AN EPIDEMIOLOGIC MODEL OF THE INCIDENCE OF ACUTE ILLNESS IN PLASMODIUM FALCIPARUM MALARIA

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Abstract. We propose a stochastic model for simulating malaria tolerance. The model relates the probability of a clinical attack of malaria to the peripheral parasite densities via a pyrogenic threshold that itself responds dynamically to the parasite load. The parameters of the model have been estimated by fitting it to the relationship between incidence of clinical episodes and the entomologic inoculation rate, using age-specific incidence data from two villages in Senegal and one village in Tanzania. The model reproduces the shifts in age distribution of clinical episodes associated with variation in transmission intensity, and in keeping with the data, predicts a slightly higher lifetime number of episodes in the mesoendemic village of Ndiop than in the holoendemic village of Dielmo. This model provides a parsimonious explanation of counter-intuitive relationships between the overall incidence of clinical malaria and transmission intensity. In contrast to the theory of endemic stability, recently proposed to apply to *P. falciparum*, it does not assume any intrinsic age dependence in the outcome of infection. This model can be used to explore the consequences for predictions of the effects of different anti-malarial interventions on the incidence of clinical malaria.

INTRODUCTION

The clinical outcome of *Plasmodium falciparum* malaria infection can range from an absence of detectable morbidity to rapid death.¹ In naive hosts, symptoms occur before the first peak of parasitemia, but untreated infections can persist for many months, with intermittent periods of acute illness. In malaria-endemic areas of sub-Saharan Africa, exposed people are subjected to frequent superinfections, and develop partial immunity that leads to control both of parasite densities and to reduction in the frequency of clinical episodes. Malaria morbidity is shifted into older ages as transmission intensity is reduced. This has been studied intensively in two villages in Senegal.^{2,3} In Dielmo, where the annual entomologic inoculation rate (EIR) is estimated to be approximately 200,^{3,4} almost all episodes are concentrated in the first years of life. In Ndiop, with an annual EIR of 20,5 there is a substantial peak shift, with a high incidence in adolescents and adults. In Ndiop, the EIR was detectable only during the short rainy season, whereas in Dielmo it was detectable throughout the year. The published data from Ndiop and Dielmo do not provide a breakdown of the age-pattern in the first year of life. In Idete in Tanzania, where transmission intensity is similar to Dielmo,^{3,6} the incidence of clinical attacks in the first three months of life is very low, but increased strongly with age.⁶ A higher number of lifetime episodes occurred in the lower transmission setting of Ndiop compared with Dielmo (even assuming the same life expectancy), a pattern seen elsewhere.⁷ To predict the potential impact of interventions that affect parasitemia, mathematical models are needed that predict not only the likely incidence of infections but also how frequently these will result in clinical episodes of malaria.

There is abundant evidence that most clinical episodes are caused by newly inoculated genetically distinct parasites.^{8,9} One proposed model is that parasite populations are structured into a limited number of strains, each stimulating long-

term clinical immunity.^{10,11} However most analyses of the population biology of *P. falciparum* have concluded that there is frequent genetic exchange,^{12–15} many malaria antigens are extremely polymorphic,^{16–18} cross-protection is clearly important, and natural immunity to the immunodominant epitopes is not necessarily lifelong.^{19–21}

The adequate modeling of all these complex immunologic phenomena represents a major challenge. However epidemiologic analyses of the tolerance of parasites can be used to predict the likelihood of clinical episodes as a function of densities of peripheral parasitemia without explicitly considering how those densities occur.^{22–25} In a study carried out in Dielmo, where parasitemia was assessed twice weekly Rogier and others estimated well-defined pyrogenic thresholds for different ages of human host.²⁴ We have now further analyzed these data to derive predictions of the thresholds as functions of recent levels of parasitemia, rather than of the age of the host. We have linked these predictions to a stochastic model that predicts parasite densities in endemic areas as a function of the pattern of transmission^{26,27} and fitted the model for the incidence of clinical episodes to field data from different epidemiologic settings in Ndiop, Dielmo, and Idete. The resulting model enables us to predict, for a wide range of malaria transmission settings, the occurrence of clinical episodes and to assess the likely effects of interventions on the incidence of clinical attacks.

