Bull Math Biol
DOI 10.1007/s11538-012-9775-4

ORIGINAL ARTICLE

The Time Distribution of Sulfadoxine-Pyrimethamine Protection from Malaria

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Received: 30 January 2012 / Accepted: 20 September 2012

Abstract Sulfadoxine-pyrimethamine (SP) has been one of the most widely used antimalarial treatments world-wide, and is also used prophylactically in vulnerable populations. In this paper, we develop a mathematical model which allows us to infer the time distribution of SP protection from drug-trial data. Fitting our model to data from a controlled field study in Mali, we find that SP provided protection from malaria for an average of 37.9 days in this pediatric population. We demonstrate that the duration of SP protection is not well described by an exponential distribution, and in fact has a much narrower dispersal about the mean; the best-fit standard deviation predicted by our model was only 17.0 days, as opposed to 41.8 days for the exponential model. We estimate the monthly entomological inoculation rate and the basic reproductive number for malaria in this population, and demonstrate that extremely high SP treatment rates would be necessary to maintain an effective reproductive number below one throughout a single rainy season. These results have implications for further efforts to model the impact of SP treatment, or for investigations of the optimal timing of prophylactic SP.

Keywords Mathematical model · Malaria · Sulfadoxine-pyrimethamine · Vaccine trial · Prophylaxis

1 Introduction

Malaria is the fifth leading cause of death from infectious disease worldwide (Centers for Disease Control and Prevention 2010); in Africa, it is second only to HIV. The

Electronic supplementary material The online version of this article (doi:10.1007/s11538-012-9775-4) contains supplementary material, which is available to authorized users.

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Published online: 19 October 2012

disease kills about 1 million people a year, 89 % of whom are in Africa (Centers for Disease Control and Prevention 2010). Malaria is spread through contact with infectious mosquitoes; after an infectious mosquito bite, malaria parasites multiply in the human liver and blood-stream, and are then able to spread to susceptible mosquitoes through further mosquito bites. Common symptoms of malaria are headache, fever and vomiting; untreated infections progress and can become life-threatening, particularly in children (Dicko et al. 2011).

Due to increasing parasite drug-resistance and mosquito insecticide-resistance, malaria poses one of the biggest burdens for global health management (Barnes et al. 2006; Chitnis et al. 2006; Koella and Antia 2003; ter Kuile et al. 2007). Therefore, it is critically important to understand the dynamics of disease transmission, and in particular to understand the impacts of drug therapy on these dynamic processes.

For decades, chloroquine was the most common treatment for malaria, but chloroquine resistance has increased to such an extent that it has become ineffective in almost all malaria-endemic countries (Barnes et al. 2006). As an alternative, a fixed-dose combination of sulfadoxine and pyrimethamine was widely implemented, and became one of the most widely used antimalarial treatments in the world (Barnes et al. 2006). Sulfadoxine-pyrimethamine (SP) is very effective (99 % efficacy in treating uncomplicated malaria) and has the advantage that the entire treatment can be given as a single dose (Coulibaly et al. 2002). Once an infected person receives SP treatment, recovery is typically rapid and protection against reinfection is maintained for several weeks (Coulibaly et al. 2002).

While the use of SP monotherapy is now strongly discouraged due to the development of drug-resistance, SP still continues to be available as monotherapy in many countries, and it is used as one of the primary antimalarial agents in preventive treatment (Coulibaly et al. 2002; World Health Organization 2010). The World Health Organization currently recommends artiminisin-based combination therapies (including artesunate plus SP) as the first line of treatment against uncomplicated *P. falciparum* malaria. The use of SP alone, however, is still recommended for the preventive treatment of malaria in infants (World Health Organization 2010), administered at the time of routine vaccines during the first year of life in some endemic areas, regardless of the presence of symptoms or infection (Egan et al. 2005). Intermittent preventative doses of SP are also recommended for pregnant women in almost all malaria-endemic countries in Africa; SP is the only antimalarial drug used in this way (ter Kuile et al. 2007). In addition, due to the high success rate of SP as an antimalarial therapy, prophylactic SP has also been considered in many drug trials (Coulibaly et al. 2002; World Health Organization 2010). Although SP-based treatment and prevention strategies have been widely accepted, much uncertainty remains regarding SP efficacy and the duration of SP protection (Dicko et al. 2011; Coulibaly et al. 2002).

A detailed understanding of the influence of SP on malaria transmission and dynamics is critical. In the sections which follow, we develop a mathematical model which allows us to estimate the duration of SP protection from drug-trial survey data. We use our approach to determine the distribution of SP protection in a pediatric population after a single prophylactic dose, using data from a study of the effects of SP in children and teenagers in Bandiagara, Mali (Coulibaly et al. 2002). Using our

model, we also estimate the entomological inoculation rate and the reproductive numbers for Bandiagara, Mali, where SP is the approved second-line antimalarial agent (Coulibaly et al. 2002). An important feature of this work is the development of a modeling approach for prophylactic drug-trial data, in which comparatively small treatment and control groups are coupled to a larger, but unsurveyed, population in an endemic area.

2 Methods

2.1 Population-Wide Malaria Model

The dynamics of standard epidemiological models for malaria are well known (Anderson and May 1991; Dietz et al. 1974; Koella and Antia 2003; Macdonald 1957), and are described by the following system:

$$\begin{aligned}
\frac{dS_h}{dt} &= \lambda_h N_h + \beta_h R_h - \mu_h S_h - \frac{(\alpha_{mh} b_m I_m) S_h}{N_h}, \\
\frac{dI_h}{dt} &= \frac{(\alpha_{mh} b_m I_m) S_h}{N_h} - (\mu_h + \alpha_h + \mu_d) I_h, \\
\frac{dR_h}{dt} &= \alpha_h I_h - (\mu_h + \beta_h) R_h,
\end{aligned} \tag{1}$$

and

$$\begin{aligned}
\frac{dS_m}{dt} &= \lambda_m N_m - \mu_m S_m - \frac{(\alpha_{hm} b_m I_h) S_m}{N_h}, \\
\frac{dE_m}{dt} &= \frac{(\alpha_{hm} b_m I_h) S_m}{N_h} - (\gamma_m + \mu_m) E_m, \\
\frac{dI_m}{dt} &= \gamma_m E_m - \mu_m I_m.
\end{aligned} \tag{2}$$

