
Acquired immunity and postnatal clinical protection in childhood cerebral malaria

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By analysing data on the age distribution of cerebral malaria among sites of different transmission intensities, we conclude that the most plausible explanation for the epidemiological patterns seen is that (i) cerebral malaria is caused by a distinct set of *Plasmodium falciparum* antigenic types; (ii) these antigenic types or 'CM strains' are very common and induce strong strain-specific immunity; and (iii) the post-natal period of protection against cerebral malaria is much longer than the period of protection against other forms of severe disease. The alternative hypothesis that cerebral malaria may be caused by any 'strain' of *P. falciparum* is compatible with the data only if a single exposure is sufficient to protect against further episodes. This is not consistent with observations on the history of exposure of patients with cerebral malaria. Finally, it is clear that although the delayed peak in incidence of cerebral malaria (with age) can be generated by assuming that subsequent exposures carry a higher risk of disease, such an explanation is not compatible with the observation that severe disease rates are low among infants and young children in areas of high transmissibility.

Keywords: cerebral malaria; clinical immunity; postnatal protection; *Plasmodium falciparum*; strain-specific immunity

1. INTRODUCTION

In recent years, there has been a shift in focus in malaria epidemiology towards the study of the clinical consequences of *Plasmodium falciparum* infection rather than the dynamics of infection risk *per se* (Marsh 1992; Marsh & Snow 1997). Under conditions of stable endemic transmission, mild, self-limiting morbidity is a normal outcome of infection, whereas severe, life-threatening disease is a rare event. The precise definition of life-threatening morbidity among African children has only recently been adequately defined (Marsh *et al.* 1995). Severe morbidity, with a high risk of a fatal outcome even under optimal treatment, comprises a series of overlapping syndromes with different pathological mechanisms. One discrete syndrome, known as cerebral malaria (CM), involves several pathologies (metabolic disturbances and/or brain-specific parasite adhesion causing obstruction of vasculature) that impair consciousness, resulting in coma (Marsh *et al.* 1995). Under the conditions of stable transmission common to sub-Saharan Africa, the risk of CM has been shown to peak at a considerably later age compared with other severe forms of morbidity (Greenwood *et al.* 1991; Snow *et al.* 1997). The simplest explanation for the disjunction in age profiles is that the dynamics of CM and other clinical manifestations are fundamentally different, as may be the case if (i) CM is caused by a distinct strain or set of strains to which immunity develops independently from other malarial strains (Gupta *et al.* 1994);

(ii) the development of immunity to CM, although strain-transcending, is distinct from the development of immunity to other severe diseases; or (iii) the probability of developing this severe syndrome increases with past exposure, as has been proposed for the Dengue virus (Halstead 1988).

In this paper, we attempt to assess these different hypotheses by using data on age-specific patterns of disease in five different areas of sub-Saharan Africa. Two of these sites were located on the Kenyan coast: Kilifi North (with perennial, low to moderate transmission) and Kilifi South (with perennial high transmission). Two others were located in The Gambia: Sukuta (a community that experiences acutely seasonal low to moderate transmission along the Atlantic coast) and Bakau (a peri-urban area with very low transmission). A fifth site was Siaya, Kenya, on the coast of Lake Victoria, with intense perennial transmission. The data we analysed have been described elsewhere (Snow *et al.* 1997) and show that CM admission rates decline with increasing endemicity from 2.6 per thousand children per annum in Sukuta to 0.1 per thousand children per annum in Siaya.

It has been postulated that the decline in rates of CM and other severe disease with increasing transmission intensity may be explained by a period of innate clinical protection following birth, which allows an individual to acquire immunity without developing severe disease. In this paper, we attempt to characterize the period of post-natal protection against CM in the context of the different hypotheses described above.

