AN EPIDEMIOLOGIC MODEL OF SEVERE MORBIDITY AND MORTALITY CAUSED BY PLASMODIUM FALCIPARUM

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Abstract. The intensity of Plasmodium falciparum transmission has multifarious and sometimes counter-intuitive effects on age-specific rates of severe morbidity and mortality in endemic areas. This has led to conflicting speculations about the likely impact of malaria control interventions. We propose a quantitative framework to reconcile the various apparently contradictory observations relating morbidity and mortality rates to malaria transmission. Our model considers two sub-categories of severe malaria episodes. These comprise episodes with extremely high parasite densities in hosts with little previous exposure, and acute malaria episodes accompanied by co-morbidity or other risk factors enhancing susceptibility. In addition to direct malaria mortality from severe malaria episodes, the model also considers the enhanced risk of indirect mortality following acute episodes accompanied by co-morbidity after the parasites have been cleared. We fit this model to summaries of field data from endemic areas of Africa, and show that it can account for the observed age- and exposure-specific patterns of pediatric severe malaria and malaria-associated mortality in children. The model will allow us to make predictions of the long-term impact of potential malaria interventions. Predictions for children will be more reliable than those for older people because there is a paucity of epidemiologic studies of adults and adolescents.

INTRODUCTION

The outcomes of Plasmodium falciparum infections range from self-limiting asymptomatic parasitemia to rapid death. It is not well understood why some infections have much worse consequences than others and this makes it difficult to predict the epidemiologic effects of malaria interventions.

Different outcomes have different age patterns: the more severe the outcome, the younger the age group most affected. The age-pattern of each outcome also varies with the intensity of transmission. In stable endemic areas, the incidence of clinical malaria episodes is highest at intermediate levels of transmission. Hospital-diagnosed severe malaria in children also appears to be most frequent at intermediate transmission, but in infants shows an increase with transmission intensity, as does all-cause mortality. Hospital case fatality rates are age-dependent, with the highest rates in young infants and older children and minimum rates in an intermediate age group. Malaria-specific mortality rates might therefore be expected to show different relationships with age and transmission intensity than do morbidity rates. Community-based estimates of malaria-specific mortality rates have been estimated using verbal autopsies for a number of endemic areas but the relationships with transmission intensity are unclear. One reason may be that verbal autopsies have poor sensitivity and specificity for malaria.

The risk of malaria-diagnosable morbidity and mortality is thought to depend on other risk factors such as malnutrition and co-infections. It has been suggested that approximately 60% of malaria mortality is attributable to low weight, vitamin A deficiency and/or zinc deficiency. Eight percent of severe malaria cases in Kenya were found to be bacteremic.

In addition to causing direct malaria mortality, P. falciparum is likely to be a contributory factor in many deaths that would not be diagnosed as malaria by a physician. Many malaria control or local elimination programs decreased all-cause mortality by more than the initial estimates of malaria specific mortality. The differential mortality required to explain frequencies of sickle cell hemoglobin (HbAS) is substantially greater than that generally attributed to malaria alone. However, the relative contribution of this indirect mortality has been debated. We propose a model to explain these patterns as consequences of two processes with different relationships to host age and the level of malaria transmission. The first of these is the level of immunity to asexual blood stages of the malaria parasite. The second is the chance that the host defenses are compromised by some co-morbidity or enhanced susceptibility around the time of the clinical malaria attack.

To predict the long-term impact of potential interventions on P. falciparum malaria, there is a need for dynamic models linking severe and fatal malaria to transmission. We now incorporate our proposal for the causes of severe malaria and malaria attributable mortality into a simulation model of malaria transmission, parasitemia, and acute morbidity. We fit the model to published data and show that the apparently conflicting observations relating morbidity and mortality rates to malaria transmission can be reconciled within a coherent framework that corresponds to current knowledge of malaria biology.