Here S_h denotes the number of susceptible humans, I_h, infectious humans, and R_h, recovered humans, while S_m, E_m, and I_m denote susceptible, exposed and infectious mosquitoes, respectively. The parameters λ_h and μ_h are the human birth rate and natural death rate, while λ_m and μ_m are the mosquito birth rate and death rate, respectively. The parameter α_h is the recovery rate for humans, β_h is the rate of loss of immunity for recovered humans, and μ_d is disease-induced death rate for humans. We use γ_m to denote the rate of progression of exposed mosquitoes to the infectious class. Finally, α_{mh} denotes the infection probability, per bite, from an infectious mosquito to a susceptible human, and α_{hm} denotes the infection probability, per bite, from an infectious human to a susceptible mosquito. The total number of mosquito bites per mosquito per day is represented by b_m.

The simple SIR model described above obscures several of the complicating features of malaria infection in humans. Infected humans may be symptomatic or asymptomatic, and asymptomatic infections may or may not be detectable in diagnostic tests, depending on the parasite concentration in the blood. Thus, new episodes of

malaria disease, as measured in the study groups described in the following subsection, are not equivalent to new infections. More complex malaria models include asymptomatic carriers (Chitnis et al. 2006; Wyse et al. 2007; Ducrot et al. 2009), as well as other refinements such as spatial heterogeneity (Smith et al. 2005b; Auger et al. 2008; Arino et al. 2012), incubation delays (Ruan et al. 2008), seasonality (Griffin et al. 2010; Lou and Zhao 2010), or parasite life-history (Griffin et al. 2010; Chitnis et al. 2008, 2012). With the goal of fitting our model to survey data, however, we aim to minimize the number of unknown parameters. We thus use the simple SIR system for humans in the population-wide model. In the supplementary material, we also examine the effects of including an exposed compartment in the human population.

We let $N_h = S_h + I_h + R_h$ be the total number of humans and $N_m = S_m + E_m + I_m$ be the total number of mosquitoes. To simplify the model, we express systems (1) and (2) in transformed variables $s_h = \frac{S_h}{N_h}$, $i_h = \frac{I_h}{N_h}$, $r_h = \frac{R_h}{N_h}$, $s_m = \frac{S_m}{N_m}$, $e_m = \frac{E_m}{N_m}$, and $i_m = \frac{I_m}{N_m}$. This allows the standard simplification $r_h = 1 - s_h - i_h$ and $s_m = 1 - e_m - i_m$, reducing the population-wide malaria model to:

$$\begin{aligned}
\frac{ds_h}{dt} &= \beta_h(1 - s_h - i_h) + \lambda_h(1 - s_h) + \mu_d i_h s_h - \beta_{mh} i_m s_h,\\
\frac{di_h}{dt} &= \beta_{mh} i_m s_h - (\lambda_h + \alpha_h + \mu_d) i_h + \mu_d i_h^2,\\
\frac{de_m}{dt} &= \beta_{hm} i_h (1 - e_m - i_m) - (\gamma_m + \lambda_m) e_m,\\
\frac{di_m}{dt} &= \gamma_m e_m - \lambda_m i_m
\end{aligned} \tag{3}$$

where $\beta_{hm} = \alpha_{hm} b_m$ and $\beta_{mh} = \alpha_{mh} b_m N_m / N_h$.

We note that under this transformation, the system is nonautonomous, since β_{mh} depends on the mosquito population density per human, $N_m(t)/N_h(t)$. However, in Sect. 2.4, we demonstrate that this ratio is very close to constant in the dataset under consideration, and thus β_{mh} is effectively a constant. We therefore impose the simplifying assumption that β_{mh} is time-independent, and study the resulting autonomous system in the sections to follow.

2.2 Study-Group Malaria Model

We next develop a modeling approach to describe the data collected in a clinical study in Bandiagara, Mali. Coulibaly et al. (2002) studied 202 subjects, aged 3 months to 20 years, who received a single prophylactic dose of SP, as well as an untreated control group of 199 subjects of similar ages. Consistent with Coulibaly et al., we model two study groups—SP-treated and control—in addition to the overall population in the town. The population-wide malaria model described above, with variables s_h, i_h, e_m, and i_m, describes the transmission dynamics and prevalence of malaria among humans who live in the study *area*, but are not part of the (comparatively small) SP study groups. However, the population-wide disease dynamics determine disease prevalence in the mosquito population. This common population of infectious