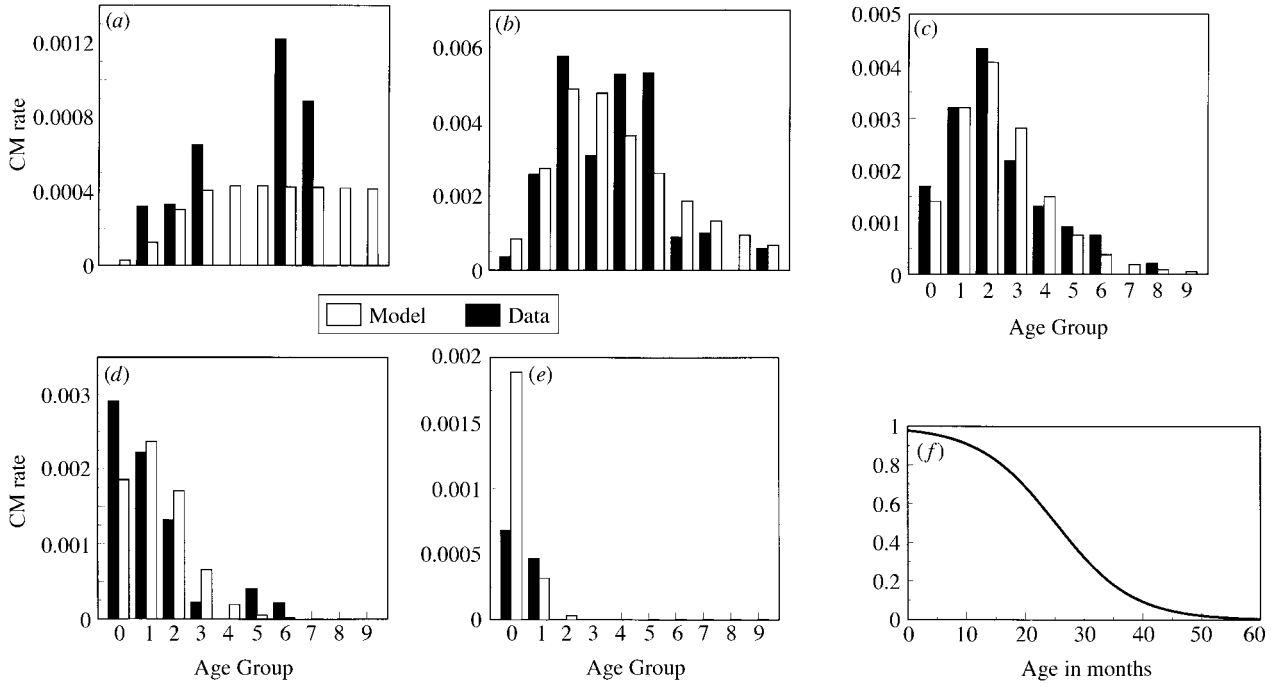


Figure 1. The output of a model that assumes that first infection induces lifelong strain-specific protection. Model output (open bars) is compared with data (closed bars) on CM rates in Bakau (a), Sukuta (b), Kilifi North (c), Kilifi South (d) and Siaya (e). The number associated with each age category indicates the upper bound of that age band. The corresponding maximum-likelihood estimate of the decay of postnatal protection with age is also shown (f).

Table 1. Maximum-likelihood parameter estimates for the force of infection at each of the five sites, β , ρ and π

(95% likelihood ratio confidence intervals were obtained for all eight fitted parameters simultaneously.)

site-specific force of infection (per person per month)				
Bakau	Sukuta	Kilifi North	Kilifi South	Siaya
0.0008 (0.0001, 0.0032)	0.0284 (0.0087, 0.0749)	0.0584 (0.0337, 0.0984)	0.1060 (0.0699, 0.1574)	0.2833 (0.1345, 0.7057)
model goodness-of-fit		β	ρ	π
$\chi^2 = 55.66$ (d.f. = 42); $p = 0.091$		0.0211 (0.0049, 0.0707)	0.1526 (0.0794, 0.3400)	0.0497 (0.0242, 0.6514)

2. STRAIN-SPECIFIC IMMUNITY TO CM

It has been postulated that *P. falciparum* may be structured by host immune responses into a set of discrete strains (Gupta *et al.* 1996) and that certain of these may be specifically associated with CM (in that infection with these strains may precipitate the syndrome, albeit usually with a low probability). This hypothesis may be explored through the abstraction of a single strain system with force of infection λ . The proportion exposed to such a strain at any age is given by the equation

$$\frac{dx}{da} = -\lambda x,$$

which has the solution $x(a) = 1 - e^{-\lambda a}$.

We assume that the age-specific disease risk function is logistic in form such that:

$$\theta(a) = \frac{\beta}{1 + (\beta - 1)e^{-\rho a}}.$$

The age-specific model log likelihood, $l(a)$, for each age a was obtained from the binomial likelihood

$$l(a) = x(a) \ln \left[\pi \sum_{a_i} (1 - e^{-\lambda a_i}) \theta(a_i) \right] + (n(a) - x(a)) \ln \left[1 - \pi \sum_{a_i} (1 - e^{-\lambda a_i}) \theta(a_i) \right],$$

where $n(a)$ is the number of children at age a in the study and $x(a)$ is the number of those affected by CM. The full model log likelihood is the sum of the age-specific model log likelihoods. Parameter estimates (table 1) were obtained for the site-specific forces of infection, the disease risk parameters and the probability of CM disease upon infection, π , by maximizing the full model log likelihood.