MATERIALS AND METHODS

Model for parasite densities. The starting point for our model for the incidence of clinical malaria is an individualbased stochastic simulation model for *P. falciparum* parasitology.^{26,27} This model makes predictions of the parasite density for each member of the simulated population using a five-day time step, with the seasonal pattern of the EIR as input. The parasite densities are sampled from log normal distributions. We compared the observed parasitologic data to the predictions of this model for the Ndiop and Dielmo transmission patterns^{3,5} to evaluate its appropriateness as a basis for the predicting clinical episodes in this setting.

Model for clinical malaria episodes. The parasitologic simu-

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lation includes stochastic variation between individual humans in average parasite densities and also stochastic variation around that average.²⁶ We model clinical immunity as a function of these stochastically varying parasite densities, and of a set of five parameters that are independent of the individual and of the transmission setting.

To predict the clinical outcome, for each five-day time step we draw five independent samples from the simulated parasite density distribution for each concurrent infection (to simulate potential daily changes in morbidity status) and consider only the maximum, $Y_{max}(i,t)$, of the simulated densities to determine whether a clinical episode occurred. When the host is infected by several concurrent infections it is likely that one of these contributes the bulk of the parasite load, so it is logical to define $Y_{max}(i,t)$ as the maximum over all infections.

A simple model is to assume that for each host there is a specific parasite density, or pyrogenic threshold, at which symptoms (e.g., fever) are triggered. Rogier and others²⁴ considered a cohort of the inhabitants of the holoendemic village of Dielmo, Senegal and fitted a step function to the probability of fever as a function of parasite density. The parasite density at which the step occurs corresponds to the pyrogenic threshold, which was shown to vary with age.

In general, it is not realistic to assume that all individuals of the same age will have exactly the same pyrogenic threshold,^{28–31} so it is more reasonable to expect a sigmoidal relationship between the risk of fever and the parasite density than a step function. We therefore propose a model in which the probability that an episode occurs in individual *i*, at time *t*, is related to the parasite density via a function of the following form:

$$P_{m}(i,t) = \frac{Y_{\max}(i,t)}{Y^{*}(i,t) + Y_{\max}(i,t)}$$
(1)

where $Y^*(i,t)$, the pyrogenic threshold for individual *i* at time *t*, is defined as the parasite density at which the probability of a clinical episode reaches 0.5, and $Y_{max}(i,t)$ is the maximum density during the time interval *t* (note that we present only the formulae for our final choice of models).

The age pattern in the pyrogenic threshold in Dielmo, together with data derived from other study sites,^{29,32,33} supports the idea that the density of parasites required to stimulate acute pathology is higher in individuals who have been recently exposed to high parasite densities. This may be a result of stimulation of immune responses to toxins released at schizogony, and very likely involves physiologic tolerance of cytokines.³⁴ The mechanism must be consistent with both rapid acquisition and rapid loss of tolerance and cannot be a simple function of antibody against toxin, which have a completely different age-pattern from that of the pyrogenic threshold.³⁵

We model the dynamics of the pyrogenic threshold with a function of the form

$$\frac{dY^{*}(i,t)}{dt} = f_{1}(Y(i,t)) f_{2}(Y^{*}(i,t)) - \varpi Y^{*}(i,t)$$
(2)

where $f_1(Y(i,t))$ is a function describing the relationship between accrual of tolerance and the parasite density Y(i,t); $f_2(Y^*(i,t))$ describes saturation of this accrual process at high values of Y^* , and the term $\varpi Y^*(i,t)$ leads to decay of the threshold with first-order kinetics. The decay ensures that the model conforms to the epidemiologic evidence suggesting that parasite tolerance is short lived.