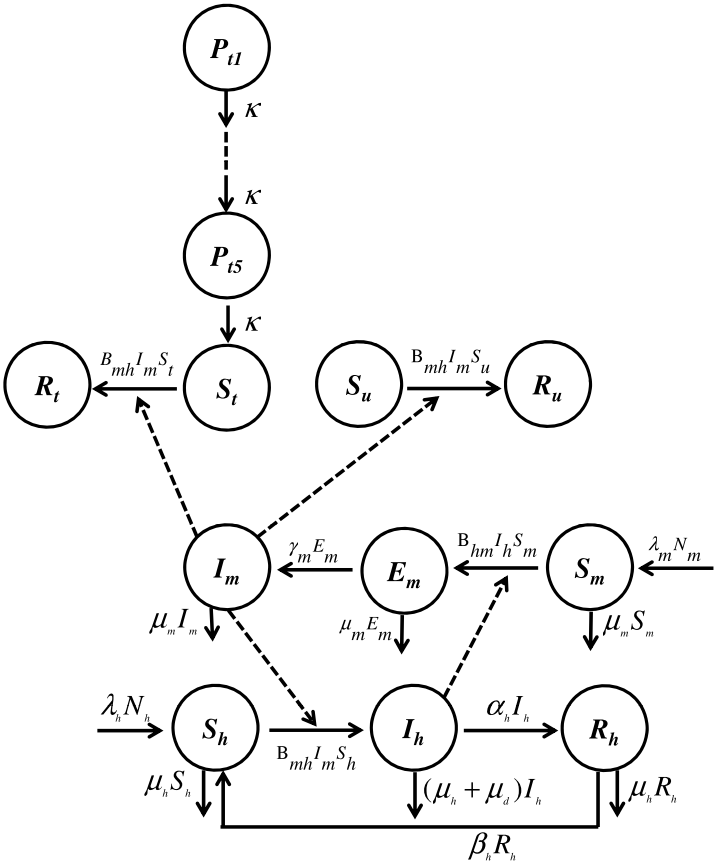

Fig. 1 Schematic diagram of the full model. Here, $B_{mh} = \alpha_{mh} b_m / N_h$ and $B_{hm} = \alpha_{hm} b_m / N_h$

mosquitoes, in turn, drives the infection dynamics in the study groups. We assume that the study groups are sufficiently small that individuals in these groups have no effect on the population-wide disease dynamics. Figure 1 provides a schematic illustrating the population-wide and study group models, described in greater detail below.

For SP-treated individuals (subscripted t), we assume that the dose of SP received at the beginning of the study confers protection from infection for some unknown time interval. We assume that individuals who are initially in this SP-protected group eventually become susceptible to infection. Let P_t denote the number of individuals in the SP-treated group who are protected by SP, while S_t denotes treated individuals who have become susceptible. In the simplest model, we assume that treated individuals who begin in the P_t class progress to the S_t class at a constant rate κ, yielding an exponential distribution for the duration of SP protection, with mean $1/\kappa$. We then relax this assumption by allowing the duration of SP protection to be gamma-distributed, finding the parameters of this gamma distribution which best fit the data (see the following section).

For individuals in the study groups, as soon as a malaria infection was detected in the clinical study, the infected individual was immediately treated and is no longer part of the susceptible class. Since we are only interested in the timing of first infection in the study groups, there is no infectious class in these groups; upon infection, individuals move directly from the S_t group to the "removed" class, denoted R_t. Thus, we use "removed" in a nonstandard sense, to indicate any individuals who are no longer candidates for a first infection. Similarly, for untreated individuals in the control study group (subscript u), we use two compartments, S_u and R_u, denoting the number of susceptible individuals and removed individuals, respectively. As in the population-wide model, we scale study group populations by their corresponding total populations to obtain scaled variables s_u, r_u, p_t, s_t, and r_t. Note that although we include natural mortality in the population-wide model, we neglect it in the study group models because there were no deaths in either study group during the study.

The population-wide and study-group models are linked by a common population of infected mosquitoes. Combining the models, we arrive at the following system:

$$\begin{aligned}
\frac{ds_h}{dt} &= \lambda_h(1-s_h) + \beta_h(1-s_h-i_h) + \mu_d i_h s_h - \beta_{mh} i_m s_h,\\
\frac{di_h}{dt} &= \beta_{mh} i_m s_h - (\lambda_h + \alpha_h + \mu_d) i_h + \mu_d i_h^2,\\
\frac{de_m}{dt} &= \beta_{hm} i_h (1-e_m-i_m) - (\gamma_m + \lambda_m) e_m,\\
\frac{di_m}{dt} &= \gamma_m e_m - \lambda_m i_m,\\
\frac{ds_u}{dt} &= -\beta_{mh} i_m s_u,\\
\frac{dr_u}{dt} &= \beta_{mh} i_m s_u,\\
\frac{dp_t}{dt} &= -\kappa p_t,\\
\frac{ds_t}{dt} &= \kappa p_t - \beta_{mh} i_m s_t,\\
\frac{dr_t}{dt} &= \beta_{mh} i_m s_t.
\end{aligned} \tag{4}$$

Note that r_u and r_t, although included in the system (4) for clarity, are decoupled, and the full system has seven coupled equations.

2.3 Duration of Drug Protection

We are interested in the duration of protection conferred by SP. A limitation of system (4) is the assumption that this duration is exponentially distributed, that is, protection is lost at a constant rate κ. We relax this assumption by using a linear chain approximation, a chain of n linear compartments, allowing the duration of protection

to be gamma-distributed. In practice, we replace the equations for drug-protected and susceptible individuals in the treatment group in system (4) with the following:

$$\begin{aligned}\frac{dp_{t1}}{dt} &= -\kappa p_{t1},\\ \frac{dp_{ti}}{dt} &= \kappa p_{t(i-1)} - \kappa p_{ti}, \quad i = 2,\ldots,n,\\ \frac{ds_t}{dt} &= \kappa p_{tn} - \beta_{mh} i_m s_t.\end{aligned} \tag{5}$$

We note that the linear chain approximation has the same number of known and unknown parameters as system (4), and clearly system (4) is recovered by the linear chain approximation when $n = 1$. Using this approximation, the mean duration of SP protection is n/κ, and the duration of protection is gamma-distributed with shape parameter n.

2.4 Parameter Values and Initial Conditions

Following Aguas et al. (2008), we set the rate of immunity loss to 0.0029 per day and the human recovery rate to 0.038 per day. This recovery rate corresponds to an average infectious period of 26 days; we note that longer infectious periods, associated with asymptomatic infections, have also been reported (Smith et al. 2005a, 2007). To estimate the disease-induced death rate, μ_d, we note that a 2-year study of malaria in Bandiagara (Lyke et al. 2004), followed the entire population of children under the age of six (i.e., 2,284 children aged ≤ 6 in Bandiagara); of these, 104 developed severe malaria and 5 died. This gives an estimated mortality, for those infected, of 5 %, yielding $\mu_d \approx 0.05\alpha_h$. This is an upper bound considering that mortality for those under 6 years is presumably higher than mortality for those under 20 years. At this rate of mortality, the total population size N_h is nearly constant over the 168 day study period, as shown in Fig. 4; thus our assumption that β_{mh} is constant holds.