The goodness-of-fit was judged by using a χ^2 -test comparing the maximized full model log likelihood with the sum of the age-specific saturated log likelihoods

$$l_{\text{sat}}(a) = x(a) \ln \left[\frac{x(a)}{n(a)} \right] + (n(a) - x(a)) \ln \left[\frac{n(a) - x(a)}{n(a)} \right].$$

Figure 1 presents the maximum likelihood estimated age-specific CM rates as well as the observed age-specific CM rates in all five sites, under the assumption that exposure (i.e. first infection) induces lifelong strain-specific immunity against further CM disease episodes involving the same strain. The figure illustrates that high values of force of infection coupled with a low probability

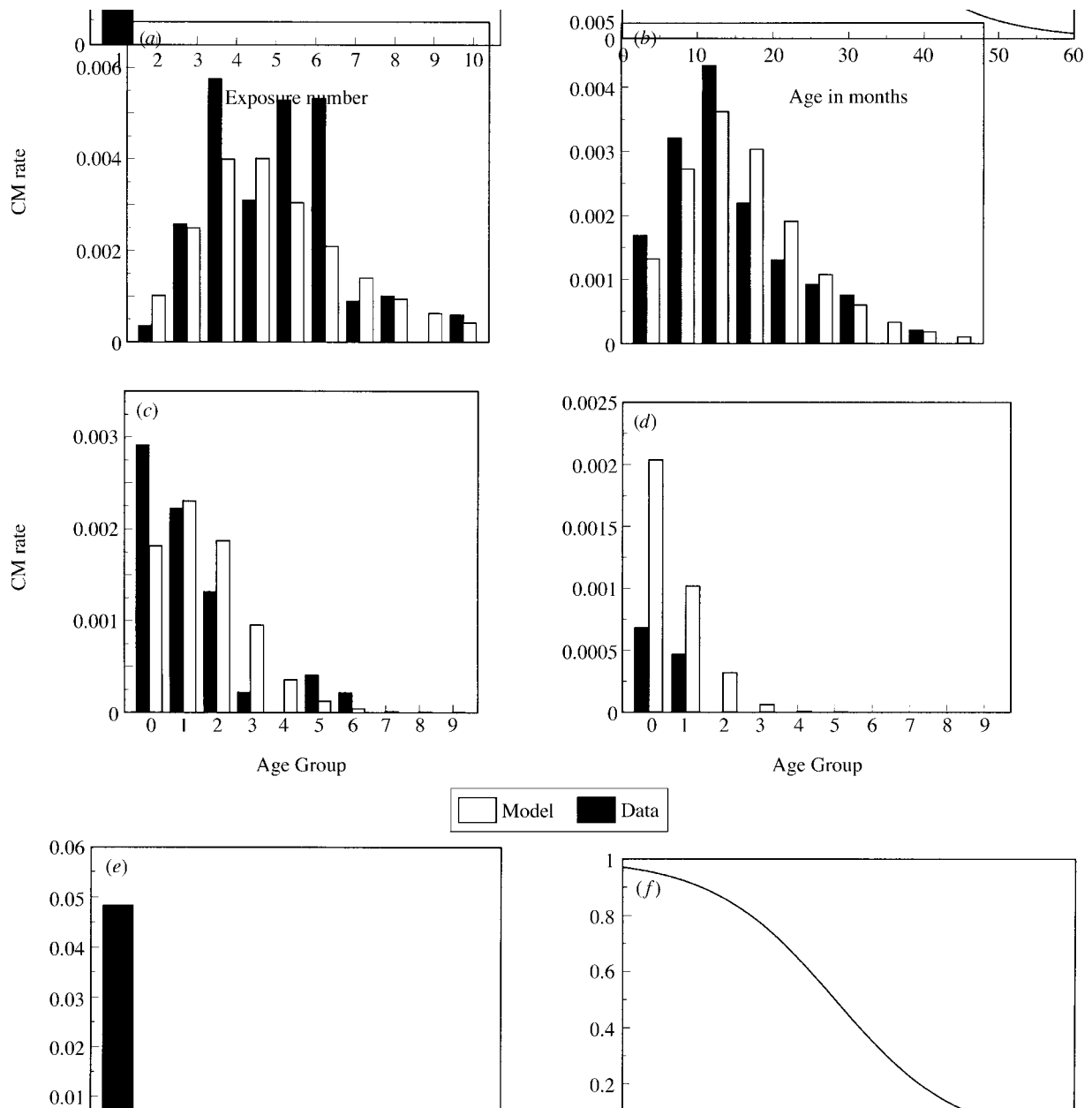


Figure 2. The output of a model that assumes that CM may be caused by any *P. falciparum* strain. Model output (in white) is compared with data (in black) on CM rates in Sukuta (a), Kilifi North (b), Kilifi South (c) and Siaya (d). The number associated with each age category indicates the upper bound of that age band. Also shown are (e) the corresponding maximum-likelihood estimates of the change in disease risk with exposure (due to acquired immunity) and (f) the decay of postnatal protection with age.

of disease upon infection and a long period of postnatal protection against CM symptoms are compatible with the observed age distribution of CM in the five sites. These values of the force of infection are similar to the estimates obtained through infant conversion rates (i.e. the rate of increase with age in proportion exposed to the parasite) for *P. falciparum* in these areas (Snow *et al.* 1997). This result suggests that a large proportion of circulating *P. falciparum* strains is capable of causing CM. The relatively high forces of infection are necessary to cause the observed decline in CM in older children. As indicated in figure 1, under such high values of force of

infection, the period of postnatal protection must be very long to generate the late peak in CM cases.

3. STRAIN-TRANSCENDING IMMUNITY TO CM

We then tested the alternative hypothesis that CM is a rare outcome of infection with any *P. falciparum* parasite strain by using an exposure-dependent model, essentially charting the progress of individuals from an unexposed state to a state of having been exposed once, through several states where *i* indicates the number of exposures to the parasite (i.e. number of infections). The following set

of equations describes the age profile of exposure in a stable endemic state

$$\frac{dx_i}{da} = \lambda(x_{i-1} - x_i),$$