We define the function $f_1(Y(i,t))$ in such a way as to ensure that the stimulus is not directly proportional to Y but rather that it asymptotically reaches a maximum at high values of Y, using

$$f_1(Y(i,t)) = \frac{\alpha Y(i,t)}{Y_1^* + Y(i,t)}$$
(3)

To ensure saturation of the accrual process, we require that at high values of Y^* , a higher parasite load is required to achieve the same increase by defining

$$f_2(Y^*(i,t)) = \frac{1}{Y_2^* + Y^*(i,t)},\tag{4}$$

Overall therefore we propose the following dynamics for Y^* :

$$\frac{dY^{*}(i,t)}{dt} = \frac{\alpha Y(i,t)}{(Y_{1}^{*} + Y(i,t)) (Y_{2}^{*} + Y^{*}(i,t))} - \varpi Y^{*}(i,t)$$
(5)

where αY_1^* , and Y_2^* are constants to be estimated. To complete the specification of the model, we set the initial conditions to be $Y^*(i,0) = Y_0^*$ at the birth of the host, thus defining a further parameter Y_0^* .

Data sources. We fitted the model for acute episodes to two distinct datasets. The first was published data on the age pattern of clinical episodes in the villages of Ndiop and Dielmo in Senegal.² The village populations were visited daily to detect and treat any clinical malaria attacks (with quinine). Thus, effectively all acute episodes were thought to be treated in these villages. In the simulations of Dielmo and Ndiop we assumed that there had been no treatment of clinical malaria prior to the start of the follow-up period. To ensure that the analysis remains tractable, we approximate the patterns of transmission with recurring annual cycles (although there was variation between years in the predominant vectors and seasonality of transmission).

We also compared the predicted patterns from the simulation model for *P. falciparum* parasitology with those from parasitologic surveys in these two villages to evaluate its appropriateness as a basis for the predicting clinical episodes in this setting. In Dielmo, two thick blood smears were prepared per week for each individual from May 29, 1990 to September 30, 1990. In Ndiop, one thick blood smear was prepared per week for each individual from July 15, 1993 to January 15, 1994 and one per month from January 2, 1994 to July 15, 1995. Slides were only declared negative after 200 high-power fields had been scanned for parasites. Parasite densities were originally expressed as the parasite:leukocyte ratio. To adjust these densities to the same scale as that used in fitting the simulation model to other datasets, the parasite:leukocyte ratios were then multiplied by a factor of 1,416 to give a notional density in parasites/microliter of blood.26

The model was fitted to a second dataset of age-incidence rates for clinical malaria in infants less than one year of age recorded at the health center in the village of Idete, Tanzania from June 1993 to October 1994.^{6,25} These data were included to estimate the initial conditions (the value of Y_0^*) and to ensure that the model predicts the age pattern of acute episodes that is actually observed in infants. For the Idete data we used the case definitions and age groups in the paper by Vounatsou and others²⁵ and the annual pattern of inoculations reported by Charlwood and others³⁶ as input. We assume a common value of Y_0^* across all sites and therefore require data for infants from only a single transmission setting.

Implementation and fitting of the simulation model. To obtain estimates of the five parameters α , ϖ , Y_0^* , Y_1^* , and Y_2^* we fitted the model to the age-pattern of clinical malaria in all three villages (i.e., Ndiop and Dielmo in Senegal, and Idete in Tanzania) and simultaneously to the pyrogenic thresholds for Dielmo estimated by Rogier and others²⁴ (Table 1).

