Tropical Medicine and International Health

VOLUME 7 NO 10 PP 823–830 OCTOBER 2002

Risk factors for presentation to hospital with severe anaemia in Tanzanian children: a case–control study

Elizeus Kahigwa[1,2], David Schellenberg[1,3], Sergi Sanz[3], John J. Aponte[3], John Wigayi[1], Hassan Mshinda[1], Pedro Alonso[3] and Clara Menendez[3]

1 *Ifakara Health Research and Development Centre, Ifakara, Tanzania*
2 *St Francis Designated District Hospital, Ifakara, Tanzania*
3 *Unidad de Epidemiologia y Bioestadistica, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clinic, Barcelona, Spain*

Summary In malaria endemic areas anaemia is a usually silent condition that nevertheless places a considerable burden on health services. Cases of severe anaemia often require hospitalization and blood transfusions. The objective of this study was to assess risk factors for admission with anaemia to facilitate the design of anaemia control programmes. We conducted a prospective case–control study of children aged 2–59 months admitted to a district hospital in southern Tanzania. There were 216 cases of severe anaemia [packed cell volume (PCV) < 25%] and 234 age-matched controls (PCV ≥ 25%). Most cases [55.6% (n = 120)] were < 1 year of age. Anaemia was significantly associated with the educational level of parents, type of accommodation, health-seeking behaviour, the child's nutritional status and recent and current medical history. Of these, the single most important factor was *Plasmodium falciparum* parasitaemia [OR 4.3, 95% confidence interval (CI) 2.9–6.5, P < 0.001]. Multivariate analysis showed that increased recent health expenditure [OR 2.2 (95% CI 1.3–3.9), P = 0.005], malnutrition [OR 2.4 (95%CI 1.3–4.3), P < 0.001], living > 10 km from the hospital [OR 3.0 (95% CI 1.9–4.9), P < 0.001], a history of previous blood transfusion [OR 3.8 (95% CI 1.7–9.1), P < 0.001] and *P. falciparum* parasitaemia [OR 9.5 (95% CI 4.3–21.3), P < 0.001] were independently related to risk of being admitted with anaemia. These findings are considered in terms of the pathophysiological pathway leading to anaemia. The concentration of anaemia in infants and problems of access to health services and adequate case management underline the need for targeted preventive strategies for anaemia control.

keywords anaemia, malaria, case–control study, Tanzania, risk factors

correspondence Dr C. Menendez, Unidad de Epidemiologia, Hospital Clinic, Villaroel 170, Barcelona 08036, Spain. Fax: +34 93 451 5272; E-mail: cmenende@medicina.ub.es

Introduction

Anaemia is an important cause of paediatric hospital admission and death in many parts of the world. The prevalence of Hb < 5 g/dl in a number of hospital-based studies ranged from 8% to 29% and was associated with case fatality rates of 9–18% (Emerton 1992; Lackritz *et al.* 1992; Brewster & Greenwood 1993; Craighead & Knowles 1993; Hedberg *et al.* 1993; Slutsker *et al.* 1994; Marsh *et al.* 1995; Bojang *et al.* 1997a,b; Schellenberg *et al.* 1999; Biemba *et al.* 2000). In some settings anaemia was responsible for about 20% of inpatient paediatric deaths. The non-specific signs and symptoms associated with anaemia lead to under-recognition of the anaemia-related burden of disease and death. This is supported by the observation that more than 20% of anaemic infants [packed cell volume (PCV) < 25%] in one cohort study were only diagnosed at cross-sectional surveys (Menendez *et al.* 1997).

Anaemia is a multifactorial problem. Causes may be classified according to their position in the pathophysiological process. Socio-economic causes (Tshikuka *et al.* 1996) and genetic factors such as sickle cell disease and thalassaemia (Fleming & Werblinska 1982; Rana *et al.* 1993; Thuilliez & Vierin 1997; Koko *et al.* 1998; Mockenhaupt *et al.* 2000) may be important underlying factors, although hard to target in anaemia control programmes. Socio-economic factors such as poor housing, crowding and poor education level predispose to illness in parts of Asia and Latin America (Banguero 1984; Buttraporn *et al.* 1986), although no such association was found in two West African studies of severe anaemia (Koram *et al.* 1995; Luckner *et al.* 1998). This may be a reflection of the homogeneity of the West African communities investigated in terms of their socio-economic status. Other socio-cultural factors may be important risk factors for anaemia, such as delayed treatment-seeking and inappropriate medication, both of which are common among the people of sub-Saharan Africa (Mwenesi *et al.* 1995; Hausmann *et al.* 1998).

