Tropical Medicine and International Health

VOLUME 9 NO 10 PP 1050–1065 OCTOBER 2004

Impact of malaria control on childhood anaemia in Africa – a quantitative review

Eline L. Korenromp[1], Joanna R. M. Armstrong-Schellenberg[2], Brian G. Williams[3], Bernard L. Nahlen[1] and Robert W. Snow[4]

1 *World Health Organization, Roll Back Malaria, Geneva, Switzerland*
2 *Ifakara Health Research and Development Centre, Ifakara, Tanzania, and London School of Hygiene & Tropical Medicine, London, UK*
3 *World Health Organization, Stop TB, Geneva, Switzerland*
4 *KEMRI Wellcome Trust Collaborative Programme, Nairobi, Kenya, and Centre for Tropical Medicine, University of Oxford, Oxford, UK*

Summary

OBJECTIVE To review the impact of malaria control on haemoglobin (Hb) distributions and anaemia prevalences in children under 5 in malaria-endemic Africa.

METHODS Literature review of community-based studies of insecticide-treated bednets, antimalarial chemoprophylaxis and insecticide residual spraying that reported the impact on childhood anaemia. Anaemia outcomes were standardized by conversion of packed cell volumes into Hb values assuming a fixed threefold difference, and by estimation of anaemia prevalences from mean Hb values by applying normal distributions. Determinants of impact were assessed in multivariate analysis.

RESULTS Across 29 studies, malaria control increased Hb among children by, on average, 0.76 g/dl [95% confidence interval (CI): 0.61–0.91], from a mean baseline level of 10.5 g/dl, after a mean of 1–2 years of intervention. This response corresponded to a relative risk for Hb < 11 g/dl of 0.73 (95% CI: 0.64–0.81) and for Hb < 8 g/dl of 0.40 (95% CI: 0.25–0.55). The anaemia response was positively correlated with the impact on parasitaemia ($P = 0.005$, $P = 0.008$ and $P = 0.01$ for the three outcome measures), but no relationship with the type or duration of malaria intervention was apparent. Impact on the prevalence of Hb < 11 g/dl was larger in sites with a higher baseline parasite prevalence. Although no age pattern in impact was apparent across the studies, some individual trials found larger impacts on anaemia in children aged 6–35 months than in older children.

CONCLUSION In malaria-endemic Africa, malaria control reduces childhood anaemia. Childhood anaemia may be a useful indicator of the burden of malaria and of the progress in malaria control.

keywords malaria/prevention and control, anaemia, Africa, children, insecticide-treated mosquito nets, insecticide residual spraying, chemoprophylaxis, intermittent preventive therapy

Introduction

Malaria is one of the factors that contribute to anaemia in children under 5 in sub-Saharan Africa, accounting for 18% of the disability-adjusted life-years (DALYs) lost because of anaemia [defined as haemoglobin (Hb) below 11 g/dl] according to the Global Burden of Disease for 1990 (Murray & Lopez 1996). Anaemia among African children is a haematological state determined by combinations of nutritional deficiencies (iron, folic acid, other micronutrients and protein-calorie malnutrition), iron loss through helminth infections, the destruction and decreased production of red blood cells by infectious diseases and the genetic constitution of red cell Hb (Menendez *et al.* 2000; Stoltzfus *et al.* 2000; Nussenblatt & Semba 2002). Anaemia is an important contributor to malaria-attributable deaths in hospitals, with severe anaemia accounting for between 17% and 54% of malaria-attributed deaths in children under 5 years of age (Slutsker *et al.* 1994; Marsh *et al.* 1995; Biemba *et al.* 2000). Furthermore, both severe and more moderate or mild anaemia may act as risk factors that predispose children to fatal outcomes because of other conditions (McDermott *et al.* 1996; Brabin *et al.* 2001, 2003). The prevalence of anaemia might therefore serve as a predictor of malaria-related mortality. Just as the deaths from acute severe malaria in hospitals do not capture the full burden of malaria-related mortality (Greenwood *et al.* 1987; Breman 2001), the incidence of severe malarial anaemia in hospitals constitutes only part of the morbidity burden to which malaria contributes. Therefore, the prevalence of (symptomatic and asymptomatic) anaemia in the community, as measured in population-based surveys,

is taken as the candidate indicator of the total malaria-related disease burden.

It is important to understand the impact that malaria control is likely to have on anaemia prevalences in children in malaria-endemic Africa, for a number of reasons. First, there has been an unprecedented increase in investment in malaria control in Africa, led largely by the Roll Back Malaria (RBM) movement (Nabarro & Taylor 1998). One major initiative is to cover at least 60% of children under 5 with insecticide-treated mosquito nets (ITNs) by the year 2010. Over the coming years, the increasing ITN coverage (Curtis *et al.* 2003; Lines *et al.* 2003) should substantially reduce malaria-related morbidity and mortality at the community level. However, there has not been any systematic, contemporary review of the likely impact upon anaemia across Africa should this target be reached.

Secondly, there is still a paucity of reliable indicators that can be used to measure short-term, malaria-specific health impacts at country levels. Most importantly, malaria-attributable mortality, an important aspect of the burden of malaria and the overall RBM target (Nabarro & Taylor 1998), is difficult to define and diagnose, especially in young children (O'Dempsey *et al.* 1993; Mung'ala & Snow 1994; Todd *et al.* 1994; Breman 2001). Its measurement is confined to clinics – which capture only a small and variable fraction of the malaria burden (Breman 2001) – and, at a population level, to selected, small-scale sentinel 'demographic surveillance' sites (INDEPTH Editorial Team 2002). Indicators collected more widely through population-based surveys have, on the other hand, largely been confined to non-specific health outcomes, such as all-cause child mortality, fever and other self-reported symptoms, and anthropometric measurements. If the response of anaemia to various malaria interventions is known, anaemia might serve as an indicator of the success of malaria programmes. This would be a useful addition to the limited list of current indicators that can be used to measure the burden of malaria and the impact of malaria control over time, particularly for African populations living at endemic malaria risk.

Several trials of interventions that suppress or prevent malaria infection, including insecticide-treated bednets, antimalarial chemoprophylaxis and insecticide residual spraying (IRS) measured the effect on anaemia in African children (Draper 1960; Bradley-Moore *et al.* 1985b; Snow *et al.* 1987, 1988; Greenwood *et al.* 1988; Bradley 1991; Alonso *et al.* 1993; D'Alessandro *et al.* 1995; Premji *et al.* 1995; Binka *et al.* 1996; Shiff *et al.* 1996; Menendez *et al.* 1997; Marbiah *et al.* 1998; Fraser-Hurt *et al.* 1999; Abdulla *et al.* 2001; Schellenberg *et al.* 2001; Maxwell *et al.* 2002; ter Kuile *et al.* 2003b; Massaga *et al.* 2003). They have generally found a marked impact, in terms of increased mean Hb or packed cell volume (PCV), or a reduced prevalence or incidence of anaemia. Comparing these impacts is, however, not straightforward, because of the multiplicity of definitions and cut-off values used to define anaemia and differences in the age groups studied and in the intensity or success of malaria suppression.

We review community-based, controlled studies in malaria-endemic parts of Africa that measured the effect of malaria interventions on increasing Hb or PCV distributions, or in reducing the prevalence of anaemia in children. Anaemia impacts were standardized across studies and, in multivariate regression, related to the type and duration of the intervention, the corresponding impact on malaria infection prevalence and background characteristics of the study populations. Comparing the estimated impact on anaemia that might typically be expected from improved malaria control with Hb distributions found in recent large-scale surveys among African children under 5 years of age, we explore the possible impact of widely implemented malaria control on Hb outcomes from national surveys, and we consider whether such Hb shifts in surveys could be used as the target or benchmark for the success of RBM programmes.

Methods

Search and review of malaria intervention studies

Studies were identified via a PubMed search using combinations of the keywords: 'h(a)emoglobin, h(a)ematocrit, packed cell volume, an(a)emia, malaria, trial, control, intervention, bednet, residual/insecticide spraying, chemoprophylaxis, and intermittent preventive or presumptive therapy or treatment'. References in eligible publications and relevant reviews (Prinsen Geerligs *et al.* 2003) were checked to identify further studies that might have been missed in the electronic search. We included malaria intervention studies that fulfilled the following eligibility criteria:

- Dealing with malaria control with ITN, IRS, antimalarial chemoprophylaxis or intermittent preventive treatment (IPT). Chemoprophylaxis studies with drugs that were found by the authors to be locally ineffective, because of parasite resistance, were excluded (e.g. the pyrimethamine arms in Bjorkman *et al.* 1980, 1986, where pyrimethamine, in contrast to chlorproguanil and chloroquine, did not reduce malaria parasite rates below the level of the control group).
- Randomization undergone by community (for any intervention) or individual subjects (for chemo-

prophylaxis or IPT). Because few randomized studies were available, five non-randomized, controlled studies (Bjorkman *et al.* 1986; Alonso *et al.* 1993; D'Alessandro *et al.* 1995; Premji *et al.* 1995; Shiff *et al.* 1996; Maxwell *et al.* 2002) and three longitudinal studies that did pre–post-comparisons were also included (Draper 1960; Bradley 1991; Abdulla *et al.* 2001; McClean & Senthilselvan 2002).