where x_i refers to the proportion of individuals of age a who have been exposed i times to *P. falciparum*, such that the proportion unexposed, $x(0) = 1 - \sum x_i$. The force of infection, λ , determines the rate of exposure. The proportion exposed i times or more within a given age class, y_i , is given by

$$\frac{dy_i}{da} = \lambda x_{i-1}.$$

The risk of developing disease upon n th exposure at age a is denoted by $\theta(n, a)$. The proportion developing disease within a given age class ($a_1 - a_2$) is thus $\sum [y_i(a_2) - y_i(a_1)]\theta(i, a)$. We assume that the disease risk function may be broken down into two components: an age-specific risk, as described above, and an exposure-dependent risk $\theta(i) = \alpha e^{-\gamma i}$, such that $\theta(i, a) = \theta(a)\theta(i)$. This allows us to independently estimate the effects of age dependence and exposure dependence.

Estimates of the force of infection of *P. falciparum* were available for all the sites, with the exception of Bakau, from previous analysis (Snow *et al.* 1998) of the rise in proportions seropositive among infants (infant conversion rates, or ICR). Disease risk parameters were estimated by maximum-likelihood methods using these independent estimates of the forces of infection: 0.41, 0.6, 1.12 and 2.11 infections per person per year in Sukuta, Kilifi North, Kilifi South and Siaya, respectively (for more details see Snow *et al.* 1998). Disease risk may be disaggregated into its exposure and age-specific components as shown in figure 2. The model output corresponding to these disease risk functions is contrasted in figure 2 with data on the incidence of CM for each of the four sites. These results suggest that the age distribution of CM can be explained by assuming that immunity to CM develops upon a single exposure to the parasite, and that the period of postnatal protection against CM extends well into the third year of life.

4. STRAIN-TRANSCENDING IMMUNITY AND INVERSE EXPOSURE DEPENDENCE IN DISEASE RISK

Finally, we examined the hypothesis that CM is a complication following previous exposure to *P. falciparum*. Figure 3 shows the predicted age distributions of CM in the Sukuta, and Kilifi North and South (using the same independent estimates of force of infection as in the previous section), under the assumptions that (i) CM is more likely to occur upon second exposure and (ii) CM is more likely to occur upon third exposure. It is clear that the qualitative patterns generated by these assumptions do not conform to the observed distributions of CM. The main difference is that the earlier peak in areas of high endemicity would be accompanied by very high rates in these young age groups; this is patently not the case. Thus, some degree of postnatal protection is essential to explain the increase in rates of CM with decreasing endemicity.

