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Maternal anaemia as an indicator for monitoring malaria control in pregnancy in sub-Saharan Africa

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Design Malarial anaemia is a major problem in many developing countries and often occurs more frequently in first pregnancies, as primigravidae are more susceptible to *Plasmodium falciparum* malaria and are at excess risk of malarial anaemia.

Objective and methods To analyse the excess risk of anaemia in primigravidae as a potential indicator of malaria control and exposure in pregnant women living in sub-Saharan Africa. The sensitivity, specificity and predictive values for anaemia in first compared with later pregnancies are calculated for 27 studies from malarious and 7 studies from nonmalarious areas.

Setting Surveys of pregnancy anaemia reported for highly malarious and nonmalarious areas.

Results In malarious areas, the weighted odds ratio for excess anaemia (haemoglobin [Hb] <11 g/dl) in primigravidae compared with multigravidae for all studies was 1.34 (95% CI 1.14–1.58). At an Hb cutoff below 8 g/dl, the weighted odds ratio was 1.79 (95% CI 1.52–2.10). In nonmalarious areas, there was no increased risk of anaemia in primigravidae with Hb below 11 g/dl (OR 0.80; 95% CI 0.63–1.90) or below 8 g/dl (OR 0.82, 95% CI 0.51–1.28).

Conclusions In view of the consistency of results across highly malarious areas compared with nonmalarious areas, maternal anaemia has the potential to be used for surveillance of malaria control in pregnancy. Based on the analysis, an anaemia nomogram is developed for use as a surveillance indicator in malarious areas in sub-Saharan Africa.

Keywords Anaemia, indicators, malaria, nomogram, pregnancy.

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Introduction

Anaemia is a major problem in all developing countries, especially in pregnant or lactating women and in children. In 1992, the estimated prevalence of anaemia in pregnant women was 56% in developing countries, and in Africa, the overall prevalence ranged from 35% in Southern to 56% in Western Africa.[1] The World Health Organization (WHO) defines anaemia in pregnancy as a haemoglobin (Hb) concentration less than 11 g/dl and severe anaemia as less than 7 g/dl. The high prevalence of anaemia is of major importance because if untreated it can lead to preterm delivery, low birthweight and if severe maternal mortality.[2,3]

The aetiology of anaemia in pregnancy is often multifactorial with causes related to nutritional deficiency of iron, folate, vitamin A or other nutrients, haemoglobinopathies, HIV infection or parasitic diseases, such as hookworm, schistosomiasis and malaria.

In sub-Saharan Africa, malaria is a major contributory cause of anaemia, especially among primigravidae living under holoendemic or perennial malaria exposure. It is well documented that primigravidae have greatly increased susceptibility to *Plasmodium falciparum* malaria compared with multigravidae living under these malaria endemic conditions,[4] and this difference in susceptibility could be reflected in increased prevalence or excess anaemia risk in primigravidae compared with multigravidae. This increased risk in first pregnancies should occur despite variation in genetic factors, influencing Hb, which should be equivalent across parity groups. Nutritional deficiencies would be expected to be more prevalent in

multigravidae due to the cumulative nutritional cost of successive pregnancies.

Hb measurements that are often routinely available at first antenatal visits, or at delivery, could potentially provide a surveillance indicator for evaluating the effectiveness of malaria control in pregnancy or of population malaria control programmes. This would be based on the degree of excess risk of anaemia in primigravidae compared with multigravidae for women living under malarious conditions.

To compare the sensitivity of this risk ratio in relation to malaria exposure, this analysis compares the degree of excess risk of anaemia in first compared with later pregnancies in women living under malarious and nonmalarious conditions. The assessment forms the basis for developing a simple anaemia chart or nomogram, which could be used as a tool for estimating malaria exposure in pregnancy. A previous analysis using this methodological approach has been proposed using birthweight as an indicator of malaria control in pregnancy.[5,6]

Materials and methods

A review was undertaken to identify published and unpublished studies that reported data on maternal Hb, anaemia and parity in pregnant women for populations from both malarious and nonmalarious countries. The analysis was based on malarious areas with high transmission, or which are considered holoendemic, and these were all from sub-Saharan Africa except for two from Papua New Guinea (PNG). A comprehensive search of the Medline database was completed between 1966 and 2003, which included papers in English or other European languages. Papers identified without parity data were excluded. The search terms used were: haemoglobin, pregnancy, pregnant, nonpregnant, anaemia, parity, gravida, obstetric and maternal. Data were also obtained from the Demographic and Health Surveys (DHS). The DHS is a programme funded by the US Agency for International Development and implemented by ORC Macro International Inc. DHS+ are conducted in numerous countries approximately every 5 years. They are nationally representative household surveys with large sample sizes (usually between 5000 and 30 000). The surveys provide data in the areas of population, health and nutrition (Measure DHS+; ORC Macro; Macro International Inc., Calverton, MD, USA; http://www.measuredhs.com). In recent years, DHS+ have also conducted anaemia surveys testing finger prick blood samples using the HemoCue technique.