MATERIALS AND METHODS

Model. Severe malaria episodes. We consider severe malaria episodes as those events that would have led to an admission diagnosis of severe malaria, had the patient presented to a health facility. The probability that a clinical malaria episode occurs in individual i at time t, \( P_m(i,t) \), depends on both the simulated parasite density, \( Y(i,t) \), and the modeled pyrogenic threshold \( Y^*(i,t) \). These episodes (A, Figure 1) include a subset that are severe (B, Figure 1). We propose that severe malaria episodes can occur as a result of one or other of two distinct processes (B1 and B2). These categories do not necessarily correspond to any of the specific syndromes of severe malaria.

One subset of the severe malaria episodes (B1, Figure 1) comprises those that occur when the host experiences an overwhelming parasite density. We define \( H(i,t) \) to be the...
We assume that 48% of severe malaria episodes arise because of co-
infected malaria exposure. The term \( P_B(i,t) \) \( P_B(i,t) \) is subdivided into \( P_B(i,t) \) and \( P_B(i,t) \), which is then used to calculate unconditional risk of severe malaria morbidity and mortality conditional on a clinical episode is then given by

\[
P_B(i,t) = P_B(i,t) + P_B(i,t) - P_B(i,t) \]  

for an insult, but that the risk of severe malaria does depend on \( F(a(i,t)) \). The probability that an episode belonging to class \( B_2 \) occurs at time \( t \), conditional on there being a clinical episode at that time is \( P_B(i,t) \) defined as

\[
P_B(i,t) = \Pr(\text{H}(i,t) \in B_2|\text{H}(i,t) \in A)  
\]

and calculated as

\[
P_B(i,t) = F(a(i,t)).  
\]

The age and time specific risk of severe malaria morbidity and mortality conditional on a clinical episode is then given by

\[
P_B(i,t) = P_B(i,t) + P_B(i,t) - P_B(i,t) \]  

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\]

and calculated as

\[
P_B(i,t) = F(a(i,t)).  
\]
which together with other co-morbidity or enhanced susceptibility, leads to subsequent death.

The insults contributing to a death in class $D_2$ could be sequential or they could occur together. Since this makes little difference to the predicted incidence, for mathematical convenience we use a model analogous to that for severe malaria in class $B_2$. In this model, an event in class $D_2$ is instigated at time $t$, conditional on there being a clinical episode at that time, with probability $P_{D_2}(i,t)$ defined as

$$P_{D_2}(i,t) = \Pr(H(i,t) \in D_2 | H(i,t) \in A)$$

and calculated as

$$P_{D_2}(i,t) = \frac{Q_D}{1 + \left( \frac{a(i,t)}{a_E} \right)}$$

where $Q_D$ is the limiting value of $P_{D_2}(i,t)$ at birth.

The deaths in class $D_2$ are simulated as occurring 30 days after time $t$. This allows for the possibility that the host dies of an event in class $C_1$ or $C_2$ before the indirect death occurs.

**Data and fitting of the model.** Severe morbidity. Data on the relative incidence of severe malaria in children less than nine years of age across different transmission intensities have been collated by Marsh and Snow. They summarize the relationship between severe malaria hospital admission rates and *P. falciparum* prevalence in children less than nine years of age. To obtain a continuous function relating hospital incidence to prevalence, we linearly interpolated between data points. To convert the hospital incidence rates to community incidence to prevalence, we linearly interpolated between data points. To obtain a continuous function relating hospital incidence to prevalence, we linearly interpolated between data points.

The Gambia data and fitting of the model.