A recent model of the Bandiagara study (Dembele et al. 2010) estimated the vital dynamics for both human and mosquito populations in this village during the study period, finding that both were approximately constant. Following Dembele et al. (2010), we therefore take $\lambda_h = \mu_h = 10^{-4}$ day^{-1}. The lifetime of a mosquito is approximately one month (Centers for Disease Control and Prevention 2012) and assuming demographic equilibrium we therefore take $\lambda_m = \mu_m = 0.033$ day^{-1}. The latent period for malaria infection in mosquitoes is approximately 10 days (Beier 1998; Chitnis et al. 2006; Koella and Antia 2003), yielding $\gamma_m = 0.1$ day^{-1}. Values of these known parameters are provided for reference in Table 1.

Coulibaly et al. (2002) report that at the beginning of the study, *Plasmodium falciparum* was detected in the blood samples of 17.1 % of control subjects. These individuals are not candidates for a *first* malaria episode of the season, as tracked by Coulibaly et al., and thus the initial fraction of susceptible humans in the untreated group, $s_u(0)$, is $1 - 0.171 = 0.829$.

Similar to the control group, 17.8 % of individuals in the SP-treated group were not candidates for a first malaria episode due to a preexisting infection. We thus take $p_t(0)$, the initial fraction of the treatment group who are protected by SP and will

Table 1 Parameter values from the literature

Parameter	Description	Value (per day)	Source
λ_h, μ_h	human birth/death rate	10^{-4}	Dembele et al. (2010)
λ_m, μ_m	mosquito birth/death rate	0.033	Centers for Disease Control and Prevention (2012)
α_h	human recovery rate	0.038	Aguas et al. (2008)
β_h	human loss of immunity rate	2.9×10^{-3}	Aguas et al. (2008)
μ_d	disease-induced death rate	1.9×10^{-3}	Lyke et al. (2004), see text
γ_m	rate of progression, e_m to i_m	0.1	Beier (1998), Chitnis et al. (2006), Koella and Antia (2003)

later become susceptible to first infection, to be $1 - 0.178 = 0.822$. The fraction of the SP-treated group that is susceptible to infection, s_t, is initially zero since all treated individuals are either protected or are already infected at the beginning of the study.

Assuming that initial conditions in the control group are representative of initial conditions in the population at large, we set $s_h(0)$, the initial proportion of susceptible humans, to be $1 - 0.171 = 0.829$. The remaining parameters β_{hm}, β_{mh}, κ, and n and initial values $i_h(0)$, $e_m(0)$, and $i_m(0)$ are estimated by fitting our model to the data obtained by Coulibaly et al. (2002). Although we allowed $i_h(0)$ and $e_m(0)$ to be free parameters in this data fitting, preliminary results allowed us to fix these values, as described in detail in Sect. 3.

2.5 Data and Model Fitting

In the field survey study (Coulibaly et al. 2002), the two study groups were monitored during the malaria season and the timing of the first malaria episode for each individual was recorded. This dataset thus provides the cumulative number of new infections, which occurred in each study group up to a given day. From our model, we can likewise estimate $U(t)$ and $T(t)$, the total number of new infections which have occurred up to time t in the control and SP-treated groups, respectively:

$$\begin{aligned} U(t) &= \int_0^t \beta_{mh}\, i_m(s)\, s_u(s)\, ds = r_u(t) - r_u(0), \\ T(t) &= \int_0^t \beta_{mh}\, i_m(s)\, s_t(s)\, ds = r_t(t) - r_t(0). \end{aligned} \tag{6}$$

Table 2 summarizes the unknown parameters and initial conditions of the full model. To estimate these unknowns, we first take $n = 1$ (system 4), and simultaneously integrate system (4) and system (6) numerically (fourth-order Runge–Kutta). We then evaluate $U(t)$ and $T(t)$, as predicted by the model, at the times reported in the clinical data set, that is, at 28, 56, 84, 112, 140, and 168 days. We compare the model predictions to the clinical data and use constrained nonlinear optimization (in particular, a gradient descent algorithm) to find values of the unknown parameters and initial conditions which best describe the clinical data. We then compute the Akaike

Table 2 Initial conditions and estimated (best-fit) parameters

Parameter	Description	Value
$i_m(0)$	initial fraction of infected mosquitoes	0.0346
$\beta_{hm} = \alpha_{hm} b_m$	infection rate, human to mosquito	0.0221 d^{-1}
$\beta_{mh} = \alpha_{mh} b_m \frac{N_m}{N_h}$	infection rate, mosquito to human	0.453 d^{-1}
κ	rate of loss of drug protection	0.132 d^{-1}
n	shape parameter for time distribution of drug protection	5

information criterion (AIC_c) to assess the relative goodness-of-fit, where lower AIC_c values indicate a significantly better fit.

We repeat this procedure for integer values of n up to 15, using AIC_c values for model comparison.

3 Results

3.1 Initial Infectious Fraction, Population-Wide

As described previously, we allowed the initial fraction of infected humans, $i_h(0)$, to vary as a free parameter. However, results of data fitting for system (4) ($n = 1$) indicated that the model most closely matched the data when $i_h(0) \approx 0$, and including $i_h(0)$ as an additional free parameter caused the AIC_c value to increase. Even for more complex models ($n = 2, \ldots, 15$), the best fit value for $i_h(0)$ was consistently negligible, and the AIC_c was larger when $i_h(0)$ was taken as a free parameter, irrespective of the number of compartments in the linear chain, or the initial estimates for unknown parameters. Since this result was robust, we chose to set $i_h(0) = 0$. We address the possible explanations for this preliminary result in the discussion. Similar results were obtained for the initial fraction of exposed mosquitoes, $e_m(0)$. Allowing this parameter to vary improved model fit slightly (e.g., at $n = 5$, SSE = 6.80 versus 6.84 when $e_m(0)$ was fixed to zero), but substantially increased the AIC_c (13.2 versus 6.97). We thus set $e_m(0) = 0$ and restricted our attention to the resulting model, which retains five free parameters (Table 2).