Information on the level of malaria transmission in study areas was recorded if reported. If not reported, a study was classified as located in a malarious or nonmalarious area by identification of its geographical location in relation to reported malaria transmission patterns for tropical countries. Methods used for Hb estimation were recorded. If packed cell volume was reported, this was divided by three to obtain an estimated Hb value.

Odds ratios and 95% confidence intervals were calculated for the excess anaemia risk in primigravidae compared with multigravidae for each study identified and using different Hb cutoff levels (<7, <8, <9, <10 and <11 g/dl). A weighted stratified analysis was completed using the Cochrane Collaboration software, RevMan 4.2, to obtain a pooled odds ratio for each Hb cutoff value. Weighted values were proportional to sample sizes available. This was performed separately for the pregnancies occurring in both malarious and nonmalarious areas. An anaemia nomogram was constructed describing the association between the odds ratios for excess anaemia risk in primigravidae compared with multigravidae, in relation to anaemia prevalence in primigravidae.

A sensitivity and specificity analysis was completed for different odds ratios and anaemia prevalence values in primigravidae to determine the optimal cutoff values using these indicators for detecting malaria exposure in pregnancy. The Youden index was calculated to determine the optimal cutoff to select based on sensitivity and specificity measurements.[7] The Youden index measures the effectiveness of a diagnostic marker or test based on its false-positive and false-negative rates and enables the selection of an optimal threshold value (cutoff point) for the marker. It is defined as (sensitivity + specificity – 1). A Youden index of +1 would indicate an ideal test. The Youden index gives equal weight to sensitivity and specificity, although in clinical practice this is not usually the case. Sensitivity was defined as the proportion of primiparous malarious populations correctly identified from malarious areas using either specific odds ratio values or primigravidae anaemia prevalence. Specificity was defined as the proportion of primiparous populations correctly identified from nonmalarious areas. The positive predictive value is the probability that the primiparous malarious population is actually from a malarious area, and the negative predictive value is the probability that the primiparous nonmalarious population is from a nonmalarious area.

Results

A total of 27 studies were identified from malarious countries, which reported anaemia and parity data in categories suitable for analysis. Data from four published and two unpublished studies for nonmalarious countries were identified, which was suitable for inclusion. These studies represented data from 15 malarious and 7 nonmalarious countries (Table 1). Nineteen studies undertaken in malarious countries provided data using an Hb concentration of <11 g/dl as cutoff. The total sample size was 40 513, with 12 010 primigravidae and 28 503 multigravidae. Six studies from nonmalarious countries used this same Hb cutoff and provided a total sample size of 15 942. The prevalence of mild anaemia in primigravidae

Table 1. List of studies included in analysis

References	Country	Hb method	Gestation
Malarious areas			
Ogbeide *et al.*[8]	Benin	Cyanomethaemoglobin	Booking
DHS[9]	Benin	HemoCue	Survey
Cot *et al.*[10]	Burkina Faso	Haematocrit	Delivery
Meda *et al.*[11]	Burkina Faso	Coulter counter	Booking
Ramon *et al.*[12]	Cote d'Ivoire	Coulter counter	Booking
Haidar *et al.*[13]	Ethiopia	Cyanomethaemoglobin	Village
Mockenhaupt *et al.*[14]	Ghana	HemoCue	Booking
Geelhoed *et al.*[15]	Ghana	Talqvist paper method	Delivery
Browne *et al.*[16]	Ghana	HemoCue	ANC July–November
Browne *et al.*[16]	Ghana	HemoCue	ANC December–April
Shulman *et al.*[17]	Kenya	Coulter counter	Booking
Rogerson *et al.*[18]	Malawi	HemoCue	Booking
Verhoeff *et al.*[19]	Malawi	Cyanomethaemoglobin	Booking
van den Broek *et al.*[20]	Malawi	HemoCue	Booking
DHS[21]	Mali	HemoCue	Survey
Thompson[22]	Namibia	Coulter counter	Booking
Ojo *et al.*[23]	Nigeria	NK	Delivery
Osuhor[24]	Nigeria	Spencer hemoglobinometer	Booking
Isah *et al.*[25]	Nigeria	Coulter model ZF	Booking
Brabin *et al.*[26]	PNG (coastal)	Cyanomethaemoglobin	Booking
Chaita (pers. comm.)[27]	PNG (coastal)	Cyanomethaemoglobin	Booking
Mutabingwa *et al.*[28]	Tanzania	Cyanomethaemoglobin	Enrolment
Matteelli *et al.*[29]	Tanzania	NK	Delivery
Mnyika *et al.*[30]	Tanzania	NK	Booking $\leq$ 24 weeks
Kasumba *et al.*[31]	Uganda	PCV	Delivery
Jackson *et al.*[32]	Zaire	Cyanomethaemoglobin	Booking
van Dongen and van't Hof[33]	Zambia	Colorimetric method	Booking
Nonmalarious areas			
Xiong *et al.*[34]	China	NK	Booking
Gies *et al.*[35]	Ethiopia	HemoCue	Booking
Bondevik *et al.*[36]	Nepal	Haematocrit	Booking
Chaita (pers. comm.)[27]	PNG (highlands)	Cyanomethaemoglobin	Booking
Ross *et al.*[37]	South Africa	Coulter counter	Booking
Hibbard and Hibbard[38]	Singapore	Oxyhaemoglobin	Booking
Forrester (pers. comm.)[39]	West Indies	NK	Booking

