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Maternal malaria during pregnancy and infant mortality rate: critical literature review and a new analytical approach

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Abstract

Background & objectives: Malaria during pregnancy is a recognised risk factor for low birth weight and probably decreases the survival of offspring, particularly during their first month of life. On the other hand, acquired maternal immunity may protect infants against malaria infection or disease. This study assesses these two opposite effects simultaneously.

Methods: We used the data of a large epidemiological study on malaria (Garki project) to analyse the impact of malaria during pregnancy on survival of offspring in their first year of life. The dataset contains 138,197 survey records, representing 12,849 subjects. Of 663 reported deliveries, 417 could be linked to survival data for the newborn.

Results: The mortality rate during the first year of life was independent of maternal malaria infection during pregnancy (crude rate ratio 1.0). After adjustment for malaria in infancy, the rate ratio was 1.2. The corresponding rate ratios for maternal malaria during the second half of pregnancy were 1.46 and 1.73. None of these rate ratios was statistically significant. This may be due to the small number of deaths in the first year of life with a complete record of maternal malaria (27 deaths). The infants during the first four months of life had the lowest risk for *Plasmodium falciparum, P. malariae* and *P. ovale* infections which may be partly due to acquired maternal immunity. There was a positive association between malaria during pregnancy and malaria during first year of life which might be due to similarity in exposure risks within a family, or confounding effects of socioeconomic status. However, this association was weaker in the first four months of life, and in those women who contracted infection during the second half of pregnancy. This may indicate that acquired immunity is stronger in this group and partially protects babies for a few months.

Interpretation & conclusion: It seems that on the whole, malaria during pregnancy was not a major risk factor for infant mortality in the Garki project. These results suggest that ignoring acquired maternal immunity may overestimate the hazard of malaria during pregnancy on infant survival.

Key words Garki project – infant mortality – maternal malaria

Introduction

Malaria during pregnancy, particularly close to term, may entail two opposite effects on child survival. It may protect the infant against malaria infection and severe disease via acquired maternal immunity (AMI)[1–5]. Or it may increase the risk of infant mortality, particularly neonatal mortality, mostly by increasing the risk of low birth weight, premature labour, intra-uterine growth retardation, placental infection and stillbirth[6–14].

Few papers have quantified the impact of maternal malaria on infant mortality (IM) directly based on the survival of offspring in the first year of life[6,11]. These studies mostly showed no significant association between IM and maternal malaria. However, in a review, Steketee *et al*[7] suggested that 3–8% of infant mortality (mortality during the first year of life) might be due to maternal malaria in endemic areas. Some authors have suggested that malaria accounts for even more infant deaths than this[12,13,15]. None of these predictions was directly derived from field data.

Most clinical trials assessed the efficacy of antimalaria drugs during pregnancy by measuring their impacts on low birth weight or neonatal mortality rate[9, 11–19]. These studies mostly did not take account of the possible decreasing effect of antimalaria drugs on the AMI; therefore, they may overestimate the impact of malaria during pregnancy on IMR. In this paper, we present one of the few published analyses of the effect of malaria infection during pregnancy on the first year survival of offspring and assess the impact of AMI.

Material & Methods

The Garki project was carried out in a malaria-endemic area of northern Nigeria from 1969–76 by the World Health Organization (WHO) and an epidemiology research team from the Government of Nigeria[20]. The anonomised Garki data are in the public domain and the version used can be downloaded from:http://www.sti.ch/en/research/biostatistics/downloads.html.

The main objectives of the Garki project were to assess malaria epidemiology, quantify the impact of different interventions, and estimate required parameters for modelling of malaria transmission. Data were recorded at cross-sectional malariological surveys of the entire population of the study villages, during which malaria slides were prepared from all individuals and recent deliveries and their outcomes were recorded. These surveys were administrated every 10 weeks between 1970 and 73; some intervals between 1974 and 76 were longer than 10 weeks. The dataset contains 138,197 records, representing 12,849 subjects in 23 surveys in both interventions and non-intervention arms. In our analysis, we included all records of subjects in the non-intervention arm and those records from intervention arms before and after the interventions (71,270 records). We excluded those data because interventions such as mass drug administration might change the impact of malaria during pregnancy on infant mortality rate.

Based on these data we constructed a cohort of infants whose births were recorded retrospectively by interviewing the mothers, and whose survival during the first year of life was monitored at the cross-sectional surveys. Originally, there was no direct link between maternal and child records. We created such a link by matching on delivery date and residence of new mothers. If, in a neonate's compound, there had been only one delivery since the previous survey, then the mother was inferred to be the woman who reported that delivery. Out of 663 reported deliveries, 417 were linked to neonates. Among them, 37 mothers had twins and two had triplets recorded. More than 96% of mothers had at least one blood slide in their first half of pregnancy; the corresponding percent for the second half of pregnancy was 91%. Of the 458 live births, 34 deaths were recorded before age of one year. On average, infants were followed 232 days before contracting malaria or death or reaching age one year.