- Conducted in African countries.
- Measured the impact on anaemia in children under 5 years with minimum and maximum age specified in months.
- As outcome measures reported increase in mean Hb level, the increase in mean PCV, or the reduction in the prevalence of Hb below 8 g/dl or 11 g/dl or of PCV below 25% or 33%, as measured in community-based surveys.
- Prevalence of infection with *Plasmodium falciparum* in the study subjects at baseline, or alternatively in the comparison arm during the study, was known.
- Mean Hb value in the study subjects at baseline, or alternatively in the comparison arm during the study, was reported or could be estimated from reported mean PCV level or from anaemia prevalence (see below).

Standardization and analysis

Comparison of the results of the trials was not straightforward, because of the different criteria used for classifying anaemia: mean PCV, mean Hb or the prevalence of severe or moderate anaemia according to defined thresholds of PCV or Hb concentration. The studies were standardized in three ways. First, PCV outcomes were converted to Hb levels by dividing them by a factor of 3. This commonly used conversion (World Health Organization 1959; Lundsgaard-Hansen 1996; Menendez *et al.* 2000; Brabin *et al.* 2001; Stoltzfus *et al.* 2003) is supported by numerous population-based studies that showed a stable threefold difference at individual level between Hb and PCV, including among newborns in the USA (Herzog & Felton 1994), among young adult men and women living at high altitude in Bolivia (Vasquez & Villena 2001), and among children in Indonesia (Mustaring *et al.* 1990) and the Gambia (McGregor *et al.* 1966). Secondly, in studies that did not report a mean Hb or PCV level but did report anaemia prevalences according to certain cut-offs, a prevalence of PCV < 25% was taken to correspond to a prevalence of Hb < 8 g/dl, and a prevalence of PCV < 33% was assumed to correspond to a prevalence of Hb < 11 g/dl.

Thirdly, when studies reported the mean Hb or PCV level in the population as well as the SD, we derived the proportion of children with Hb below 8 g/dl and below 11 g/dl, or the proportion of children with PCV below 25% or below 33% from these mean values by assuming normal distributions. This conversion is valid for various African childhood populations (Asobayire *et al.* 2001; ORC Macro – MEASURE *DHS*+ 2001; Mwaniki *et al.* 2002). Haemoglobin distributions are often skewed at their lower end, which might invalidate conversions based on the assumption of normality for the more severe anaemias. Therefore, we pre-tested the validity of this conversion on databases from four large Demographic and Health Surveys (DHS) conducted in African under five populations (Madagascar, Benin, Uganda and Mali; ORC Macro – MEASURE *DHS*+ 2001). These survey populations can be considered to be indicative of the populations tested in the intervention trials considered in our analysis. Across the four survey populations, when deriving the prevalence of Hb < 8 g/dl from the mean Hb level and its SD, the mean relative error in estimated prevalence was only 2.9% (range: 0.4–8) of the true prevalence. For lower Hb cut-offs, however, larger errors were observed (results not shown), and for this reason our analysis did not consider lower Hb cut-offs.

We considered three outcome measures in turn: mean Hb level, the prevalence of Hb below 8 g/dl or of PCV < 25% (reflecting moderate-to-severe anaemia), and the prevalence of Hb below 11 g/dl or of PCV < 33% (reflecting any mild, moderate or severe anaemia) (World Health Organization Communicable Diseases Cluster 2000). For each outcome measure, the determinants of intervention impact were assessed using ordinary least-squares regression in SPSS software, version 11.5 (SPSS, Inc.). The following continuous variables were considered: the duration of the intervention before anaemia impact was tested, the prevalence of *P. falciparum* infection at baseline of the study or in the control arm, the proportional reduction in *P. falciparum* infection prevalence in the intervention arm compared with the control arm, and the Hb level at baseline of the study or in the control arm. The following categorical variables were considered: the type of intervention and the age range of the study subjects. For this purpose, the interventions were classified as ITN, IRS, chemoprophylaxis of any frequency and any (locally effective) antimalarial drug or ITN plus chemoprophylaxis combined.

Based on the age distribution of malaria infection prevalence and anaemia prevalence in endemic areas (Brewster & Greenwood 1993; Cornet *et al.* 1998), we hypothesized that the impact of malaria control would be

greatest in the youngest children, under age 2 or 3 years. The studies were therefore categorized by the age range of the children (at the start of the study), into the following groups: (0) lower age limit between 0 and 5 months and an upper limit between 24 and 36 months, (1) lower limit 3–6 months and upper limit 40–72 months, and (2) lower limit 12 months and upper limit 119 months. Most studies were in category (1). Analysis was at the level of intervention studies, not at the level of individual study subjects; all studies were weighted equally.

Results

All eligible studies (Table 1) were conducted in malaria-endemic parts of Africa. The 23 studies evaluated a total of 29 interventions, with four studies each measuring two interventions (Bjorkman *et al.* 1986; Fuller *et al.* 1988; Greenwood *et al.* 1989; Alonso *et al.* 1993) and one study measuring three interventions (Marbiah *et al.* 1998). For one study, impact was reported at two different time-points after the intervention started (Greenwood *et al.* 1988; Menon *et al.* 1990); here, the report over the longest period was included (Menon *et al.* 1990). Parasite prevalences among under 5s, at baseline varied from 32 to 94% (Table 2). Impact was evaluated mostly 1 or 2 years after the onset of interventions (mean 1.6 years, range: 0.5–4). All studies except one (Maxwell *et al.* 2002) recorded the mean increase in Hb or PCV; one study recorded the mean increase in Hb and in PCV (Bradley-Moore *et al.* 1985a,b), and for this study the Hb outcome was used.

Across the 28 study outcomes, the mean observed increase in Hb was 0.76 g/dl, in a range from 0.1 to 1.8 g/dl (Table 2). Besides increasing mean Hb, the interventions tended to decrease the relative variability in Hb levels within the study populations, with the SD after intervention being on average 1.5 g/dl over a mean of 11.2 g/dl, compared with 1.5 g/dl over a mean of 10.5 g/dl in the comparison groups. The reduced within-population variation in Hb levels can be explained by a proportionally larger Hb increase among those children with the lowest Hb at baseline (data not shown). The mean observed relative risk (RR) of Hb below 11 g/dl or PCV < 33% was 0.73 (range: 0.27–1.00). The mean observed RR of Hb below 8 g/dl or PCV < 25% was 0.40 (range: 0.02–0.93).

Table 3 shows the determinants of anaemia impact estimated from multivariate regression. For the mean increase in Hb, little of the variation between studies could be explained from the characteristics that were tested. In particular, the magnitude of the increase was similar for the three age groups ($P = 0.69$). However, the Hb response increased with the corresponding impact on parasite prevalence ($P = 0.005$). For a median reduction in parasite prevalence of 42% (RR of 0.58), the mean estimated increase in Hb was 0.76 g/dl [95% confidence interval (CI): 0.61–0.91].

For the prevalence of Hb below 11 g/dl or PCV < 33%, in multivariate analysis, the impact was also similar for all age groups ($P = 0.98$). The reduction in anaemia was larger in sites with higher baseline Hb levels ($P = 0.001$), which is expected mathematically when using a fixed anaemia cut-off and given the finding above that the mean Hb increase did not vary with the baseline Hb level. Impact was also larger in sites of higher malaria endemicity, as defined by high baseline parasite prevalence ($P = 0.012$), and it increased with the corresponding impact on parasitaemia ($P = 0.008$). The mean estimated RR across 14 studies was 0.73 (95% CI: 0.64–0.81).

The impact on Hb below 8 g/dl or PCV < 25%, at an estimated mean RR of 0.40 (95% CI: 0.25–0.55) across 14 studies, was larger than that for Hb below 11 g/dl or PCV < 33%. As for the other two outcomes, the impact on Hb below 8 g/dl did not vary by age group ($P = 0.72$), but increased with the impact on parasite prevalence ($P = 0.01$).