More immediate factors in the pathophysiological process may be relatively amenable to control measures. For example, *Plasmodium falciparum* malaria is a common cause of anaemia in children living in endemic areas (Menendez *et al.* 1997, 2000; Murphy & Breman 2001) and malaria control with insecticide-treated mosquito nets and chemoprophylaxis reduces the level of anaemia (Alonso *et al.* 1993; Menendez *et al.* 1997; Abdulla *et al.* 2001). Iron deficiency is the most common nutritional cause of anaemia worldwide (Stoltzfus & Dreyfuss 1998). Although iron supplementation is now recommended between the ages of 6 months and 2 years (Stoltzfus & Dreyfuss 1998), this policy is not widely implemented. Even low birthweight children who have limited iron stores (Stockman & Oski 1978; Dallman *et al.* 1980) are rarely given iron supplements. Marked deficiencies of other minerals, such as zinc, copper and vitamin B12, which are also necessary for haematopoiesis, are also associated with anaemia (Said *et al.* 1975; Singla *et al.* 1996). Apart from specific nutritional deficiencies, protein energy malnutrition is a common nutritional disorder in Africa and is also associated with anaemia (Biemba *et al.* 2000). Some intestinal parasites, in particular hookworm, contribute to the development of anaemia, for example in school-age children (Brooker *et al.* 1999; Stoltzfus *et al.* 2000).

In order to optimize effective anaemia control it would be useful to know the relative contribution of the different aetiological factors. In this paper we present a case–control study of the risk factors for admission with severe anaemia in children under 5 years of age in south-eastern Tanzania.

Materials and methods

Study area and population

The study was conducted in Ifakara in Kilombero District, Morogoro Region, southern Tanzania. The district has a population of 250 000, predominantly subsistence farmers growing rice and maize. Malaria transmission is perennial and the mean annual entomological inoculation rate in a nearby village was more than 300 infectious bites/person/year (Smith *et al.* 1993), although this may be less in Ifakara town. Malaria control is based on early detection and treatment of cases. Chloroquine resistance is common with a treatment cure rate of only 35.4% on day 7 and 10.3% on day 14 (Hatz *et al.* 1998).

St Francis Designated District Hospital (SFDDH) is situated in Ifakara town (population 55 000) and has a paediatric department with 70 beds. Among the 6500 annual paediatric admissions the four most common primary clinical diagnoses are malaria (40%), anaemia (20%), pneumonia (20%) and protein energy malnutrition (10%) (unpublished observations).

Study design

This was a case–control study frequency matched for age with a target of one control per case. Children aged between 2 and 59 months admitted to the paediatric ward between July and October 2000, whose guardians gave informed consent, were enrolled in the study as cases if their PCV on admission was < 25%, or as controls if their PCV was ≥ 25% and if they had not had a blood transfusion in the last 4 weeks. We used a standard questionnaire to document exposure to risk factors: information on maternal and paternal factors, health-seeking behaviour and socio-economic status (Table 1), length (< 2 years) or height (≥ 2 years), weight, mid upper arm circumference (MUAC) and birthweight of the child (from the growth card).

Laboratory procedures

A finger prick blood sample was collected in a microcapillary tube for the measurement of PCV and haemoglobin electrophoresis. Thick blood smears were prepared to look for malaria parasites after staining with Giemsa. Blood slides were read according to standard procedures (Alonso *et al.* 1994). Briefly, the number of asexual forms per 200 leucocytes was counted independently by at least two slide readers and a parasite concentration calculated by assuming a white cell count of 8000/μl and multiplying by the geometric mean parasite count. Sickle cell status was assessed by electrophoresis on cellulose acetate gel with an alkaline buffer. Wet preparations of stool samples were prepared and read under direct microscopy.

