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THE EFFECT OF MALARIA TRANSMISSION INTENSITY ON NEONATAL MORTALITY IN ENDEMIC AREAS

AMANDA ROSS AND THOMAS SMITH*
Swiss Tropical Institute, Basel, Switzerland

Abstract. Estimates of the impact of *Plasmodium falciparum* infections during pregnancy on neonatal mortality have not taken into account how this varies with the level of malaria endemicity and thus do not indicate the possible effects of malaria control strategies that reduce transmission. We now review the relevant literature, and propose a mathematical model for the association between *P. falciparum* transmission and neonatal death. The excess risk of neonatal mortality in malaria-endemic areas appears to be insensitive to the intensity of *P. falciparum* transmission over a wide range of endemicity. Moderate reductions in the overall level of malaria transmission in endemic areas are therefore unlikely to significantly reduce neonatal mortality. The magnitude of the excess risk is very uncertain because existing estimates are heavily dependent on the questionable assumption that the effects are mediated by birth weight. Accurate prediction of the impact of malaria control measures targeted at pregnant women requires direct estimates of malaria-attributable neonatal mortality rates.

INTRODUCTION

In malaria-endemic areas, infants are at high risk of mortality due to *Plasmodium falciparum*, and there is a strong association between all-cause infant mortality and malaria transmission intensity.[1] Infections received in early infancy are unlikely to result in death;[2] however, maternal infections during the first, and to a lesser extent later, pregnancies increase the risk of mortality in the newborn.[3–5]

The indirect mortality due to maternal infection could affect estimates of the impact of a malaria intervention. It may not, in the short-term, be amenable to interventions targeted at infants. Nevertheless, effective malaria control may reduce transmission in the community and therefore might be expected to reduce the risk of such mortality. As one component of a project to develop a comprehensive simulation of the likely impact of potential malaria vaccines delivered to infants via the expanded program on immunization,[6] we develop a model for the relationship between malaria transmission and indirect mortality in the neonatal period (birth to 28 days). Most deaths due to post-natal malaria infection occur after the first month of life and a model for these is described in an accompanying paper.[7]

The magnitude of the impact of maternal malaria infection on neonatal mortality is unclear, as is the mechanism by which it occurs.[5,8] There is little data with which to make direct estimates due in part to the enormous sample size requirements. In the absence of such data, previous studies have used estimates of the effect of maternal malaria on birth weight, and combined these with independent measures of the association between low birth weight and mortality. The resulting estimates apply either to all endemic areas in Africa taken together or to a single site (Table 1).

Previous estimates of the impact of *P. falciparum* malaria on neonatal mortality have not considered how it varies with the level of transmission. Forecasting the effects of malaria control in endemic areas needs estimates not only of the average contribution of malaria to neonatal mortality, but also of the quantitative relationship between transmission intensity and neonatal mortality. To estimate this relationship, we have now summarized available data from clinical trials on birth weight, from between-site comparisons for sites with either entomologic or prevalence data together with estimates of mortality, and from observational studies and reviews. We have used these summaries to develop a simple model of neonatal mortality due to malaria in pregnancy over a range of transmission intensities.

MATERIALS AND METHODS

Our model relates neonatal mortality resulting from malaria infection during pregnancy to the age-specific prevalence of *P. falciparum* in the general population. This allows it to be integrated into a comprehensive simulation[6] and uses our parasitologic model[9,10] as a foundation. We model neonatal mortality rather than perinatal mortality (28 weeks gestation to 7 days after birth) so that the predictions can be included in disability-adjusted life year calculations.[11] However, we acknowledge that the increased risk of mortality associated with maternal infection is not necessarily confined to the neonatal period.

There is little data with which to directly relate the risk of indirect malaria neonatal mortality to *P. falciparum* prevalence in young adults. Where available we used proxy variables for the exposure or outcome, which led us to consider separately the relationship between malaria infection in primigravidae and neonatal mortality and the relationship between parasite prevalence in young adults in the general population and primigravidae. We focus on primigravidae because they show the most pronounced effects and have the most data available, and we compute the overall impact on the neonatal mortality rate by assuming that 30% of live births are born to primigravidae.

