Tropical Medicine and International Health

VOLUME 8 NO 6 PP 507–511 JUNE 2003

The association between protein–energy malnutrition, malaria morbidity and all-cause mortality in West African children

Olaf Müller[1], Michel Garenne[2], Bocar Kouyaté[3] and Heiko Becher[1]

1 *Department of Tropical Hygiene and Public Health, Ruprecht-Karls-University, Heidelberg, Germany*
2 *Institut Pasteur, Paris, France*
3 *Centre de Recherche en Santé de Nouna, Burkina*

Summary Both malaria and protein–energy malnutrition (PEM) are highly prevalent in young children of sub-Saharan Africa, and the association between PEM and malaria continues to be discussed controversially. We analysed the association between PEM, malaria morbidity and all-cause mortality in a cohort of 709 children aged 6–30 months in a malaria holoendemic rural area of Burkina Faso. Study children were followed over the main malaria transmission period (June–December) in 1999 through longitudinal malaria surveillance complemented by three cross-sectional clinical surveys. There was no association between PEM and malaria morbidity, but malnourished children had a more than two-fold higher risk of dying than non-malnourished children.

keywords Africa, Burkina Faso, malaria, malnutrition, mortality

Introduction

Nutritional status is considered to be one of the major determinants of host resistance to infection (Keusch 1979; Gershwin *et al* . 1985). Malnutrition is estimated to cause about half of the world's 12 million annual deaths in children less than 5 years of age as well as substantial proportions of infectious disease morbidity (Pinstrup-Andersen *et al.* 1993; Rice *et al.* 2000). The relation between nutritional status and mortality is well documented, with decreasing nutritional status being associated with increasing risk ratios of mortality (Van den Broek *et al.* 1993; Garenne *et al* . 2000; Rice *et al.* 2000). More than half of the global burden of childhood deaths is caused by diarrhoea, acute respiratory illness (ARI), malaria and measles, conditions which can easily be prevented or treated (Tulloch 1999). In sub-Saharan Africa (SSA), malaria alone is estimated to kill around one million children every year (Snow *et al.* 1999).

Young children of SSA are the group most affected by both poor nutrition and malaria, and the relation between both conditions continues to be discussed very controversially. While a number of studies provided substantial evidence for protein–energy malnutrition (PEM) being associated with reduced malaria morbidity, others have not seen such associations or even demonstrated that PEM is associated with more severe manifestations of malaria (McGregor 1988; Shankar 2000). Against this background we studied the association between PEM, malaria morbidity and all-cause mortality in a cohort of West African pre-school children.

Subjects and methods

Study area

The study was conducted in Nouna Health District in northwestern Burkina Faso. Nouna is a dry orchard savannah, populated almost exclusively by subsistence farmers of different ethnic groups. There is a short rainy season, which usually lasts from June to October. Malnutrition is highly prevalent in the study area and malaria is holoendemic, with most transmission occurring during or shortly after the rainy season. HIV/AIDS is still a rare disease in this rural area of Nouna Health District.

Patients

In 1999, we had undertaken a randomized double-blind placebo-controlled trial on the effects of zinc supplementation on malaria morbidity. The main finding was that zinc supplementation had no effect on malaria morbidity (Müller *et al.* 2001). During this trial, 709 children aged 6–30 months were recruited from 18 villages of the Nouna Health Research Centre (CRSN) study area in Nouna Health District. Anthropometric and malariometric data were systematically collected during three cross-sectional surveys (6 of 99, 9 of 99, 12 of 99), and

685 children were successfully followed up over the 6-month study period.