Figure 1 shows the estimated correlations in the impact of malaria control on anaemia and on parasite prevalence, for all three anaemia outcome measures. In contrast to the clear influence of the interventions' efficacy in reducing parasite prevalence, none of the anaemia outcomes depended on the type or the duration of intervention. This is in line with the findings from two of the chemoprophylaxis trials where the rise in Hb did not detectably vary over the first 40 months (Bjorkman *et al.* 1986; Greenwood *et al.* 1988; Menon *et al.* 1990). In contrast, two other studies found the rise in Hb to increase over the first 18 months larger at 18 months compared with 6 months after onset of chemoprophylaxis (Fuller *et al.* 1988) or over 3 years of IRS (Draper 1960; Bradley 1991).

Age pattern in anaemia impact

Across the studies, no differences in anaemia impacts were detected among the age groups that were tested. This unexpected finding may be because the lower and upper age limits of these groups were variable and the studies were difficult to classify. More insight into the relative anaemia impacts at different ages could be obtained from some of the individual studies (Figure 2).

Three trials measured anaemia reductions related to ITN usage, all in holoendemic sites (as indicated by baseline parasite prevalences between 70 and 84%). The trial in Muheza, Tanzania, found a greater reduction at age 6–23 months compared with 24–49 months. The trial in Asembo, Kenya, found a greater reduction at age

Table 1 African malaria intervention studies with anaemia outcomes for children under 5

Study site	Intervention	Age (months)	Study duration (years)	Parasite prevalence*	Relative risk of parasitaemia†	Outcome measure	Anaemia impact	Anaemia prevalence, or mean Hb or mean PCV‡		Sample size§	Reported data or normal approximation¶
								Intervention group	Control group		
Bagamoyo, Tanzania (Premji *et al.* 1995; Shiff *et al.* 1996)	ITN	6–40	1.33	84	0.45	Mean PCV	+2.0%	34%	32%	146	Data. Intervention and control villages not randomized
						PCV < 33%	0.51	28%	55%		Data
Muheza, Tanzania (Maxwell *et al.* 2002)	ITN	6–59	4	82	0.62	Hb < 8 g/dl	0.43	7.6%	17.7%	329	Data. Intervention and control villages not randomized
Kilombero, Tanzania (Fraser-Hurt *et al.* 1999)	ITN	5–24	0.5	66	0.75	Mean Hb	+0.52	9.34% (0.67)	8.82% (0.63)	60	Data
						Hb < 11 g/dl	0.99	99.3%	100%		Approximation
						Hb < 8 g/dl	0.24	2.3%	9.7%		Approximation
Oubritenga, Burkina Faso (Habluetzel *et al.* 1999)	ITN	6–59	1	87	0.94	Mean Hb	+0.45	9.4% (1.2)	8.9% (1.0)	267**	Mean: data, SD: approximation based on mean Hb and the prevalence of Hb < 11 g/dl
						Hb < 11 g/dl	0.93	91%	98%		Data
						Hb < 8 g/dl	0.71	12.6%	17.7%		Approximation
National Programme, The Gambia (D'Alessandro *et al.* 1995)	ITN	12–119	1	40	0.93	Mean PCV	+0.3%	32.9% (4.6)	32.6% (4.7)	156	Data. Intervention and control villages not randomized
						PCV < 33%	0.95	50.9%	53.4%		Approximation
						PCV < 25%	0.81	4.3%	5.3%		Approximation
Katchang, The Gambia (Snow *et al.* 1987)	ITN	12–119	1	43	0.83	Mean PCV	+0.6%	34.7%	34.1%	121	Data. Comparison group is users of untreated nets
Farafenni North Bank, The Gambia (Snow *et al.* 1988)	ITN	12–119	1	35	0.68	Mean PCV	+2.7%	35.8% (12)	33.1% (9.2)	189	Data. Comparison group is users of untreated nets
Farafenni South Bank, The Gambia (Alonso *et al.* 1993)	ITN	6–59	0.5	40	0.60	Mean PCV	+1.6%	32.2% (3.4)	30.6% (4.4)	357	Data. ITNs were not randomized but systematically allocated to the larger villages (in which also primary health care had been implemented)

Table 1 Continued

Study site	Intervention	Age (months)	Study duration (years)	Parasite prevalence*	Relative risk of parasitaemia†	Outcome measure	Anaemia impact	Anaemia prevalence, or mean Hb or mean PCV‡		Sample size§	Reported data or normal approximation¶
								Intervention group	Control group		
						PCV < 33%	0.84	59.4%	70.6%		Approximation
						PCV < 25%	0.16	1.6%	10.3%		Approximation
	ITN + chemoprophylaxis (pyrimethamine-dapsone)	6–59	0.5	40	0.07	Mean PCV	+2.8%	33.4% (3.9)	30.6% (4.4)	367	Data. Chemoprophylaxis randomized by individual child
						PCV < 33%	0.65	45.9%	70.6%		Approximation
						PCV < 25%	0.15	1.6%	10.3%		Approximation
Farafenni North Bank, The Gambia (Greenwood *et al.* 1988; Menon *et al.* 1990)	Chemoprophylaxis (pyrimethamine-dapsone)	3–59	3.33	32	0.22	Mean PCV	+1.6%	33.5% (3.8)	31.9% (5.8)	154	Data
						PCV < 33%	0.76	44.8%	59.1%		Approximation
						PCV < 25%	0.17	1.3%	7.5%		Approximation
Kassena-Nankana, Ghana (Binka *et al.* 1996 and F. Binka, personal communication)	ITN	6–59	2	69	0.96	Mean PCV	+1.2%	24.3% (4.7)	23.1% (5.3)	396	Data
						PCV < 33%	1.00	96.8%	96.9%		Approximation
						PCV < 25%	0.87	55.9%	64.0%		Approximation
Asembo, Kenya (ter Kuile *et al.* 2003b)	ITN	0–36	Mean of 1.2 and 1.8 years	70	0.81	Mean Hb	+0.5	10.0	9.5	978	Data
Bo, Sierra Leone (Marbiah *et al.* 1998)	ITN	3–72	0.75	48	0.72	Mean PCV	+5.4%	43.4% (7.1)	38.0% (7.2)	470	Data
						PCV < 33%	0.29	7.1%	24.4%		Approximation
						PCV < 25%	0.13	0.5%	3.5%		Approximation
	Chemoprophylaxis (pyrimethamine-dapsone)	3–72	0.75	48	0.71	Mean PCV	+2.0%	40.0%	38.0%	436	
	ITN + chemoprophylaxis	3–72	0.75	48	0.43	Mean PCV	+4.2%	42.2%	38.0%	467	

Table 1 Continued

Study site	Intervention	Age (months)	Study duration (years)	Parasite prevalence*	Relative risk of parasitaemia†	Outcome measure	Anaemia impact	Anaemia prevalence, or mean Hb or mean PCV‡		Sample size§	Reported data or normal approximation¶
								Intervention group	Control group		
Gamazago, Nigeria (Bradley-Moore *et al.* 1985a,b)	Chemo-prophylaxis (chloroqouine)	3–24	50% 1, 50% 2	41	0.22	Mean Hb	+1.1	10.9% (1.8)	9.8% (1.6)	88	Data
						Hb < 11 g/dl	0.68	52.2%	77.3%		Approximation
						Hb < 8 g/dl	0.41	5.4%	13.0%		Approximation
Ruwan Sanyi & Gamazago, Nigeria (Bradley-Moore *et al.* 1985a)	Chemopophylaxis (pyrimethamine)	3–24	50% 1, 50% 2	41	0.068	Mean Hb	+0.9	10.75	9.8% (1.6)	38	Data
Pare-Taveta, Tanzania/ Kenya (Draper 1960; Bradley 1991)	IRS	3–48	3	80	0.04	Mean Hb	+1.6	11.4% (1.24)	9.8% (1.64)	295	Data. Pre–post-comparison in programme
						Hb < 11 g/dl	0.47	36.1%	76.8%		Approximation
						Hb < 8 g/dl	0.02	0.3%	13.6%		Approximation
Kilombero & Ulanga, Tanzania (Abdulla *et al.* 2001)	ITN	0–24	2	63	0.60	Mean Hb	+0.9	8.9% (1.2)	8.0% (1.0)	330	Data. Pre–post-comparison in social marketing project
						Hb < 11 g/dl	0.96	95.5%	99.9%		Approximation
						Hb < 8 g/dl	0.53	25.9%	49.2%		Data
Kabompo, Zambia (McClean & Senthilselvan 2002)	ITN	0–60	1	38	0.20	Mean Hb	+1.09	8.14	7.05	44	Data. Pre–post-comparison in ITN promotion project
Yekepa, Liberia (Bjorkman *et al.* 1986)	Chemoprophylaxis (chloroquine)	24–119	2	91	0.26	Mean PCV	+2.0%	38.3%	36.3%	46	Data. Intervention and control villages not randomized
	Chemoprophylaxis (chlorproguanil)				0.83	Mean PCV	+1.4%	37.7%	36.3%	42	Data
Yekepa, Liberia (Bjorkman *et al.* 1980)	Chemoprophylaxis (chlorproguanil)	24–119	2	94	0.79	Mean PCV	+3.2%	37.7% (3.5)	34.5% (3.5)	42	Data
						PCV < 33%	0.27	9.0%	33.3%		Approximation
						PCV < 25%	0.05	0.02%	0.4%		Approximation

