American Journal of Epidemiology

Vol. 154, No. 5
Printed in U.S.A.

Effects of Malaria during Pregnancy on Infant Mortality in an Area of Low Malaria Transmission

Christine Luxemburger,[1–3] Rose McGready,[1–3] Am Kham,[1] Linda Morison,[4] Thein Cho,[1] Tan Chongsuphajaisiddhi,[2] Nicholas J. White,[1–3] and François Nosten[1–3]

Malaria during pregnancy reduces birth weight, and low birth weight is a major determinant of infant mortality. The authors estimated the impact of malaria during pregnancy on infant mortality in a Karen population living in Thailand. Between 1993 and 1996, a cohort of 1,495 mothers and their infants was followed weekly from admission of the mother to antenatal clinics until the first birthday of the infant. Both falciparum malaria and vivax malaria during pregnancy were associated with low birth weight but did not shorten gestation. Febrile illness in the week before delivery was associated with premature birth. Preterm and full-term low birth weight and fever in the week before delivery were associated with neonatal mortality. Maternal fevers close to term were also associated with the deaths of infants aged between 1 and 3 months, whereas no risk factors could be identified for deaths that occurred later in infancy. Thus, malaria during pregnancy increased neonatal mortality by lowering birth weight, whereas fever in the week before birth had a further independent effect in addition to inducing premature birth. The prevention of malaria in pregnancy and, thus, of malaria-attributable low birth weight should increase the survival of young babies. *Am J Epidemiol* 2001;154:459–65.

infant, low birth weight; infant mortality; malaria; pregnancy

Falciparum malaria during pregnancy has long been recognized as an important determinant of low birth weight (1, 2). The reduction in birth weight is usually more marked in primigravidae (1) but can extend to second and third gravidae in areas of low malaria transmission (3). A recent study conducted in Thailand has shown that *Plasmodium vivax* malaria during pregnancy also reduces birth weight (4). In most studies designed to investigate the relation between malaria during pregnancy and birth weight, potential confounding factors, such as socioeconomic status, maternal nutrition, and smoking, have not been taken into account. However, a number of randomized controlled trials of preventive antimalarial measures during pregnancy have confirmed this causal effect by showing that preventing malaria increases birth weight (5–7).

The major adverse effect of malaria in pregnancy on the mother is anemia. In malarious areas, malaria and anemia are likely to act together to reduce birth weight. Their independent effects are difficult to distinguish. In a study conducted in a highly malarious area of Papua New Guinea, severe maternal anemia was associated with low birth weight in primigravidae, whereas there was no obvious consistent association between parasite positivity and low birth weight (8). However, a more recent study, conducted in the same country, which attempted to quantitate the separate effects of anemia- and malaria-attributable low birth weight, concluded that, in malarious areas, malaria was a more important risk factor for low birth weight than was anemia (9).

Until recently, the distinction between full-term and preterm low birth weight was difficult in the tropics. As a consequence, the relative contributions of malaria-associated intrauterine growth retardation and preterm delivery were not clearly established. Since the introduction of accurate methods for the estimation of gestational age, it has been suggested that the relative importance of these causes of low birth weight may depend on the level of malaria transmission and the timing of malaria infection during pregnancy. Premature birth results commonly from symptomatic malaria and is usual in severe malaria. It is therefore common in low-transmission areas, where acquired premunition is poor, and in epidemics (10–14). However, in prospective studies conducted in a low-malaria-transmission setting in Thailand, infection with malaria (which was most often asymptomatic) was associated with low birth weight, resulting mainly from intrauterine growth retardation rather than preterm delivery (3, 15, 16). In sub-Saharan Africa where malarial transmission is generally much higher and maternal malaria is rarely

Received for publication March 8, 2000, and accepted for publication April 16, 2001.

Abbreviations: CI, confidence interval; OR, odds ratio; PAF, population-attributable fraction; pc, prevalence among cases; SD, standard deviation.

[1] Shoklo Malaria Research Unit, Mae Sod, Thailand.
[2] Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.
[3] Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, United Kingdom.
[4] London School of Hygiene and Tropical Medicine, London, United Kingdom.