ANC, antenatal clinic; DHS, demographic health survey; NK, not known; PCV, packed cell volume.

from malarious areas ranged from 6.7% (Uganda)[31] to 94.3% (Malawi).[19] In nonmalarious areas, the prevalence of anaemia ranged from 6.3% (Ethiopia)[35] to 62.2% (Nepal).[36] Seven studies from malarious areas and two studies from nonmalarious areas were available for analysis, using an Hb cutoff of <8 g/dl. In malarious areas, the prevalence of anaemia (<8 g/dl) ranged from 3.4% (Ghana)[15] to 38.3% (PNG).[26] In the two studies from nonmalarious areas which used an Hb cutoff of <8 g/dl, 3.6% of primigravidae in Nepal,[36] but none in Ethiopia,[35] had anaemia at this level.

There was a significant excess risk of anaemia, as defined using different Hb cutoff values, in primigravidae compared with multigravidae for women living in malarious areas. This difference was not observed for women from nonmalarious areas (Table 2). The odds ratios and their confidence intervals were calculated for Hb cutoff values of: <7, <8, <9, <10 and <11 g/dl and are plotted in Figure 1. The mean odds ratios were 1.73, 1.79, 1.40, 1.35 and 1.32 for each successively higher Hb cutoff for women from malarious areas. For nonmalarious areas, the corresponding mean values were: 0.89, 0.82, 1.09, 0.99 and 0.80. A significant difference between mean odds ratio estimates for malarious or nonmalarious areas was observed at the <11 and <8 g/dl Hb cutoff levels.

For malarious areas at the <11 g/dl cutoff, the odds ratio values ranged in individual studies from 0.82 to 3.03, with a weighted mean value of 1.32 (95% CI 1.15–1.52) (Table 3). When delivery Hb values were excluded, the weighted odds ratio remained almost unchanged at 1.31 (95% CI 1.15–1.51).

Table 2. Mean risk of anaemia in primigravidae compared with multigravidae for different Hb cutoff values

Hb cutoff g/dl	Malarious areas			Nonmalarious areas		
	n	No. of studies	OR (95% CI)	*n*	No. of studies	OR (95% CI)
<11	40 513	19	1.32 (1.15–1.52)	15 942	6	0.80 (0.63–1.00)
<10	11 657	10	1.35 (0.92–1.97)	19 077	4	0.99 (0.71–1.37)
<9	19 750	6	1.4 (1.06–1.83)	12 282	3	1.09 (0.9–1.33)
<8	12 635	7	1.79 (1.52–2.1)	2521	2	0.82 (0.52–1.28)
<7	34 006	12	1.73 (1.34–2.24)	12 282	3	0.89 (0.54–1.45)

n, sample size.

The odds ratio increased to 1.34 (95% CI 1.14–1.58) when the DHS surveys were also excluded, as some of these may have measured Hb values close to delivery. In nonmalarious areas, there was no increased risk of anaemia at this level in primigravidae with a mean odds ratio of 0.80 (95% CI 0.63–1.0). Heterogeneity was considerable in both the malarious and nonmalarious areas (I^2 = 80.9 and 75.2%, respectively).

