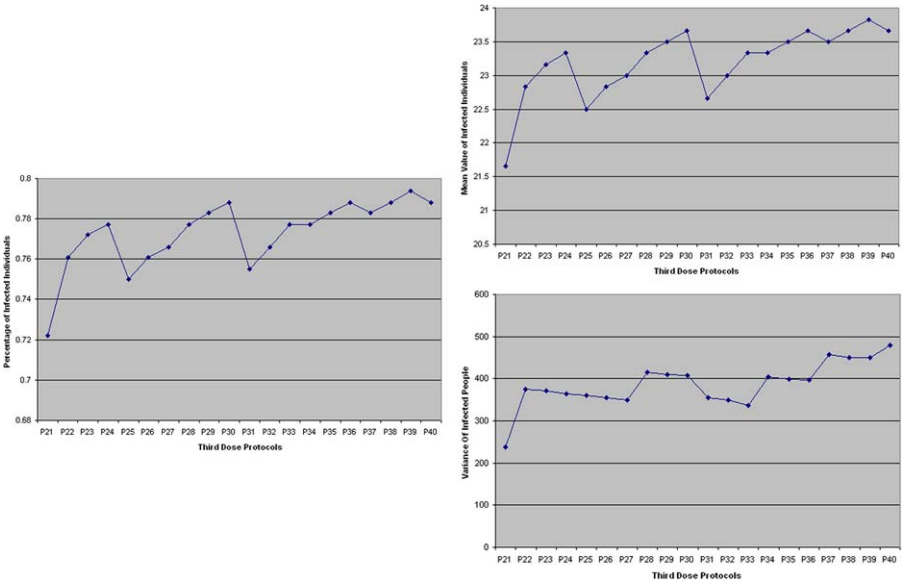

Fig. 7 Protocols 21–40: Percentage, mean, and variance of infected persons during the wet season.

6. Conclusion

We used a simple deterministic malaria model to study the potential effects of a "generic" malaria drug administration under two policies, Policy 0 (no drug) and Policy 1 (drug). Under Policy 1, we defined 40 protocols (Protocol 1–40) based on the clinical trials of Coulibaly et al. at a site in Mali. The conclusion of the model results are as follows.

- If one full dose of the drug is given once during the wet season, then administering it on Day 1 of the wet season (Protocol 1) leads to the lowest malaria episodes, namely 77.22% of the population will incur the first malaria episode. This model result agrees with the clinical results of Coulibaly et al.
- If a half dose of the drug is given twice, then administering them on Days 1 and 56 of the wet season (Protocol 7) leads to the lowest percentage of first malaria episode, namely, 73.89%. The mean and variance of the first malaria episodes of Protocol 7 are 22.17 and 285.37, respectively.
- If a one-third dose of the drug is given three times, then administering them on Days 1, 28 and 56 of the wet season (Protocol 21) has the lowest percentage of first episode occurrence, namely, 72.22%. The mean and variance of the first malaria episodes of Protocol 21 are 21.67 and 237.47, respectively.

The above results suggest that the best policy is Protocol 21, of administering the drug in three equal portions on Days 1, 28 and 56. The next best policy is Protocol 7, of administering the drug in two equal portions on Days 1 and 56. It seems intuitive that when administering one full dose, the earliest the dose is given the better the results will be, i.e., Protocol 1 is better than Protocol 2–5. However, we do not have an intuitive explanation of why Protocol 7 does better, and why Protocol 21 is the best, as our model

results predict. These conclusions of our model should be tested clinically. If it turns out that Protocol 21 (or 7) is indeed the best, then the extra cost of drug distributions should be considered and taken into account when policy on drug protocol is evaluated.

In this paper, we assume that when a half dose is given at day x, the protection afforded, in terms of the infection rate $\gamma(t)$, is half of the protection afforded by the full dose (that is, $\frac{1}{2}\gamma_1(t-x)$), whereas the previous rate $\gamma(t)$ persists at half the level. Similarly, with the one-third dose, the new infection rate for $t > x$ is $\frac{1}{4}\gamma_1(t-x)$ plus three-fourths of the previous infection rate. We do not take into account that the immune system is somewhat weakened by the drug. When data becomes available on the direct effect of partial dose on the infection rate, the model equation for $\gamma(t)$ could be extended to fit these data.

To compare our results with the clinical studies of Coulibaly et al., the days on which the drug is administered in each of the 40 protocols are always informed directly by the clinical studies. However, our model framework allows for finding the optimal days for different treatment schedules (how many days to be determined by how many doses would work best). To obtain our results, we first estimated the infection functions $\gamma_0(t)$ and $\gamma_1(t)$. These functions are allowed to vary with time and they fit well the clinical data of Coulibaly et al. Estimating the "range" of infection functions that would be consistent with the observed data and determining how our results depend on these functions are interesting questions for future studies.