Relationship between malaria infection among primigravidae and neonatal mortality. *Data summaries.* Data summaries were used to provide information on the relationship between malaria infection among the population of primigravidae and the risk of neonatal mortality. We used various sources of information on malaria infection during pregnancy, for both the entomologic inoculation rate (EIR) and *P. falciparum* prevalence. To dissect the observed association between infant mortality and transmission intensity[1] into neonatal and post-neonatal mortality, we carried out a literature

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* Address correspondence to Thomas Smith, Swiss Tropical Institute, Socinstrasse 57, Postfach, 4002 Basel, Switzerland. E-mail: amanda.ross@unibas.ch and Thomas-A.Smith@unibas.ch

TABLE 1

Estimates of neonatal and infant mortality due to malaria in pregnancy derived using birth weight measures*

	Primigravidae		Multigravidae		All gravidities	
Reference	%†	Rate‡	%†	Rate‡	%†	Rate‡
Neonatal mortality						
Greenwood and others[57]§¶	42	–	6	–	–	–
Goodman and others[58]§	24	11	–	–	–	–
Guyatt and Snow 2001[59]#	18	7	–	–	11	4
Infant Mortality						
Greenwood and others[57]§¶	18	14	4	2	–	–
Guyatt and Snow[59]#	10	8	–	–	6	4
Steketee and others[60]**	–	–	–	–	3–8	–
Murphy and Breman[61]#	–	–	–	–	–	3–17

* The perinatal mortality rate for countries with a human development index between 500 and 800 has been estimated;[13] non-endemic countries had a mean perinatal mortality rate of 30/1,000 and endemic countries had a mean perinatal mortality rate of 50.5/1,000.

† Estimated percentage of mortality attributable to malaria in pregnancy.

‡ Estimated deaths per 1,000 live births attributable to malaria in pregnancy.

§ Estimates are based on the changes in the proportion of low birth wieght[57] or in mean birth weight[58] associated with antimalarial drugs during pregnancy in clinical trials.

¶ Estimates apply to The Gambia; all other estimates apply to sub-Saharan Africa.

\# Estimates are based on observational studies of maternal infection and low birth weight.

** 8% is a composite of 18% and 4% from Greenwood and others.[57] 3% is derived from the estimated reduction in low birth weight associated with clearing placental and peripheral parasites, and does not include anemia.

search for sub-Saharan Africa sites with information on both the EIR and neonatal or post-neonatal mortality rates. The mortality rates were not parity specific.

In addition, birth weight has been previously used as a proxy in a number of studies estimating mortality in the newborn (Table 1) using both observational data and data from controlled clinical trials of anti-malarial drugs in pregnancy. We use data from the trials and assume that for a particular trial setting the difference in mean birth weight between the intervention and control groups is an approximate measure of the impact that malaria infection in pregnancy has on birth weight. Although women are not necessarily 100% protected from malaria throughout their pregnancy, the drugs have a large impact on peripheral and placental prevalence.[12] To examine the association between the estimated birth weight difference and EIR, we matched entomologic data to the sites of the trials. We also examined meta-analyses of perinatal mortality rates by maternal peripheral parasite prevalence in malaria-endemic areas,[13] of birth weight by childhood parasite prevalence,[14] and of birth weight by placental prevalence.[15]

Model. From the analyses of neonatal mortality and transmission intensity (see Results) using the data summaries above, we propose that the risk of neonatal mortality attributable to malaria in pregnancy, μ_{PG}, saturates at low transmission levels. Therefore we propose a relationship for primigravidae between the prevalence x_{PG} and the neonatal mortality rate μ_{PG} of the form

$$\mu_{PG} = \mu_{\max}\left[1 - \exp\left(-\frac{x_{PG}}{x^*_{PG}}\right)\right] \tag{1}$$

where $\mu_{\max}$ and x^*_{PG} are constants, and which satisfies the additional constraint that in the absence of malaria $\mu_{PG} = 0$. We use an estimate of the efficacy of antimalarial drugs in pregnancy[16] to assign a value of $\mu_{\max} = 0.011$ (11/1,000 live births among primigravidae). To compute the overall effect on the neonatal mortality rate, we assume that 30% of live births are born to primigravidae and thus our model predicts an overall risk of malaria-attributable neonatal mortality of 0.3 μ_{PG}.