3.2 Exponential Model ($n = 1$)

Our results for this 5-parameter model are succinctly demonstrated in Figs. 2, 3, and 4. First, the top panel of Fig. 2 shows the results of data-fitting to systems (4) and (6), with exponentially-distributed drug protection. The model predicts that the mean duration of SP protection, κ^{-1} is 41.8 days with a standard deviation of 41.8 days.

We varied the shape parameter in the gamma distribution by taking the number of drug-protected classes $n = 1, 2, 3, \ldots, 15$. Figure 3 plots the AIC_c values thus obtained. We find that the clinical data are best described when we approximate the time distribution of SP protection by five linear compartments, although six compartments also provide an excellent fit to the experimental data.

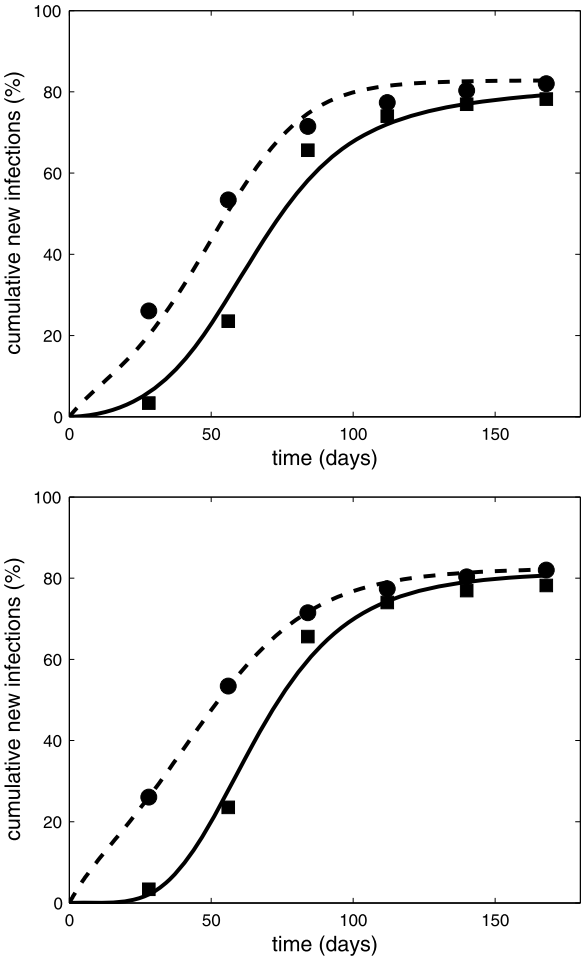

Fig. 2 Results of data-fitting. The cumulative number of new infections which occurred in the experimental study are plotted for the control group (*circles*) and for the SP-treated group (*squares*). The best-fit model predictions for $U(t)$ (*dashed*) and $T(t)$ (*solid*) are shown for comparison. The *top panel* shows the best fit obtained for the exponential model ($n = 1$); the *lower panel* shows the same for the gamma-distributed model ($n = 5$). The fit in the latter case is significantly better, as measured by the Akaike information criterion

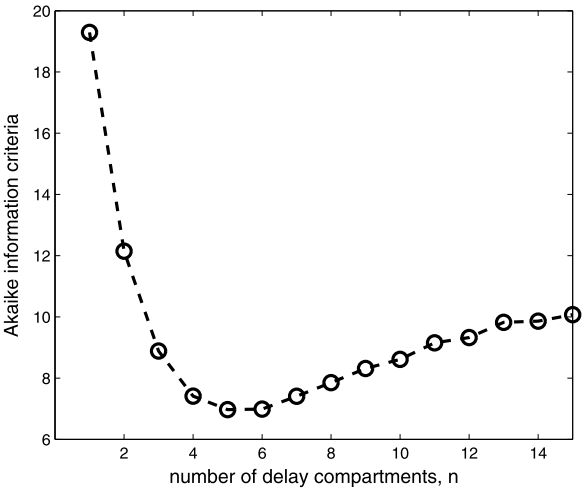

Fig. 3 Akaike information criteria (AIC_c, see text for details) versus number of delay compartments, n

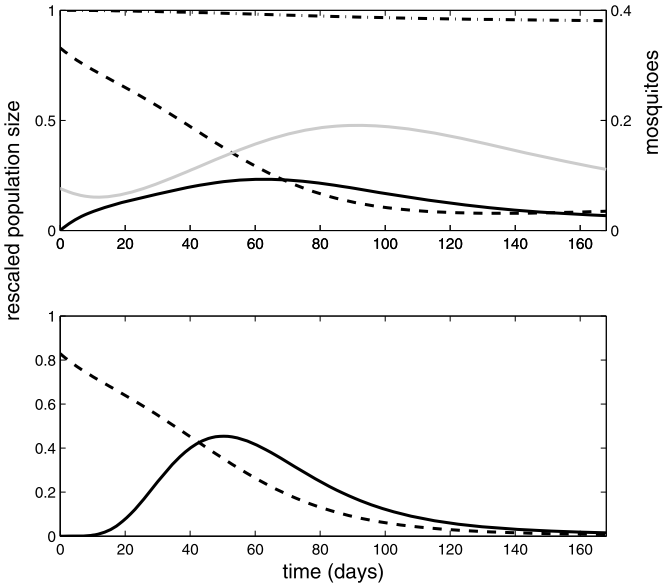

Fig. 4 Population dynamics for the best-fit model ($n = 5$). In the *top panel*, the time course of susceptible humans (*dashed*), infected humans (*solid*) and infected mosquitoes (*grey*) are illustrated. The total population size of humans, $N_h(t)/N_h(0)$ is also shown for comparison (*dot-dashed*); note that it is nearly constant over the course of the study. The *lower panel* shows the time course of susceptible humans in the untreated study group (*dashed*) and in the treatment group (*solid*)

The model fit when $n = 5$ is illustrated for comparison with the exponential case in the lower panel of Fig. 2. The values of the best fit parameters are $i_m(0) = 0.0346$, $\kappa = 0.132$, $\beta_{mh} = 0.4529$, $\beta_{hm} = 0.0221$.