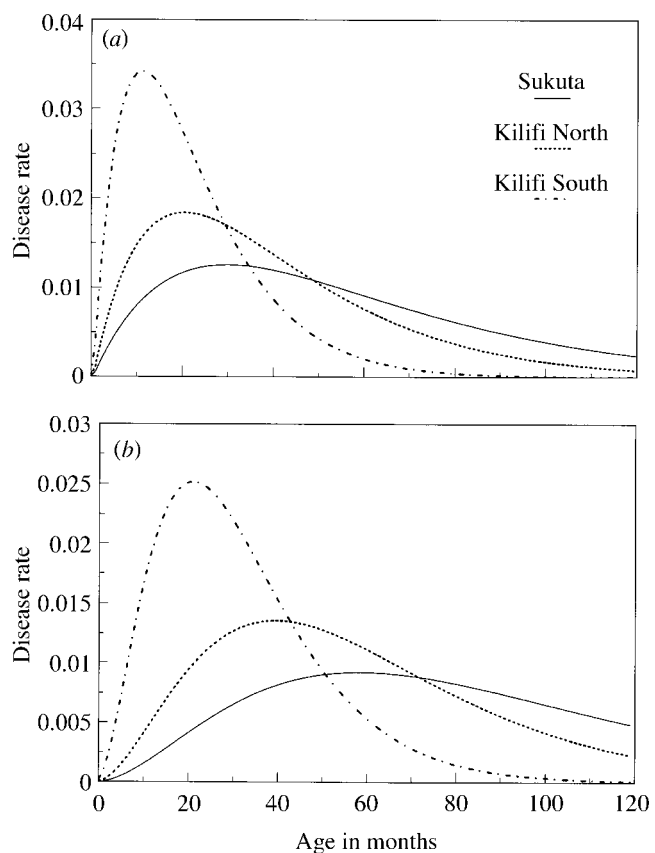


Figure 3. The predicted age distributions of CM in the three areas under the assumption that (a) CM is more likely to occur upon second exposure and (b) CM is more likely to occur upon third exposure.

5. DISCUSSION

Two models of the development of immunity to cerebral malaria appear to be compatible with the age distribution of this severe malaria syndrome across a wide range of malaria endemicities. Immunity to CM may develop in a strain-specific fashion against certain strains or 'antigenic types' that are uniquely capable of causing CM. Relatively high forces of infection are required for CM cases to decline solely as a consequence of the development of strain-specific immunity. This is compatible with recent data from Kilifi, Kenya, showing that isolates from individuals with severe disease have a high likelihood of being recognized (and agglutinated) by antibodies in heterologous plasma (Bull *et al.* 1998). If CM were caused by a very rare strain, we would expect very few individuals to agglutinate isolates taken from CM cases.

The observed age distribution of CM may also be generated by assuming that immunity to CM can be generated by infection with any malaria strain. Analysing the data with respect to the latter scenario, we found that the best fit was obtained when immunity to CM developed upon first infection with any strain. However, this is not compatible with observations on past history of CM cases; lack of previous exposure is not a risk factor for the development of CM (Erunkulu *et al.* 1992). Erunkulu *et al.* (1992) measured titres of a wide range of anti-*P. falciparum* antibodies in plasma samples obtained from children with severe and mild malaria and found no

significant differences. More importantly, plasma samples obtained from children with cerebral malaria recognized (in agglutination assays) as many isolates as did samples obtained from children with mild disease.