Relationship between the prevalence of *P. falciparum* in the general population and prevalence in primigravidae. We relate the prevalence of *P. falciparum* in primigravidae to the age-specific prevalence in the general population. We use data from a review of 27 cross-sectional studies comparing the peripheral prevalence either at antenatal attendance or at delivery in primigravidae and multigravidae.[5] We approximate the prevalence in multigravidae by that of the general population of the same age. We could find little evidence to support this assumption, but it is not a critical assumption for the model predictions and we believe it to be a closer approximation than using the prevalence in the general population for that in primigravidae directly. We fit a statistical model to estimate the prevalence in primigravidae from that in multigravidae. The predicted prevalence in primigravidae, x_{PG}, is constrained to be zero when x_{MG}, the prevalence in multigravidae, is zero. To allow x_{PG} either to increase or saturate at high values of x_{MG}, we fit a curve of the form

$$x_{PG} = 1 - \frac{1}{1 + \left(\frac{x_{MG}}{x^*_{MG}}\right)} \tag{2}$$

where x^*_{MG} is a critical value of x_{MG}. This model was fitted in WinBUGS version 1.4 (Biostatistics Unit, University of Cambridge, Cambridge, United Kingdom). The proportions of women with placental and peripheral parasitemia at delivery are approximately equal in the same settings,[5] even though in individual women peripheral blood slides are not a good indicator of placental infection.[17,18]

RESULTS

Relationship between malaria infection in primigravidae and neonatal mortality. As reported by Hyder and others,[19] we found few reported neonatal mortality rates from sub-Saharan Africa and we could locate entomologic data for only those given in Table 2. Among these sites, there is no evidence of an association between neonatal mortality and malaria transmission intensity (Figure 1a), yet such an association is evident for both post-neonatal and overall infant mortality (Figure 1b and c). We acknowledge that there are many differences other than malaria transmission intensity between the studies included in the ecologic comparison of mortality rates, and there may be an association between malaria transmission and other diseases, availability of effective treatment, or poverty that may serve to overestimate or underestimate the effect of maternal malaria infection. We conclude that the relationship of transmission intensity with the risk of neonatal mortality is much weaker than that that with post-neonatal mortality, although there are few reported post-neonatal mortality rates from settings with entomologic data.

We found no evidence of an association between the estimated effect of antimalarial drug interventions on birth weight and EIR (Figure 2). The overall pattern observed may be biased by confounders such as drug resistance. Since none of the trial settings had very low transmission intensity, this is not inconsistent with a review of studies where the proportion of low birth weight (<2500g) babies was lower for studies set in areas with an EIR < 1 compared with settings with an EIR ≥ 1.

TABLE 2

All-cause neonatal, post-neonatal, and infant mortality rates from sites with entomologic data*