Reprint requests to Dr. Christine Luxemburger, Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, OX3 9DU Oxford, United Kingdom (e-mail: christine.luxemburger@wanadoo.fr).

associated with symptoms, two studies have demonstrated that there were different consequences on the newborn infant, depending on the timing of infection. Parasitemia in the antenatal period was associated with intrauterine growth retardation, whereas cord blood parasitemia, probably reflecting a recent active infection, was associated with premature birth (17, 18). In an area of much higher rates of transmission, chronic placental infection was associated with both mechanisms, and low birth weight resulting from premature birth was more common than usually thought (19).

Malaria during pregnancy has not been associated directly with an increase in infant mortality, whereas severe maternal anemia has been associated with an increased risk of infant death in the perinatal (8) and postneonatal periods (15, 16). However, as low birth weight is a major determinant of infant mortality (20), it has been assumed that malaria and anemia during pregnancy would increase infant mortality indirectly by lowering birth weight. Nevertheless, the relative importance of maternal malaria and anemia as contributors to infant mortality has not been measured previously. In areas of low malarial transmission, infants born to malaria-infected mothers are growth retarded rather than premature, and the latter are at much higher risk of dying in infancy than are the former (21). However, premature births are common where maternal malaria is associated with symptoms. We have followed a cohort of pregnant women and their liveborn singletons in an area of low malarial transmission to determine the role of maternal malaria and anemia on infant survival.

MATERIALS AND METHODS

Study area

The study was conducted in five camps for refugees of the Karen ethnic group (total population, circa 30,000), situated on the western border of Thailand. The camps are located in forested areas where malarial transmission is low (on average, one infection per person and per year) and occurs year-round with two seasonal peaks: May-July and December-January. *P. vivax* coexists with multidrug-resistant *Plasmodium falciparum* (on average, 50 percent and 40 percent, respectively, with 10 percent of the infections mixed with both species). As a consequence of the low transmission, symptomatic and severe falciparum malaria cases are seen at all ages (14, 22). Malaria during pregnancy is an important public health problem. Before the introduction of the antenatal clinics that had as their principal objectives the early detection and treatment of malaria, malaria during pregnancy was associated with a significant maternal morbidity and mortality (3). The control program reduced the incidence of severe malaria. However, one third of women are still infected with either of the two main *Plasmodium* species during pregnancy. Most infected women develop oligosymptomatic malaria. Both species of *Plasmodium* are associated with a reduction in birth weight (3, 4).

In this population the level of literacy is relatively high (70 percent). Food, school furniture, blankets, and mosquito nets are given by a consortium of charities (Burma Border Consortium). Health care is provided by the French medical organization, Médecins Sans Frontières, and by the Shoklo Malaria Research Unit. The malaria control program relies on early detection and treatment. Only slide-confirmed cases of malaria are treated, and the availability of antimalarial drugs is restricted to the health structures. Antenatal clinics have been in existence since 1986. These consist of weekly consultations with active detection of malarial infection by microscopic examination of a blood smear and treatment of all parasitemic episodes irrespective of the presence of symptoms. Nearly all (90 percent) pregnant women are registered. Infants are seen regularly, and immunization coverage is high (80 percent).