Two approaches were used to analyse the data. In the first approach, the age pattern of malaria infection risk was assessed (in all selected records) to consider whether the AMI could decrease the risk of infection in the first few months of life. A slide positive for malaria was used as a proxy for AMI. Logistic regression with random effects was used to adjust odds ratios (ORs) for repeated observations on the same person.

In the second approach, the impact of malaria infection during pregnancy on IMR and AMI were as-

sessed. Separate analyses were done for each half of pregnancy and for pregnancy as a whole, using Cox regression. For each analysis, women were included if they had at least one slide result, and they were classified as positive if at least one of the slides was positive. These models were run in Stata version 8.0.

Maternal infection status is imperfectly observed in this study, being based on slides made at intervals of approximately 2–4 months, and with some mothers having more slides than others. To quantify the uncertainity resulting from this variable sampling, we fitted a Bayesian model by Markov Chain Monte Carlo using WinBUGS version 1.3. The IMR was defined as the number of deaths per year of follow-up in the first year of life. This differs from the common definition, i.e. the number of deaths in first year of life as a proportion of the number of births.

Results

The mean age, and the frequency of malaria infections among pregnant women in the three surveys before delivery, did not differ significantly between women whose pregnancies could be matched with a baby and those whose could not (p = 0.41 and 0.58 respectively).

The mean and standard deviation of age of mothers at the beginning of their pregnancies were 28.6 and 6.6 yr, respectively (minimum and maximum of 12.2 and 48.1 yr). Around 29.4% of pregnant women had at least one positive slide for malaria [30% (112 slides) and 28.6% (109 slides) in the first and second halves of pregnancy] and around 47% *P. falciparum*.

The frequency of *P. falciparum* infection in infants (less than one year of age) was 53%, while the corresponding frequencies for *P. malariae* and *P. ovale* were 9 and 2%, respectively. Around 23.5% of infant deaths were below the age of one month (8 deaths), while only 1% of positive blood slides of babies belonged to this age group. Overall, the risk of malaria in those who died as infants was 30.2%, while in the first year of life for those who reached age one year, it was 8.8% (p = 0.009 by Fisher's exact test).

The risk ratios for maternal malaria infection in the first and second halves of pregnancy for IMR were 0.74 and 1.46, respectively, but neither was statistically significant (Table 1). For maternal infection at any time during pregnancy, taking into account the varying number of slides by the Bayesian model, produced a rate ratio for IMR of 1.05 with a wider 95% confidence interval (0.32–4.1).

Adjusting for the infant's malaria infection increased the rate ratios, more so for the second half of pregnancy (crude RR = 1.46, adjusted RR = 1.73) than the first. In other words, having adjusted for a potential protective effect of maternal acquired immunity, malaria infection during pregnancy was a stronger risk factor for IM.

Table 1. Infant mortality rates according to maternal malaria infection during pregnancy

Time of infection during pregnancy	No. of deaths in slide-negative group (person-years)	No. of deaths in slide-positive group (person-years)	Rate ratio (95% CI)	Adjusted rate ratio (95% CI)
First half	22 (169.1)	7 (79.9)	0.74 (0.31–1.72)	0.83 (0.36–1.96)
Second half	19 (188.1)	11 (74.2)	1.46 (0.7–3.07)	1.73 (0.8–3.58)
Any time	14 (125.12)	13 (123.89)	1.00 (0.47–2.14)	1.20 (0.56–2.56)

Due to their definitions, the numbers in last row is not the sum of the numbers in two first rows (see the last paragraph of subjects and methods section).