Study site	Reference for entomology data	Year of entomology data	EIR	Reference for mortality data	Year of mortality data	No. of livebirths	Neonatal mortality rate	Post-neonatal mortality rate	Infant mortality rate
Areas I–V, The Gambia	62	1991	3.7	35	1992	3,063	35.9	43	83
Upper River Division, The Gambia	62	1991	5.3	63	1989–1993	26,894	37.7	42.4	80.2
Farafenni, The Gambia	64	1987	8.9	36	1984–1987	610	52.5	–	–
Niakhar, Senegal	65	1995	11.6	66	1995–1999	5,997	31	48	80
Kilifi, Kenya	67	1997–1998	20	68	1999–2003	2,189	29.7	–	–
Bo, Sierra Leone	69	1990–1991	34.7	70	1990	< 100	–	–	74.0
Mlomp, Senegal	71	1995–1996	30	71	1995	–	–	–	61
Mlomp, Senegal	71	1995–1996	30	72	1985–1989	917	36	–	–
Manhica, Mozambique	Aponte J, unpublished data	–	38	66	1998–1999	1,280	–	–	78.5
Yombo, Tanzania	73	1992	234	73	1992–1994	1,130	25.7	–	131.0
Saradidi, Kenya	74	1986–1987	239	75	1981–1983	1,168	36.8	72.8	109.4
Karangasso,	76	1985	244	77	1986–1988	–	–	–	121
Nyanza-Lac, Burundi	78	1990–1991	312	78	1990–1991	813	–	–	108
Bandafassi, Senegal	71	1995–1996	363	79	1989–1992	1,448	71	–	–
Bandafassi, Senegal	71	1995–1996	363	66	1995–1999	2,122	–	–	124.9
Namawala, Tanzania	80	1990–1991	329	81	1902	1,902	–	–	95.2
Navrongo, Ghana	82	2001–2002	418	66	1994–1999	20,462	–	–	111.9
Muheza, Tanzania	83	1987–1988	639	84	1992–1993	361	11.1	121.9	133

* EIR = entomologic inoculation rate.

However, among settings with EIR ≥ 1 there was no clear association.[14]

We conclude that there is little or no association between neonatal mortality and transmission intensity once the transmission is above a very low level. This lack of an association enables us to infer that there can be little association also between the prevalence in primigravidae and neonatal mortality. The prevalence of *P. falciparum* in young adults is itself insensitive to transmission intensity.[20]

Our conclusion is supported by reviews of related outcomes and prevalence. A review of observational studies that found that there was no obvious linear trend between perinatal mortality (28 weeks gestation to the first 7 days) and maternal peripheral parasite prevalence in endemic areas.[13] The association between the proportion of primigravidae with placental parasitemia and birth weight is weak (Figure 3) after accounting for highly influential points (data from Brabin and others[15]), although this may be confounded by the inclusion of studies from southeast Asia.

These observations contribute only to the shape of our model of the relationship of malaria-attributable neonatal mortality with transmission. Since the malaria-attributable neonatal mortality rate in primigravidae, μ_{PG}, appears to be independent of the transmission intensity across the settings for which we have data, we were not able to use a formal fit to data to obtain estimates of the parameters $\mu_{\max}$ and x^*_{PG} (equation 1). We follow Goodman and others[16] in assigning a value of $\mu_{\max} = 0.011$ (11/1,000 live births among primigravidae). Since saturation seems to occur at lower prevalence than any measured in endemic areas, the data only suggest an approximate idea of the upper limit of the quantity x^*_{PG}. In the absence of more relevant data, we set $x^*_{PG} = 0.25$.

Relationship between the prevalence of *P. falciparum* in the general population and prevalence in primigravid women. We relate the prevalence of infection in primigravidae, x_{PG}, to that in the multigravidae, x_{MG} (Equation 2). We obtained a good fit to relationship between x_{PG} and x_{MG} with a value of $x^*_{MG} = 0.19$ (95% confidence interval = 0.16–0.23), which corresponds to the observation that x_{PG} and x_{MG} are approximately proportional when both are low, but as prevalence increases in multigravidae, it approaches 100% in primigravidae and cannot continue to be proportional (Figure 4).

To compute the overall effect on the neonatal mortality rate, we assume that 30% of live births are born to primigravidae and thus our model predicts an overall risk of malaria-attributable neonatal mortality of 0.3 μ_{PG}. Assuming x_{MG} to be equivalent to the prevalence of patent *P. falciparum* in adults 20–24 years of age in the general population, we can thus combine equations 1 and 2 to obtain predictions of the malaria-attributable neonatal mortality rate as a function of prevalence as shown in Figure 5. Our model predicts little effect of transmission intensity on neonatal mortality.