<table>
<thead>
<tr>
<th>Site</th>
<th>Entomology reference</th>
<th>EIR data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkina Faso</td>
<td>48,49</td>
<td>1994–1995</td>
</tr>
<tr>
<td>ITC control</td>
<td>50</td>
<td>1985</td>
</tr>
<tr>
<td>Karangasso</td>
<td>51</td>
<td>1984</td>
</tr>
<tr>
<td>Kongodjan</td>
<td>52</td>
<td>1994–1995</td>
</tr>
<tr>
<td>Zimari</td>
<td>53</td>
<td>1983</td>
</tr>
<tr>
<td>Gihanga</td>
<td>53</td>
<td>1982</td>
</tr>
<tr>
<td>Katumba</td>
<td>55</td>
<td>1992</td>
</tr>
<tr>
<td>Kenya</td>
<td>54,55</td>
<td>1992–1993</td>
</tr>
<tr>
<td>Chonyi</td>
<td>54,55</td>
<td>1992–1993</td>
</tr>
<tr>
<td>Kilifi North</td>
<td>54</td>
<td>1990–1991</td>
</tr>
<tr>
<td>Kilifi Town</td>
<td>55</td>
<td>1991</td>
</tr>
<tr>
<td>Saradidi</td>
<td>56</td>
<td>1986–1987</td>
</tr>
<tr>
<td>Senegal</td>
<td>57,58</td>
<td>1995–1996</td>
</tr>
<tr>
<td>Bandalafi</td>
<td>57,58</td>
<td>1995</td>
</tr>
<tr>
<td>Mlomp</td>
<td>57,58</td>
<td>1995</td>
</tr>
<tr>
<td>Niakhar</td>
<td>59</td>
<td>1995</td>
</tr>
<tr>
<td>Tanzania</td>
<td>47</td>
<td>1990–1991</td>
</tr>
<tr>
<td>Namawala</td>
<td>60</td>
<td>1992</td>
</tr>
<tr>
<td>The Gambia</td>
<td>61,62</td>
<td>1991</td>
</tr>
<tr>
<td>Areas I–V</td>
<td>61</td>
<td>1987</td>
</tr>
<tr>
<td>Others</td>
<td>61</td>
<td>1992</td>
</tr>
<tr>
<td>Bo, Sierra Leone</td>
<td>61</td>
<td>1990–1991</td>
</tr>
<tr>
<td>Guanv, Benin</td>
<td>64</td>
<td>1993–1995</td>
</tr>
<tr>
<td>Manhica, Mozambique</td>
<td>65</td>
<td>2001–2002</td>
</tr>
<tr>
<td>Matsari, Nigeria</td>
<td>66</td>
<td>1971</td>
</tr>
<tr>
<td>Navrongo, Ghana</td>
<td>66</td>
<td>2001–2002</td>
</tr>
</tbody>
</table>

*EIR = entomologic inoculation rate, ITC = control group of randomized trial of insecticide-treated curtains.

† Five sites with annual EIR between 1 and 10.

Simulated annealing was used to identify the parameter values that minimized the weighted residual sum of squares. Approximate confidence intervals were obtained by estimating the Fisher information for the parameters from a least squares fit of local quadratic approximations to the (stochastic) log likelihood. In addition to considering the formal model fit, we also assessed the biologic plausibility of the models and the predictions for the age groups for which we had no data.

**Direct malaria mortality.** The odds ratio for death in class $C$ predicted by the model could not account for the relationship observed between EIR and infant mortality, and we propose that the

squares of the log-transformed rates, where the weights were chosen so that the two analyses were weighted approximately equally.

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**Indirect malaria mortality.** The deaths in class $C$ predicted by the model could not account for the relationship observed between EIR and infant mortality, and we propose that the
difference is due to deaths in class D. We assembled a library of sites for which entomologic data were collected at least monthly and all-cause infant mortality rates (IMR) were available (Table 2). We use the entomologic data as input and estimate $Q_D$ and the infant mortality that is independent of malaria $Q_n$ by the same fitting algorithm that was used for the severe malaria and direct mortality components. The model for indirect mortality is conditional on our models for severe malaria and direct mortality components. The model for indirect mortality is conditional on our models for severe malaria and direct mortality, and assumes no effective treatment of uncomplicated malaria episodes.

Since a study found no clear relationship between all-cause mortality for children 1–4 years of age and transmission intensity, we did not use data for children more than one year of age to estimate the parameters of the model for indirect mortality.

## RESULTS

### Severe malaria.
We compared the best-fitting models of the two forms proposed (Table 3). Both models produced similar predictions (Figure 2). Both gave a good fit to most of the data, and in particular they reproduced the decrease in incidence with transmission intensity in highly endemic areas.