At the <8 g/dl cutoff, the mean weighted odds ratio for malarious areas was 1.79 (95% CI 1.52–2.10) (n = 12 635). If delivery samples were excluded, the odds ratio decreased slightly to 1.72 (95% CI 1.47–2.00). Estimates for individual studies ranged from 0.93 in a survey from Mali[21] to 2.32 in a survey from Benin[9] (Table 4). For the studies from China and Ethiopia that were assigned as nonmalarious areas,[34,35] the combined sample size was 2521, and the mean odds ratio was 0.82 (95% CI 0.52–1.28).

The results of the sensitivity analyses and Youden index scores are summarised in Table 5. At the <11 g/dl cutoff, the highest sensitivity observed at odds ratio of 0.9 was 79%, with a corresponding specificity of 66.7% (Table 5). The highest specificity of 100% was observed at odds ratios of 1.2 and 1.3, but these odds ratio values corresponded to lower sensitivities (53 and 37%, respectively). Positive predictive values ranged from 71.7 to 100%, with negative predictive values ranging from 33.3 to 44.4%. At the <8 g/dl Hb cutoff, all odds ratios had 100% specificity, with positive predictive values of 100%. The odds ratio of 1.3 showed the highest sensitivity (85.7%) and the highest negative predictive value (66.7%). Sensitivity and specificity for anaemia prevalence in primigravidae ranged from 10.5 to 94.7% and from 33.3 to 100%, respectively, for anaemia using the <11 g/dl cutoff (Table 5). At the <8 g/dl, there was 100% specificity and 57.1% sensitivity for a corresponding anaemia prevalence in primigravidae of 10 or 20%, respectively.

Figures 2 and 3 present the scatter plot of the data in Tables 3 and 4, illustrating the relationship between anaemia prevalence in primigravidae (y axis) and the odds ratio for excess risk of anaemia in primigravidae compared with multigravidae (x axis). On the basis of the sensitivity analysis using the Youden index (Table 5), values of 40% anaemia prevalence and an odds ratio of 1.2 were selected for optimally distinguishing between malarious and nonmalarious populations at the Hb cutoff of 11 g/dl. For the Hb cutoff of <8 g/dl, an odds ratio of 1.3 and anaemia prevalence of 10% were selected (Table 5).

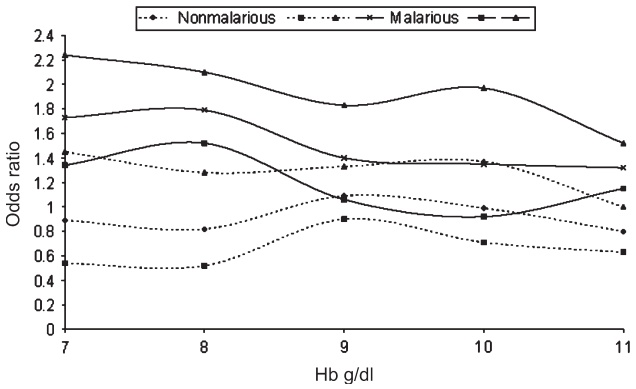

Figure 1. Mean risk of anaemia in primigravidae compared with multigravidae in malarious and nonmalarious regions with upper and lower 95% CI.

Discussion

This study raised two questions: first, was there an excess anaemia risk in primigravidae compared with multigravidae for women living mostly in highly malarious areas but no excess risk for women living in nonmalarious areas. The second question related to the potential for anaemia to be used as an indicator of malaria control.

There was a greater excess risk of anaemia at all Hb cutoff values in primigravidae compared with multigravidae from the malarious areas. This was not observed in studies reporting data from nonmalarious areas. This clearly indicates that there is a significant parity difference in anaemia risk between these malarious and nonmalarious regions. This difference can be attributed to malaria-associated anaemia as maternal nutritional causes of anaemia, conversely should affect