Table 2. The risk of infection with *Plasmodium* spp classified by age

Age group	<4 months No. (%)	4–7 months No. (%)	8–12 months No. (%)	1–9 year No. (%)	≥10 year No. (%)	Total
P. falciparum						
Negative	484 (70.7)	356 (42)	272 (31.6)	2,220 (13.5)	27,902 (64.6)	31,234
Positive	201 (29.3)	492 (58)	558 (68.4)	14,224 (86.5)	15,299 (35.4)	30,804
OR	0.75	2.52	3.9	11.68	1	χ^2=1270*
(95% CI)	(0.64–0.9)	(2.2–2.9)	(3.41–4.56)	(11.13–12.27)	–	p <0.001
OR for the whole first year: 2.1 (1.8–2.4)						
P. malariae						
Negative	654 (95.9)	763 (90)	738 (85.8)	10,957 (66.6)	39,826 (92.2)	52,938
Positive	31 (4.5)	85 (10)	122 (14.2)	5,486 (33.4)	3,375 (7.8)	9,099
OR	0.56	1.31	1.95	5.9	1	χ^2=6285*
(95% CI)	(0.39–0.8)	(1.04–1.65)	(1.6–2.37)	(5.63–6.2)	–	p <0.001
OR for the whole first year: 1.3 (1.1–1.5)						
P. ovale						
Negative	678 (99)	826 (97.4)	841 (97.8)	15,761 (95.8)	42,761(99)	60,867
Positive	7 (1)	22 (2.6)	19 (2.2)	682 (4.2)	440 (1)	1,170
OR	1	2.59	2.2	4.2	1	χ^2=630*
(95% CI)	(0.47–2.12)	(1.68–4)	(1.38–3.49)	(3.72–4.75)	–	p <0.001
OR for the whole first year: 4.2 (3.6–5.0)						

*Using χ^2 test the associations between age group and the frequencies of each *Plasmodium* species were checked; the infection risk in the last age group (≥10 yr) is the baseline.

The population attributable fraction (PAF) for malaria infection during pregnancy was – 0.01 (95% CI: – 0.09 to 0.08). The corresponding PAF for the second half of pregnancy was 0.12 (95% CI: – 0.16 to 0.33). The adjusted PAFs for infant malaria infection status were 0.06 (95% CI: – 0.034 to 0.34) and 0.16 (95% CI: – 0.11 to 0.36) respectively.

The frequency of *P. falciparum* infection in infants was 53%, while the corresponding frequencies in 1–9 and 10 or more year old subjects were 86.5 and 35.4% respectively. These age-group specific frequencies were 9, 33.4 and 7.8% for *P. malariae*, and 2, 4.2 and 1% for *P. ovale* correspondingly. These frequencies show that the infection risks in the first year of life were much less than the risks in 1–9 yr old children (Table 2). In addition, the infection risks in the first year of life had an increasing trend, i.e. these frequencies were much lower in those aged less than four months than those aged 8–12 months.

Table 2 also compares the age-specific infection frequencies, taking those aged at least ten years as the baseline group. Compared to the ORs in the 1–9 yr age group, lower ORs in the first year of life might be due to either less exposure to vectors, or partial protection via AMI abbreviation, or both.

To explore this issue more deeply, the ORs of infections in the <4, 4–7 and 8–12 months of life were computed. The ORs for babies aged less than four months were 0.75, 0.56 and one for *P. falciparum*, *P. malariae* and *P. ovale*, respectively which were much lower than the ORs for the rest of first year of life (Table 2).

Malaria infections during pregnancy and infection in their offspring showed a positive association (OR=2.4, 95% CI: 1.48–3.88). This positive association could be explained by the correlation between exposure risk of mothers and infants; i.e. in highly exposed families, both mothers and infants had higher

Table 3. The odds ratios between maternal malaria infection during pregnancy and infections in their off spring

Malaria during pregnancy	Malaria in infants		
	<4 months	4–8 months	>8 months
P. falciparum			
First half	2.8 (0.84–9.3)	2 (0.79–5.03)	1.78 (0.8–3.98)
Second half	1.55 (0.52–4.6)	3.1 (1.05–9.13)	2.1 (0.98–4.42)
Any time	1.58 (0.6–4.1)	2.6 (1.12–6.1)	1.94 (0.96–3.9)
P. malariae			
First half	–	0.31 (0.03–3.2)	1.28 (0.26–6.25)
Second half	0.84 (0.16–4.55)	1.05 (0.26–4.2)	1.93 (0.57–6.6)
Any time	0.63 (0.12–3.3)	0.73 (0.23–2.37)	1.97 (0.71–5.4)
Any species			
First half	2.8 (0.86–9.2)	2.2 (0.87–5.52)	1.87 (0.85–4.1)
Second half	1.43 (0.5–4.1)	1.96 (0.77–4.98)	2.2 (1.06–4.58)
Any time	1.63 (0.59–4.52)	3.1 (1.23–7.81)	2.48 (1.14–5.37)

infection risks. However, this positive association was weaker in infants with less than four months age; and for those mothers who contracted infection in the second half of their pregnancies (Table 3). These findings were comparable for *P. falciparum* and *P. malariae* infections and may imply that AMI generated stronger protection in the first four months of infant life, particularly in those pregnant women who contracted infection in second half of pregnancy.