Neither model reproduced the sharp peak in incidence associated with a prevalence of just under 20%, which is most pronounced in the rate reported from a hospital in Ethiopia. Model 1, with the severe malaria threshold as a multiple of the individual’s pyrogenic threshold, had a better fit (weighted residual sum of squares 3.35 versus 8.97). However, it predicted a rather high incidence of severe episodes in adults (for whom few data are available) (Figure 3), and this led to estimates of malaria mortality rates that exceed recorded all-cause mortality rates in some age groups. Predicted mortality rates in older age groups were lower with model 2. The assumption of a constant parasitemia threshold for severe malaria in model 2 is also more attractive because of the evidence that total parasite biomass is critical in precipitating severe malaria episodes. The estimate of this threshold of 784,000 parasites/μL is high, but within the range observed in severe malaria patients. We do not attach much credibility to the precise value of this threshold because our simulation model only reproduces distributions of parasite densities very approximately.

Model 2 reproduces the age patterns from the four sites with different transmission intensities reasonably well (Figure 4). The proportion of predicted severe malaria cases that be-

## Table 2
Sites used for fitting the model for direct and indirect malaria mortality

| Site, country                  | Estimated malaria mortality (< 5 years old)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>Deaths/1,000 person years</td>
</tr>
<tr>
<td>Kilifi North</td>
<td>1991–1993</td>
</tr>
<tr>
<td>Bo, Sierra Leone</td>
<td>1990</td>
</tr>
<tr>
<td>Karangasso, Burkina Faso</td>
<td>–</td>
</tr>
<tr>
<td>Manhica, Mozambique</td>
<td>–</td>
</tr>
<tr>
<td>Navrongo, Ghana</td>
<td>1990</td>
</tr>
<tr>
<td>Bandafassi, Senegal</td>
<td>1984–1989</td>
</tr>
<tr>
<td>Mlomp, Senegal</td>
<td>–</td>
</tr>
<tr>
<td>Kongodjan, Burkina Faso</td>
<td>1982–1986</td>
</tr>
<tr>
<td>Namawala, Tanzania</td>
<td>–</td>
</tr>
</tbody>
</table>

* Used for direct malaria mortality model.
† Used for indirect malaria mortality model. IMR = all-cause infant mortality rate/1,000 livebirths.

## Table 3
Parameter estimates and 95% confidence intervals

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe malaria model parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Threshold density multiplier (model 1); threshold (model 2)</td>
<td>$\alpha_p$ = 983 (518, 1,869)</td>
<td>$\alpha_p$ = 983 (518, 1,869)</td>
</tr>
<tr>
<td>Prevalence at birth of co-morbidity contributing to severe episodes</td>
<td>$Q_0$ = 0.127 (0.060, 0.258)</td>
<td>$Q_0$ = 0.127 (0.060, 0.258)</td>
</tr>
<tr>
<td>Critical age for co-morbidity (years)</td>
<td>$a^F = 0.078 (0.053, 0.113)$</td>
<td>$a^F = 0.078 (0.053, 0.113)$</td>
</tr>
<tr>
<td>Weighted residual sum of squares</td>
<td>3.35</td>
<td>3.35</td>
</tr>
<tr>
<td>Malaria mortality model parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio for case fatality in the community compared to in hospital</td>
<td>$\psi_1$ = 2.00 (1.33, 5.26)</td>
<td>$\psi_1$ = 2.00 (1.33, 5.26)</td>
</tr>
<tr>
<td>Weighted residual sum of squares</td>
<td>3.24</td>
<td>3.24</td>
</tr>
<tr>
<td>Indirect malaria mortality model parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-malaria intercept for infant mortality rate</td>
<td>$Q_n$ = 58.2 (30.5, 111.0)</td>
<td>$Q_n$ = 58.2 (30.5, 111.0)</td>
</tr>
<tr>
<td>Prevalence at birth of co-morbidity contributing to indirect mortality</td>
<td>$Q_D$ = 0.018 (0.006, 0.047)</td>
<td>$Q_D$ = 0.018 (0.006, 0.047)</td>
</tr>
<tr>
<td>Weighted residual sum of squares</td>
<td>0.31</td>
<td>0.31</td>
</tr>
</tbody>
</table>
long to class $B_2$ in this model increases with transmission intensity because the infections tend to occur at younger ages (Figure 5).