In their clinical study, Coulibaly et al. found that although parasite densities were no different between asymptomatic subjects in the two groups at regular 4-weekly intervals, malaria infected subjects had significantly lower parasite densities if they had SP treatment at the beginning of the malaria season. They observed the persistence of this effect throughout the 24-week period. Moreover, the effect was more pronounced in older children and young adults. Using age-structured mathematical malaria models to study cumulative and age-specific incidence of malaria episodes could be useful for future malaria investigations.

In the development of Model (1), we used data from Coulibaly et al. (2002) (see Fig. 1) in order to determine the infection rates $\gamma_0(t)$ and $\gamma_1(t)$ as in Eqs. (3) and (4). These data were based on the fact that Sulfadoxine-Pyrimethamine is a single-compound cure for malaria. WHO now recommends combination therapy whereby this drug is used in combination with another active ingredient to fight resistance. When data based on this combined vaccine (therapy) becomes available, new infection rates for $\gamma_0(t)$ and $\gamma_1(t)$ could be derived as before to replace Eqs. (3) and (4). With these new rates and the same $i_m(t)$ as in Fig. 2, the method of the present paper can immediately be extended to determine the optimal use of the combined vaccine.

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Appendix

Following Dembele et al. (2009), we model the spread of the malaria disease by the following system of equations.

$$\begin{aligned}
\frac{dS_h}{dt} &= \lambda_h N_h + \beta_h R_h - \mu_h S_h - \frac{(\alpha_{mh} b_m I_m) S_h}{N_h},\\
\frac{dI_h}{dt} &= \frac{(\alpha_{mh} b_m I_m) S_h}{N_h} - (\mu_h + \alpha_h + \mu_d) I_h,\\
\frac{dR_h}{dt} &= \alpha_h I_h - (\mu_h + \beta_h) R_h,\\
\frac{dS_m}{dt} &= \lambda_m N_m - \mu_m S_m - \frac{(\alpha_{hm} b_m I_h) S_m}{N_h},\\
\frac{dI_m}{dt} &= \frac{(\alpha_{hm} b_m I_h) S_m}{N_h} - \mu_m I_m,\\
\frac{dN_h}{dt} &= (\lambda_h - \mu_h) N_h - \mu_d I_h,\\
\frac{dN_m}{dt} &= (\lambda_m - \mu_m) N_m,
\end{aligned} \tag{A.1}$$

where $N_h = S_h + I_h + R_h$ and $N_m = S_m + I_m$.

To analyze Model (A.1), we introduce the following variables:

$$s_h = \frac{S_h}{N_h}, \qquad i_h = \frac{I_h}{N_h}, \qquad r_h = \frac{R_h}{N_h}, \qquad s_m = \frac{S_m}{N_m}, \quad \text{and} \quad i_m = \frac{I_m}{N_m}.$$

Then $s_h + i_h + r_h = 1$ and $s_m + i_m = 1$ so that $r_h = 1 - s_h - i_h$ and $i_m = 1 - s_m$. In the new variables, our system becomes

$$\begin{aligned}
\frac{ds_h}{dt} &= (\lambda_h + \beta_h)(1 - s_h) - \beta_h i_h - \gamma s_h i_m + \mu_d s_h i_h,\\
\frac{di_h}{dt} &= \gamma s_h i_m - (\lambda_h + \alpha_h + \mu_d) i_h + \mu_d i_h^2,\\
\frac{di_m}{dt} &= \alpha i_h (1 - i_m) - \lambda_m i_m.
\end{aligned} \tag{A.2}$$

The initial conditions at the start of the wet season are taken to be $s_h(0) = 0.8$, $i_h(0) = 0.1$ and $i_m(0) = 0.1$.

The parameters of Model (A.2) are estimated in Table A.1, as will be discussed below. In Table A.1,

$$\widetilde{\lambda}_m(t) = \frac{9(-t^2 + 4900)}{(4900 + t^2)(2t^2 + 9t + 9800)}.$$

Table A.1 Model (A.1) and (A.2) parameters

Parameter	Description	Value in $(\text{day})^{-1}$
α_{hm}	Infectivity of human	$4 * 10^{-1}$
α_{mh}	Infectivity of mosquito	$4 * 10^{-1}$
λ_h	Human birth rate	10^{-4}
b_m	Human-biting rate of mosquito	1 bite per day
λ_m	Mosquito birth rate	$\widetilde{\lambda}_m + \mu_m + \lambda_h - \mu_h$
α_h	Human recovery rate	$2.5 * 10^{-1}$
β_h	Human loss of immunity rate	$3.0 * 10^{-2}$
$\alpha = b_m \alpha_{hm}$	Infection rate of mosquitoes	$4.0 * 10^{-1}$
$\gamma = b_m \alpha_{mh} \frac{N_m}{N_h}$	Infection rate of humans relative to human/mosquito population	$\frac{18t}{4900+t^2} + 0.4$
μ_d	Disease induced death rate	0
μ_h	Death rate of susceptibles	$9 * 10^{-5}$
μ_m	Death rate of mosquitoes	$3.3 * 10^{-2}$

Mali has the sixth highest birth rate in Africa. In Mali; the average number of annual births per 1,000 persons is 48.1. In Table A.1, we divided 48.1 by $1000 * 365$ to get the average human birth rate per day $\lambda_h \approx 10^{-4}$.