Discussion

We did not find evidence for a detrimental effect of malaria in pregnancy on infant survival. The data are consistent with a moderate to large risk, but the 95% confidence interval for the rate ratio is wide even from the model without allowing for variable number of slides (0.44–2.0). The point estimate allowing for this was similar, but had an even wider confidence interval. On the whole, malaria infection during pregnancy could account for around 6% of the IMR. Our analysis suggests that the effect of malaria infection on offspring survival in the second half of pregnancy is stronger than in the first half, which might be due to its effect on birth-weight. In addition, infection during pregnancy may produce partial immunity in infants, particularly in their first four months life.

The short protective effect of AMI which observed in this study is compatible with other published results[2–5,21]. Sehgal *et al*[3] showed that maternal immunoglobulin G (IgG) was detectable in newborn babies for around 4–7 months and its level had a negative association with the risk of malaria infection. Kitua *et al*[5] found that age profiles of malaria disease and of the density of parasitaemia also complement those of maternal IgG. It seems that infants obtain partial protection against malaria if the mother contracted infection in late part of her pregnancy; but this protection is effective for only a few months.

There is a great deal of research on the hazards of malaria during pregnancy on mothers and babies health[22]. Most clinical trials have found that prophylaxis with antimalaria during pregnancy increased birth weight and decreased the frequency of neonatal mortality[9,11,13,16-19]. Greenwood *et al*[12] concluded that maternal malaria prophylaxis could reduce IMR by around 18% among the children of primigravidae, and by around 4% among the children of multi-

gravidae. However, this prediction was based on the effect of prophylaxis on the birth weight and was not adjusted for presumably protective effect of AMI.

It is not clear whether low birth weight is on the causal pathway between maternal malaria and infant mortality, and accurate prediction of the impact of malaria control measures targeted at pregnant women requires direct estimates of malaria attributable neonatal mortality rates[22]. We estimate that malaria during the whole pregnancy did not have any contribution on IMR (PAF = – 0.01) which is compatible with the results of studies which followed babies for one year[6,11]. However, the adjusted PAF for maternal immunity was 0.06, which may imply that without allowing for AMI effect, malaria during pregnancy slightly increased the IMR. The adjusted OR is close to the prediction of Steketee *et al*[7] (3–8%). Therefore, the observed difference between studies might be due to the impact of AMI.

It should be mentioned that our definition of IMR is the number of deaths divided by the person months of follow-up, which is different to its conventional definition. However, we do not expect this difference had any impact on the final conclusion.

The crude and adjusted PAF of malaria during the second half of pregnancy on IMR were 0.12 and 0.16 respectively, showing that malaria during the second half of pregnancy is a stronger risk factor for IM. Nonetheless, perhaps due to the low number of deaths in first year of life, none of these PAFs was statistically significant.

It seems that even the large database from Garki is inadequate for accurately measuring the specific association between malaria during pregnancy and IM. This association was not a primary objective in the Garki project; and the number of births that could be linked to maternal malaria status was nevertheless small, so the confidence limits for the estimates are wide.

Conclusion

Around 6% of IMR could be attributed to maternal malaria during pregnancy. It seems that most previous studies over-estimated the impact of malaria on survival of infants because they do not consider protective effect of AMI. To demonstrate unequivocally an excess risk of infant mortality would require a large longitudinal study, which would also need to measure possible confounding factors such as socioeconomic status and to take account of AMI.

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References

1. Desowitz RS, Elm J, Alpers MP. *Plasmodium falciparum*-specific immunoglobulin G (IgG), IgM, and IgE antibodies in paired maternal-cord sera from east Sepik Province, Papua New Guinea. *Infect Immun* 1993; *61*(3): 988–93.

2. Okoko BJ, Enwere G, Ota MO. The epidemiology and consequences of maternal malaria: a review of immunological basis. *Acta Trop* 2003; *87*(2): 193–205.

3. Sehgal VM, Siddjiqui WA, Alpers MP. A seroepidemiological study to evaluate the role of passive maternal immunity to malaria in infants. *Trans R Soc Trop Med Hyg* 1989; *83*(Suppl): 105–6.

4. Rasheed FN, Bulmer JN, De Francisco A, Jawla MF, Jakobsen PH, Jepson A, *et al*. Relationships between maternal malaria and malarial immune responses in mothers and neonates. *Parasit Immunol* 1995; *17*(1): 1–10.

5. Kitua AY, Smith T, Alonso PL, Masanja H, Urassa H, Menendez C, *et al*. *Plasmodium falciparum* malaria in the first year of life in an area of intense and perennial transmission. *Trop Med Int Hlth* 1996; *1*(4): 475–84.