Study population and data collection

Between 1993 and 1996, all pregnant women who delivered a singleton liveborn infant were enrolled in the study after they gave informed consent. Data regarding their pregnancy had been collected prospectively from their first consultation at antenatal clinics until delivery as part of a large routine follow-up of pregnancies that has been described previously (4). In summary, the following procedures were performed. On admission, information was obtained about maternal demographic data, past obstetric history, and malarial history. The record of malarial attacks that occurred between conception and admission to the study was obtained by history recall and checked against the dispensaries' registers. In this area most patients with malaria would develop symptoms (22). Thus, history recall of microscopically confirmed cases of malaria is considered a good proxy for patients' history of malaria. Pregnant women were then followed weekly. At each consultation, they were asked to report the presence of any symptoms during the previous week, and a blood capillary sample was taken for a malarial smear weekly and hematocrit fortnightly. Symptomatic malarial cases were defined as the presence of asexual forms of *Plasmodium* species on a blood smear, associated with fever (axillary temperature, above 37.5°C) or history of fever with one or more of the following: headache, chills, joint pain. Malarial cases were asymptomatic when none of the symptoms listed above was reported. All women with a positive malarial smear were treated. Women with vivax malaria were given chloroquine (25-mg base/kg over 3 days), whereas the first-line treatment for falciparum malaria was quinine (30-mg salt/kg/day for 7 days) during the first trimester of pregnancy and a 3-day combination of artesunate-mefloquine (12 mg/kg of artesunate and 25-mg base of mefloquine/kg) later in pregnancy. Women who presented with recrudescent falciparum malarial episodes were treated with artesunate alone (4 mg/kg and then 2 mg/kg/day for a total of 7 days). During the period of follow-up in antenatal clinics, the majority of the women who developed malaria remained oligosymptomatic, because malaria was detected actively before they developed fever. Iron and folic acid treatments were given to all women who developed anemia, defined as a hematocrit of less than 30 percent. Women with severe anemia (hematocrit of less than 20 percent) received a blood transfusion. Oral hematinics were continued until delivery.

All women were encouraged to deliver at a hospital. When they delivered at home, home visitors brought the babies to the clinic within 3 days. The newborn infants were weighed (to the nearest 50 g), and a Dubowitz score (23) was assigned within 6–24 hours. The use of this score in the Karen population was validated by Dr. Dubowitz who trained Karen staff to perform it. Low birth weight was defined as a birth weight of less than 2,500 g, and premature birth was defined as gestational age of less than 37 weeks.

Infants were then followed weekly at home until they were 1 year of age. During these weekly visits, mothers were asked if the child had been ill and, when this was the case, if he/she attended a dispensary. Absence and deaths that occurred at home were recorded. The duration of follow-up was determined in days, until completion of the study (365 days) or the age at death or withdrawal from the study.

Analysis

Analysis was restricted to the pairs of mothers and liveborn singletons. The mothers' characteristics and their morbidity during pregnancy were described to identify potential confounders for further analysis of infant survival. Determinants of low birth weight and risk factors for malaria and/or anemia during pregnancy were identified by bivariate statistics and multivariate logistic regression. Population-attributable fractions (PAFs) were calculated and adjusted for other explanatory variables, assuming that the exposure had a causal effect on the outcome. The formula was as follows: PAF = pc (adjusted odds ratio (OR) – 1)/adjusted OR, where pc is the prevalence of the factor among the cases (24). Risk factors for infant mortality were identified using survival methods that were performed for three different periods of infancy: neonatal, 1–3 months, and >3–12 months of age. Kaplan-Meyer plots, log-rank tests, and hazards ratios were used to examine the univariate association between each potential factor and infant mortality. All factors associated with survival ($p < 0.10$) were subsequently included in a Cox regression. The hierarchy among the numerous confounding variables was taken into account by fitting the model in three stages (25). The first model did not contain anemia at delivery nor low birth weight and prematurity, because these variables could be on the causal pathway between the effects of the other variables in the model and survival. Anemia at delivery was added in the second model, and low birth weight and prematurity were added in the third model. Thus, in addition to correctly estimating the effect of each variable, it was also possible to estimate how much of the effect was mediated through the intermediate variables of anemia, low birth weight, and prematurity.

RESULTS

Figure 1 summarizes the study's profile. Between 1993 and 1996, 2,097 pregnant women were admitted into the study. Information on pregnancy outcome was available for 86 percent. After selection of the women with liveborn singletons and exclusion of those who did not reside in the camps or for whom data during pregnancy were lost, a cohort of 1,495 mothers and infants was recruited. Overall, 25 percent ($n = 368$) of the infants were lost to follow-up, but the reasons for withdrawal seemed unrelated to the study. More than half of them (58 percent; 212 of 368 infants) left during insecure periods when some armed groups attacked the camps. Other babies moved or followed their mothers who went working outside the camps. Only one mother refused to pursue the follow-up after the older brother of the index child died in the Research Unit's hospital.