Table 3. Anaemia risk at Hb <11 g/dl

Study	PG *n/N*	MG *n/N*	Weight %	OR (95% CI)
Malarious areas*				
DHS[9]	64/81	204/291	3.35	1.61 (0.89–2.90)
Meda *et al.*[11]	314/460	1210/1848	6.91	1.13 (0.91–1.41)
Ramon *et al.*[12]	219/285	939/1360	6.03	1.49 (1.10–2.00)
Haidar *et al.*[13]	64/349	202/1100	5.89	1.00 (0.73–1.36)
Mockenhaupt *et al.*[14]	95/130	189/400	4.61	3.03 (1.96–4.68)
Geelhoed *et al.*[15]	543/1966	735/3921	7.78	1.65 (1.46–1.88)
Shulman *et al.*[17]	54/73	154/202	3.19	0.89 (0.48–1.64)
Rogerson *et al.*[18]	943/1563	1754/3148	7.81	1.21 (1.07–1.37)
Verhoeff *et al.*[19]	755/801	2618/2887	5.76	1.69 (1.22–2.33)
van den Broek *et al.*[20]	936/1554	1723/3092	7.81	1.20 (1.06–1.36)
van den Broek *et al.*[20]	557/681	1119/1612	6.88	1.98 (1.59–2.47)
DHS[21]	63/258	310/1391	5.89	1.00 (0.73–1.36)
Thompson[22]	27/68	44/103	3.13	0.88 (0.47–1.65)
Isah *et al.*[25]	17/33	28/62	2.05	1.29 (0.55–3.01)
Brabin *et al.*[26]	56/60	221/234	1.24	0.82 (0.26–2.62)
Chaita (pers. comm.)[27]	2417/2774	3373/3833	7.61	0.92 (0.80–1.07)
Kasumba *et al.*[31]	10/150	29/369	2.47	0.84 (0.40–1.76)
Jackson *et al.*[32]	439/610	1685/2340	7.13	1.00 (0.82–1.22)
van Dongen and van't Hof[33]	50/114	73/310	4.43	2.54 (1.61–3.99)
Total	7623/12 010	16 610/28 503	100	1.32 (1.15–1.52)
Nonmalarious areas**				
Gies *et al.*[35]	9/142	23/261	6.33	0.70 (0.31–1.56)
Bondevik *et al.*[36]	820/1319	497/799	24.12	1.00 (0.83–1.20)
Chaita (pers. comm.)[27]	1121/4440	1895/6747	27.38	0.86 (0.79–0.94)
Ross *et al.*[37]	98/261	271/785	19.48	1.14 (0.85–1.52)
Hibbard and Hibbard[38]	12/185	58/630	8.61	0.36 (0.19–0.69)
Forrester (pers. comm.)[39]	39/341	64/302	14.05	0.48 (0.31–0.74)
Total	2099/6688	2808/9254	100	0.80 (0.63–1.00)

DHS, demographic health survey; MG, multigravidae; PG, primigravidae.
*Test for heterogeneity: $Chi^2 = 94.05$, $df = 18$ ($P < 0.00001$); $I^2 = 80.9\%$; Test for overall effect: $Z = 3.9$ ($P < 0.0001$).
**Test for heterogeneity: $Chi^2 = 20.13$, $df = 5$ ($P = 0.001$); $I^2 = 75.2\%$; Test for overall effect: $Z = 1.96$ ($P = 0.05$).

multigravidae to a greater extent than primigravidae, due to the cumulative nutritional cost of successive pregnancies. In view of the consistency of the results across several malaria endemic areas, it is concluded that maternal anaemia has the potential to be used as an indicator of malaria exposure and control in pregnant women.

Figure 1 shows that in malarious areas there is a higher risk of anaemia than in nonmalarious areas for all Hb cutoff values. This difference in risk was significant only at the <11 and <8 g/dl cutoff values. At the WHO recommended Hb values for severe anaemia of <7 g/dl, the difference was not statistically significant. At the <8 g/dl level, the largest excess risk of anaemia in primigravidae in malarious countries was observed (79% increased risk). The analysis is limited by the fact that there were few studies available from nonmalarious areas that were suitable for inclusion. This was especially the case for severe anaemia as the number of women with severe anaemia in each study was small. In the study from Ethiopia, no primigravidae had severe anaemia.

The allocation of a study area as malarious or as nonmalarious was based primarily on geographical location of the study site, as not all reports provided exact information on the levels of malaria transmission in the study location. Entomological inoculation rates (EIRs) for mosquito biting frequencies in these areas were mostly not available. The results are, however, consistent with the reported decline in Hb levels with increases in the *P. falciparum* parasite ratio in children less than 15 years old (a measure of the intensity of transmission) in sub-Saharan Africa.[40] Although mixed infections with *Plasmodium vivax* occur in these locations, *P. falciparum* is the predominant parasite. Outside sub-Saharan Africa this pattern alters, first because *P. vivax* is more often the primary infection as in India and much of South-East Asia and second because malaria endemicity may be lower leading to less frequent infection in women in their first pregnancies with