6. Luxemburger C, McGready R, Kham A, Morison L, Cho T, Chongsuphajaisiddhi T, White NJ, Nosten F. Effects of malaria during pregnancy on infant mortality in an area

of low malaria transmission. *Am J Epidemiol* 2001; *154*(5): 459–65.

7. Steketee RW, Nahlen BL, Parise ME, Menendez C. The burden of malaria in pregnancy in malaria-endemic areas. *Am J Trop Med Hyg* 2001; *64*(Suppl 1–2): 28–35.

8. Newman RD, Hailemariam A, Jimma D, Degifie A, Kebede D, Rietveld AE, *et al*. Burden of malaria during pregnancy in areas of stable and unstable transmission in Ethiopia during a nonepidemic year. *J Infect Dis* 2003; *187*(11): 1765–72.

9. Parise ME, Ayisi JG, Nahlen BL, Schultz LJ, Roberts JM, Misore A, *et al*. Efficacy of sulfadoxine-pyrimethamine for prevention of placental malaria in an area of Kenya with a high prevalence of malaria and human immunodeficiency virus infection. *Am J Trop Med Hyg* 1998; *59*(5): 813–22.

10. Cot M, Brutus L, Pinell V, Ramaroson H, Raveloson A, Rabeson D, Rakotonjanabelo AL. Malaria prevention during pregnancy in unstable transmission areas: the highlands of Madagascar. *Trop Med Int Hlth* 2002; *7*(7): 565–72.

11. Nosten F, Ter Kuile F, Maelankiri L, Chongsuphajaisiddhi T, Nopdonrattakoon L, Tangkitchot S, *et al*. Mefloquine prophylaxis prevents malaria during pregnancy: a double-blind, placebo-controlled study. *J Infect Dis* 1994; *169*(3): 595–603.

12. Greenwood AM, Armstrong JR, Byass P, Snow RW, Greenwood BM. Malaria chemoprophylaxis, birth weight and child survival. *Trans R Soc Trop Med Hyg* 1992; *86*(5): 483–5.

13. Greenwood AM, Menendez C, Todd J, Greenwood BM. The distribution of birth weights in Gambian women who received malaria chemoprophylaxis during their first pregnancy and in control women. *Trans R Soc Trop Med Hyg* 1994; *88*(3): 311–2.

14. Greenwood BM, Greenwood AM, Snow RW, Byass P, Bennett S, Hatib-N'Jie AB. 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*(5): 589–94.

15. Phillips-Howard PA, Nahlen BL, Kolczak MS, Hightower AW, Ter Kuile FO, Alaii JA, *et al*. Efficacy of permethrin-treated bednets in the prevention of mortality in young children in an area of high perennial malaria transmission in western Kenya. *Am J Trop Med Hyg* 2003; *68*(Suppl 4): 23–9.

16. Menendez C, Todd J, Alonso PL, Lulat S, Francis N, Greenwood BM. Malaria chemoprophylaxis, infection of the placenta and birth weight in Gambian primigravidae. *J Trop Med Hyg* 1994; *97*(4): 244–8.

17. Steketee RW, Wirima JJ, Hightower AW, Slutsker L, Heymann DL, Breman JG. The effect of malaria and malaria prevention in pregnancy on offspring birth weight, prematurity, and intrauterine growth retardation in rural Malawi. *Am J Trop Med Hyg* 1996; *55*(Supp1): 33–41.

18. Cot M, Le Hesran JY, Miailhes P, Esveld M, Etya'ale D, Breart G. Increase of birth weight following chloroquine chemoprophylaxis during the first pregnancy: results of a randomized trial in Cameroon. *Am J Trop Med Hyg* 1995; *53*(6): 581–5.

19. Bouvier P, Breslow N, Doumbo O, Robert CF, Picquet M, Mauris A, Dolo A, Dembele HK, Delley V, Rougemont A. Seasonality, malaria, and impact of prophylaxis in a West African village. II: Effect on birth weight. *Am J Trop Med Hyg* 1997; *56*(4): 384–9.

20. Molyneux L, Gramicca G. *The Garki project: research on the epidemiology and control of malaria in the Sudan Savanna of West Africa*. Geneva: World Health Organization 1980.

21. Riley EM, Wagner GE, Ofori MF, Wheeler JG, Akanmori BD, Tetteh K, *et al*. Lack of association between maternal antibody and protection of African infants from malaria infection. *Infect Immun* 2000; *68*(10): 5856–63.

22. Ross A, Smith T. The effect of malaria transmission intensity on neonatal mortality in endemic areas. *Am J Trop Med Hyg* 2006; *75*(Suppl 2): 74–81.

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