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

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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. Infections received in early infancy are unlikely to result in death; however, maternal infections during the first, and to a lesser extent later, pregnancies increase the risk of mortality in the newborn. 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, 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.

The magnitude of the impact of maternal malaria infection on neonatal mortality is unclear, as is the mechanism by which it occurs. There is little data with which to make direct estimates due 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 and uses our parasitologic model 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. 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 into neonatal and post-neonatal mortality, we carried out a literature

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MALARIA TRANSMISSION INTENSITY AND NEONATAL MORTALITY

Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Primigravidae</th>
<th>Multigravidae</th>
<th>All gravidities</th>
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<tbody>
<tr>
<td>Neatrnal mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greenwood and others (1998)</td>
<td>42</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Goodman and others (2000)</td>
<td>24</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Guyatt and Snow (2001)</td>
<td>18</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Infant Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greenwood and others (1998)</td>
<td>18</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Guyatt and Snow (2000)</td>
<td>10</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Steketee and others (2000)</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Murphy and Breman (2011)</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>

Notes:

1. The total mortality rate for countries with a human development index between 500 and 1000 has been estimated; non-endemic countries had a mean total mortality rate of 200,000 and endemic countries had a mean total mortality rate of 50,000.
2. Estimates based on observational studies of maternal infection and low birth weight.
3. Estimated percentage of mortality attributable to malaria in pregnancy.
4. Estimated number of deaths per 1,000 live births attributable to malaria in pregnancy.
5. Estimated percentage of mortality attributable to malaria in pregnancy.
6. The estimated percentage of mortality attributable to malaria in pregnancy.
7. All estimates are based on the changes in the proportion of low birth weight.
8. The estimated percentage of mortality attributable to malaria in pregnancy.
9. 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 parasitemia prevalence in malaria-endemic areas, and of birth weight by childhood parasite prevalence, and of birth weight by placental prevalence.
10. 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, \( \mu_{PG} \), saturates at low transmission levels. Therefore we propose a relationship for primigravidas between the prevalence \( x_{PG} \) and the neonatal morality rate \( \mu_{PG} \) of the form

\[
\mu_{PG} = \mu_{\text{max}} \left( 1 - \exp \left( -\frac{x_{PG}}{x_{PG}} \right) \right)
\]

where \( \mu_{\text{max}} \) 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 to assign a value of \( \mu_{\text{max}} = 0.011 \) (11/1,000 live births among primigravidas). To compute the overall effect on the neonatal mortality rate, we assume that 30% of live births are born to primigravidas and thus our model predicts an overall risk of malaria-attributable neonatal mortality of 0.3 \( \mu_{\text{PG}} \).

Relationship between the prevalence of \( P. falciparum \) in the general population and prevalence in primigravidas. We relate the prevalence of \( P. falciparum \) in primigravidas 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 primigravidas and multigravidas. We approximate the prevalence in primigravidas 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 primigravidas directly. We fit a statistical model to estimate the prevalence in primigravidas from that in multigravidas. The predicted prevalence in primigravidas, \( x_{PG} \), is constrained to be zero when \( x_{MG} \), the prevalence in multigravidas, is zero. To allow \( x_{PG} \) either to increase or saturate at high values of \( x_{MG} \), we fit a curve of the form

\[
x_{PG} = \frac{1 - \frac{1}{1 + \frac{x_{MG}}{x_{MG}}}}{1 - \frac{x_{MG}}{x_{MG}}}
\]

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, even though in individual women peripheral blood slides are not a good indicator of placental infection.

RESULTS

Relationship between malaria infection in primigravidas and neonatal mortality. As reported by Hyde and others, 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.
However, among settings with $\text{EIR} \geq 1$ 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 \textit{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, $\mu_{\text{PG}}$, 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 $\mu_{\text{max}}$ and $x_{\text{PG}}$ (equation 1). We follow Goodman and others$^{16}$ in assigning a value of $\mu_{\text{max}} = 0.011$ (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 $x_{\text{PG}}$. In the absence of more relevant data, we set $x_{\text{PG}} = 0.25$.

\textbf{Relationship between the prevalence of \textit{P. falciparum} in the general population and prevalence in primigravidae women.} We relate the prevalence of infection in primigravidae, $x_{\text{PG}}$, to that in the multigravidae, $x_{\text{MG}}$ (Equation 2). We obtained a good fit to relationship between $x_{\text{PG}}$ and $x_{\text{MG}}$ with a value of $x_{\text{MG}} = 0.19$ (95% confidence interval = 0.16–0.23), which corresponds to the observation that $x_{\text{PG}}$ and $x_{\text{MG}}$ 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 $\mu_{\text{PG}}$. Assuming $x_{\text{MG}}$ to be equivalent to the prevalence of patent \textit{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.

\textbf{DISCUSSION}

Although \textit{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,$^{7}$ although this is not known. This may both explain why the adverse consequences of maternal infection mainly occur in first, and to a lesser

\begin{table}
\centering
\caption{All-cause neonatal, post-neonatal, and infant mortality rates from sites with entomologic data$^{*}$}
\begin{tabular}{cccccccc}
\hline
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 \\
\hline
Bo, Sierra Leone & 69 & 1990–1991 & 34.7 & 70 & 1990 & < 100 & – & – & 74.0 \\
\hline
\end{tabular}

$^{*}$ EIR = entomologic inoculation rate.
\end{table}
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),\textsuperscript{26,27} results from areas with more intense transmission are mixed. No impact was observed in Kilifi, Kenya and Navrongo, Ghana,\textsuperscript{18,28} but a reduction in the proportion of low birth weight babies was found in western Kenya.\textsuperscript{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 \textit{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.\textsuperscript{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.\textsuperscript{31} It is the relative size of this residual distribution that is the feature associated with mortality.\textsuperscript{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.\textsuperscript{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

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.pdf}
\caption{Mortality rates by transmission intensity. EIR = entomologic inoculation rate.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.pdf}
\caption{Estimated effect of antimalarial drug interventions on birth weight. \textbf{a}, Estimated mean change in birth weight due to intervention. \textbf{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\textsuperscript{36,44–52} were analyzed. Trials were not included if they compared multiple drugs with no inactive control\textsuperscript{36,44–52} or could not be matched to entomologic data.\textsuperscript{36} The estimates refer to primigravidae, or primigravidae and secundigravidae together in the case of one trial. \textbullet = chloroquine; \textblacksquare = dapsone-pyrimethamine; \texttriangle = sulfadoxine-pyrimethamine; \textbullet = pyrimethamine. EIR = entomologic inoculation rate. Error bars show 95% confidence intervals.}
\end{figure}
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, 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. 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, and HIV infection is associated both with an increased prevalence of malaria parasitemia during pregnancy for all gravities and with increased rates of adverse perinatal outcomes.

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,
which may be substantial (although the prevalence of anemia in pregnancy is considered by our model of anemia).

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 \textit{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 \textit{P. falciparum}. 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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