Table 1 Continued

Study site	Intervention	Age (months)	Study duration (years)	Parasite prevalence*	Relative risk of parasitaemia†	Outcome measure	Anaemia impact	Anaemia prevalence, or mean Hb or mean PCV‡		Sample size§	Reported data or normal approximation¶
								Intervention group	Control group		
Farafenni North Bank, The Gambia (Greenwood *et al.* 1989)	Chemoprophylaxis (pyrimethamine-dapsone)	3–59	3	55	0.55	Mean PCV	+1.5%	34.0%	32.5%	51**	Data. Study subsidiary to Greenwood *et al.* 1988; Menon *et al.* 1990)
	Chemoprophylaxis (chlorproguanil)				0.49	Mean PCV	+1.0%	33.5%	32.5%	51**	
Muheza, Tanzania (Lemnge *et al.* 1997)	Chemoprophylaxis (pyrimethamine-dapsone)	12–59	2	80	0.97	Mean PCV	+0.60%	33.9% (3.4)	33.3% (3.2)	55	Data
						PCV < 33%	0.86	39.6%	46.3%		Approximation
						PCV < 25%	0.93	0.4%	0.5%		Approximation
Farafenni North bank, The Gambia (Fuller *et al.* 1988)	Chemoprophylaxis (pyrimethamine-dapsone)	3–59	3	44	0.36	Mean PCV	5.0%	35.9%	30.9%	22	Data
	Chemoprophylaxis (chlorproguanil)				0.57	Mean PCV	+2.5%	33.4%	30.9%	25	Data
Farafenni, The Gambia (Otoo *et al.* 1988)	Chemoprophylaxis (pyrimethamine)	3–59	2	46	0.73	Mean PCV	+1.2%	36.3%	35.1%	48	Data

* Denotes the prevalence of *Plasmodium falciparum* infection at baseline of the study (in %).
† Being the single malariometric impact measure that all studies reported in common, the reduction in the prevalence of *P. falciparum* infection (intervention group/control group) was considered as a covariate of anaemia impacts.
‡ Mean Hb is in g/dl; SD in brackets.
§ The number of children remaining in the study intervention arm at follow-up.
¶ Approximation assuming Hb or PCV concentrations to be normally distributed around the reported mean, with the reported SD.
PCV, packed cell volume; Hb, haemoglobin; ITN, insecticide-treated mosquito net; IRS, indoor residual spraying with insecticide; chemoprophylaxis, weekly or monthly antimalarial chemoprophylaxis (with the drug in brackets).
Anaemia impact is the increase in mean Hb or in mean PCV, or the relative risk of Hb < 8 g/dl, Hb < 11 g/dl, PCV < 25% or PCV < 33%. Unless indicated, the control group is the comparison arm of a randomized trial.
** Average sample size per group estimated by authors based on reported across-group total.

Table 2 Summary of African malaria intervention studies with anaemia outcomes for children under 5

	Number of studies	Mean (range)
Sites	Burkina Faso: 1 The Gambia: 11 Ghana: 1 Kenya: 2 Liberia: 3 Nigeria: 2 Sierra Leone: 3 Tanzania: 5 Zambia: 1	
Intervention		
ITN	13	
Chemoprophylaxis	13	
ITN + chemo-prophylaxis	2	
IRS	1	
Age category		
0–5 to 24–36 months	5	
3–6 to 40–72 months	17	
12–119 months	7	
Study duration	29	1.6 years (0.5–4)
Mean baseline parasite prevalence	29	58% (32–94)
Mean relative risk of parasitaemia	29	0.56 (0.04–0.97)
Comparison arm mean Hb*	28	10.5 g/dl (7.1–12.7), SD 1.5
Intervention arm mean Hb*	28	11.2 g/dl (8.1–14.5), SD 1.5
Increase in mean Hb*	28	0.76 g/dl (0.1–1.8)
Mean relative risk of Hb < 11 g/dl	14	0.73 (0.27–1.00)
Mean relative risk of Hb < 8 g/dl	14	0.40 (0.02–0.93)

Hb, haemoglobin; ITN, insecticide-treated mosquito net; IRS, indoor residual spraying; PCV, packed cell volume.
* Including PCV divided by 3 as an approximation of Hb level for studies that reported mean PCV but no mean Hb.

6–35 months compared with 0–5 months (ter Kuile *et al.* 2003b), but in Bagamoyo, Tanzania, no clear age pattern was apparent (Shiff *et al.* 1996) (Figure 2a).

For the mean increase in Hb, an IRS trial in Tanzania/Kenya and a chemoprophylaxis trial in Nigeria found a fairly consistent impact throughout age 6–35 months (Draper 1960; Bradley-Moore *et al.* 1985b; Bradley 1991), but ITN trials in Burkina and Zambia found a greater increase at ages 6–23 and 6–40 months compared with older children (Habluetzel *et al.* 1997; McClean & Senthilselvan 2002) (Figure 2b). This difference could not be explained by differing endemicity (as indicated in the Figure 2b legend as the baseline parasite prevalences), which were high in Tanzania and Burkina and more moderate in Nigeria and Zambia.

Discussion

Across 29 interventions studied in malaria-endemic Africa, malaria control increased Hb and reduced anaemia among under 5, with the largest anaemia impact in studies where the impact on malaria infection prevalence was also largest (Figure 1). A mean increase in Hb across studies of 0.76 g/dl corresponded to RRs of Hb below 11 g/dl of 0.73 (27% reduction) or for Hb below 8 g/dl of 0.40 (60% reduction).

Several limitations must be recognized in this quantitative review. Results were standardized across trials by converting mean PCV into mean Hb using a fixed factor threefold difference. Although this conversion is conventionally undergone and is supported by numerous studies throughout the world (McGregor *et al.* 1966; Mustaring *et al.* 1990; Herzog & Felton 1994; Vasquez & Villena 2001), there appear to be exceptions to this relationship. Among the studies analysed here, a chemoprophylaxis trial in Nigeria that measured both Hb and PCV found a mean increase in Hb of 1.1 g/dl, whereas PCV increased by only 2.7%, i.e. less than threefold as much (Table 1) (Bradley-Moore *et al.* 1985b). For chemoprophylaxis with pyrimethamine, PCV actually decreased while Hb increased, and this was explained by a decreased mean cell volume (Bradley-Moore *et al.* 1985a). If malaria intervention had a lesser impact on PCV than on Hb, our inclusion of converted PCV outcomes may have slightly deflated the estimated mean Hb response to malaria control. However, the main results remained unchanged when only studies with directly observed Hb outcomes were included (not shown).

The second standardization performed on trial outcomes, the inference of reductions in anaemia prevalence from reported increases in Hb, depends critically on the reported SDs (Table 1). In some studies, however, the SDs were imprecisely reported, or they had to be calculated from a reported SE, or they could not be meaningfully interpreted. This introduced additional uncertainty in our analysis, although the main outcomes were unchanged when only studies with directly reported anaemia prevalence were included (not shown).

Finally, these results cannot necessarily be extrapolated beyond Africa, or to areas of Africa where malaria transmission is not stable. In an ITN trial in meso-endemic Thailand (Dolan *et al.* 1993), ITN use reduced the prevalence of PCV < 30% among pregnant women by

Table 3 Anaemia impacts in children under-five observed in 29 malaria control studies and determinants, estimated by multivariate analysis

	Increase in Hb or PCV	Reduction in the prevalence of Hb < 11 g/dl or PCV < 33%	Reduction in the prevalence of Hb < 8 g/dl or PCV < 25%
Estimated overall impact (95% CI)*	+0.76 g/dl (0.61–0.91)	RR = 0.73 (0.64–0.81)	RR = 0.40 (0.25–0.55)
Determinants of impact			
Intervention's impact on parasite prevalence	The larger the impact on parasite prevalence, the larger the anaemia impact ($P = 0.005$)	The larger the impact on parasite prevalence, the larger the anaemia impact ($P = 0.008$)	The larger the impact on parasite prevalence, the larger the anaemia impact ($P = 0.01$)
Hb level at baseline	ns	The higher Hb at baseline, the larger the anaemia impact ($P = 0.001$)	ns
Parasite prevalence at baseline	ns	The higher parasite prevalence, the larger the anaemia impact ($P = 0.012$)	ns
Duration of intervention	ns	ns	ns
Type of intervention†	ns	ns	ns
Age group‡	ns	ns	ns
Proportion of between-study variation explained (R^2)	27%	77%	43%

ns, not significant; RR, relative risk; Hb, haemoglobin (in g/dl); PCV, packed cell volume; R^2, correlation coefficient; CI, confidence interval.