DISCUSSION

Although *P. falciparum* infections during pregnancy in primigravidae have an important impact on the newborn, there is little or no association between neonatal mortality and malaria transmission intensity in stable transmission areas. This lack of association with transmission intensity is to be expected, if, as is likely, most women in these areas are infected at some stage in their pregnancy, and also that immunity to pregnancy-associated malaria is gained through relatively few infections. Despite problems with the sensitivity of histology,[21] the proportion of placenta with histologic evidence of active or past infection is very high even in endemic areas with relatively low transmission: in primigravidae in Kilifi, Kenya it was 77%[18] and in The Gambia it was 76%.[22] A subset of parasites expressing particular cytoadherence properties are thought to account for much of the pathology of malaria in pregnancy.[23–25] It has been suggested that a single infection with such a phenotype may be sufficient to stimulate an immunologic reaction,[5] although this is not known. This may both explain why the adverse consequences of maternal infection mainly occur in first, and to a lesser

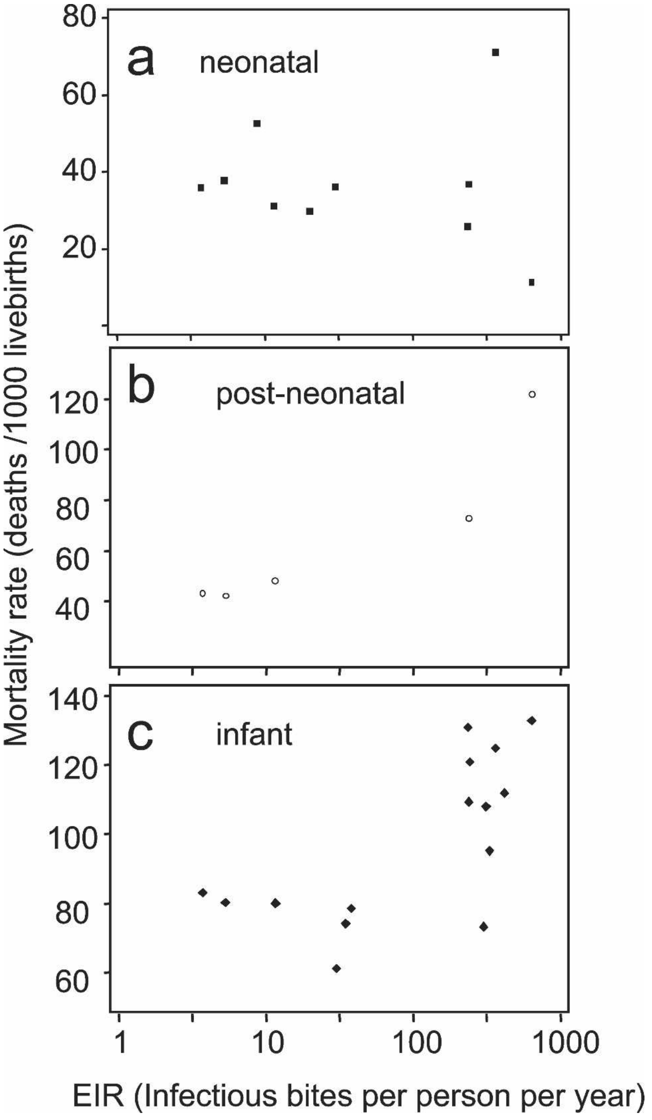

FIGURE 1. Mortality rates by transmission intensity. EIR = entomologic inoculation rate.