Case definitions and statistical methods

Severe anaemia was defined as a PCV < 25%. This cut-off for anaemia was chosen because it has been

Table 1 Potential anaemia risk factors investigated

Socio-economic
Mother's literacy, number of years in school, age at delivery, marital status, parity, number of children alive, birth interval, birth order of this child
Father's literacy and number of years in school
Number of family members, number of meals family gets per day, number of meals child gets per day, food source (bought/grown), type of child care
House owner, type of roof, walls and floor, number of people sleeping in the room with the child
Family source of income, monthly income in shillings, amount of crops harvested, mother's income, father's occupation
Family assets: number of cows, pigs, chickens/ducks, radio, bicycle, TV, fridge
Access to hospital
Distance from hospital > 10 km, duration of illness > 3 days before admission, previous hospital admissions
Health seeking behaviour
Choice of place for treatment: where was the child taken first for treatment
Completion of EPI vaccinations
Weighing contacts: number of weighing contacts
Place this child delivered (home or health facility)
Child factors
Sickle cell status
Low birthweight
Nutritional factors: MUAC, weight/age, weight/height, height/age
Previous blood transfusions
Use of mosquito net
Intestinal parasites: hookworms
P. falciparum parasitaemia & clinical malaria

associated with increased mortality (Stoltzfus *et al.* 1997; Schellenberg *et al.* 1999) and to facilitate comparability with other studies carried out in the area (Menendez *et al.* 1997; Schellenberg *et al.* 2001). Clinical malaria was defined as an axillary temperature equal to or higher than 37.5 °C plus asexual *P. falciparum* parasitaemia of any density. Malnutrition assessed by MUAC was defined as mild if MUAC was 12.5–13.5 cm and severe if MUAC was < 12.5 cm (Shakir & Morley 1974). The NCHS growth standards were used to express measurements as *Z*-scores for weight for height, weight for age and height for age (WHO 1983). A *Z*-score of < −1 was considered mild malnutrition, < −2 moderate malnutrition and < −3 severe malnutrition. Data were double entered in a menu driven system written in FoxPro 2.6 (Microsoft Corporation). Statistical analysis was performed using EPI-Info 2000 (v1.0, CDC Atlanta, USA) and Stata version 5.0 (Stata Corp, TX, USA). Multivariate analysis was performed using a logistic regression model adjusting for the possible confounding variables identified on univariate analysis. Two sets of multivariate analysis were performed to ensure that malaria, known to be a major determinant of anaemia in this setting (Menendez *et al.* 1997) did not obscure the effect of less marked but important upstream determinants.

Results

Two hundred and sixteen cases and 234 controls were enrolled in the study. Cases and controls alike were from poor families. The mean average total household expenditure for cases and controls was equivalent to US$ 7.65/month. The mean family size was 6.5, with 3.8 adults and 2.7 children. Most families depended on subsistence agriculture, harvesting an average of 10 (SD = 11.8) sacks of rice from 2.3 (SD = 2.4) acres of land. The majority owned the dwellings in which they lived, but these were simple constructions with leaf roofs, mud walls and mud floors. Very few ($n = 16$; 3.6%) households had electricity and only two had a refrigerator or television/video.

Most cases (55.6%, $n = 120$) were younger than 1 year (Figure 1). Table 2 shows the risk factors statistically significantly associated with severe anaemia. Anaemic children were more likely than controls to have mothers and fathers who had not completed primary education and fathers who were illiterate. Most children ($n = 350$, 77.8%) came from families normally growing their own food, but the mean number of meals consumed in the households of controls (2.40, SD = 0.78) was higher than that in the homes of cases [2.22 (SD = 0.80)] ($P = 0.02$).