* For a median reduction in parasitaemia of 58%, and, for the reduction in the prevalence of Hb < 11 g/dl or PCV < 33%, baseline parasite prevalence of 62% and baseline Hb level of 10.0 g/dl.

† Categorized as: insecticide-treated nets (ITNs), chemoprophylaxis, ITNs plus chemoprophylaxis, and insecticide-residual spraying (IRS).

‡ Categorized according to the age at start, as: (0) lower age limit between 0 and 5 months and an upper limit between 24 and 36 months, (1) lower limit 3–6 months and upper limit 40–72 months, and (2) lower limit 12 months and upper limit 119 months.

between 34 and 62%. A similarly impressive response was found in a highly endemic area in India (Yadav *et al.* 1998), where ITN use among children 2–9 years reduced the prevalence of any anaemia (Hb < 11 g/dl) up to 85%, increasing mean Hb from 11.0 to 14.5 g/dl. Among the studies in stable endemic African settings, however, the impact tended to be higher at higher endemicity (Table 3 for the outcome measure Hb < 11 g/dl), which confirms the intuitive notion that in less endemic areas, anaemia will respond less to malaria control than estimated here.

In some of the trials in highly endemic areas, malaria control had its greatest impact on anaemia between 6 months and around 3 years of age (Figure 2). Such an age pattern could be explained from the corresponding young peak age of symptomatic malaria episodes (Snow *et al.* 1994) and anaemia prevalence (Schellenberg *et al.* 2003) in these areas. Here, the high exposure to malaria infection from birth onwards leads to a rapid build up of immunity against morbidity and sequelae over the first years of life. In line with this young age range, trials in highly endemic settings found that in birth cohorts, IPT or ITN gave better protection against incident severe anaemia than did iron supplementation (average reductions of 60% and 46%, respectively) (Menendez *et al.* 1997; Schellenberg *et al.* 2001; ter Kuile *et al.* 2003a; Massaga *et al.* 2003).

Implications for malaria monitoring

While malaria control is being intensified, and malaria is recognized as being among the major contributors to ill-health in developing countries by The Global Fund against AIDS, TB and Malaria 2003 and the UN's Millennium Development Goals (Millennium Assembly of the United Nations 2003), there is an urgent need for indicators to track burden and demonstrate timely impact, at national and subnational levels.

In view of the limitations of alternative malaria indicators, we suggest that childhood anaemia might be a suitable indicator of the burden of malaria in malaria-endemic parts of Africa. As only a small and variable fraction of malaria and anaemia patients in Africa are seen in health facilities (Mung'ala & Snow 1994; Breman 2001; Schellenberg *et al.* 2003), population-based indicators are preferred. Monitoring of anaemia prevalence through population-based surveys has become a more viable option recently with the development of the HemoCue test (HemoCue Angelholm Sweden, http://www.hemocue.co.uk/) on fingerprick blood, which is increasingly used to measure Hb distributions in large-scale household surveys. In particular, the nationally representative DHS, which are conducted in an increasing number of malarious

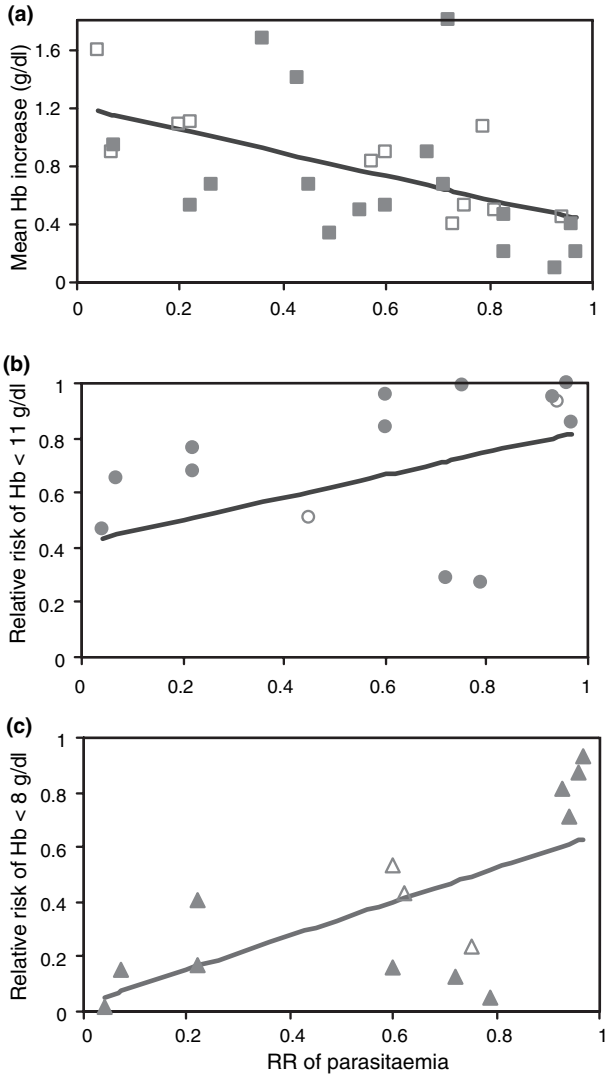

Figure 1 Correlation between the impact of malaria control on anaemia and its impact on the prevalence of *Plasmodium falciparum* parasitaemia. Solid symbols: data from intervention trials (summarized in Table 1); open symbols: estimates from intervention trials (summarized in Table 1), in (a) haemoglobin (Hb) increase inferred from packed cell volume (PCV) increase, in (b) and (c) anaemia reductions inferred from mean increase in Hb or PCV level. Lines: prediction from multivariate analysis, where the significance of the correlations was: $P = 0.005$, $P = 0.008$ and $P = 0.01$, respectively (Table 3). RR = relative risk. Result for Hb < 11 g/dl is for a median baseline Hb level of 10.0 g/dl and baseline parasite prevalence of 62%.

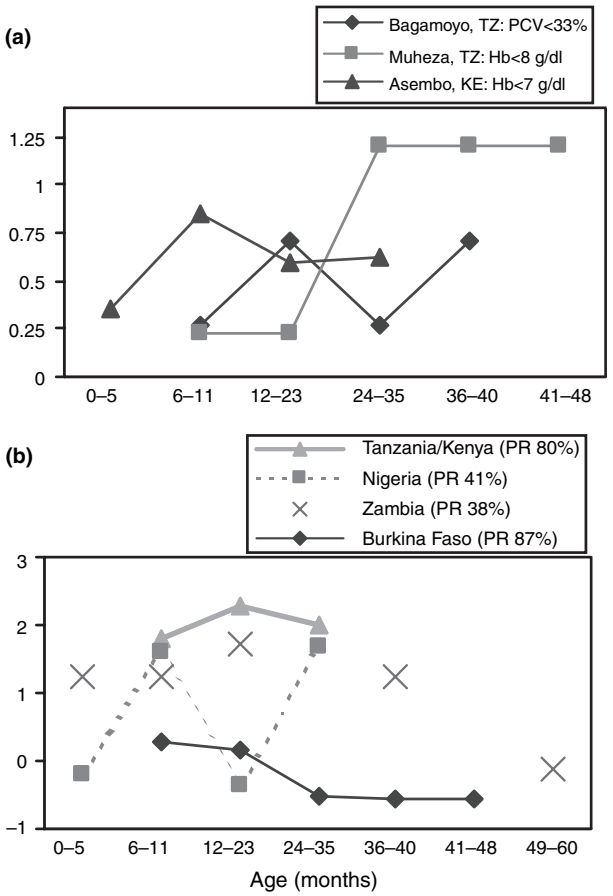

Figure 2 Age pattern in impact of malaria interventions on anaemia among children under 5, from African trials. (a) Relative risk of anaemia, in various definitions, in insecticide-treated mosquito net (ITN) trials in holoendemic sites (parasite prevalence between 70 and 84%) (Shiff *et al.* 1996; Maxwell *et al.* 2002; ter Kuile *et al.* 2003b). (b) Mean increases in haemoglobin (g/dl) after insecticide residual spraying (IRS), chemoprophylaxis or ITN distribution in sites of varying malaria endemicity (Draper 1960; Bradley-Moore *et al.* 1985a,b; Bradley 1991; Habluetzel *et al.* 1999; McClean & Senthilselvan 2002). Hb, haemoglobin; PCV, packed cell volume; TZ, Tanzania; KE, Kenya; PR, parasite prevalence.

countries at approximately 5-year intervals, now include Hb testing (Sharmanov 2000; ORC Macro – MEASURE *DHS*+ 2001). Recent DHS in Benin, Mali, Madagascar and Uganda, with sample sizes of between 2300 and 6000 children under 5 years of age, measured Hb distributions with SE of between 0.058 and 0.087 g/dl (at mean values ranging between 9.4 and 10.2 g/dl). At this level of precision, Hb shifts such as might be expected from intensified malaria control would be easily detectable. Also more modest reductions than in the efficacy trials, which might result from less intensive intervention or a more limited area of the total country (and survey population) exposed to malaria, are likely to be picked up.