For Dielmo and Ndiop we further predicted parasite densities for a sample of 10,000 individuals over a 10-year period drawn from the age-groups of interest. For Idete, where we were concerned only with infants less than one year of age, we used a sample size of 2,000. In each village we assumed a typical sub-Saharan African age-distribution taken from the demographic surveillance area that includes Idete.³⁷

Simulated clinical episodes of malaria occurred with probability $P_m(i,t)$, which was dependent on both the simulated maximum density and the current value of $Y^*(i,t)$ for each individual and each five-day time point in the 10-year followup period. In the simulations of Ndiop and Dielmo we simulated effective treatment of all clinical episodes within the five-day period in which they occurred. In the simulation of Idete we assumed that some proportion, P_{r} , of the episodes were effectively treated (i.e., the parasites were cleared within the course of one time interval), and that this proportion corresponded to the proportion of episodes reported to the village dispensary. In Idete village, simulated episodes occurring within 30 days of a preceding episode were not counted (these have been registered in the surveillance system as recrudescence, rather than new episodes). In Ndiop and Dielmo this restriction did not hold.38

For each simulated individual in each village the model thus predicted the incidence of clinical malaria as a stochastic function of the inoculation rate. These incidences were summarized over age groups and compared with the published values.^{2,25} Similarly, the model predicted the pyrogenic threshold, $Y^*(i,t)$, at each time point for each individual. The geometric mean of these values was calculated for each age group in the simulation of Dielmo village, and the logarithms of these values compared with the logarithms of the agespecific pyrogenic thresholds estimated by Rogier and others.²⁴ Simulated annealing^{39,40} was used to identify the parameter values that minimized the residual sum of squares summed over all three villages and both outcomes for Dielmo. The Fisher information estimated from a least squares quadratic fit to the residual sum of squares was used to give approximate confidence intervals.

RESULTS

The parameter estimates are given in Table 1. Our model was able to reproduce the age incidence patterns very well considering that only five parameters were fitted across three datasets (Figure 1).

The value of ϖ , estimated as 2.5/year, implied that in the absence of stimulation, the pyrogenic threshold decays with a half life of 0.33 years. The predicted total numbers of episodes up to age 60 were 56 for Ndiop (EIR = 20) and 53 for Dielmo (EIR = 200) compared with the published overall incidence of clinical malaria cumulative numbers of episodes up to the age of sixty of 62 and 43, respectively.² In the simulations of both villages the age of peak incidence was a little younger than in the data predicted incidence and incidence was rather lower in the youngest individuals than the observed values, and higher in adults. The extent of the peak shift was similar in the model to the data.

Although the model was not fitted to the patterns of age prevalence and of age density in Dielmo or Ndiop, it does make predictions of these quantities, which we could therefore compare with the observed curves. The predicted ageprevalence curve for Dielmo was very similar to that observed (Figure 2a), as were the predicted geometric mean densities in children in that village (Figure 3a). In adults the model predicted rather higher densities than those observed in Dielmo, while for adults in Ndiop the model predicted higher prevalence in adults (Figure 2b) but lower densities (Figure 3b) than those observed. This would be expected if the burden of malaria is concentrated in a smaller proportion of individuals in Ndiop than in the dataset to which the parasitologic model was fitted. A reasonably good fit was obtained for the average pyrogenic threshold, but the model did not give a very good fit to the age-trend in $Y^*(i,t)$, predicting that the peak was at a greater age than the estimates of Rogier and others²⁴ (Figure 4).

DISCUSSION

Our model can reproduce the patterns of the age-specific incidence of acute episodes from the three transmission settings. In particular, we were able to reproduce both the shape of the age-specific incidence curves and total the lifetime incidence of acute episodes for sites with very different transmission intensities with a model with only five parameters. Within this model, the higher incidence of clinical attacks in older individuals in Ndiop than in Dielmo arises both because of lower immunologic control of asexual blood stages and less clinical tolerance.