Most (69%) children lived in houses with grass roofs, but anaemic children were significantly less likely to live

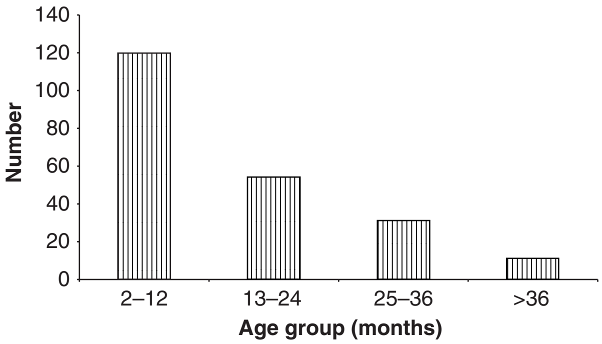

Figure 1 Age pattern of anaemia.

under a corrugated iron roof. The minority (13.8%) of children living in a house with a cement floor were also less likely to be anaemic than the majority of children whose houses had earth floors. The 67% of children living in a house with mud and wood walls were more likely to be anaemic than children living in brick-built houses.

There were no significant differences between cases and controls in the numbers of sacks of rice or maize harvested. The proportion of families with a monthly salary below the national minimum wage (TSh 30 000/= – approximately US$ 37.50) was similar for cases (24%) and controls (21%). In the 6 months leading up to the admission, cases spent significantly less on their

Table 2 Univariate analysis of risk factors for severe anaemia

	Controls		Cases			
Variable	*n*/*N*	%	*n*/*N*	%	Odds Ratio (95% CI)	*P*-value
Socio-economic						
Mother's years in school						
< 7	45/234	(19.2)	63/216	(29.2)	1	
7	161/234	(68.8)	142/216	(65.7)	0.64 (0.41; 1.00)	0.026
8–10	7/234	(3.0)	3/216	(1.4)	0.34 (0.08; 1.45)	
≥ 11	21/234	(9.0)	8/216	(3.7)	0.29 (0.12; 0.71)	
Father's years in school						
< 7	45/234	(19.2)	62/216	(28.8)	1	
7	161/234	(68.8)	142/216	(66.2)	0.65 (0.41; 1.01)	0.031
8–10	7/234	(3.0)	3/216	(1.4)	0.35 (0.08; 1.43)	
≥ 11	21/234	(9.0)	8/216	(3.7)	0.29 (0.12; 0.72)	
Father illiterate	25/234	(10.7)	39/215	(18.1)	1.83 (1.06; 3.16)	0.031
House factors						
Family own a house	158/234	(64.5)	166/216	(76.9)	1.54 (1.01; 2.4)	0.043
Paid for housing previous 6 months	33/234	(14.1)	13/216	(6.01)	0.41 (0.21; 0.80)	0.009
Grass roofing	143/234	(61.1)	169/216	(78.2)	2.22 (1.46; 3.38)	< 0.001
Earth floor	192/234	(82.1)	196/216	(90.7)	2.07 (1.17; 3.66)	0.013
Mud & wood wall	116/234	(49.6)	144/216	(66.7)	2.00 (1.36; 2.95)	< 0.001
Health-seeking & access to hospital						
Distance to hospital > 10 km	118/234	(50.4)	170/216	(78.7)	3.66 (2.42; 5.55)	< 0.001
Duration of illness > 6 days	66/234	(28.2)	69/216	(31.9)	1.90 (1.16; 3.12)	0.004
Home delivery	63/234	(26.9)	90/216	(41.7)	1.94 (1.30; 2.89)	0.002
Expenditure last 6 months > 5000 Tsh on health	44/234	(18.8)	60/216	(27.8)	1.78 (1.14; 2.80)	0.012
Child factors						
MUAC						
Reference	127/233	(54.5)	83/216	(38.4)	1	
Mild (< 13.5 cm)	50/233	(21.5)	69/216	(31.9)	2.18 (1.36; 3.49)	0.002
Severe (< 12.5 cm)	56/233	(24.0)	64/216	(29.6)	1.88 (1.16; 3.04)	
Not sleeping under a mosquito net	33/234	(14.1)	48/216	(22.2)	1.80 (1.10; 2.94)	0.020
Previous blood transfusion	11/234	(4.7)	37/216	(17.1)	4.34 (2.17; 9.09)	< 0.001
P. falciparum parasitaemia	69/228	(29.5)	138/213	(63.9)	4.33 (2.88; 6.49)	< 0.001
Clinical malaria	55/227	(24.2)	14/211	(44.5)	2.51 (1.67; 3.79)	< 0.001