Table 4. Anaemia risk at Hb <8 g/dl

Study	PG *n/N*	MG *n/N*	Weight %	OR (95% CI)
Malarious areas*				
Ogbeide *et al.*[8]	5/118	7/317	1.89	1.96 (0.61–6.30)
DHS[9]	19/81	34/291	6.39	2.32 (1.24–4.33)
Geelhoed *et al.*[15]	67/1966	62/3921	18.78	2.20 (1.55–3.12)
Verhoeff *et al.*[19]	239/801	563/2887	54.14	1.76 (1.52–2.10)
DHS[21]	10/258	58/1391	5.38	0.93 (0.47–1.84)
Brabin *et al.*[26]	23/60	73/234	7.18	1.37 (0.76–2.47)
Mutabingwa *et al.*[28]	22/105	24/205	6.24	2.00 (1.06–3.77)
Total	385/3389	821/9246	100	1.79 (1.52–2.10)
Nonmalarious areas**				
Bondevik *et al.*[36]	47/1319	34/799	97.86	0.83 (0.53–1.30
Gies *et al.*[35]	0/142	2/261	2.14	0.36 (0.02–7.64
Total	47/1461	36/1060	100	0.82 (0.52–1.28)

DHS, demographic health survey; MG, multigravidae; PG, primigravidae.
*Test for heterogeneity: $Chi^2 = 6.49$, $df = 6$ ($P = 0.37$); $I^2 = 7.5\%$; Test for overall effect: $Z = 7.04$ ($P = 0.00001$).
**Test for heterogeneity: $Chi^2 = 0.28$, $df = 1$ ($P = 0.60$); $I^2 = 0\%$; Test for overall effect: $Z = 0.89$ ($P = 0.37$).

reduced risk of anaemia in primigravidae. This pattern is described, for example, in some malarious areas of Thailand.[41,42] For these reasons, the findings reported in this analysis would not apply to countries where transmission is lower than that in sub-Saharan Africa.

Maternal HIV infection is a potential confounding factor but HIV prevalence in Africa is often higher in older women in malaria endemic areas and HIV-associated anaemia risk would therefore be greater in multigravidae. HIV as a contributory factor to malarial anaemia must be considered, as *P. falciparum* parasitaemia is more frequent in HIV-infected women.[43] This implies that HIV-related malarial anaemia would occur more commonly in those with highest HIV prevalence. The magnitude of these effects could not be assessed in the present study, as maternal HIV status was not reported for most of these studies. Significant differences in parity-specific anaemia risk were identified despite the considerable expected variation between these studies in maternal HIV

Table 5. Predictive estimates for identification of malaria exposure in pregnancy in relation to odds ratios for excess anaemia primigravidae and anaemia prevalence

Odds ratio						Primigravidae anaemia prevalence					
OR	Sensitivity	Specificity	Youden index	PPV	NPV	% PG	Sensitivity	Specificity	Youden index	PPV	NPV
Hb <11 g/dl											
0.9	79.0	66.7	0.46	88.2	50.0	10	94.7	33.3	0.28	81.8	66.7
1.0	74.0	66.7	0.41	87.5	44.4	20	89.5	50.0	0.40	85.0	60.0
1.1	57.9	83.3	0.41	71.7	38.5	30	79.0	66.7	0.46	88.2	50.0
1.2	53.0	100	0.53*	100	40.0	40	73.7	83.3	0.57*	93.3	50.0
1.3	36.9	100	0.37	100	33.3	50	68.4	83.3	0.52	92.9	41.7
						60	63.2	83.3	0.47	92.9	45.5
						70	47.4	100	0.47	100	60.0
						80	21.1	100	0.21	100	28.6
						90	10.5	100	0.11	100	35.5
Hb <8 g/dl											
1.3	85.7	100	0.86	100	66.7	10	57.1	100	0.57	100	40.0
1.4	71.4	100	0.71	100	50.0	20	57.1	100	0.57	100	40.0

NPV, negative predictive value; OR, odds ratio for excess risk of anaemia in primigravidae compared with multigravidae;
% PG, primigravidae who are anaemic; PPV, positive predictive value.
*Optimal threshold value.