Neither of these models for the development of immunity to CM can successfully generate the observed age distribution in the absence of a period of postnatal protection against severe disease. It is widely believed that infants in malarial endemic areas are less prone to severe life-threatening illness (Garnham 1949; Brabin 1990). In the absence of a period of postnatal protection, the incidence of severe disease would decline monotonically with age. Instead, it appears to peak between approximately six months and two years of age, depending on the intensity of transmission. CM, as a distinct syndrome, also exhibits a peak rather than a monotonic decline with age. Our analysis suggests that the period of postnatal protection against CM is very long, extending well into the third year of life. However, recent data on the age distribution of severe disease cases among infants in these areas strongly suggest that the period of postnatal protection against severe disease is very short (Snow *et al.* 1998), falling to normal levels within the first eight months of life. In the case where immunity to CM is not strain-specific, the two observations may only be reconciled by postulating that postnatal protection against CM operates independently of postnatal protection against other forms of severe disease. The precipitating event in the development of CM is the selective accumulation of infected red cells in the brain as a result of their specific adhesion to cerebral endothelium (Berendt *et al.* 1990). Therefore, one possible explanation for an extended period of postnatal protection from this syndrome is that the pattern of adhesion-molecule expression and its regulation by cytokines is sufficiently different in younger children to prevent the development of CM. However, where CM is caused by a distinct subset of strains, a long period of postnatal protection operating against all forms of severe disease can adequately account for the patterns of cerebral and non-cerebral disease together on an annual scale between zero and nine years (Gupta *et al.* 1994), but would fail to explain the changes in disease patterns recently recorded by Snow *et al.* (1998) within the first year of life in these areas. Under a short period of postnatal protection, the average age of CM cases can only be high if the CM strain has a considerably lower force of infection. However, this would mean that CM cases would continue to occur at moderately high rates for a large age range, instead of declining rapidly in the five-to-nine age group. It may be postulated that the decline in case rates in the older children is a consequence of the delayed development of strain-transcending clinical immunity. However, even with a very low force of infection, and strong levels of strain-transcending clinical immunity, the period of postnatal protection would have to extend beyond the first year of life to generate the appropriate peaks in CM incidence. Thus, although there is very limited biological support for the notion that postnatal protection against CM might operate independently of postnatal protection against other forms of severe disease, our results indicate that the period of postnatal protection against CM must be longer than the

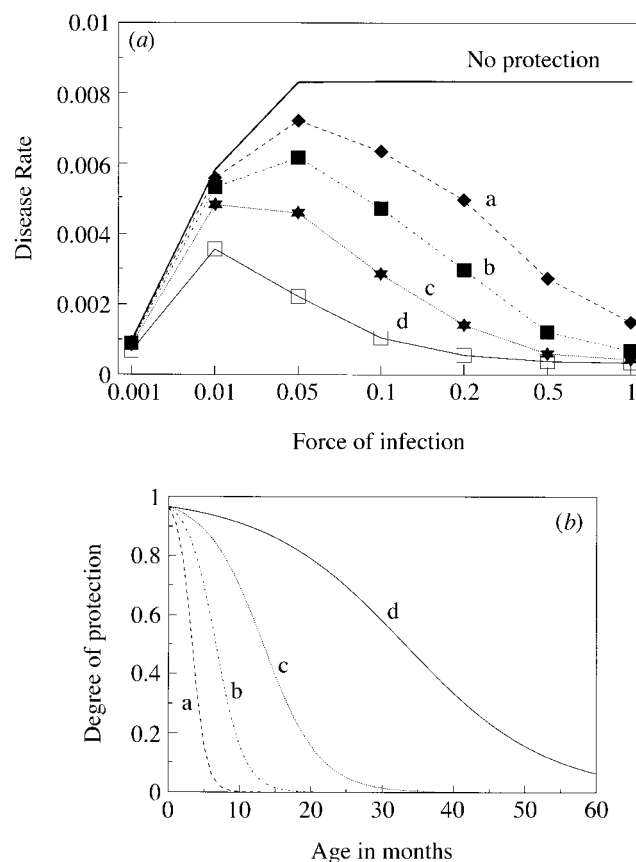


Figure 4. Changes in severe disease rates in children under the age of 10 with force of infection or endemicity for different durations of the period of postnatal protection (indicated by the corresponding letters a-d).

average of six months as suggested by disease patterns in infants.

The precise duration of the period of postnatal protection is critical to the outcome of intervention. Figure 4 shows how severe disease rates in children under the age of ten years change with force of infection or endemicity for different durations of the period of postnatal protection. In the absence of postnatal protection, the rates simply rise and plateau with increasing endemicity. With the introduction of a period of postnatal protection, the disease rates tend to peak at intermediate values, because the cases in the highly endemic areas are reduced to a proportionately greater extent. As the period of postnatal protection increases, the peak shifts in the direction of lower endemicity. Thus if the period of postnatal protection is long, interventions that reduce force of infection are likely to increase disease rates over a larger range of endemicity, but the magnitude of the increase will be small. By contrast, if the period of postnatal protection is short, reducing the force of infection will increase disease rates quite dramatically, but over a shorter range of endemicities. Finally, if different periods of postnatal protection are associated with different syndromes, the incidence of one syndrome may rise while the other falls. Information on the precise duration of protection against each syndrome is therefore essential for the rational design of intervention strategies where the goal is to reduce the total burden of malarial disease.

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