**Direct malaria mortality.** To reconcile the field estimates of malaria-specific mortality rates with either model for severe malaria, odds ratios of approximately 2 were estimated for case fatality in the community compared with in hospital (Table 3). The predicted age-specific community case fatality is shown in Figure 6.

**Figure 2.** Model predictions of the incidence of severe disease compared with observed data. a, Model 1. b, Model 2. —— = data reported by Marsh and Snow. The hospital incidence rates have been divided by 0.48 to provide estimates of the incidence in the community.

**Figure 3.** Predicted incidence of severe malaria in adults 20–39 years of age by transmission intensity. Solid line = Model 1; dashed line = Model 2. The seasonal pattern of transmission intensity follows that of Namawala, Tanzania scaled to sum to different values of infectious bites per person per year.

**Figure 4.** Age-specific incidence of severe malaria. a, Community incidence rates calculated from the hospital data reported by Snow and others by dividing by the notional hospital attendance rate of 0.48. b, Predicted incidence rates from model 2 for the four scenarios chosen on the basis of similar parasite prevalence values (1–9 years) to the sites above.

**Figure 5.** Percentage of severe malaria episodes due to age-dependent cofactors ($B_2$) by transmission intensity. These predictions are from model 2 and include all age groups. The seasonal pattern of transmission intensity follows that of Namawala, Tanzania scaled to sum to eight different values of infectious bites per person per year.
Empirical malaria mortality rates for children less than five years of age are shown in Figure 7, together with the predictions for the same sites using the severe malaria model that we have adopted (model 2). Both the observed data and predictions show no obvious trend with transmission intensity, and there is a large variation between the sites in the verbal autopsy-based rates.

The predicted malaria mortality rates show a clear increase with transmission intensity in infants and no apparent trend for 1–4-year-old children for both models (Figure 8a and b). Using the severe malaria model with a multiplier for the pyrogenic threshold (model 1), adults 20–39 years of age had a rather high predicted malaria mortality rate (Figure 8c). This is the result of the high predictions for incidence of severe malaria with this model.

Indirect malaria mortality. We estimate that in the absence of \( P. falciparum \), the IMR for the sites included in the analysis, \( Q_m \), would average approximately 50 per 1,000 live births (Table 3). However, this quantity was estimated very imprecisely because the parameters \( Q_D \) and \( Q_n \) are highly correlated.

There was an association between the observed all-cause IMR and transmission intensity, as previously reported using broader inclusion criteria\(^5\) (Figure 9). The predicted IMR for these sites using model 2 (incorporating the effects of severe malaria and malaria mortality models as above) reproduces this apparent trend.

Predictions of indirect malaria mortality for different age groups show similar patterns with transmission intensity to those of the direct malaria mortality (Figure 10). Although the deaths in infants tend to increase, this is not the case for either direct or indirect malaria mortality for older age groups. Taking all age groups together, the ratio of indirect: direct malaria deaths was 0.6 for an EIR of 5. This increased to 1.4 for an EIR of approximately 100 and did not increase further for higher transmission intensities.
DISCUSSION

Our model replicates reasonably well the associations of severe malaria incidence and transmission intensity in sub-Saharan Africa. Severe episodes resulting simply from very high parasite densities ($B_1$ in Figure 1) represent malaria-specific morbidity. These are more frequent at moderate levels of transmission and account for the peak in the incidence of pediatric severe malaria at intermediate levels of transmission. Within our model, this is mainly because maternal immunity helps to control the first infections at very high levels of transmission, so that the initial infections are less well controlled if they occur later in life.\(^{25}\)

The patterns of events in classes $B_1$ and $B_2$ with age and with transmission have similarities to those described for severe malaria anemia, and for patterns for cerebral malaria,\(^{32}\) respectively. However, our simple structure for the different classes of events does not aim to map onto the pathophysiology of these syndromes. Recent work has suggested that the different syndromes of severe malaria are overlapping.\(^{33}\) A major uncertainty lies in the choice between models 1 and 2 for the relationship between parasite density and severity of disease. This is likely to have an important effect on our predictions of the impact on interventions that affect blood stage densities, and points to a gap in our knowledge of pathogenesis.