To survey malaria morbidity, children were seen daily except on Sundays by village-based fieldworkers who took the axillary temperature with an electronic thermometer (Digital Classic, Hartmann, Germany) and filled in a structured questionnaire on further parent-reported information. If a temperature of 37.5 °C or higher was measured, a finger prick blood sample was taken and a thick and thin blood film were prepared. The parents of children found to be sick during daily visits were advised to take them to the nearest local health centre for diagnosis and treatment. During cross-sectional surveys, children were seen and examined by the same physician during all visits. Children found sick during surveys were treated appropriately or referred to Nouna Hospital free of charge. Mothers of malnourished children received intensive advice on feeding practice, and were offered admission to the Nouna Hospital Feeding Centre in case of severe malnutrition. Demographic and risk factor data (age, sex, ethnicity, mosquito net protection in September, socio-economic status defined through possession of radio/bicycle/motorbike), clinical data (history, symptoms, temperature, spleen size by Hackett grade, weight, height/length, mid-arm circumference), and parasitological data (thin and thick blood films) were collected from all children. Demographic and socio-economic baseline variables are shown in Table 1.

Table 1 Distribution of demographic and socio-economic baseline variables

	n	%
Sex		
Male	335	48.9
Female	350	51.1
Age (months) (6/1999)		
6–12	174	25.4
13–18	185	27.0
19–24	181	26.4
>24	145	21.2
Ethnic group		
Dafing	311	45.4
Bwaba	141	20.6
Mossi	132	19.3
Peulh	79	11.5
Samo	12	1.8
Others	10	1.5
Bednet use (9/1999)		
No	489	71.4
Yes	168	24.5
Missings	28	4.1
Socio-economic status		
Low	67	9.8
Middle	229	33.4
High	299	43.7
Missing	90	13.1
Total	685	100.0

Laboratory procedures

Blood films were Giemsa-stained at Nouna Hospital Laboratory and then transported to the Centre National de Recherche et de Formation sur le Paludisme in Ouagadougou for reading. All films were examined by two experienced laboratory technicians using a × 100 oil immersion lens and × 10 eyepieces. In case of significant discrepancy between the results of the two technicians, blood slides were read by a third investigator. Blood films were analysed for the species-specific parasite density per microlitre by counting against 500 white blood cells and multiplying by 16 (assuming 8000 white blood cells per microlitre of blood). Slides were declared negative if no parasites were seen in 400 fields on the thick film.

Anthropometric measurements

Weight was measured during each of the three surveys, while height/length was measured only during the baseline and the end-of-study survey. Weight was measured with one Salter hanging spring scale with 100-g gradations, which was calibrated and checked daily before and after use. Children were allowed to wear a minimum of light clothes. Recumbent length and standing height were measured with a locally produced length board with an upright wooden base and a movable headpiece and a simple anthropometer, respectively. Measures included weight to 0.1 kg and height/length to 1.0 cm. Anthropometric measurements were usually performed by the same fieldworker following standard techniques. The SD scores for height-for-age (HAZ), weight-for-age (WAZ), and weight-for-height (WHZ) were calculated in comparison with the NCHS reference population, using Epi Info, version 6.0. Stunting, underweight and wasting were defined as HAZ ≤ −2, WAZ ≤ −2, and WHZ ≤ −2, respectively (WHO Working Group 1986).

Mortality follow-up

Mortality follow-up took place through the existing Demographic Surveillance System (DSS) of the CRSN (Sankoh *et al.* 2001). The routine activities of the DSS include three-monthly visits to all households in the CRSN study area, with registration of all births, deaths and migrations.

Statistical analysis

Malaria incidence was calculated by dividing the number of falciparum malaria episodes by the number of days of observation. A falciparum malaria episode was defined as an axillary temperature of 37.5 °C or higher with at least 5000 parasites per microlitre and no other obvious causes for the fever. Additional definitions of fever and parasite counts of ≥1 and ≥100 000/µl were also applied. To exclude recrudescent malaria episodes, the individual observation time was defined as the time interval from the first to last day of observation minus 20 days for each defined episode.