Although most DHS measure Hb levels in all children aged 0–59 months, for the purpose of malaria monitoring the appropriate lower age limit in analyses of anaemia prevalences would be 6 months. This is, first, because Hb levels change rapidly over the first 6 months of life, a physiological process, which makes definitions of anaemia in this age group problematic. Secondly, anaemia in infants younger than 6 months may, in contrast to older children, relate more to the general conditions of pregnancy and birth than to the impact of malaria control. For the highest endemic African sites where malaria burden and the impact of malaria control are largely concentrated in infancy and early childhood (Snow *et al.* 1994), analysis of survey data could be further restricted to include an upper age limit of 24 or 36 (instead of 59) months.

Besides its modest sample size requirements, its fast response to malaria control makes Hb distribution an attractive indicator. As a predictor of subsequent (malaria-attributable and malaria-related) mortality, anaemia will respond more quickly than mortality to malaria control – especially if mortality is measured retrospectively, as it is in household surveys with birth histories.

Although severe anaemia is one of the most important syndromes responsible for malaria-attributed deaths in African children admitted to clinics, the evidence that (less severe) anaemia predisposes to childhood mortality remains inconclusive (Brabin *et al.* 2001, 2003). A large-scale study in rural Gambia did not confirm an association between moderate anaemia (Hb between 7 and 11 g/dl) and subsequent mortality, apart from an acute effect in the last week of life (Ghattas *et al.* 2003). Nevertheless, even if (asymptomatic) anaemia as measured in population-based surveys would not predict malaria-related mortality, its marked correlation with poor cognitive and motor development, retarded growth (World Health Organization *et al.* 2001) and, via impaired immunity, subsequent morbidity from infectious diseases (Nacher 2002; Verhoef *et al.* 2002) make it a relevant indicator of malaria-related disease burden.

A potential drawback is the seasonal variation in malaria-related anaemia (McGregor *et al.* 1966; Delmont *et al.* 1981; Bouvier *et al.* 1997; Koram *et al.* 2003), which makes survey outcomes sensitive to the season of measurement. Figure 3 gives an example from The Gambia, which shows also that the seasonal fluctuation in anaemia prevalence is greatest in the age group 6–23 months, where most malaria-related anaemia is expected. Most intervention trials (Table 1) measured Hb impact at the end of the rainy season, i.e. when malaria-related anaemia had reached its peak. In two trials that reported on the seasonal pattern in impact, anaemia impact appeared to be stable over the seasons (Bjorkman *et al.* 1986; ter Kuile *et al.*

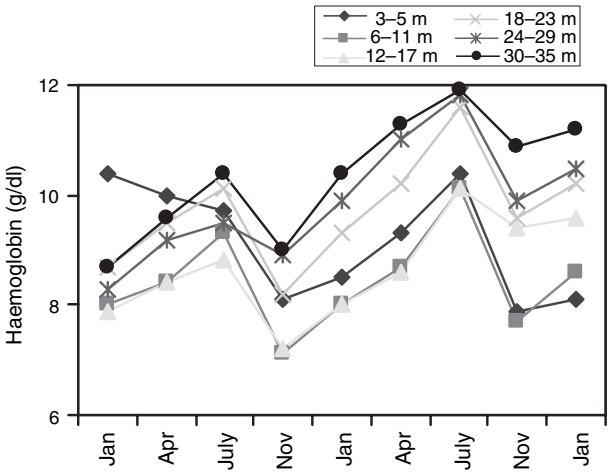

Figure 3 Example of seasonal variation in anaemia in a malaria-endemic area of the Gambia in the 1960s, by age group (in months) (McGregor *et al.* 1966). The malaria season in this area is between July and December (Craig *et al.* 1999; MARA/ARMA (Mapping Malaria Risk in Africa) 2002).

2003b). These data remain difficult to interpret given the confounding of season with the duration of intervention and the ageing of the children, but they suggest that anaemia prevalences in surveys will reflect both the season of measurement and the success of malaria control. In contrast to most intervention trials, survey fieldwork in DHS takes place throughout the year and, for logistical reasons, usually avoids the wet season. The variation in Hb levels at different times of the year might, across differently timed surveys, thus easily offset and obscure any trends related to malaria control.

Furthermore, the use of anaemia as a malaria indicator would inevitably be compromised by a lack of specificity, given other anaemia determinants like paediatric HIV/AIDS (Villamor *et al.* 2000; van Eijk *et al.* 2002; Totin *et al.* 2002), malnutrition and micronutrition supplementation programmes (Villamor *et al.* 2000; Muller *et al.* 2003). Even in areas of intense malaria transmission, anaemia in young children may depend more on malnutrition than on malaria (Muller *et al.* 2003) – although the interpretation of risk factor analyses based on observational data is complicated as malnutrition and malaria mutually enhance each other (El Samani *et al.* 1987; Shankar 2000; Deen *et al.* 2002; Nussenblatt & Semba 2002) and increased intake of micronutrients may not only reduce nutritional anaemia but, via improved immune function, also reduce malaria-associated anaemia (Verhoef *et al.* 2002). Currently, there are no major iron supplementation programmes in place in African countries, but the increasing prevalence of paediatric HIV/AIDS (Walker

et al. 2002) is likely to confound trends in malaria-related anaemia. In African school children, helminth infections such as hookworm are important contributors to anaemia, but among the age groups concerned here, especially at an upper limit of 2 or 3 years, helminth infections have a low prevalence and low average density and contribute little to anaemia (Stoltzfus *et al.* 2000).

In conclusion, the prevention or treatment of malaria infection in malaria-endemic Africa is likely to increase mean Hb values substantially and to reduce the prevalence anaemia in under 5. As Hb measurement is increasingly common in population-based surveys, anaemia in under 5s, may be a useful additional indicator of the burden of malaria and the progress in its control.

Acknowledgements

Authors thank the Roll Back Malaria Monitoring and Evaluation Reference Group (MERG) Task Force on anaemia for comments on an earlier version of this review. This work forms part of the Burden of Malaria in Africa (BOMA) project funded by the Wellcome Trust, UK, The Bill & Melinda Gates Foundation and the Kenya Medical Research Institute. RWS is supported as Wellcome Trust Senior Research Fellow (No. 058992).

References

Abdulla S, Armstrong Schellenberg J, Nathan R *et al.* (2001) Impact on malaria morbidity of a programme supplying insecticide treated nets in children aged under 2 years in Tanzania: community cross-sectional study. *British Medical Journal* **322**, 270–273.

Alonso PL, Lindsay SW, Armstrong Schellenberg JR *et al.* (1993) A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of the Gambia, West Africa: 6. The impact of the interventions on mortality and morbidity from malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **87** (Suppl. 2), 37–44.

Asobayire FS, Adou P, Davidsson L, Cook JD & Hurrell RF (2001) Prevalence of iron deficiency with and without concurrent anemia in population groups with high prevalences of malaria and other infections: a study in Cote d'Ivoire. *The American Journal of Clinical Nutrition* **74**, 776–782.

Biemba G, Dolmans D, Thuma PE, Weiss G & Gordeuk VR (2000) Severe anaemia in Zambian children with *Plasmodium falciparum* malaria. *Tropical Medicine and International Health* **5**, 9–16.

Binka FN, Kubaje A, Adjuik M *et al.* (1996) Impact of permethrin impregnated bednets on child mortality in Kassena-Nankana district, Ghana: a randomized controlled trial. *Tropical Medicine and International Health* **1**, 147–154.

Bjorkman A, Brohult J, Sirleaf V, Willcox M & Bengtsson E (1980) *Plasmodium falciparum* resistance to pyrimethamine and chlorproguanil – host or parasite dependent? *Annals of Tropical Medicine and Parasitology* **74**, 245–248.

Bjorkman A, Brohult J, Pehrson PO *et al.* (1986) Monthly antimalarial chemotherapy to children in a holoendemic area of Liberia. *Annals of Tropical Medicine and Parasitology* **80**, 155–167.

Bouvier P, Rougemont A, Breslow N *et al.* (1997) Seasonality and malaria in a west African village: does high parasite density predict fever incidence? *American Journal of Epidemiology* **145**, 850–857.