The fitting of these models suggests that a substantial proportion of severe malaria episodes involve age-dependent cofactors that are concentrated in the youngest children. This is consistent with the fact that these children have the least immunity to other infections and are also at highest risk of nutritional problems.

We assumed the same age dependence in co-morbidity in estimating the contribution of malaria to indirect deaths ($D_2$ in Figure 1) and thus the effects of co-morbidity dominate those with high parasite densities in determining the impact of P. falciparum on all-cause mortality in the youngest children. The strong age dependence is supported by ecologic comparisons of all-cause mortality rates and malaria transmission intensity, where there is no clear association after the first year of life.\(^5\) It is also in agreement with analyses of HbAS frequencies that have suggested that indirect malaria mortality is likely to be concentrated in the youngest children.\(^{20}\)

Clinical malaria episodes are also more concentrated in younger children as the transmission intensity increases.\(^{23}\) Therefore, within our model, the probability that these risks coincide to cause either severe malaria episodes ($B_2$) or subsequent indirect mortality ($D_2$) increases with transmission level. We used clinical malaria episodes for the predisposing factor for indirect deaths, but it is also possible that asymptomatic parasitemia plays this role.\(^{21}\)

The model points to other important areas of uncertainty. Malaria in adults is an example of this. It is generally thought that severe malaria occurs only infrequently in adults in the

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**Figure 9.** Observed and predicted infant mortality rates $\square =$ infant mortality rates from field data; $\bigcirc =$ predictions using model 2.

**Figure 10.** Predicted mortality rates by transmission intensity. **a.** Direct malaria mortality. **b.** Indirect malaria mortality. Age groups: small dashed line = 0–1 years of age; solid line = 1–4 years of age; dotted line = 5–20 years of age; large dashed line = 20–39 years of age. Predictions from model 2 using as input the seasonal pattern of inoculations for Namawala, Tanzania scaled to different numbers of infectious bites per person per year.
stable endemic conditions prevailing in much of Africa, and although severe malaria is commonly diagnosed in African adults, many of these represent misdiagnoses. In a randomized trial, insecticide-impregnated nets did not reduce mortality in Ghanaian adults, suggesting that malaria is not a major cause of death in this age group. However, immunologically naive adult visitors to endemic areas are highly susceptible and major epidemics with high case fatality may occur in areas of initially low transmission to which malaria returns after having been nearly eliminated. A recent observational study in an endemic area of Papua New Guinea suggested that mosquito nets have a substantial effect in reducing all-cause mortality in adults in an area of moderate transmission. These results suggest that malaria may be an important cause of adult mortality in areas of low endemicity.

We expect that severe malaria is infrequent in those adults with a substantial history of exposure to *Plasmodium falciparum* because they control parasite densities and thus rarely develop any acute clinical episodes. Major epidemics should not occur as a rebound if malaria control is abandoned in areas of very high previous exposure because of persistence of immunity against asexual stages of the parasite. In contrast, people who become infected with *P. falciparum* after spending most of their lives without being exposed are highly susceptible to severe episodes. Current efforts to control malaria may lead to sustained reductions in malaria transmission without eliminating the parasite, and this could place many older children and adults in this position. The shape of our function for co-morbidity is critical in our predictions of the public health burden that this implies. If co-morbidity follows the strong increase in infectious disease mortality with age that is observed in adults, then we would predict that in low and unstable transmission settings where most adults never acquire much immunity *P. falciparum* may be an important cause of mortality in elderly people. There is a need to test whether this is the case.