TABLE 1							
Parameter	estimates	from	the	best	fitting model*		

Parameter	Meaning of parameter	Estimate	95% confidence interval	
α	Factor determining increase in $Y^*(i,t)$	143,000 parasites ² μ L ⁻² day ⁻¹	103,000-197,000	
យ	Decay rate of pyrogenic threshold	2.5 year^{-1}	2.1-3.0	
Y_0^*	Pyrogenic threshold at birth	296.3 parasites/µL	3-30,000	
Y_{1}^{*}	Critical value of parasite density in determining increase in Y^*	0.60 parasites/µL	0.17-2.13	
Y_{2}^{1}	Critical value of $Y^*(i,t)$ in determining increase in $Y^*(i,t)$	6.5×10^3 parasites/µL	$5.2 \times 10^{3} - 8.2 \times 10^{3}$	
P_t^2	Compliance in Idete (proportion of episodes detected and treated)	0.36	0.27–0.48	

* The residual sums of squares for the three datasets were 0.2 (Idete), 4.4 (Ndiop), and 3.4 (Dielmo), computed from 4, 22, and 22 distinct age groups, respectively (corresponding to 43 residual degrees of freedom. The residual sum of squares for the pyrogenic threshold for Dielmo was 3.3.



FIGURE 1. Age incidence curves. **a**, Idete, Tanzania. $\blacksquare - \blacksquare =$ measured incidence of clinical malaria at health center; thick line = model prediction for overall incidence of clinical malaria; $\square - \square =$ model prediction for incidence of clinical malaria at health center. **b**, Ndiop and Dielmo, Senegal. Thin black line = observed incidence of clinical malaria in Ndiop; thin gray line = observed incidence of clinical malaria in Dielmo; thick black line = model prediction of incidence of clinical malaria in Ndiop; thick gray line = model prediction of incidence of clinical malaria in Dielmo.

This good fit was obtained despite the use of a parasitologic model that only crudely reproduces within-host parasite dy-namics, since we fitted it to cross-sectional data.²⁶ Day-to-day variation in parasite densities may be critical in determining

levels of tolerance, and our model, based on five-day time steps, did not aim to simulate this accurately. This may explain why the density of patent parasitemia did not appear to be very important, and may also be the explanation of why we



FIGURE 2. Parasite prevalence. **a**, Dielmo. Points and error bars show prevalence of patent parasitemia and 95% confidence intervals determined in surveys from 1990 to 1994. Continuous line = model predictions. **b**, Ndiop. Points and error bars show prevalence of patent parasitemia and 95% confidence intervals determined in surveys from 1990 to 1994. Continuous line = model predictions. Pervalence is assessed as the proportion of individuals with parasite density (simulated or observed) above the actual level of detection used in the field study.



FIGURE 3. Geometric mean parasite densities **a**, Dielmo. Points and error bars show geometric mean and 95% confidence intervals of densities of patent parasitemia determined in surveys from 1990 to 1994. Continuous line = model predictions of the geometric means. **b**, Ndiop. Points and error bars show geometric mean and 95% confidence intervals of densities of patent parasitemia determined in surveys from 1990 to 1994. Continuous line = model predictions of the geometric means. **b**, Ndiop. Points and error bars show geometric mean and 95% confidence intervals of densities of patent parasitemia determined in surveys from 1990 to 1994. Continuous line = model predictions of the geometric means.

could not obtain a better fit for the age-pattern of the pyrogenic threshold. It is possible that the important variations in density and levels of tolerance are much more rapid than our model could capture, especially if they involve physiologic tolerance of cytokines.³⁴

The relatively poor prediction of parasite prevalence and density in adults in Ndiop is possibly because the model assumes the degree of within-village heterogeneity in transmission to be the same in each village. Focality of transmission leads to lower prevalence, but higher densities in those who are infected, because of increased levels of superinfection. Based on these criteria, transmission in Ndiop appears to be more focal than that in the villages to which we fitted the parasitologic model.²⁶ Within our model effects of focal transmission on incidence of clinical episodes should be only of secondary importance because there is little interaction be-



FIGURE 4. Pyrogenic threshold in the village of Dielmo, Senegal. Filled circles = the pyrogenic threshold $(Y \times a)$ by age in Dielmo (results of Rogier and others²⁴). Line = model prediction.

tween concurrent co-infections. Thus, at any given level of immunity the incidence of clinical episodes depends primarily on the overall force of infection and not on how the infections are distributed between individuals.