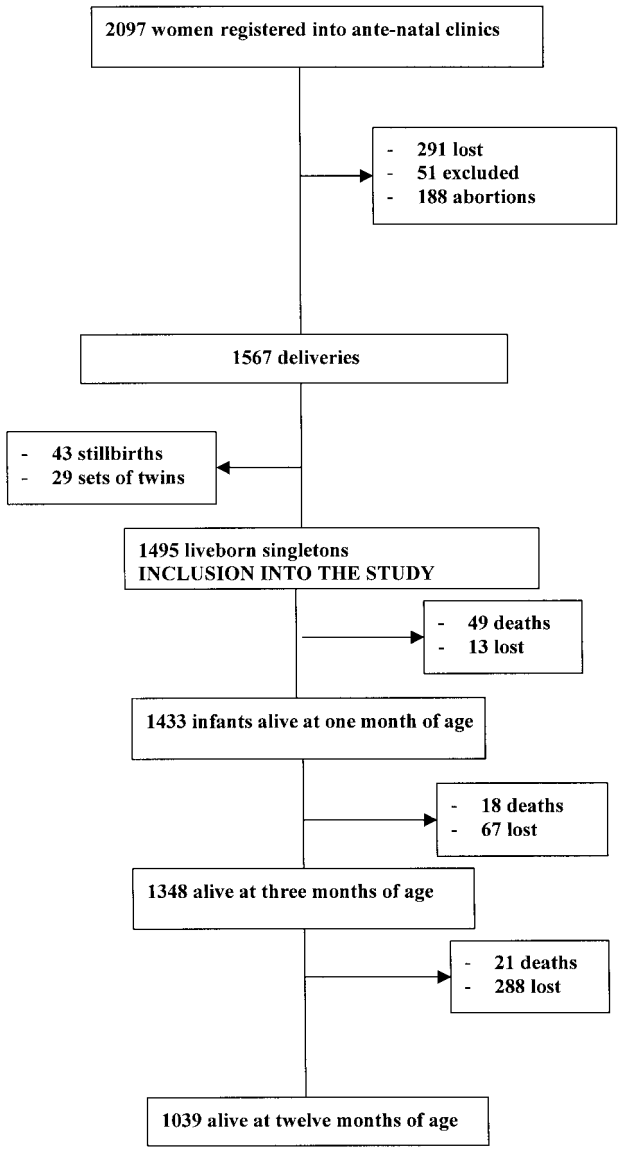

FIGURE 1. Study's profile, Thailand, 1993–1996.

Maternal malaria and anemia

Thirty-seven percent (555 of 1,495) of the women developed malaria during pregnancy. There were 1,096 parasitemic episodes (range, 1–8 episodes/woman) in the 555

malaria-infected women (491 episodes of *P. falciparum*, 570 episodes of *P. vivax*, 34 episodes of mixed infection with *P. falciparum* and *P. vivax*, and one episode of malaria from unrecorded species). Symptoms were present in 59 percent (566 of 960) of the episodes for which this information was available. Falciparum malaria was more common in primigravidae than in multigravidae (28 percent vs. 20 percent, $\chi^2 = 10$, $p = 0.002$), whereas *P. vivax* malarial prevalence rates were similar in all gravidae.

Maternal anemia was extremely common. One fourth ($n = 374$) of the women were anemic on admission, and 69 percent of the women who were not anemic at that time developed anemia later in pregnancy. Thus, overall, 77 percent (1,132 of 1,466) of the women developed anemia at some stage of pregnancy, for a mean duration of 7.7 (standard deviation (SD), 5.9) weeks. At delivery, 24 percent (353 of 1,444) of the women remained anemic despite hematinics. However, only 1 percent were severely anemic. Malaria during pregnancy was the strongest independent risk factor of anemia during pregnancy (PAF = 27 percent, 95 percent confidence interval (CI): 16, 30). At delivery, malaria remained associated with anemia, and the PAF of anemia due to malaria was 17 percent (95 percent CI: 9, 23). Multigravidae, Karen ethnicity, and respiratory infections during pregnancy were also associated independently with anemia during pregnancy (table 1). Other maternal infections, such as urinary tract infections, and the month of conception were not associated with maternal anaemia.