There are many other factors influencing the risk and outcome of severe malaria that we have not been able to consider explicitly. These include effects of host genetic markers and of seasonality. In addition, field estimates of malaria morbidity and mortality rates are unavoidably plagued by effects of attendance bias and diagnostic uncertainties. The empirical basis for estimating the effect of in-patient care on case fatality rates is particularly weak. There are estimates of four relevant models for estimating the effect of in-patient care on case fatality rates, but these do not provide a basis for convincing estimation of the case fatality rate in the community. This adds considerable uncertainty when our model is used to estimate the likely public health impact of improving curative services.

In the context of recent developments in malaria control, there is a need for comparisons of the likely epidemiologic impact of different intervention strategies. Randomized controlled trials provide a solid basis for predictions of the short-term impact but these cannot necessarily be extrapolated beyond the time horizon of the trial, which is rarely more than 1–2 years. Adverse consequences resulting from interference with the acquisition of natural immunity may take much longer than this to become apparent, and the full impact of malaria interventions on human-vector transmission is also only likely to be seen over longer periods. The model we propose represents a first step towards making predictions of longer term effects that can allow for these factors.

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REFERENCES

SEVERE MORBIDITY AND MORTALITY DUE TO P. FALCIPARUM


**APPENDIX 1**

Candidate functions for co-morbidity contributing to type B2 severe malaria, $F(a(i,t))$

We considered three proposals for the age pattern of events that, when co-incident with a malaria attack lead to a severe episode (Figure 11). Infectious disease morbidity in rural African sites decreases strongly over the first few years of life so we require that, at least over this period, $F(a(i,t))$ should be a decreasing function of the age $a(i,t)$ of individual $i$ at time $t$.

A simple proposal is an exponential decay with age

$$F(a(i,t)) = \beta_1 \exp(-\beta_2 a(i,t))$$

where $\beta_1$ and $\beta_2$ are constants.

An alternative is to use an empirical function. We explored a function based on the first principal component of the life tables for demographic surveillance sites in predominantly rural communities in Africa. This curve decreases with age in very young children but increases with age in adults. We expect this to represent mainly the age-pattern of infectious disease mortality (excluding that due to human immunodeficiency virus), but it is not necessarily an appropriate curve to represent the age-pattern of relevant co-morbidity. We scale the risk of an insult that would convert an uncomplicated episode to a severe attack by assuming in our model that

$$\text{logit}(P_{B2}(i,t)) = F(a(i,t)) + \beta_3.$$  (9)

The age patterns were best reproduced using the hyperbolic curve (option ii), and adopt this proposal as part of our model. The estimates for $a_2^p$ and $F_0$ are given in Table 3. We assumed the same function for co-morbidity contributing to indirect deaths (equation 7). For this, we estimate the prevalence and long-term survival.
ence at birth of co-morbidity $Q_{Dw}$, but the same value for $a^2_0$ was used because we fit the indirect model only to infant data that does not give information about the decrease of the function with age (Table 3).

APPENDIX 2

Effect of the health system on the case fatality rate

The evidence base for estimating the effect of in-patient care on case fatality rates is weak, largely because the incidence of severe episodes and case fatality in the community are not known. Formulæ for the community case fatality rates can be derived from the overall incidence of severe malaria, proportion of cases admitted to hospital, and the hospital case fatality rates (Table 4). For simplicity, they ignore age and season dependence and consider very approximate average rates for children.

The inpatient case fatality rate in rural hospitals in sub-Saharan Africa, $Q_h$, is relatively well defined at approximately 0.1 (Figure 6). Pediatric hospital admission rates for the studies reported by Marsh and Snow\(^4,6\) (Figure 2) average approximately 30/1,000 person-years, and overall malaria mortality rates (from VA studies) is approximately 10 per 1,000\(^28\) (Figure 7). Combining $Q_{h=1}$ with the ratio of inpatient admissions to overall malaria deaths, $P_i/P_o = 30/10 =0.3$, gives an estimate of $Q_hP_i/P_o$, the proportion of deaths that occur in hospital, of 0.3. This is similar to the results of a retrospective study of VAs in Tanzania\(^48\) that found that about 33% of children less than five years of age who died of malaria had attended the hospital at some time during their terminal illness, though the proportion who died there was lower.