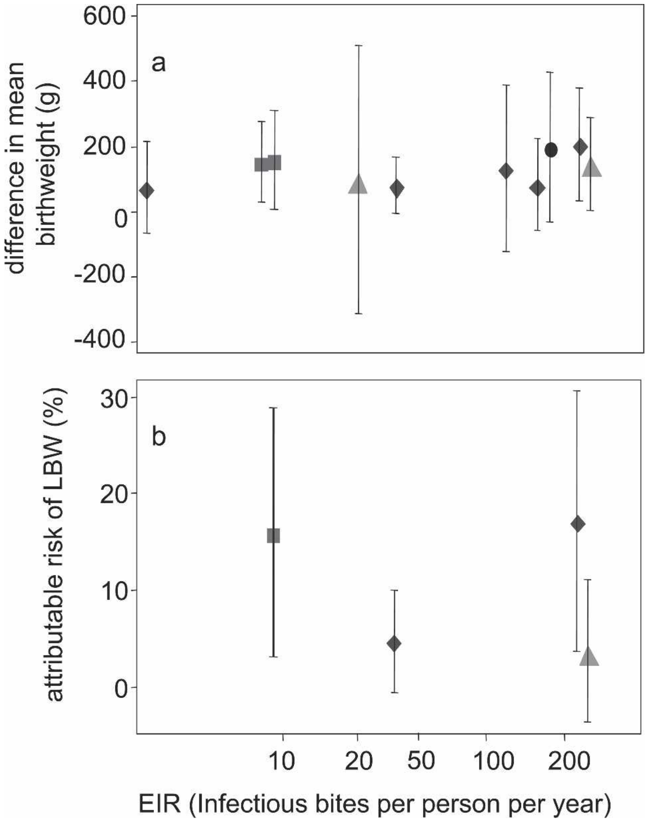

FIGURE 2. Estimated effect of antimalarial drug interventions on birth weight. **a**, Estimated mean change in birth weight due to intervention. **b**, Excess risk of low birth weight (LBW) (% LBW in controls – % LBW in drug group). Data from 10 trials comparing antimalarial drug use to control either placebo or no drug controls[36,44–52] were analyzed. Trials were not included if they compared multiple drugs with no inactive control[53–55] or could not be matched to entomologic data.[56] The estimates refer to primigravidae, or primigravidae and secundigavidae together in the case of one trial. ◆ = chloroquine; ■ = dapsone-pyrimethamine; ▲ = sulfadoxine-pyrimethamine; ● = pyrimethamine. EIR = entomologic inoculation rate. Error bars show 95% confidence intervals.

extent second, pregnancies, and why the intensity of superinfection appears to have little effect.

The model would predict little change in mortality from a decrease in transmission intensity unless it reaches a very low level. Trials of insecticide-treated nets provide some data: while increased birth weight was observed in areas with low transmission (Thailand and The Gambia),[26,27] results from areas with more intense transmission are mixed. No impact was observed in Kilifi, Kenya and Navrongo, Ghana,[18,28] but a reduction in the proportion of low birth weight babies was found in western Kenya.[29] However, the transmission intensity after the introduction of the nets would be more relevant than the baseline transmission intensity.

Since there is considerable uncertainty about the pathophysiology of the effects of *P. falciparum* infection on neonatal mortality, we attempted to avoid assumptions about mechanisms in formulating our predictive model. However, all the available estimates of this effect (Table 1), including the one we use, depend on associations with birth weight and assume that the risk of death in babies of the same birth weight is the same whether their mothers had placental malaria or not, and that the relevant effect on the birth weight distribution can easily be summarized either by the mean or by the proportion of birth weights below a standard cut-off. Both these assumptions have been questioned.[12,30] If the full distribution of birth weights is available, this should be analyzed as a mixture of the predominant normal distribution and a residual distribution in the form of a tail at low birth weights.[31] It is the relative size of this residual distribution that is the feature associated with mortality.[30] Comparison of three birth weight distributions from areas of high, medium, and low transmission settings suggest that the overall mean and size of the residual tail may move in tandem.[32] However, this is indirect support for models that assume the maternal effect to be adequately captured by simple summaries of the effect on birth weight when there is not even convincing evidence of that birth weight is on the causal pathway between maternal infection and neonatal death.