We compared children with malnutrition (mean HAZ/WAZ/WHZ ≤ −2) and without malnutrition (mean HAZ/WAZ/WHZ > −2) for falciparum malaria incidence over the 6-month study period using Poisson regression and all-cause mortality (over a 1-year follow-up period) using logistic regression; children with no anthropometric measurements to calculate the HAZ/WAZ/WHZ scores at the first survey were excluded from the respective analyses. Possible confounding factors (age, sex, ethnicity, village, mosquito net use, and socio-economic status) were taken into account. Relative risks, 95% confidence intervals, and *P*-values were calculated using the statistical software package SAS and using PROC GENMOD for Poisson Regression, PROC LOGISTIC for logistic regression and PROC CORR SPEARMAN for assessing the relation between age and number of malaria episodes.

Ethical aspects

Approval was granted by the Ethical Committee of Heidelberg University Medical School, the Ethical Committee of the World Health Organization and the Ministry of Health in Burkina Faso. Prior to study participants' recruitment, the trial was explained in detail to all district authorities and village meetings were held to explain the purpose, methods, benefits and risks of the study to the population. The trial was also explained to the respective head of each participating compound and oral consent was sought from the parents and caretakers of study children before enrolment.

Results

Of 685 children followed up for malaria incidence over the 6-month observation period, 232 (36%), were stunted, 314 (48%) underweight and 132 (20%) wasted based on the respective mean HAZ, WAZ and WHZ values. The median number of falciparum malaria episodes over the observation period according to the three case definitions (≥37.5 °C + ≥1 *P. falciparum* parasites/microlitre; ≥37.5 °C + ≥5000 *P. falciparum* parasites/microlitre; ≥37.5 °C + ≥100 000 *P. falciparum* parasites/microlitre) were 2 (range 0–5), 1 (0–5) and 0 (0–2) respectively. The mean SD scores for HAZ, WAZ, and WHZ were −1.6, −2.0, and −1.2 at baseline, respectively; and −1.5, −2.0, and −1.3 after 6-month follow-up, respectively (Table 2). There were no differences in falciparum malaria incidence between malnourished and non-malnourished children after adjustment for possible confounding variables (Table 3).

During the 6 months of the randomized controlled trial 17 of 685 (2.5%) study children died; after 12 months of observation, 28 of 685 (4.1%) of the study children had died. After adjustment for possible confounding variables, malnourished children had a more than two-fold higher risk of dying than non-malnourished children, with a

Table 2 Distribution of anthropometric variables by sex and survey

	Male			Female		
	n	mean	SD	*n*	mean	SD
First survey (6/1999)						
HAZ	322	−1.69	1.49	326	−1.42	1.39
WAZ	321	−2.03	1.29	332	−1.87	1.15
WHZ	320	−1.28	1.09	325	−1.20	0.95
Second survey (9/1999)						
HAZ						
WAZ	292	−1.89	1.26	307	−1.73	1.12
WHZ						
Third survey (12/1999)						
HAZ	309	−1.60	1.43	307	−1.45	1.34
WAZ	307	−1.99	1.18	319	−1.93	1.13
WHZ	305	−1.30	0.95	306	−1.33	0.83

SD = standard deviation; HAZ = height for age; WAZ = weight for age; WHZ = weight for height.

Table 3 Association between protein–energy malnutrition, falciparum malaria and all-cause mortality