Newborn infants

Most children (91 percent; $n = 1,355$) were seen within the first 3 days of life, and information on birth weight and gestational age was available simultaneously in 80 percent of them ($n = 1,201$). The mean birth weight was 2,872 (SD, 490) g, and the mean gestational age was 38.5 (SD, 1.6) weeks. Of the newborn infants, 190 (16 percent) weighed less than 2,500 g, including 88 (7 percent) infants born prematurely and 102 (9 percent) full-term infants. Overall, 135 infants (11 percent) were born prematurely.

Table 2 shows the determinants of low birth weight. Univariate analysis was performed on maternal (age, gravidae, ethnic group, malaria, anemia, respiratory and urinary infections, hypertension), infant (sex, gestational age), and other (season of birth) variables. Malaria during pregnancy was an independent risk factor of low birth weight, with a PAF of 20 percent (95 percent CI: 7, 29). All anthropometric markers (weight, height, and head circumference) were

TABLE 1. Risk factors of maternal anemia during pregnancy in Karen women, Thailand, 1993–1996

Factors	Prevalence of anemia		Crude OR*	95% CI*	Adjusted OR†	95% CI
	No./total	%				
Maternal anemia during pregnancy						
Multigravidae						
Yes	883/1,093	81	2.1	1.6, 2.7	2.1	1.6, 2.7
No	251/375	67				
Karen ethnic group						
Yes	1,012/1,296	79	1.8	1.2, 2.5	1.7	1.2, 2.4
No	116/172	67				
Malaria during pregnancy						
Yes	479/550	87	2.7	2.0, 3.6	2.9	2.1, 3.9
No	655/918	76				
Respiratory infection during pregnancy						
Yes	335/410	82	1.5	1.1, 1.9	1.1	0.9, 1.6
No	799/1,058	76				
Maternal anemia at delivery						
Multigravidae						
Yes	289/1,078	27	1.7	1.3, 2.4	2.0	1.5, 2.7
No	64/366	18				
Karen ethnic group						
Yes	321/1,274	25	1.5	1.0, 2.2	1.6	1.0, 2.4
No	32/170	19				
Malaria during pregnancy						
Yes	157/537	29	1.5	1.2, 1.9	1.6	1.3, 2.1
No	196/907	22				
Respiratory infection during pregnancy						
Yes	114/405	28	1.3	1.0, 1.7	1.4	1.1, 1.9
No	239/1,039	23				

* OR, odds ratio; CI, confidence interval.

† Adjusted for all other variables included in the table (variables are shown in the table only if $p < 0.10$ in univariate analysis).

TABLE 2. Determinants of low birth weight in Karen newborn infants, Thailand, 1993–1996

Factors	Prevalence of low birth weight		Crude OR*	95% CI*	Adjusted OR†	95% CI
	No./total	%				
Primigravidae						
Yes	90/346	26	2.3	1.7, 3.1	2.3	1.6, 3.4
No	134/1,000	13				
Premature birth						
Yes	88/135	65	17.7	11.5, 27.2	16.6	10.8, 25.5
No	102/1,066	10				
Malaria during pregnancy						
Yes	109/496	22	1.8	1.4, 2.4	1.7	1.2, 2.4
No	115/850	14				
Maternal anemia at the time of delivery						
Yes	67/319	21	1.5	1.1, 2.9	1.3	0.8, 2.0
No	151/990	15				

* OR, odds ratio; CI, confidence interval.
† Adjusted for all other variables included in the table (variables are shown in the table only if $p < 0.10$ in univariate analysis).

affected in children born to malaria-infected mothers, indicating a chronic symmetric growth retardation. Maternal anemia had no independent effect in reducing birth weight.