An additional highly uncertain element of our model is the value of 0.25 assigned to the parameter x^*_{PG}. x^*_{PG} determines the prevalence at which neonatal mortality saturates, and data from endemic areas provide only an approximate idea of

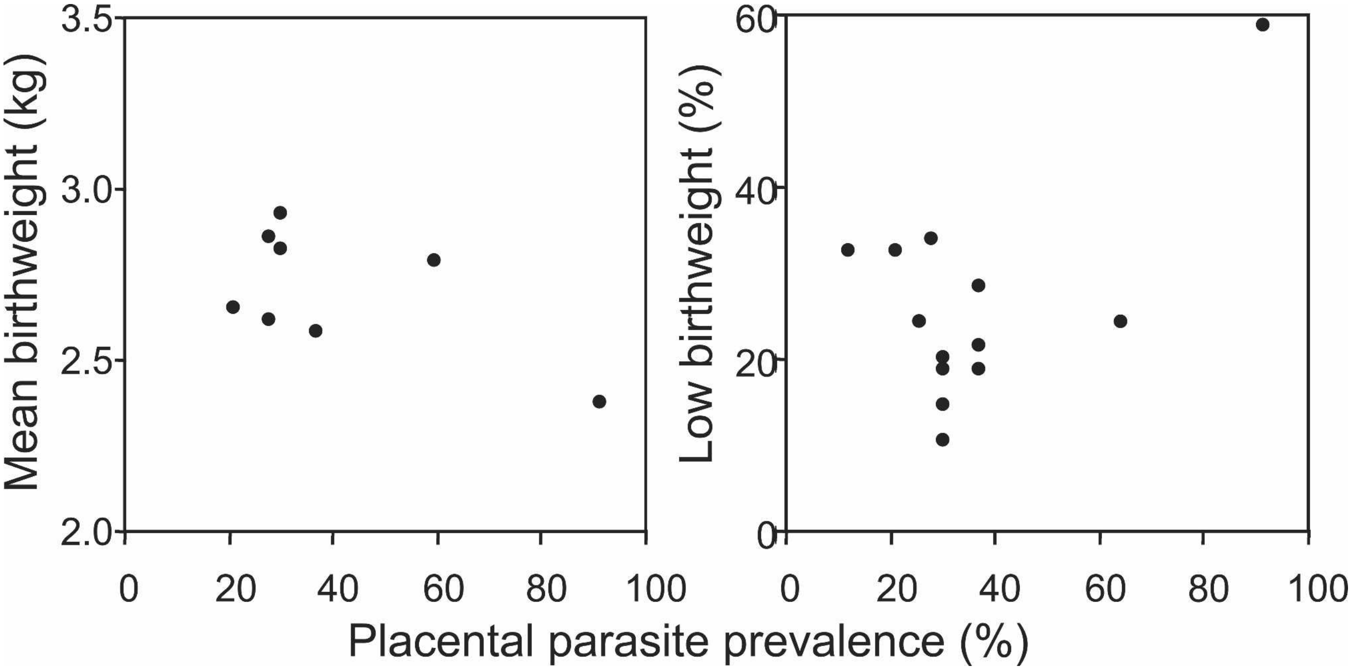

FIGURE 3. Placental prevalence and birth weight.
Data for primigravidae from Brabin and others.[15]

the upper limit of this quantity because saturation seems to occur at lower prevalence than any measured in endemic areas. This is one of several reasons why our model is in any case unlikely to be appropriate in areas of unstable transmission such as southeast Asia. In such areas, the impact of malaria in pregnancy on the mother is likely to be more severe, and thus the risk associated with individual infections may be higher. In stable endemic areas, acute effects on the mother are less frequent[21,33] presumably because of immunity that has already been acquired prior to pregnancy.