Brabin BJ, Premji Z & Verhoeff F (2001) An analysis of anemia and child mortality. *Journal of Nutrition* **131**, 636S–648S.

Brabin B, Prinsen-Geerligs P, Verhoeff F & Kazembe P (2003) Anaemia prevention for reduction of mortality in mothers and children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **97**, 36–38.

Bradley DJ (1991) Morbidity and mortality at Pare-Taveta, Kenya and Tanzania, 1954–66: the effects of a period of malaria control. In: *Disease and Mortality in sub-Saharan Africa* (eds RG Feachem & DT Jamison). Oxford University Press, Washington, pp. 248–263. Published for the World Bank.

Bradley-Moore AM, Greenwood BM, Bradley AK *et al.* (1985a) A comparison of chloroquine and pyrimethamine as malaria chemoprophylactics in young Nigerian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **79**, 722–727.

Bradley-Moore AM, Greenwood BM, Bradley AK *et al.* (1985b) Malaria chemoprophylaxis with chloroquine in young Nigerian children: IV. Its effect on haematological measurements. *Annals of Tropical Medicine and Parasitology* **79**, 585–595.

Breman JG (2001) The ears of the hippopotamus: manifestations, determinants, and estimates of the malaria burden. *American Journal of Tropical Medicine and Hygiene* **64**, 1–11.

Brewster DR & Greenwood BM (1993) Seasonal variation of paediatric diseases in the Gambia, West Africa. *Annals of Tropical Paediatrics* **13**, 133–146.

Cornet M, Le Hesran J-Y, Fievet N *et al.* (1998) Prevalence of and risk factors for anemia in young children in Southern Cameroon. *American Journal of Tropical Medicine and Hygiene* **58**, 606–611.

Craig MH, Snow RW & le Sueur D (1999) A climate-based distribution model of malaria transmission in sub-Saharan Africa. *Parasitology Today* **15**, 105–111.

Curtis C, Maxwell C, Lemnge M *et al.* (2003) Scaling-up coverage with insecticide-treated nets against malaria in Africa: who should pay? *Lancet Infectious Diseases* **3**, 304–307.

D'Alessandro U, Olaleye BO, McGuire W *et al.* (1995) Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme [see comments]. *Lancet* **345**, 479–483.

Deen JL, Walraven GE & von Seidlein L (2002) Increased risk for malaria in chronically malnourished children under 5 years of age in rural Gambia. *Journal of Tropical Pediatrics* **48**, 78–83.

Delmont J, Ranque P, Balique H *et al.* (1981) The influence of malaria chemoprophylaxis on health of a rural community in West Africa (author's translation). *Bulletin de la Societé de Pathologie Exotique Filiales* **74**, 600–610.

Dolan G, ter Kuile FO, Jacoutot-V J *et al.* (1993) Bed nets for the prevention of malaria and anaemia in pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **87**, 620–626.

Draper CC (1960) Effect of malaria control on haemoglobin levels. *Brookhaven Symposium Biology* **5184**, 1480–1483.

van Eijk AM, Ayisi JG, ter Kuile FO *et al.* (2002) Malaria and human immunodeficiency virus infection as risk factors for anemia in infants in Kisumu, western Kenya. *American Journal of Tropical Medicine and Hygiene* **67**, 44–53.

El Samani FZ, Willett WC & Ware JH (1987) Nutritional and socio-demographic risk indicators of malaria in children under five: a cross-sectional study in a Sudanese rural community. *Journal of Tropical Medicine and Hygiene* **90**, 69–78.

Fraser-Hurt N, Felger I, Edoh D *et al.* (1999) Effect of insecticide-treated bed nets on haemoglobin values, prevalence and multiplicity of infection with *Plasmodium falciparum* in a randomized controlled trial in Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **93** (Suppl. 1), 47–51.

Fuller NJ, Bates CJ, Hayes RJ *et al.* (1988) The effects of antimalarials and folate supplements on haematological indices and red cell folate levels in Gambian children. *Annals of Tropical Paediatrics* **8**, 61–67.

Ghattas H, Fulford T & Prentice A (2003) Effect of moderate anaemia on later mortality in rural African children. *Lancet* **361**, 2048–2050.

Greenwood BM, Bradley AK, Greenwood AM *et al.* (1987) Mortality and morbidity from malaria among children in a rural area of the Gambia, West Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **81**, 478–486.

Greenwood BM, Greenwood AM, Bradley AK *et al.* (1988) Comparison of two strategies for control of malaria within a primary health care programme in the Gambia. *Lancet* **1**, 1121–1127.

Greenwood BM, Greenwood AM, Smith AW *et al.* (1989) A comparative study of Lapudrine (chlorproguanil) and Maloprim (pyrimethamine and dapsone) as chemoprophylactics against malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **83**, 182–188.

Habluetzel A, Diallo DA, Esposito F *et al.* (1997) Do insecticide-treated curtains reduce all-cause child mortality in Burkina Faso? *Tropical Medicine and International Health* **2**, 855–862.

Habluetzel A, Cuzin N, Diallo DA *et al.* (1999) Insecticide-treated curtains reduce the prevalence and intensity of malaria infection in Burkina Faso. *Tropical Medicine and International Health* **4**, 557–564.

Herzog B & Felton B (1994) Hemoglobin screening for normal newborns. *Journal of Perinatology* **14**, 285–289.

INDEPTH Editorial Team (Sankoh OA, Kahn K, Mwageni E, Ngom P & Nyarko P) (2002) *Population and Health in Developing Countries. Vol. I. Population, Health and Survival at INDEPTH Sites*. International Development Research Centre, Ottawa.

Koram KA, Owusu-Agyei S, Fryauff DJ *et al.* (2003) Seasonal profiles of malaria infection, anaemia, and bednet use among age groups and communities in northern Ghana. *Tropical Medicine and International Health* **8**, 793–802.

ter Kuile F, Terlouw DJ, Kariuki S *et al.* (2003a) Impact of permethrin-treated bed nets on malaria, anemia and growth in infants in an area of intense perennial malaria. *American Journal of Tropical Medicine and Hygiene* **68** (Suppl. 4), 68–77.

ter Kuile FO, Terlouw DJ, Phillips-Howard PA *et al.* (2003b) Impact of permethrin-treated bed nets on malaria and all-cause morbidity in young children in an area of intense perennial malaria transmission in western Kenya: cross-sectional survey. *American Journal of Tropical Medicine and Hygiene* **68** (Suppl. 4), 100–107.

Lemnge MM, Msangeni HA, Ronn AM *et al.* (1997) Maloprim malaria prophylaxis in children living in a holoendemic village in north-eastern Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **91**, 68–73.

Lines J, Lengeler C, Cham K *et al.* (2003) Scaling-up and sustaining insecticide-treated net coverage. *Lancet Infectious Diseases* **3**, 465–466.

Lundsgaard-Hansen P (1996) Safe hemoglobin or hematocrit levels in surgical patients. *World Journal of Surgery* **20**, 1182–1188.

MARA/ARMA (Mapping Malaria Risk in Africa)2002) *Modelled Maps of Malaria Transmission in West Africa*. http://www.mara.org.za, accessed 2002.

Marbiah NT, Petersen E, David K, Magbity E, Lines J & Bradley DJ (1998) A controlled trial of lambda-cyhalothrin-impregnated bed nets and/or dapsone/pyrimethamine for malaria control in Sierra Leone. *American Journal of Tropical Medicine and Hygiene* **58**, 1–6.

Marsh K, Forster D, Waruiru C *et al.* (1995) Indicators of life-threatening malaria in African children. *New England Journal of Medicine* **332**, 1399–1404.

Massaga JJ, Kitua AY, Lemnge MM *et al.* (2003) Effect of intermittent treatment with amodiaquine on anaemia and malarial fevers in infants in Tanzania: a randomised placebo-controlled trial. *Lancet* **361**, 1853–1860.

Maxwell CA, Msuya E, Sudi M, Njunwa KJ, Carneiro IA & Curtis CF (2002) Effect of community-wide use of insecticide-treated nets for 3–4 years on malarial morbidity in Tanzania. *Tropical Medicine and International Health* **7**, 1003–1008.

McClean KL & Senthilselvan A (2002) Mosquito bed nets: implementation in rural villages in Zambia and the effect on subclinical parasitaemia and haemoglobin. *Tropical Doctor* **32**, 139–142.

McDermott JM, Slutsker L, Steketee RW, Wirima JJ, Breman JG & Heymann DL (1996) Prospective assessment of mortality among a cohort of pregnant women in rural Malawi. *American Journal of Tropical Medicine and Hygiene* **55**, 66–70.