Malaria (disease or parasitization) and anemia during pregnancy did not reduce the duration of gestation. The mean number of weeks of gestation was 38.5 (SD, 1.7) weeks in malaria-infected women and 38.5 (SD, 1.4) weeks in women without malaria during pregnancy ($p = 0.33$). The durations of gestation were also similar in anemic and nonanemic women: 38.5 (SD, 1.6) weeks and 38.5 (SD, 1.6) weeks, respectively ($p = 0.40$). The prevalence of premature labor decreased with gravidity (17 percent in primigravidae, 13 percent in second gravidae, and 8 percent in gravidity of higher rank; χ^2 for trend = 18; $p < 0.001$) and with mother's age (20 percent in mothers aged less than 20 years and 10 percent in older women; $\chi^2 = 20$; $p < 0.001$). Premature birth was also associated with febrile disease within the week preceding delivery: 28 percent in febrile women compared with 10 percent in nonfebrile women ($\chi^2 = 23$; $p < 0.001$). Diagnoses of the 78 febrile episodes in the week preceding delivery were symptomatic falciparum ($n = 23$), vivax ($n = 17$), and mixed ($n = 1$) malaria; acute respiratory infection ($n = 33$); and urinary tract infection ($n = 4$). The risk of premature delivery was present for each condition, probably reflecting an effect of fever. In multivariate analysis, febrile episodes preceding delivery (adjusted OR = 3.0, 95 percent CI: 1.7, 5.3) and mothers aged less than 20 years (adjusted OR = 2.2, 95 percent CI: 1.5, 3.3) remained independently associated with the risk of delivering prematurely. The PAF of premature birth due to maternal infection close to term was 10 percent (95 percent CI: 6, 12).

Infant mortality

Of the 1,127 children who completed follow-up, 88 died before 1 year of age, giving a crude infant mortality rate of 78 per 1,000 livebirths. Sixty-seven infants (76 percent) died during the first 3 months of life, including 49 during the neonatal period and 18 between 1 and 3 months of age. Table 3 shows the risk factors for neonatal deaths. Malaria

TABLE 3. Risk factors of neonatal deaths in Karen infants, Thailand, 1993–1996

Factors	Univariate analysis		Multivariate analysis*					
			Step 1		Step 2		Step 3	
	HR†	95% CI†	HR	95% CI	HR	95% CI	HR	95% CI
Primigravidae	2.0	1.2, 3.6	NS†		NS		NS	
Mothers aged less than 20 years	2.2	1.2, 4.0	2.0	1.1, 3.6	1.9	1.1, 3.5	NS	
Birth in winter	1.9	1.1, 3.4	NS		NS		NS	
Complicated delivery	2.6	1.3, 5.1	2.3	1.1, 4.4	2.3	1.1, 4.4	NS	
Maternal infection within 1 week before delivery	5.3	2.7, 10.4	4.8	2.5, 9.5	4.0	2.0, 8.1	2.5	1.3, 5.0
Maternal anemia at the time of delivery	1.8	1.0, 3.2	Not in model		NS		NS	
Preterm low birth weight	20.8	11.2, 38.9	Not in model		Not in model		18.0	9.5, 34.1
Full-term low birth weight	3.3	1.2, 9.9	Not in model		Not in model		3.2	1.2, 8.8

* Hazards ratios adjusted for all other variables included in the table (variables are shown in the table only if $p < 0.10$ in univariate analysis).
† HR, hazard ratio; CI, confidence interval; NS, not significant.

during pregnancy affected neonatal mortality indirectly by lowering birth weight, whereas fever in the week before birth had an additional independent effect as well as inducing premature birth.

Maternal infection within the week before delivery was the only risk factor for infant death from 1 to 3 months of age, in univariate analysis, and after adjusting for birth weight and gestational age (adjusted hazards ratio = 4.0, 95 percent CI: 1.2, 13.7). No risk factors could be identified for deaths that occurred later in infancy (from 3 to 12 months).