After treatment, recovery from malaria infection takes about 4 days, so we let the human recovery rate $\alpha_h = 0.25$ per day. SP treatment provides near complete protection from malaria episodes for about 30–35 days, so we take the human loss of immunity rate to be $\beta_h \approx 0.03$. We assume that human-biting rate of mosquito is $b_m = 1$ bite per day. Humans become infected by bites from infected mosquitoes and mosquitoes become infected by biting infected humans. The severity of the infection depends on the Plasmodium species as well as other circumstances such as the state of immunity and the general health and nutritional status of the infected individual. We estimate the ability of humans to infect mosquitoes, α_{hm} (that is, human infectivity), and the ability of mosquitoes to infect humans, α_{mh} (that is, mosquito infectivity) at 0.4. We also estimate the death rate of humans at $\mu_h = 9 \times 10^{-5}$ per day and that of mosquitoes at $\mu_m = 3.3 \times 10^{-2}$ per day.

To use the experimental results of Coulibaly et al. in Model (1), we need to know the profile of the infected mosquitoes, $i_m(t)$. To find this function, we use the malaria model, (A.2), which includes the *entire* populations of infected humans and mosquitoes and of recovered humans. Note that Model (1) is for first malaria episodes and is therefore different from Model (A.2). However, both models have the *same* $i_m(t)$, since this number is unaffected by the experiment of Coulibaly et al. which dealt with a small number of the human population. So, we propose to compute the $i_m(t)$ of Model (1) from system (A.2). But to do so, we need to first determine $\gamma(t)$ and $\gamma_k(t)$.

As documented in Sagoba et al. (2007), the mosquito population in Mali increases sharply during the rainy season and then subsides toward the dry season. Based on the data from Sagoba et al. (2007), we take the graph of $\frac{N_m(t)}{N_h(0)}$ to be as in Fig. A.1, and describe it analytically in the form

$$\frac{N_m(t)}{N_h(0)} = \left(\frac{45t}{4900 + t^2} + 10\right) e^{(10^{-4} - 9 * 10^{-5})t}.$$

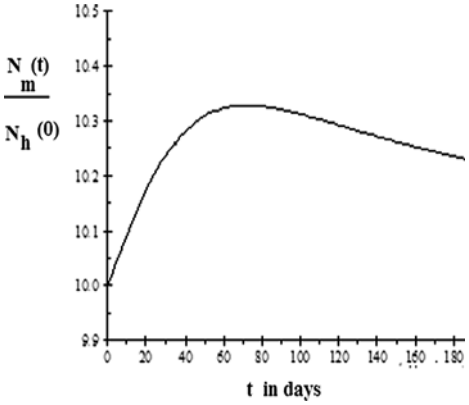

Fig. A.1 Graph of $\frac{N_m(t)}{N_h(0)}$ over the entire rainy season.

Assuming that

$$N_m(0) = 10N_h(0),$$

we compute that

$$\gamma(t) = \frac{18t}{4900 + t^2} + 0.4$$

as shown in Table A.1.

We know that

$$N_m'(t) = (\lambda_m - \mu_m)N_m(t).$$

Hence,

$$\begin{aligned}\lambda_m(t) &= \frac{N_m'(t)}{N_m(t)} + \mu_m \\ &= \frac{[\frac{45(-t^2+4900)}{(4900+t^2)^2} + (\frac{45t}{4900+t^2} + 10)(\lambda_h - \mu_h)]N_h(0)\exp((\lambda_h - \mu_h)t)}{(\frac{45t}{4900+t^2} + 10)N_h(0)\exp((\lambda_h - \mu_h)t)} + \mu_m.\end{aligned}$$

That is,

$$\lambda_m(t) = \frac{9(-t^2 + 4900)}{(4900 + t^2)(2t^2 + 9t + 9800)} + \lambda_h - \mu_h + \mu_m,$$

as shown in Table A.1.

Based on Model (A.2) and the parameter values of Table A.1, we computed the number of infected mosquitoes, i_m, and obtained the profile shown in Fig. 2.

Remark A.1. In Dembele et al. (2009), we also computed the basic reproduction number,

$$\mathcal{R}_0 = \frac{\alpha\gamma \frac{1}{T}\int_0^T \frac{N_m(t)}{N_h(t)}\,dt}{(\lambda_h + \alpha_h)\frac{1}{T}\int_0^T \lambda_m(t)\,dt}$$

for Model (A.2) provided $\lambda_m(t)$ and $\frac{N_m(t)}{N_h(t)}$ are T-*periodic*, γ is constant and $\mu_d = 0$. We proved that if $\mathcal{R}_0 < 1$ then the disease goes extinct, whereas if $\mathcal{R}_0 > 1$ then the disease persists. With data in Table A.1 for $0 < t < T$ ($T = one\ year$), one can easily check that even if we decrease $\gamma(t)$, replacing it by the constant $\min_{0<t<T}\{\gamma(t\}$, we still have $\mathcal{R}_0 > 1$, so that the malaria disease will persist.

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