McGregor IA, Williams K, Billewicz WZ & Thomson AM (1966) Haemoglobin concentration and anaemia in young west African (Gambian) children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **60**, 650–667.

Menendez C, Kahigwa E, Hirt R *et al.* (1997) Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants [see comments]. *Lancet* **350**, 844–850.

Menendez C, Fleming AF & Alonso PL (2000) Malaria-related anaemia. *Parasitology Today* **16**, 469–476.

Menon A, Snow RW, Byass P, Greenwood BM, Hayes RJ & N'jie AB (1990) Sustained protection against mortality and morbidity from malaria in rural Gambian children by chemoprophylaxis given by village health workers. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **84**, 768–772.

Millennium Assembly of the United Nations (2003) *Millennium Development Goals*. http://www.developmentgoals.org/Child_Mortality.htm, accessed October, 2003.

Muller O, Traore C, Jahn A & Becher H (2003) Severe anaemia in west African children: malaria or malnutrition? *Lancet* **361**, 86–87.

Mung'ala VO & Snow RW (1994) Death registration on the Kenyan Coast. *East African Medical Journal* **71**, 747–750.

Murray CJ & Lopez AD (1996) *Global Burden of Disease and Injury Series*. World Health Organization, Geneva, pp. 320–327, 525.

Mustaring, Tranggana S & Daud D (1990) Capillary microhematocrit measurement as a screening test for anemia in children. *Paediatrics Indonesia* **30**, 241–247.

Mwaniki DL, Omwega AM, Muniu EM *et al.* (2002) *Anemia and Status of Iron, Vitamin A and Zinc in Kenya: the 1999 National Survey Report*. Report prepared for the Ministry of Health, Government of Kenya.

Nabarro D & Taylor E (1998) The 'Roll Back Malaria' campaign. *Science* **280**, 2067–2068.

Nacher M (2002) Malarial anaemia: a crossroad? *Medical Hypotheses* **59**, 363–365.

Nussenblatt V & Semba RD (2002) Micronutrient malnutrition and the pathogenesis of malarial anemia. *Acta Tropica* **82**, 321–337.

O'Dempsey TJ, McArdle TF, Laurence BE, Lamont AC, Todd JE & Greenwood BM (1993) Overlap in the clinical features of pneumonia and malaria in African children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **87**, 662–665.

ORC Macro – MEASURE *DHS+* (2001) *Demographic and Health Surveys (DHS)*. http://www.measuredhs.com, Madagascar 1997, Mali 2000/01, Uganda 2000/01 and Benin 2001.

Otoo LN, Snow RW, Menon A, Byass P & Greenwood BM (1988) Immunity to malaria in young Gambian children after a two-year period of chemoprophylaxis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **82**, 59–65.

Premji Z, Lubega P, Hamisi Y *et al.* (1995) Changes in malaria associated morbidity in children using insecticide treated mosquito nets in the Bagamoyo district of coastal Tanzania. *Tropical Medicine and Parasitology* **46**, 147–153.

Prinsen Geerligs PD, Brabin BJ & Eggelte TA (2003) Analysis of the effects of malaria chemoprophylaxis in children on haematological responses, morbidity and mortality. *Bulletin of the World Health Organization* **81**, 205–216.

Schellenberg D, Menendez C, Kahigwa E *et al.* (2001) Intermittent treatment for malaria and anaemia control at time of routine vaccinations in Tanzanian infants: a randomised, placebo-controlled trial. *Lancet* **357**, 1471–1477.

Schellenberg D, Armstrong Schellenberg JRM, Mushi A *et al.* (2003) The silent burden of anaemia in Tanzanian children: a community-based study. *Bulletin of the World Health Organization* **81**, 581–590.

Shankar AH (2000) Nutritional modulation of malaria morbidity and mortality. *Journal of Infectious Diseases* **182**, S37–53.

Sharmanov A (2000) *Anemia Testing Manual for Population-based Surveys*. Macro International Inc., Calverton.

Shiff C, Checkley W, Winch P, Premji Z, Minjas J & Lubega P (1996) Changes in weight gain and anaemia attributable to malaria in Tanzanian children living under holoendemic conditions. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **90**, 262–265.

Slutsker L, Taylor TE, Wirima JJ & Steketee RW (1994) In-hospital morbidity and mortality due to malaria-associated severe anaemia in two areas of Malawi with different patterns of malaria infection. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **88**, 548–551.

Snow RW, Rowan KM & Greenwood BM (1987) A trial of permethrin-treated bed nets in the prevention of malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **81**, 563–567.

Snow RW, Lindsay SW, Hayes RJ & Greenwood BM (1988) Permethrin-treated bed nets (mosquito nets) prevent malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **82**, 838–842.

Snow RW, Bastos de Azevedo I, Lowe BS *et al.* (1994) Severe childhood malaria in two areas of markedly different falciparum transmission in east Africa. *Acta Tropica* **57**, 289–300.

Stoltzfus RJ, Chwaya HM, Montresor A, Albonico M, Savioli L & Tielsch JM (2000) Malaria, hookworm and recent fever are related to anemia and iron status indicators in 0- to 5-y old Zanzibari children and these relationships change with age. *Journal of Nutrition* **130**, 1724–1733.

Stoltzfus RJ, Mullany R & Black RE (2003) *Malnutrition and the Global Burden of Disease: Iron Deficiency Anaemia and Health Outcomes*. Department of International Health, Johns Hopkins University, USA.

The Global Fund against AIDS, TB and Malaria (2003) http://www.globalfundatm.org/, accessed 8 September 2003.

Todd JE, De Francisco A, O'Dempsey TJ & Greenwood BM (1994) The limitations of verbal autopsy in a malaria-endemic region. *Annals of Tropical Paediatrics* **14**, 31–36.

Totin D, Ndugwa C, Mmiro F, Perry RT, Jackson JB & Semba RD (2002) Iron deficiency anemia is highly prevalent among human immunodeficiency virus-infected and uninfected infants in Uganda. *Journal of Nutrition* **132**, 423–429.

Vasquez R & Villena M (2001) Normal hematological values for healthy persons living at 4000 meters in Bolivia. *High Altitude Medicine and Biology* **2**, 361–367.

Verhoef H, West CE, Veenemans J, Beguin Y & Kok FJ (2002) Stunting may determine the severity of malaria-associated anemia in African children. *Pediatrics* **110**, e48.

Villamor E, Mbise R, Spiegelman D, Ndossi G & Fawzi WW (2000) Vitamin A supplementation and other predictors of anemia among children from Dar es Salaam, Tanzania. *American Journal of Tropical Medicine and Hygiene* **62**, 590–597.

Walker N, Schwartlander B & Bryce J (2002) Meeting international goals in child survival and HIV/AIDS. *Lancet* **360**, 284–289.

World Health Organization (1959) *Iron Deficiency Anaemia*. Report of a Study Group. World Health Organization, Geneva, Report No. 182.

World Health Organization Communicable Diseases Cluster (2000) Severe falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **94** (Suppl. 1), S1–90.

World Health Organization, UNICEF and University of the United Nations (2001) *Iron Deficiency Anaemia. Assessment, Prevention, and Control. A Guide for Programme Managers*. WHO, Geneva, WHO/NHD/01.3.

Yadav RS, Sampath TR, Sharma VP, Adak T & Ghosh SK (1998) Evaluation of lambdacyhalothrin-impregnated bednets in a malaria endemic area of India: Part 3. Effects on malaria incidence and clinical measures. *Journal of the American Mosquito Control Association* **14**, 444–450.

Authors

Eline L. Korenromp (corresponding author) and **Bernard L. Nahlen**, World Health Organization, Roll Back Malaria (HTM/RBM), Avenue Appia 20, 1211 Geneva 27, Switzerland. Tel.: +41 22 791 1378; Fax: +41 22 791 4824; E-mail: korenrompe@who.int; nahlenb@who.int

Joanna R. M. Armstrong-Schellenberg, Ifakara Health Research and Development Centre, PO Box 53, Ifakara, Tanzania. Tel.: +255 232 625 164; Fax: +255 232 625 312 and London School of Hygiene and Tropical Medicine, 50 Bedford Square, London WC1E 7HT, UK. Tel.: +44 20 7299 4721; Fax +44 1296 681099; E-mail: dajobelo@aol.com

Brian G. Williams, World Health Organization, Stop TB, Avenue Appia 20, 1211 Geneva 27, Switzerland. Tel.: +41 22 791 4680; Fax: +41 22 791 4268; E-mail: williamsbg@who.int

Robert W. Snow, KEMRI Wellcome Trust Collaborative Programme, 00100 GPO, PO Box 43640, Nairobi, Kenya and Centre for Tropical Medicine, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK. Tel.: +254 2 2720163; E-mail: rsnow@wtnairobi.mimcom.net