accommodation (TSh 688 *vs.* TSh 2322), and significantly more on health issues (TSh 4098 *vs.* TSh 3401) than controls. Cases also tended to spend less on food and clothes, and to have a lower overall expenditure, than controls, although these differences did not reach statistical significance. Overall, 72% of patients owned a house and all of them lived in the houses they owned. These houses were significantly more likely to be made with non-corrugated roofs (246/324, $P < 0.001$), mud walls (289/324, $P < 0.001$) and mud floors (204/324, $P < 0.001$) than houses which were rented.

Anaemic children were more likely to have been delivered at home than cases. Low birthweight was not associated with an increased risk of anaemia and there was no apparent association between birth order or birth interval and risk of anaemia.

Children who lived more than 10 km away from the hospital were more likely to be anaemic than children living closer to the hospital. The duration of the illness before presenting to hospital was also longer in children admitted with anaemia. Although a history of previous admission was not associated with increased risk of anaemia, a history of previous blood transfusion was (OR 4.34, 95% CI 2.2–9.1).

The different measures of nutritional status produced similar estimates of the prevalence of malnutrition, but only children with a low MUAC were significantly more likely to be anaemic than children not malnourished on this assessment. There was a non-significant tendency for children with low WAZ and HAZ scores to be anaemic ($P = 0.07$ for each).

Reported net use was high among cases and controls (82%, $n = 369$) and children not sleeping under nets had nearly double the chance of being cases than children who used nets. Most (64%) cases were *P. falciparum* positive, a condition associated with a more than four-fold increased risk of anaemia. Increasing parasite density did not increase the risk of anaemia. Only 2.8% of cases had HbSS and 6.9% HbAS, and neither genotype was significantly associated with anaemia. Hookworm ova were only present in 2.9% of children admitted to the paediatric ward (3.7% of anaemia cases and 2.1% of controls, $P = 0.36$). The prevalence of other intestinal parasites was < 1%.

Multivariate analyses (Table 3) showed that increased health expenditure in the preceding 6 months, malnutrition defined by a reduced MUAC, living >10 km away from the hospital, history of previous blood transfusion and *P. falciparum* parasitaemia were independent risk factors for admission with severe anaemia. Repeating the analysis having removed *P. falciparum* parasitaemia did not materially alter the results.

Table 3 Multivariate analysis of risk factors for severe anaemia

Variable	OR	95% CI	*P*-value
Health expenditure last 6 months > 5000 TSh	2.23	1.3; 3. 9	0.005
Mid upper arm circumference (cm)			
Mild malnutrition		1.6; 5.1	< 0.001
Severe malnutrition	2.4	1.3; 4.3	
Distance from hospital > 10 km	3.0	1.8; 4.9	< 0.001
Previous blood transfusion	3.8	1.7; 9.1	< 0.001
Asexual *P. falciparum* parasitaemia	9.5	4.3; 21.3	< 0.001

Discussion

The results of this study show that important contributors to the pathogenesis of anaemia included the socio-cultural background, case management of previous anaemia episodes and *P. falciparum* malaria, which was the most important immediate cause of anaemia in this setting.

The controls were selected from other hospitalized children and hence the risk factors identified are related to the risk of admission with anaemia rather than admission with other conditions. Factors associated more generally with ill health may not have been identified. A striking observation was that cases and controls alike came from poor families, heavily dependent on subsistence agriculture, with very low household expenditure and living in simple dwellings. Despite the homogeneity of the study population in this respect, the study showed that the minority of children living in brick-built houses with cement floors and corrugate iron roofs were less likely to be anaemic than children living in more simple houses. It is not clear whether this is a reflection of improved socio-economic status or whether the better housing *per se* reduces risk of anaemia, e.g. by being less hospitable for *Anopheline* mosquitoes. Better nourished children, with higher MUAC and living in households where more meals were available each day, were less likely to be anaemic than their malnourished counterparts. This too may be a reflection of better socio-economic status, itself related to parental education, which was another important determinant of risk of anaemia. That cases came from poorer households is also suggested by the lower total household expenditure of cases than controls. Yet cases spent significantly more on health than controls in the 6 months before questioning, suggesting that these children were more likely to have had prior illnesses than the control children. The former illness may have been malaria, known to predispose to anaemia, or children with anaemia may have been generally less healthy than children with other problems. A potential risk factor, which could account for this observation but which we did not assess, is infection with HIV. Whatever the reason for the increased expenditure, the costs of the new illness episode would exacerbate their poverty, possibly increasing further the risk of subsequent illness episodes, locking them ever more firmly into the illness–poverty cycle.