		Malaria defined as												Total mortality		
		≥37.5 °C ≥1 parasite/microlitre				≥37.5 °C ≥5000 parasites/microlitre				≥37.5 °C ≥100 000 parasites/microlitre						
	n	RR*	ME	PDO	95% CI	RR*	ME	PDO	95% CI	RR*	ME	PDO	95% CI	Deaths *n* (%)	RR**	95% CI
HAZ																
>−2	416	1.0	753	55 901		1.0	545	60 061		1.0	48	70 001		12 (2.9)	1.0	
≤−2	232	1.0	406	30 791	0.9–1.1	1.0	300	32 911	0.9–1.2	0.8	20	38 511	0.5–1.4	15 (6.5)	2.4	1.0–5.7
P-value					0.87				0.59				0.44			0.05
WAZ																
>−2	339	1.0	620	45 616		1.0	448	49 056		1.0	38	57 256		6 (1.8)	1.0	
≤−2	314	1.0	553	41 643	0.9–1.1	1.0	407	44 563	0.9–1.2	0.8	29	52 123	0.5–1.4	21 (6.7)	2.7	1.0–7.3
P-value					0.98				0.68				0.49			0.05
WHZ																
>−2	513	1.0	926	68 911		1.0	669	74 051		1.0	53	86 371		14 (2.7)	1.0	
≤−2	132	1.0	228	17 365	0.9–1.2	1.0	172	18 485	0.9–1.2	1.0	14	21 645	0.5–1.8	13 (9.8)	2.8	1.1–6.7
P-value					0.99				0.58				0.94			0.02

* RR based on Poisson regression model adjusted for age, sex, ethnicity, village (region), mosquito net use, socio-economic status.
** RR based on logistic regression model adjusted for age, sex, ethnicity, village (region), mosquito net use, socio-economic status.
ME = number of malaria episodes; PDO = person days of observation; HAZ = height for age; WAZ = weight for age; WHZ = weight for height.

relative risk of 2.4 [confidence interval (CI) 1.0–5.7, $P = 0.05$] for stunted children, 2.7 (CI 1.0–7.3, $P = 0.05$) for underweight children, and 2.8 (CI 1.1–6.7, $P = 0.02$) for wasted children (Table 3).

Discussion

We measured the association between PEM and malaria morbidity in a well-defined population of young children exposed to high *P. falciparum* transmission intensity. There was no association between PEM and the incidence of falciparum malaria, using the case definition of fever plus at least 5000 *P. falciparum* parasites per microlitre, and after controlling for possible confounding factors. Additional comparisons using traditional case definitions for mild and heavy infections did not change this result. As zinc supplementation assigned randomly to study children was not found related with malaria, it is unlikely to be a confounder (Müller *et al.* 2001). These findings are in contrast with a number of older studies, which claimed that PEM is associated with decreased malaria morbidity, as well as with some more recent studies providing evidence for PEM being associated with increased malaria morbidity (McGregor 1988; Shankar 2000). A variety of designs have been used in such studies, ranging from hospital-based case–control studies on malaria morbidity and mortality to community-based cohort studies on malaria incidence, and from experimental studies in animals to famine interventions in human populations. Most of these studies have obvious methodological limitations, and are thus difficult to interpret (Shankar 2000). However, in our study we also have to take into account that parasitaemia is not a very good measure of malaria morbidity.

Protein–energy malnutrition is considered to be one of the most important risk factors for overall morbidity and mortality in childhood, particularly in SSA (Murray & Lopez 1997). The strongest evidence for this association comes from observational community-based cohort studies (Rice *et al.* 2000). As even in cohort studies the direction of the effect can be confused through intermittent illnesses resulting in nutritional deterioration, we chose a PEM definition likely to avoid such bias.

In our study, mortality was significantly associated with a low HAZ, WAZ and WHZ. This supports the evidence for both acute malnutrition (wasting) and chronic malnutrition (stunting) being associated with mortality (Pinstrup-Andersen *et al.* 1993; Rice *et al.* 2000). Our findings on the high prevalence of malnutrition and the association between PEM and all-cause mortality in a typical population of young West African children thus confirms the major impact of this risk factor on overall childhood mortality in SSA (Murray & Lopez 1997).