A comprehensive model for the effects of malaria in pregnancy would also need to address the question of the timing and intensity of the infections. Babies born during the rainy season were lighter than those born during the low transmission periods in The Gambia and Mali.[34–36] Maternal malaria infection is likely to contribute to this, but the implications for neonatal mortality are unclear. We also do not consider the effects of infection with human immunodeficiency virus (HIV). The prevalence of HIV in women varies between countries in sub-Saharan Africa,[37] and HIV infection is associated both with an increased prevalence of malaria parasitemia during pregnancy for all gravities[38–40] and with increased rates of adverse perinatal outcomes.[41]

We are not in a position to provide good estimates of the potential impact of interventions (such as intermittent preventive treatment or vaccination) targeted at pregnant women. This is for two reasons. First, we consider only the impact on the infant and not the health effects for the mother,

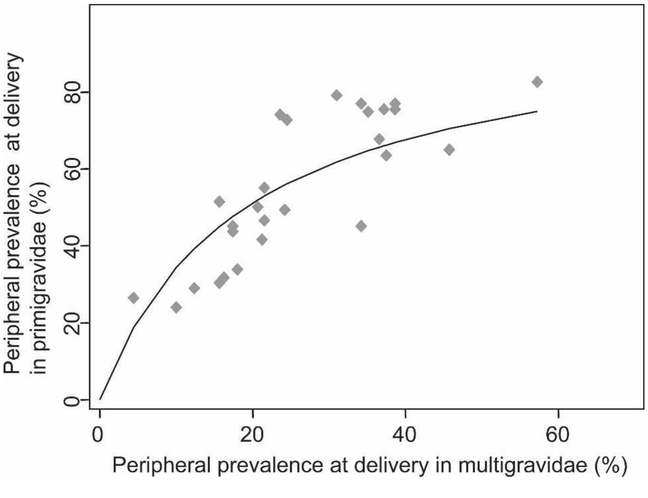

FIGURE 4. Relationship between peripheral prevalence at delivery in primigravidae and multigravidae. The points represent cross-sectional surveys collated by Brabin and Rogerson.[5] The fitted line corresponds to the model of equation 2.

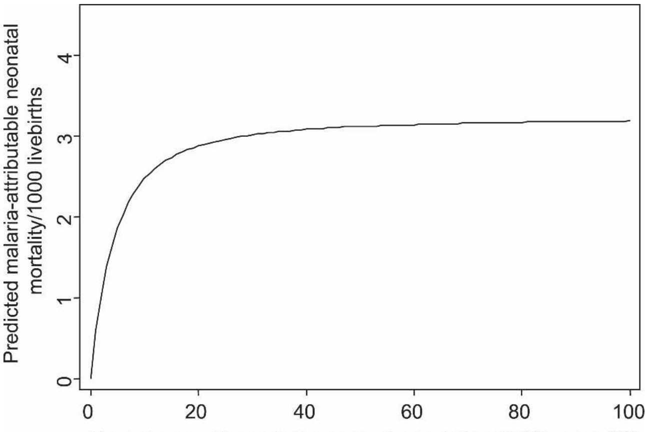

FIGURE 5. Predicted malaria attributable neonatal mortality rate as a function of prevalence in the general population aged 20–24 years.

which may be substantial[42] (although the prevalence of anemia in pregnancy is considered by our model of anemia[43]). Second and most important, there is an unacceptable level of uncertainty associated with estimates of malaria in pregnancy associated neonatal mortality that depend on the assumed relationship with birth weight. The burden of neonatal mortality caused by *P. falciparum* will remain highly uncertain as long as we are dependent on indirect assessments.

Despite these uncertainties, we propose that our model is adequate for predicting the effects of preventative interventions targeted at children or the general population on the risk of neonatal mortality associated with maternal infection, and we propose to incorporate equations 1 and 2 into our general model of the epidemiology of *P. falciparum*.[6] The main predictions relating to neonatal mortality are already evident and are clearly insensitive to the uncertainties documented above. We predict that interventions targeted at infants such as vaccination would have to reduce the infectious reservoir to very low levels to affect indirect neonatal mortality.

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Authors' address: Amanda Ross and Thomas Smith, Swiss Tropical Institute, Socinstrasse 57, Postfach, 4002 Basel, Switzerland, Telephone: 41-61-284-8273, Fax: 41-61-284-8105, E-mails: amanda.ross@unibas.ch and Thomas-A.Smith@unibas.ch.

Reprint requests: Thomas Smith, Swiss Tropical Institute, Socinstrasse 57, Postfach, 4002 Basel, Switzerland.

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