The observation that children living further away from the hospital were more likely to be anaemic persisted in the multivariate analysis. This may be a reflection of higher malaria transmission beyond the immediate vicinity of SFDDH, impaired access to hospital in those living further away, or a combination of the two factors. The importance of access may explain the finding that the delay in seeking health care, which was more common in cases than controls, did not persist in the multivariate analysis. Delay in seeking health care may therefore be more a function of time taken to travel from the remote home to the hospital, a reflection of ease of physical access to health services, than to health-seeking behaviour. The same considerations apply for the relationship between birth place and anaemia as poor access to hospital would increase the chance of a home delivery. Poor transport facilities and the costs involved in travelling from peripheral rural areas to hospital compound the physical problems of access. In Kilombero, many households are more than 150 km from the district hospital, the only transfusion-capable health facility in the district, and public transport is relatively expensive and, at best, erratic.

The long list of risk factors significantly associated with an increased risk of severe anaemia should not obscure the fact that anaemia cases were concentrated in children younger than 1 year. This is in keeping with earlier work documenting a concentration of anaemia in infants (Slutsker *et al.* 1994; Schellenberg *et al.* 1999; Menendez *et al.* 2000) and the observation that 10% of children aged 6–11 months in the community had a PCV < 15% (D. Schellenberg, unpublished). Anaemia control measures in this setting need to be targeted towards infants. An earlier study estimated that 57% of anaemia in this age group is related to malaria and that 29% is associated with iron deficiency (Menendez *et al.* 1997). The importance of malaria as a cause of anaemia is reflected by the observation that parasitaemia was associated with risk of anaemia. Increasing density of parasitaemia did not increase the risk of anaemia. Children not sleeping under nets had nearly double the chance of being cases than children sleeping under nets in the univariate analysis. It is impressive that, despite the poverty within the community studied, 82% of children slept under a mosquito net. This is likely to be a reflection of the high mosquito densities of the Kilombero flood plains, with the associated biting nuisance, and the widespread availability of mosquito nets through an active social marketing campaign (Armstrong Schellenberg *et al.* 1999).

A previous blood transfusion was strongly associated with increased risk of anaemia, suggesting that earlier episodes of anaemia were inadequately treated with a blood transfusion. Studies have shown that the effect of blood transfusion alone is short-lived, lasting only weeks (Lackritz *et al.* 1992; Holzer *et al.* 1993). This emphasizes the need for an integrated approach to the management of anaemia, particularly in ensuring that children who receive blood transfusions also receive antimalarials and ferrous sulphate treatment. In our setting, however, routine use of antihelminthics is probably not appropriate as a very low proportion of the young children with anaemia were found to harbour helminths, in keeping with earlier work from this area (Gascon *et al.* 2000).

In conclusion, this study has shown that factors well upstream in the pathogenic process, such as parental education and type of accommodation, are important determinants of risk of admission with anaemia: such factors are not easy to change and require long-term strategies. Although it was the poorest who were at highest risk of anaemia, they also had the highest health-related expenditures, illustrating their entrapment in the poverty–illness cycle. The plethora of risk factors apparently related to socio-economic status suggest that the prevalence of anaemia, or mean PCV, may be a useful marker of poverty reduction strategies in some settings. Improved case management of anaemia and malnutrition is likely to produce useful health benefits. However, the marked tendency of admitted anaemia cases to be aged < 1 year emphasizes the need to target this most vulnerable age group. Furthermore, as anaemia was more common in those with poorer access to health services, the need to develop preventive strategies is underlined. Taken together, these findings suggest that the approach to anaemia control should be revised so that preventive strategies are targeted at very young children. Several approaches have yielded promising results and are in different stages of implementation and evaluation. These include the use of insecticide treated nets (ITNs), supplementation of infants with iron syrup and intermittent antimalarial treatment delivered alongside routine vaccinations. Further evaluation and deployment of these approaches should now be a priority.