It was not possible to obtain a better fit for infants in Ndiop because the number of infection events predicted for this age group by our model of infection²⁷ is less than the number of clinical episodes. We have assumed all episodes are immediately treated so that no more than one episode can occur for any one infection event, but this was not necessarily always the case. We assumed mosquito biting to be proportional to body surface area, using Tanzanian anthropometric data to estimate age-specific surface areas.⁴¹ Different patterns of human growth or mosquito behavior may account for some of the discrepancies. Selection effects that might arise because of differential mortality of susceptible individuals are an additional factor that we did not take into account.

Our model assumes particular functional forms for the relationships between the pyrogenic threshold and the risk of clinical episodes and the pyrogenic threshold and the parasite density itself. Exploratory analyses indicated that the fitted age-incidence relationships are not very sensitive to the exact functional forms used for these relationships. Empirical relationships between parasite density and risk of illness depend on how the cases are detected. In the studies in Senegal parasitemia and fever were monitored daily, so episodes were generally detected early and this may account for the abrupt pyrogenic thresholds reported by Rogier and others.²⁴ More usually, fever cases are detected when they report to a health facility, as in the study in Idete.⁶ The arrival of the cases at the health facility is at varying intervals after the beginning of the episode and this tends to blur the relationship between fever risk and parasite density. If fever episodes are detected at household visits, which are carried out at intervals of more than a few days at times that are unrelated to the onset of disease, then the relationship between parasite densities and fever risk is weaker (e.g.,^{22,42}).

In areas endemic for P. falciparum malaria, the incidence of clinical attacks is highly age dependent, with the peak incidence occurring at younger ages the higher the transmission. Such peak shifts are not only characteristic for malaria but also for many other infectious diseases.⁴³ A superficially similar shift is also seen in patterns of age prevalence for P. fal*ciparum*,⁴⁴ but the peak in prevalence is generally reached at an older age than that of acute morbidity. Unlike the pattern for clinical episodes, reduction in transmission is associated with reduction in infection prevalence over almost all of the age range, (although in some age groups there may be a small increase). The peak shift in clinical attacks is more pronounced than that in prevalence, and the incidence of acute malaria attacks in older children and adults can be substantially greater at low transmission levels than at high ones (Figure 1).

The observation that reduction in transmission may lead to an increased incidence of disease in P. falciparum has been attributed to the phenomenon of endemic stability observed with many veterinary pathogens.45 For endemic stability to occur there must be at least two processes accounting for the age-incidence curves, one leading to an increase in incidence with age in the youngest age groups, and the other to a decreasing incidence in older individuals. Coleman and others⁴⁵ suggest that the first of these conditions must be satisfied by a worsening of the outcome of infection with age over at least part of the age range. Our model demonstrates that this assumption is not necessary, for we explain the initial increase in morbidity with age as a consequence of increase in exposure to mosquitoes as the host grows in body surface area.²⁷ Idete, Dielmo, and Ndiop are all villages with stable endemic P. falciparum. Although Ndiop is an example of mesoendemicity, contrasting with the holoendemic transmission in Idete and Dielmo, it still experiences a much higher EIR than areas of unstable transmission. The theory of endemic stability therefore needs adapting for the analysis of the case of endemic malaria.

We propose to use the sub-model of equations 1–5 as part of a comprehensive model for examining the likely consequences of a wide range of interventions, including vaccination. The incidence of acute illness is only one of these consequences, which can include severe life-threatening disease, chronic anemia, and indirect mortality. Even an intervention that leads to an increase in the incidence of uncomplicated illness in some age groups might lead to a reduction in mortality or severe disease. We know that parasite tolerance and anti-parasitic immunity have different dynamics, and conjecture that they make differential contributions to uncomplicated and severe disease, respectively.

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