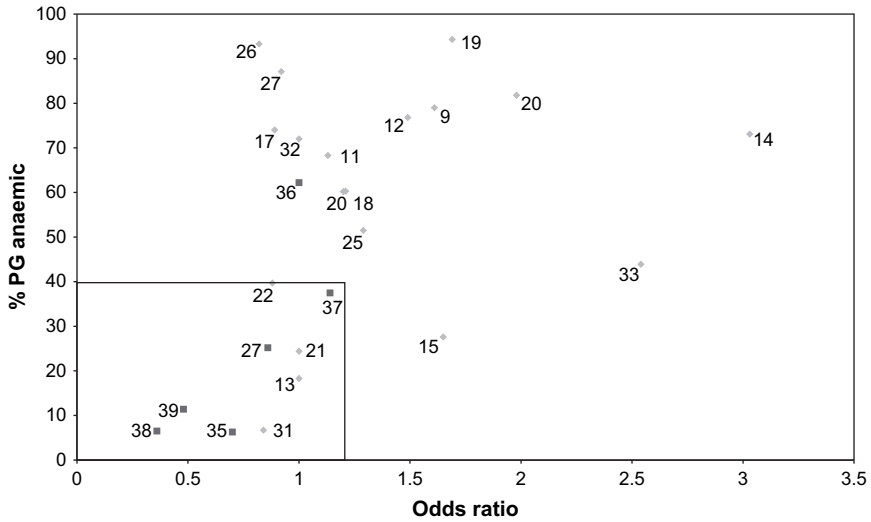

Figure 2. Anaemia nomogram (Hb <11 g/dl) for surveillance of malaria control in pregnancy. Diamond, malarious areas; square, non-malarious areas. Numbers indicate reference.

prevalence. Most studies were from countries in West Africa where HIV prevalence is still relatively low or were obtained early in the HIV epidemic when prevalence was low (e.g. Tanzania). The analysis should be repeated to include areas with high HIV prevalence (>20%) as is the case in several countries in East Africa today. The Malawi data summarised in Table 1 were from communities with high HIV prevalence and for those women in whom the excess risk of anaemia in primigravidae remained statistically significant.

In any meta-analysis, the selection criteria of the studies included in the analysis are crucial. A test has been devised that determines whether there are true differences between studies (heterogeneity) or whether the variation in the results is caused by random chance (homogeneity). This test of heterogeneity is affected by the number of studies in the analysis. The Cochrane Review group has developed a quantity, I^2, to assess consistency of these results.[44] It is proposed that heterogeneity is poor when there are a small number of studies, that a nonsignificant result does not prove homogeneity and also that the converse is true, i.e. the test has too much power when many large studies are included.[44] The parameter I^2 was devised to assess 'the percentage of total variation across studies that is due to heterogeneity rather than chance'. A value of 0% shows homogeneity with heterogeneity increasing as the percentage value increases.

The present analysis showed that there were significantly high levels of heterogeneity between studies at most Hb cutoff values for malarious areas, except for the value of <8 g/dl. The

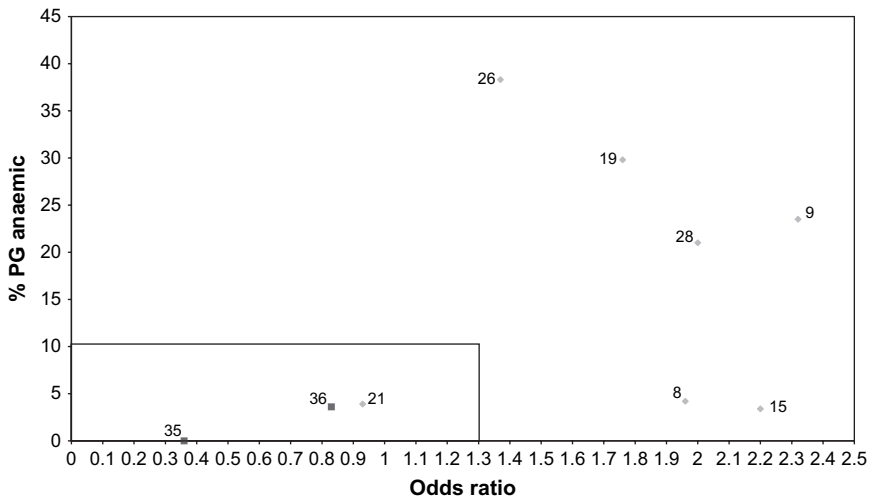

Figure 3. Anaemia nomogram (Hb <8 g/dl) for surveillance of malaria control in pregnancy. Diamond, malarious areas; square, nonmalarious areas. Numbers indicate reference.

studies from nonmalarious areas were homogeneous, with the exception of those for Hb values <7 g/dl. The large amount of heterogeneity in this analysis would seem to imply that although the overall effect is significant the findings may not necessarily be extrapolated to other populations. This can only be assessed with the availability and inclusion of further studies. The number of available studies that reported anaemia as well as parity was very limited and a wide variety of methods were used in the different studies to determine anaemia status. These included Cyanomethaemoglobin, Talqvist paper method, Coulter counter and various photometers, such as the Spencer hemoglobinometer, HemoCue and Grey-wedge photometers. The heterogeneity could in part be due to the variety of these methodologies.

A further variable characteristic between studies was the time during pregnancy when Hb was assessed. Most studies had measured Hb at the first antenatal visit, although even those assessed at antenatal booking could have substantial variation in time of gestation at first attendance. In the China report, the mean gestational age at the first antenatal visit was 10.4 ± 2.7 weeks.[34] In contrast, in Malawi, only 33.5% of primigravidae and 22.2% of multigravidae attended the antenatal clinic before 18 weeks of gestation.[19] The data were not presented in these studies in a form that made it possible to assess anaemia risk at specific gestational ages. This variation would result in heterogeneity.