Acknowledgements

We thank the parents and guardians of all children involved in the study; Dr P.Kibatala (Medical Director) and the staff of St Francis Designated District Hospital, without whose cooperation this study would not have been possible; the laboratory staff of Ifakara Health Research and Development Centre for performing the lab tests, Irene Ngoja for performing interviews and collecting samples; and the District Medical Officer, Dr F. Lwilla and his District Health Management Team for facilitating the acceptance of the research team in the local community. This study received financial support from the UNDP/World Bank/WHO Special Program for Research Training in Tropical Diseases. Ifakara Health Research and Development Centre receives funds from the Swiss Agency for Development and Cooperation.

References

Abdulla S, Schellenberg JA, 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 S, Armstrong 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**, 37–44.

Alonso PL, Smith T, Armstrong Schellenberg JRM *et al.* (1994) Randomised trial of efficacy of SPf66 vaccine against *Plasmodium falciparum* malaria in children in southern Tanzania. *Lancet* **344**, 1175–1181.

Armstrong Schellenberg JRM, Abdulla S, Minja H *et al.* (1999) KINET: a social marketing programme of treated nets and net treatment for malaria control in Tanzania, with evaluation of child health and long-term survival. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **93**, 225–231.

Banguero H (1984) Socio-economic factors associated with malaria in Colombia. *Social Science and Medicine* **19**, 1099–1104.

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.

Bojang KA, Van Hensbroek MB, Palmer A, Banya WA, Jaffar S & Greenwood BM (1997a) Predictors of mortality in Gambian children with severe malaria anaemia. *Annals of Tropical Paediatrics* **17**, 355–359.

Bojang KA, Palmer A, Boele van Hensbroek M, Banya WA & Greenwood BM (1997b) Management of severe malarial anaemia in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **91**, 557–561.

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

Brooker S, Peshu N, Warn PA *et al.* (1999) The epidemiology of hookworm infection and its contribution to anaemia among preschool children on Kenyan coast. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **93**, 240–246.

Buttraporn P, Sornmani S & Hungsapruek T (1986) Social, behavioural housing factors and their interactive effects associated with malaria occurrence in East Thailand. *South-east Asian Journal of Tropical Medicine and Public Health* **17**, 386–392.

Craighead IB & Knowles JK (1993) Prevention of transfusion-associated HIV transmission with the use of a transfusion protocol for under 5s. *Tropical Doctor* **23**, 59–61.

Dallman PR, Siimes MA & Stekel A (1980) Iron deficiency in infancy and childhood. *American Journal of Clinical Nutrition* **33**, 86–118.

Emerton DG (1992) An audit of the management of malaria in a Tanzanian district hospital. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **86**, 476–478.

Fleming AF & Werblinska B (1982) Anaemia in childhood in the guinea savanna of Nigeria. *Annals of Tropical Paediatrics* **2**, 161–173.

Gascon J, Vargas M, Schellenberg D *et al.* (2000) Diarrhoea in children under 5 from Ifakara, Tanzania: a case control study. *Journal of Clinical Microbiology* **38**, 4459–4462.

Hatz C, Abdulla S, Mull R *et al.* (1998) Efficacy and safety of CGP 56697 (artemether and benflumetol) compared with chloroquine to treat acute falciparum malaria in Tanzanian children aged 1–5 years. *Tropical Medicine and International Health* **3**, 498–504.

Hausmann-Muela S, Ribera J & Tanner M (1998) Fake malaria and hidden parasites – the ambiguity of malaria. *Anthropology and Medicine* **5**, 43–61.

Hedberg K, Shaffer N, Davachi F *et al.* (1993) *Plasmodium falciparum*-associated anemia in children at a large urban hospital in Zaire. *American Journal of Tropical Medicine and Hygiene* **48**, 365–371.