DISCUSSION

This study showed that malaria during pregnancy influenced infant mortality during the first months of life. In this area of low malarial transmission, the two main *Plasmodium* species, *P. falciparum* and *P. vivax*, are associated with low birth weight, but they do not reduce gestational age (3, 4, 15, 16). In this cohort study, malaria during pregnancy was not a direct cause of neonatal death. This finding was similar to those of previous studies in which malaria during pregnancy did not increase the risk of neonatal deaths (15, 16, 26, 27). Malaria increased neonatal mortality indirectly by reducing birth weight. In this community, malaria during pregnancy was responsible for 20 percent of low birth weight. As in other settings, low-birth-weight babies were more likely to die during the neonatal period. The main risk factor of neonatal mortality in this community was premature delivery, only a small proportion of which was attributable to malaria. Thus, prevention of malaria would be expected to have a major effect in reducing the mortality from intrauterine growth retardation but only a small effect in reducing the mortality attributable to prematurity. In this area of low transmission, malaria was associated with maternal morbidity. Women who presented with febrile illnesses close to term were at risk of premature delivery. Maternal infections that occurred close to term were an additional contributor to neonatal death, as well as inducing premature birth. This effect was present up to 3 months of age. It is not clear what caused this association. Premature delivery is a well-known consequence of symptomatic and/or severe malaria during pregnancy in areas of low malaria endemicity or during epidemics (10–14). The risk of premature delivery and/or neonatal deaths was similar for acute respiratory infections or urinary tract infections, reflecting an effect of fever and illness rather than malaria per se. Focusing on the prevention of malaria near term would have the greatest overall benefit if resources are limited.

Maternal anemia was not associated with neonatal or postneonatal deaths. This result contrasted with those of other studies. Maternal anemia in malarious areas has been shown to be related to perinatal deaths in several studies (1). However, women in these earlier studies were severely anemic, whereas most pregnant women in this cohort were moderately anemic, and all anemic women were given routine iron and folic acid treatments. Maternal anemia was also associated with infant death in the previous studies conducted at our study site (15, 16). Various explanations can be proposed for these contrasting results. The infant mortality rate was halved (from 170–160 to 78 per 1,000 livebirths) in the current cohort compared with that in previous studies we have conducted in this community. Most of the reduction occurred in the postneonatal period. The number of postneonatal deaths was very small in the current cohort and, thus, the study may have lacked power to detect an impact of maternal anemia on late infant mortality. Another explanation relates to the cause of infant deaths. Previously, the main cause of infant deaths in this area was thiamine deficiency (causing the deaths of approximately 10 percent of all babies). The number of deaths attributable to this cause has been reduced dramatically (C. Luxemburger et al., unpublished manuscript). Maternal anemia in our earlier studies may have been a marker of a broader nutritional deficiency. If anemic mothers were also more often thiamine deficient, their offspring would have had a greater risk of dying later from infantile beri beri.

In conclusion, this study suggests that malaria during pregnancy contributes to early infant mortality in this area of low malarial transmission. Malaria from both species reduces birth weight and indirectly influences neonatal mortality. All gravidae are affected. Moreover, when maternal malaria occurs close to term and is associated with symptoms, the risk of premature birth and infant death increases. Malarial control programs in areas such as this should focus on the prevention of malaria in pregnancy, because this will increase infant survival.

ACKNOWLEDGMENTS

The study was part of the Wellcome Trust-Mahidol University, Oxford Tropical Medicine Research Programme, supported by the Wellcome Trust of Great Britain.

The authors thank the Karen staff from the Shoklo Malaria Research Unit for technical support.

REFERENCES

1. Brabin BJ. The risks and severity of malaria in pregnant women. In: Applied field in malaria reports, no. 1. Geneva, Switzerland: World Health Organization, 1991. (TDR/FIELDMAL/1).
2. Menendez C. Malaria during pregnancy: a priority area of malaria research and control. Parasitol Today 1995;11:178–83.
3. Nosten F, ter Kuile FO, Maelankirri L, et al. Malaria during pregnancy in an area of unstable endemicity. Trans R Soc Trop Med Hyg 1991;85:424–9.
4. Nosten F, McGready R, Simpson JA, et al. The effects of *Plasmodium vivax* malaria in pregnancy. Lancet 1999;354:546–9.
5. Greenwood BM, Greenwood AM, Snow RW, et al. The effects of malaria chemoprophylaxis given by traditional birth attendants on the course and outcome of pregnancy. Trans R Soc Trop Med Hyg 1989;83:589–94.
6. Menendez C, Todd J, Alonso PL, et al. Malaria chemoprophylaxis, infection of the placenta and birthweight in Gambian primigravidae. J Trop Med Hyg 1994;97:244–8.
7. Cot M, Le Hesran JY, Miailhes P, et al. Increase of birth weight