Despite these possible limitations, the anaemia nomogram that was based on the sensitivity analysis showed clearly the division between malarious and nonmalarious areas based on anaemia criteria alone. At the <11 g/dl cutoff, four studies plotted in the 'nonmalarious' transmission zone, one was from Namibia,[22] which could be a low transmission malarious area, and one was from Uganda in which anaemia status was measured at delivery.[31] The two other studies[13,21] were from a DHS survey in Mali and from a village in Ethiopia in which women may have been surveyed nearer to delivery than in the other studies which were conducted at antenatal booking. The other study conducted at delivery from Ghana[15] also had a lower prevalence of anaemia among primigravidae compared with the other studies from malarious areas. This may relate to antenatal use of antimalarials or haematinics. Only one study from nonmalarious areas, a study from Nepal,[36] plotted in the malarious zone. This study reported haematocrit values only, which were adjusted for altitude. At the <8 g/dl cutoff, only one study plotted outside the expected zone that was a DHS survey from Mali which plotted in a nonmalarious area.[21] Without precise information on malaria parasitaemia or transmission intensity in this population, the validity of this plot remains uncertain.

The routine use of maternal anaemia data for malaria surveillance would be very advantageous as Hb status is routinely checked at booking in antenatal clinics in many sub-Saharan African facilities, and these data could be made available for national surveillance. The prevalence of maternal anaemia if recorded at both booking and delivery has the potential to be used to measure the effectiveness of malaria control intervention strategies in pregnancy and in pregnant women as representative of the general population. The cutoff values used in the anaemia nomogram presented in this paper are based essentially on Hb levels at booking. However, inclusion of studies reporting Hb at delivery did not substantially alter the weighted odds ratio estimates.

Further research is required to establish the optimal odds ratio values to be used both in relation to malaria endemicity and gestational age at Hb measurement. The inclusion of data from more studies in particular from areas with known malaria transmission intensities will help clarify the thresholds. Since the nomogram was derived, new data from five recent studies were obtained.[45–49] Four studies were carried out in reportedly malarious areas, in Mali, Nigeria, Cameroon and Sudan. One study from Rwanda contained data from both malarious and nonmalarious districts.[49] The prevalence of anaemia, Hb <11 g/dl, among primigravidae in the malarious areas ranged from 23.1 to 80.6%. The odds ratios ranged from 0.77 to 1.83. All of the studies from malarious area plotted in the malarious area of the nomogram. The study from the nonmalarious area, with an odds ratio of 0.69 and an anaemia prevalence among primigravidae of 3.4% would also have been correctly identified as nonmalarious area by using the nomogram. When these studies were included in the sensitivity analyses, the Youden index increased from 0.53 to 0.54 using an odds ratio of 1.2 and from 0.57 to 0.61 at the 40% prevalence cutoff.

In practice if Hb measured at booking can be used then there is a better chance that the nomogram might be adapted for practical use, as this would not overburden antenatal systems with a complicated tool for measurement. Constraints on Hb data collection would restrict its widespread use. If the nomogram is to be used as an indicator of malaria control, then it should be demonstrated that it shows a relation to transmission intensity (ideally EIR). The EIR values were not available from the referenced papers used for this analysis, and further work should be undertaken using EIR estimates to assess their correlation with anaemia indicators in pregnancy. This exercise could include online access to current data sources to enable EIR values and to current anaemia status to be correlated with the same locations.

The analysis suggests that a cutoff of Hb <8 g/dl would be more sensitive as a malaria control indicator than the current WHO recommended cutoff of <7 g/dl for severe anaemia. Using a cutoff of Hb 8 g/dl, pregnancy anaemia prevalence at delivery in southern Malawi was reduced from 28.6 to 15.5% in primigravidae and from 19.1 to 15.9% in multigravidae following the introduction of a community based programme to increase uptake of intermittent preventive antimalarials during pregnancy (unpublished data). This

corresponded to a reduction in odds ratio values from 1.7 at baseline to 0.91 2 years following introduction of the programme when *P. falciparum* parasite prevalence at delivery had also fallen. This example demonstrates the potential utility of the nomogram. A similar approach has been proposed using low birthweight surveillance as an indicator of malaria control in pregnancy,[6] and the combined use of both anaemia and birthweight indicators could enhance the utility of this approach for routine monitoring for malaria control in pregnancy in sub-Saharan Africa.

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