Holzer B, Egger M, Teuscher T, Koch S, Mboya D & Smith GD (1993) Childhood anemia in Africa: to transfuse or not transfuse? *Acta Tropica* **55**, 47–51.

Koko J, Dufillot D, M'Ba-Meyo J, Gahouma D & Kani F (1998) Mortality of children with sickle cell disease in a pediatric department in Central Africa. *Archives of Pediatrics* **5**, 965–969.

Koram KA, Bennet S, Adiamah JH & Greenwood BM (1995) Socio-economic determinants are not major risk factors for severe malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **89**, 151–154.

Lackritz EM, Campbell CC, Ruebush TK *et al.* (1992) Effect of blood transfusion on survival among children in a Kenyan hospital. *Lancet* **340**, 524–528.

Luckner D, Lell B, Greve B *et al.* (1998) No influence of socio-economic factors on severe malarial anaemia, hyperparasitaemia or reinfection. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **92**, 478–481.

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.

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

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. *Lancet* **350**, 844–850.

Mockenhaupt FP, Rong B, Gunther M *et al.* (2000) Anaemia in pregnant Ghanaian women: importance of malaria, iron deficiency, and haemoglobinopathies. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **94**, 477–483.

Murphy SC & Breman JG (2001) Gaps in the childhood malaria burden in Africa: cerebral malaria, neurological sequelae, anemia, respiratory distress, hypoglycemia, and complications of pregnancy. *American Journal of Tropical Medicine and Hygiene* **64**, S57–S67.

Mwenesi H, Harpham T & Snow RW (1995) Child malaria treatment practices among mothers in Kenya. *Social Science and Medicine* **40**, 1271–1277.

Rana SR, Sekhsaria S & Castro OL (1993) Hemoglobin S and C traits: contributing causes for decreased mean hematocrit in African-American children. *Pediatrics* **91**, 800–802.

Said A, El-Hawary MF, Sakr R, Khalek MK, El-Shobaki FA & Noseir MB (1975) Biochemical and haematological aspects of anaemia associating protein energy malnutrition (PEM). *Gazette of the Egyptian Paediatric Association* **23**, 139–144.

Schellenberg D, Menendez C, Kahigwa E *et al.* (1999) African children with malaria in an area of intense *Plasmodium falciparum* transmission: features on admission to the hospital and risk factors for death. *American Journal of Tropical Medicine and Hygiene* **61**, 431–438.

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.

Shakir A & Morley DC (1974) Measuring malnutrition. *Lancet* **i**, 758–759.

Singla PN, Chand P, Kumar A & Kachhawaha JS (1996) Serum zinc and copper levels in children with protein energy malnutrition. *Indian Journal of Pediatrics* **63**, 199–203.

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.

Smith T, Charlwood JD, Kihonda J *et al.* (1993) Absence of seasonal variation in malaria parasitaemia in an area of intense seasonal transmission. *Acta Tropica* **54**, 55–72.

Stockman JA & Oski FA (1978) Physiological anaemia of infancy and the anaemia of prematurity. *Clinics in Haematology* **7**, 3–18.

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

Stoltzfus RJ, Chwaya HM, Tielsch JM, Schulze KJ, Albonico M & Savioli L (1997) Epidemiology of iron deficiency anaemia in Zanzibari schoolchildren: the importance of hookworms. *American Journal of Clinical Nutrition* **65**, 153–159.

Stoltzfus RJ & Dreyfuss ML (1998) *Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia.* INACG, WHO and UNICEF, Geneva.

Thuilliez V & Vierin Y (1997) The importance of sickle cell anaemia in a pediatric environment in Gabon. *Sante Publique* **9**, 45–60.

Tshikuka JG, Scott ME, Gray-Donald K & Kalumba ON (1996) Multiple infection with *Plasmodium* and helminths in communities of low and relatively high socio-economic status. *Annals of Tropical Medicine and Parasitology* **90**, 277–293.

WHO (1983) *US National Centre for Health Statistics (NCHS).* WHO, Geneva.