In rural sub-Saharan Africa, since many hospitals are difficult to reach and often provide poor care, attendance is likely to be even less frequent than in the Tanzanian study where public health services have a relatively high ratio to population. However in the research settings that contributed most of the VA and hospital data (many of them the same sites) hospital attendance rates may have been higher. In view of this, we assume that proportion of cases treated is $P_i/P_o = 0.48$, in agreement with the proportion of severe episodes receiving inpatient treatment in the model of Goodman and others.\(^35\) Using the formulæ in Table 4, this gives an estimate of 31% for the case fatality rate in the community, corresponding to this level of treatment (arrows in Figure 12) and 21% for the overall case fatality rate. This implies that the health system prevents approximately 33% of malaria deaths. This compares with an estimate of 44% for the proportion of (all cause) deaths prevented by a good Kenyan district hospital.\(^46\)

We used the same figure of $P_i/P_o = 0.48$ to obtain an estimate of $\varphi_i = 2.09$ for the ratio of odds of community death to inpatient death by fitting our stochastic model to verbal autopsy data adjusted for sensitivity and specificity (see Materials and Methods).

Irrespective of the proportion of episodes resulting in admission, the low values of $\varphi_i$ that we propose at first sight appear to indicate that inpatient treatment has little benefit. The reality is undoubtedly more complex than this simple model. We dichotomized clinical malaria into severe and uncomplicated classes and assumed each class to be homogeneous in prognosis. In practice, there is a continuous range of severity and inpatients are likely to be disproportionately represented in the most severe cases, many of whom arrive at health facilities when it is too late for treatment to be effective. This selection bias leads to an underestimate the benefit of seeking treatment. Treatment may be life-saving even when administered less than optimally or based on imperfect diagnoses. Contact is made with formal health facilities at some time during the terminal illness in many more cases than those who die in hospital.\(^48\) For every case that dies despite making contact with the health services, many more may be saved.

| TABLE 4 |
| Case fatality rates for severe malaria* |
| Die | Survive | Total |
| Health facility | $Q_hP_h$ | $(1 - Q_h)P_h$ | $P_h$ |
| Community | $Q_h\varphi_i(P_i - P_h)$ | $(1 - Q_h)(P_i - P_h)$ | $P_i - P_h$ |
| Total | $1 - Q_h + Q_h\varphi_i$ | $1 - Q_h + Q_h\varphi_i$ | $P_h - P_i$ |

$Q_h$ = hospital case-fatality rate; $P_i$ = incidence of hospital admissions for malaria; $\varphi_i$ = ratio of odds of community death to in-patient death; $P_h$ = overall severe malaria incidence; $P_C$ = overall incidence of malaria mortality; $\dagger$ indicates quantities for which we have reasonable estimates. Since frequency of hospital admission per capita in rural Africa generally decreases steeply with distance from the hospital, the applicability of estimates to the whole district served is questionable.

**Figure 12.** Effects of community case fatality rate on proportion of severe cases. All values were based on an assumption of an average in-patient case-fatality rate of 0.1. Dotted line = proportion of deaths in inpatients $Q_hP_h/P_C = 0.5$; ratio of inpatient admissions to overall malaria deaths $P_i/P_C = 3.3$. Thick solid line = proportion of deaths in inpatients $Q_hP_i/P_C = 0.1$; ratio of inpatient admissions to overall malaria deaths $P_i/P_C = 0.9$. Thin solid line = proportion of deaths in inpatients $Q_hP_i/P_C = 0.3$; ratio of inpatient admissions to overall malaria deaths $P_i/P_C = 2.1$. Arrows indicate that effective treatment of 48% of severe episodes corresponds to a community case fatality rate of 31% under the assumptions given.