In Fig. 4, we illustrate the population dynamics predicted for the population-wide model, using the best-fit parameter values described above.

The time distribution of SP protection was thus best described by a gamma distribution with mean $5/\kappa = 37.9$ days, and standard deviation 17.0 days. Figure 5 illustrates this distribution, along with the best-fit exponential distribution from system (4) for comparison. Consistent with the results of the Akaike test, we see that the best-fit distribution of SP protection differs markedly from the distribution predicted by the best-fit exponential model.

3.3 Entomological Inoculation Rate

The entomological inoculation rate (EIR)—defined as the average number of infectious bites received by a person per unit time—is one of the most commonly measured indices of malaria prevalence (Smith et al. 2005a, 2007; Shaukat et al. 2010; Kelly-Hope and Mckenzie 2009). The EIR estimates the level of exposure to parasite-infected mosquitoes, and is the preferred method for assessing malaria endemicity and transmission intensity, as well as for evaluating malaria control strategies that reduce human-mosquito contact (Drakeley et al. 2003; Burkot and Graves 1995; Shaukat et al. 2010).

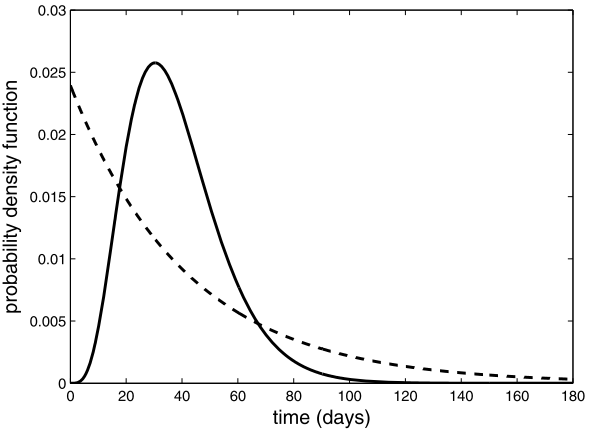

Fig. 5 The distribution of the duration SP protection for the best-fit exponential model ($n = 1$, *dashed*), and for the best-fit gamma model ($n = 5$, *solid*)

In our model, b_m and N_m represent the number of bites per mosquito per day and the total number of mosquitoes, respectively. Therefore, the total bites by all mosquitoes per day is given by $b_m N_m$. Since the fraction of infectious mosquitoes is I_m/N_m, the total infectious bites is $b_m I_m$, which are received by N_h humans. Therefore, the daily EIR is given by

$$\text{EIR} = \frac{b_m I_m}{N_h} = \frac{\beta_{mh}}{\alpha_{mh}} i_m.$$

Previous studies have used 0.05 (Smith et al. 2010), 0.02 (Chitnis et al. 2006), and 0.4 (Dembele et al. 2010) for the value of α_{mh}, the infection probability from mosquito to human per bite. Taking the average of these values, we get $\alpha_{mh} = 0.15$. Then, using our best fit values for β_{mh} and $i_m(0)$, we compute the monthly EIR in Bandiagara, Mali to be 3.1. This value is consistent with that for Sudan Savana, Mali (monthly EIR = 2.8) estimated from a survey study (Sogoba et al. 2007).

3.4 Reproductive Number

The basic reproductive number, R_0, is the average number of secondary infections that one infectious individual would cause over the duration of the infectious period, provided that everyone else is susceptible (Chitnis et al. 2006; Diekmann et al. 1990). As discussed earlier, in the context of Bandiagara, Mali, β_{mh} remains effectively constant making the model system (3) autonomous. Therefore, we can calculate R_0 for the population-wide malaria model using the next generation operator approach (Diekmann et al. 1990; van den Driessche and Watmough 2002) for the scaled system (3). The model system (3) has exactly one disease-free equilibrium $E_0 = (1, 0, 0, 0)$, and equations for the exposed and infectious compartments of the linearized system at E_0 take the form:

$$\frac{di_h}{dt} = -(\lambda_h + \alpha_h + \mu_d) i_h + \beta_{mh} i_m, \tag{7}$$

$$\frac{de_m}{dt} = \beta_{hm} i_h - (\gamma_m + \lambda_m) e_m, \tag{8}$$

$$\frac{di_m}{dt} = \gamma_m e_m - \lambda_m i_m. \tag{9}$$

We introduce the following matrices:

$$F = \begin{pmatrix} 0 & 0 & \beta_{mh} \\ \beta_{hm} & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} \lambda_h + \alpha_h + \mu_d & 0 & 0 \\ 0 & \lambda_m + \gamma_m & 0 \\ 0 & -\gamma_m & \lambda_m \end{pmatrix}.$$

These expressions give

$$FV^{-1} = \begin{pmatrix} 0 & \frac{\beta_{mh}\gamma_m}{\lambda_m(\lambda_m+\gamma_m)} & \frac{\beta_{mh}}{\lambda_m} \\ \frac{\beta_{hm}}{\lambda_h+\alpha_h+\mu_d} & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Then R_0 corresponds to the spectral radius of FV^{-1}:

$$R_0 = \rho\left(FV^{-1}\right) = \sqrt{\frac{\beta_{hm}\beta_{mh}\gamma_m}{\lambda_m(\lambda_m+\gamma_m)(\lambda_h+\alpha_h+\mu_d)}}.$$

Using our estimated parameters, we obtain $R_0 = 2.4$ for Bandiagara, Mali. Now assume that a proportion p of the human population is protected by SP treatment at the beginning of the season. In this case, the proportion of the population that is susceptible to infection is reduced by $(1-p)$. Then the reproductive number under SP protection, R_0^{SP}, is given by

$$R_0^{\mathrm{SP}} = \sqrt{\frac{\beta_{hm}\beta_{mh}\gamma_m}{\lambda_m(\lambda_m+\gamma_m)(\lambda_h+\alpha_h+\mu_d)}(1-p)} = 2.4\sqrt{1-p}.$$

We note that the malaria model (1)–(2) may exhibit backward bifurcation for sufficiently large disease-induced death rates (Chitnis et al. 2006). However, for our autonomous system with low disease-induced death rate estimated from field survey data in Bandiagara, Mali (see Table 1), we verified that the malaria epidemic will not grow at the beginning of the season if $R_0^{\mathrm{SP}} < 1$, consistent with findings in Anderson and May (1991), Chitnis et al. (2006). This implies that the minimum proportion of population that must be protected by SP, $p_{\min}$, in order to control the growth of the epidemic at the beginning of the season in Bandiagara is $p_{\min} = 0.82$, i.e., at least 82 % population needs to be protected by SP.