following chloroquine chemoprophylaxis during the first pregnancy: results of a randomised trial in Cameroon. Am J Trop Med Hyg 1995;53:581–5.
8. Brabin BJ, Ginny M, Sapau J, et al. Consequences of maternal anaemia on outcome of pregnancy in a malaria endemic area in Papua New Guinea. Ann Trop Med Parasitol 1990;84:11–24.
9. Brabin B, Piper C. Anaemia and malaria-attributable low birthweight in two populations in Papua New Guinea. Ann Hum Biol 1997;24:547–55.
10. Wickramasuriya G. Clinical features of malaria in pregnancy. In: Malaria and ankylostomiasis in pregnant women. London, United Kingdom: Oxford University Press, 1937:5–90.
11. Menon R. Pregnancy and malaria. Med J Malaysia 1972;27: 115–19.
12. Endeshaw Y. Malaria in pregnancy: clinical features and outcome of treatment. Ethiop Med J 1991;29:103–8.
13. Nair LS, Nair AS. Effects of malaria infection on pregnancy. Indian J Malariol 1993;30:207–14.
14. Luxemburger C, Ricci F, Nosten F, et al. The epidemiology of severe malaria in an area of low transmission on the western border of Thailand. Trans R Soc Trop Med Hyg 1997;91: 256–62.
15. Dolan G, ter Kuile FO, Jacoutot V, et al. Bed nets for the prevention of malaria and anaemia in pregnancy. Trans R Soc Trop Med Hyg 1993;87:620–6.
16. Nosten F, ter Kuile F, Maelankiri L, et al. Mefloquine prophylaxis prevents malaria during pregnancy: a double-blind, placebo-controlled study. J Infect Dis 1994;169:595–603.
17. Steketee RW, Wirima JJ, Hightower AW, et al. The effect of malaria and malaria prevention in pregnancy on offspring birthweight, prematurity, and intrauterine growth retardation in rural Malawi. Am J Trop Med Hyg 1996;55(suppl 1):33–41.
18. Sullivan AD, Nyirenda T, Cullinan T, et al. Malaria infection during pregnancy: intrauterine growth retardation and preterm delivery in Malawi. J Infect Dis 1999;179:1580–3.
19. Menendez C, Ordi J, Ismail MR, et al. The impact of placental malaria on gestational age and birth weight. J Infect Dis 2000; 181:1740–5.
20. Ashworth A. Effects of intrauterine growth retardation on mortality and morbidity in infants and young children. Eur J Clin Nutr 1998;52(suppl 1):S34–42.
21. Victora CG, Barros FC, Vaughan JP, et al. Birthweight and infant mortality: a longitudinal study of 5914 Brazilian children. Int J Epidemiol 1987;16:239–45.
22. Luxemburger C, Thwai KL, White NJ, et al. The epidemiology of malaria in a Karen population on the western border of Thailand. Trans R Soc Trop Med Hyg 1996;90:105–11.
23. Dubowitz LM, Dubowitz V. Gestational age of the newborn. Reading, MA: Addison-Wesley, 1977.
24. Bruzzi P, Green SB, Byar DP, et al. Estimating the population attributable risk factors using case-control data. Am J Epidemiol 1985;122:904–14.
25. Victora CG, Huttly SR, Fuchs SC, et al. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. Int J Epidemiol 1997;26:224–7.
26. Taha TET, Gray RH. Malaria and perinatal mortality in Central Sudan. Am J Epidemiol 1993;138:563–8.
27. McDermott JM, Wirima JJ, Steketee RW, et al. The effect of placental malaria infection on perinatal mortality in rural Malawi. Am J Trop Med Hyg 1996;55(suppl 1):61–5.