While this minimum 82 % SP-protection ensures that the epidemic does not grow at the beginning of the season, with this strategy epidemics later in the season cannot be avoided, since the SP-protected individuals lose their protection as time progresses. To study long-term protection by SP, a more relevant measure is the effective reproductive number, $R_e^{\mathrm{SP}}(t)$, which is defined as the average number of infectious individuals resulting from a single infective introduced at time t into the population, given the susceptible fraction at that time (Farrington and Whitaker 2003; Cintron-Arias et al. 2009). For our model, the effective reproductive number is given by (Cintron-Arias et al. 2009):

$$R_e^{\mathrm{SP}}(t) = \sqrt{\frac{\beta_{hm}\beta_{mh}\gamma_m}{\lambda_m(\lambda_m+\gamma_m)(\lambda_h+\alpha_h+\mu_d)}s_h(t)s_m(t)}.$$

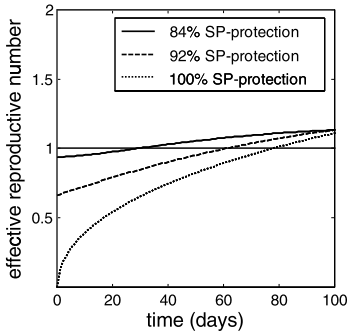

Fig. 6 Effective reproductive number in Bandiagara, Mali, with 84 %, 92 %, and 100 % SP-protection level at the beginning of the season

Figure 6 shows the effective reproductive number in Bandiagara, Mali, with initial SP-protection levels of 84 %, 92 %, and 100 %. The figure shows that although the reproductive number at the beginning of the season is less than one, the effective reproductive number eventually increases to greater than one due to the loss of SP-protection. As expected, the higher the level of SP-protection at the beginning of the season, the longer the delay for the effective reproductive number to exceed one.

3.5 Sensitivity Analysis

We examined the sensitivity of our parameter estimates to changes in the assumed values of four parameters obtained from the literature: the human and mosquito birth rates; the recovery rate; and the rate of immunity loss (see Table 1). Fixing the number of delay compartments at $n = 5$, we either increased or reduced each known parameter by 10 %, and reran the analysis obtaining new values for the fitted parameters. On average, this yielded less than a 1 percent change in the best-fit parameter values (mean absolute value: 0.66 %); the largest change we observed was a 4.8 % change in β_{hm}, when α_h was increased 10 %. We repeated this procedure using a 25 % increase or reduction in each of the known parameters. Here we found, on average, a 8.6 % magnitude change in the best-fit parameter values. This indicates that the fitted parameters are very robust to changes in the assumed parameter values.

One of our most important quantitative conclusions is that $n = 5$ compartments best describe the duration of drug protection. To investigate the sensitivity of this result, we repeated the analysis above, for 10 % changes in the known parameter values, at $n = 3, 4, 5, 6$, and 7. Figure 7 shows the Akaike information criteria (AIC_c) for the resulting best fits, versus n. We see that $n = 5$ provides the best fit in almost every case, although in several cases $n = 6$ also provides an excellent fit to the data. Our conclusion that the duration of SP protection is best fit by 5 delay compartments is thus quite robust to changes of ± 10 % in the parameters from the literature.

Finally, we wished to investigate the sensitivity of our conclusions regarding the duration of drug protection, that is, the rate of loss κ. In this case, we allowed the same four parameters to vary simultaneously. In brief, we drew four random values for these parameters, uniformly distributed between 90 % and 110 % of the assumed value in Table 1. We then fit the model to the data fixing $n = 5$. We repeated this procedure 100 times. A histogram of the resulting best-fit values of κ is provided

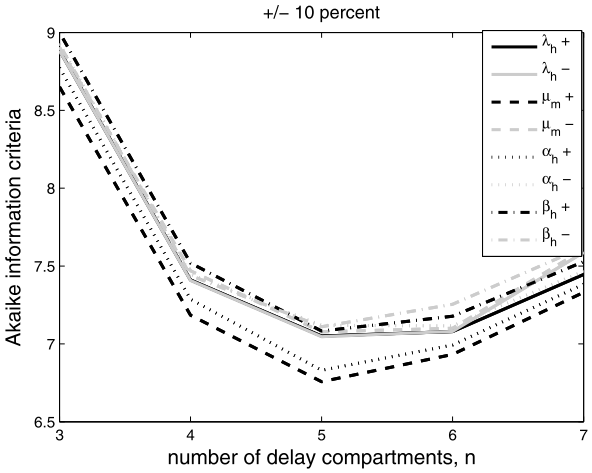

Fig. 7 The Akaike information criteria for the best-fit model versus the number of delay compartments, n. Each of the indicated parameters was either increased or decreased by 10 % (see *legend*). The conclusion that $n = 5$ yields the best fit to the data is robust to 10 % changes

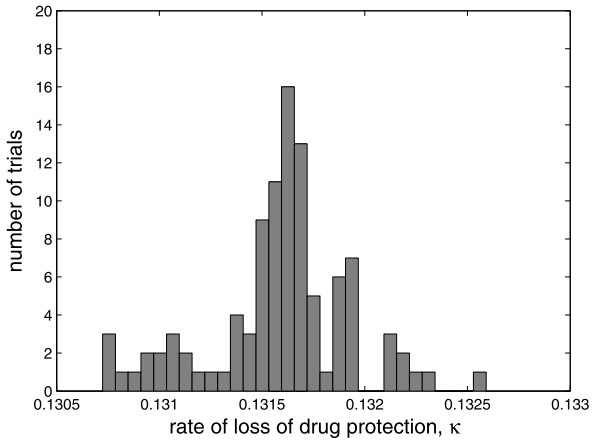

Fig. 8 Histogram of the best-fit values of the parameter κ, when parameter values from the literature were varied by ± 10 %. See text for details

in Fig. 8. We see that the values of κ are very tightly distributed around the best-fit value (0.1318) reported in Table 2. Overall the mean value obtained was $\kappa = 0.1316 \pm 3.5 \times 10^{-4}$. We conclude that our quantitative estimate for κ is very robust to changes in the assumed parameters.

4 Discussion

Sulfadoxine-pyrimethamine (SP) is one of the most widely used antimalarial treatments world-wide. Since a single dose of SP also provides protection against infection, SP has also been considered prophylactically (Coulibaly et al. 2002; World Health Organization 2010). In this paper, we describe a novel system of ordinary differential equations which allows us to infer the time distribution of SP protection from drug-trial data.

Applying our method to a study of prophylactic SP in children and young adults in Bandiagara, Mali (Coulibaly et al. 2002), we find that, on average, SP delayed infection by malaria in this cohort for 37.9 days, consistent with the estimate in the survey study (Coulibaly et al. 2002). We also demonstrate, however, that the duration of SP protection is not well described by an exponential distribution, and in fact has a much narrower dispersal about the mean; the best-fit standard deviation predicted by our model was only 17.0 days, as opposed to 41.8 days for the exponential model (see Fig. 5). This finding has implications for further efforts to model SP use, or for investigations of the optimal timing of prophylactic SP, as described in Dembele et al. (2010). Our data fitting suggests that a one-compartment model for SP protection is not adequate, while a linear chain approximation, yielding a gamma distribution, provides a more accurate description of the duration over which SP retains its protective effect.

Although the parameter estimates of Dembele et al. (2010) suggest that both mosquito and human populations were close to demographic equilibrium for the 168-day study, it is of course likely that the mosquito population density per human may change somewhat over the course of the rainy season. A field survey study (Sogoba et al. 2007) conducted in Bancoumana, Mali, shows that during the rainy season, the mosquito density can vary between 5 to 10 mosquitoes per household. With an average of 12 people per household in Bandiagara (De Groote et al. 2003), the mosquito density per human might vary between 0.4 to 0.8 during the study period. This gives bounds on the possible variation in the parameter β_{mh}, suggesting that although β_{mh} is not, in reality, constant, the range between its minimum and maximum values is at most two-fold. The literature surrounding seasonal variations in malaria transmission is well developed, and we refer the interested reader to Chitnis et al. (2012), Lou and Zhao (2010), Griffin et al. (2010) and references therein.

Another limitation of our approach is the simplicity of the population-wide model, which is necessary for meaningful data fitting. Since malaria has an incubation delay, in the infected human, of about 2 weeks (Filipe et al. 2007; Maire et al. 2006), we expected that incorporating this delay would improve data fitting. In the supplementary material, however, we demonstrate that the inclusion of exposed classes in the population-wide model, and in each of the study groups, did not significantly improve model fits to the data, nor did it change our best estimate of $n = 5$. Including an exposed human class, however, did reduce our estimate of the duration of SP protection from about 38 to 31 days (see supplementary material for details). Since the survey data quantify the *delay* in the incidence of malaria episodes due to SP treatment, as compared to an untreated group, we hypothesize that data-fitting is quite robust to changes in the structure of the model preceding the infectious compartments.

As described in Sect. 3, model-fitting consistently predicted that the initial fraction of infected humans, $i_h(0)$, was close to zero in the general population, while the initial fraction of humans in the recovered state was close to 20 %. This result was surprising, since *Plasmodium falciparum* was detected in the blood of roughly 20 % of the control group at the start of the study. This result could be an artifact of the simplified SIR model we used, which effectively assumes that all infected individuals are simultaneously infectious and symptomatic. Another possible factor here is SP

treatment availability, since recovery under treatment is rapid, of order 4 days (Bell et al. 2008). Although we assumed that SP treatment was not widely available to the general population, the model fit might be improved by including an "infected and under treatment" compartment in the population-wide model. A further possibility is transmission-blocking immunity (Arino et al. 2012), which is more common in the adult population. These factors suggest directions for future work, although we again note that the study-group results are fairly robust to changes in the population-wide model.

We estimate the monthly entomological inoculation rate for Bandiagara to be 3.1, consistent with an estimate of 2.8 from a survey study in Sudan Savana, Mali (Sogoba et al. 2007). However, we note that EIR values may vary widely from place to place (Smith et al. 2007, 2005a; Shaukat et al. 2010; Kelly-Hope and Mckenzie 2009) and also from season to season (Drakeley et al. 2003). For example, during the peak transmission period of September, the monthly EIR in Bandiagara town can reach up to 4 (Coulibaly et al. 2002). Similarly, the basic reproductive number for malaria varies widely (Smith et al. 2007); our estimate of 2.4 is consistent with previous studies (Aguas et al. 2008; Ruan et al. 2008). Although a treatment rate of 82 % would reduce R_0 below one at the beginning of the season, Fig. 6 demonstrates that extremely high rate and high frequency of treatment would be necessary to maintain this level of control of R_e throughout a single rainy season. The investigation of the optimal use of limited SP in reducing the overall impact of malaria during the season is a clear avenue for future work (see Dembele et al. 2010). Finally, the model we develop here involves two study groups (treated and untreated), as well as a population-wide model, linked by a common population of infected mosquitoes. This approach could be useful more generally for the analysis of prophylactic drug trials for malaria, or other vector-borne diseases.

Acknowledgements The authors are grateful to two referees for their insightful comments, and to the Natural Sciences and Engineering Research Council of Canada for funding.

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