Evidence points to diarrhoea and ARI being the most important causes of deaths related to malnutrition in childhood, while the association between PEM and malaria mortality continues to be discussed controversially (Rice *et al.* 2000; Shankar 2000). As the majority of young

children's deaths in SSA occur at home, verbal autopsy is the only method to estimate cause-specific mortality rates. Unfortunately, it is not very reliable for determining deaths caused by the major diseases in SSA children, and particularly not for malaria (Snow *et al.* 1992; Todd *et al.* 1994). Verbal autopsy is likely to become even more unreliable with the emergence of HIV/AIDS as a major determinant of childhood deaths in SSA (Müller & Garenne 1999).

Our results confirm PEM being a major risk factor for all-cause mortality in West African children but provide no evidence for PEM being associated with malaria morbidity.

Acknowledgements

We thank Ms Gabriele Stieglbauer at the University of Heidelberg for her assistance in data management and statistical analysis. The work was supported by a grant from the World Health Organization, and by the Deutsche Forschungsgemeinschaft (SFB 544, Control of Tropical Infectious Diseases).

References

Garenne M, Maire B, Fontaine O, Dieng K & Briend A (2000) *Risques de décès associés à différents états nutritionnels chez l'enfant d'âge préscolaire*. Etudes du CEPED, no 17. CEPED, Paris.

Gershwin ME, Beach RS & Hurley LS (1985) *Nutrition and Immunity*. Academic Press, New York.

Keusch GT (1979) Nutrition as a determinant of host response to infection and the metabolic sequelae of infectious disease. *Seminar of Infectious Diseases* **2**, 265–303.

McGregor IA (1988) Malaria and nutrition. In: *Malaria – Principles and Practice of Malariology*. (eds WH Wernsdorfer & I McGregor), Churchill Livingstone, London, pp. 753–768.

Müller O & Garenne M (1999) Childhood mortality in sub-Saharan Africa. *Lancet* **353**, 673.

Müller O, Becher H, Baltussen van Zweeden A *et al.* (2001) Effect of zinc supplementation on malaria and other causes of morbidity in west African children: randomized double blind placebo controlled trial. *British Medical Journal* **322**, 1–6.

Murray CJL & Lopez AD (1997) Global mortality, disability, and the contribution of risk factors: global burden of disease study. *Lancet* **349**, 1436–1442.

Pinstrup-Andersen P, Burger S, Habicht JP & Peterson K (1993) Protein-energy malnutrition. In: *Disease Control Priorities in Developing Countries*. (eds DT Jamison, WH Mosley, AR Measham & JL Bobadilla) Oxford University Press, Oxford, pp. 391–420.

Rice AL, Sacco L, Hyder A & Black RE (2000) Malnutrition as an underlying cause of childhood deaths associated with infectious diseases in developing countries. *Bulletin of the World Health Organization* **78**, 1207–1221.

Sankoh OA, Ye Y, Sauerborn R, Müller O & Becher H (2001) Clustering of childhood mortality in rural Burkina Faso. *International Journal of Epidemiology* **30**, 485–492.

Shankar A (2000) Nutritional modulation of malaria morbidity and mortality. *Journal of Infectious Diseases* **182** (Suppl. 1), 37–53.

Snow RW, Armstrong JRM, Forster D et al. (1992) Childhood deaths in Africa: uses and limitations of verbal autopsies. *Lancet* **340**, 351–355.

Snow RW, Craig M, Deichmann U & Marsh K (1999) Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. *Bulletin of the World Health Organization* **77**, 624–640.

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

Tulloch J (1999) Integrated approach to child health in developing countries. *Lancet* **354**, 16–20.

Van den Broek J, Eeckels R & Vuylstek J (1993) Influence of nutritional status on child mortality in rural Zaire. *Lancet* **341**, 1491–1495.

WHO Working Group (1986) Use and interpretation of anthropometric indicators of nutritional status. *Bulletin of the World Health Organization* **64**, 929–941.

Authors

Olaf Müller (corresponding author) and **Prof. Heiko Becher**, Department of Tropical Hygiene and Public Health, Ruprecht-Karls-University Heidelberg, Im Neuenheimer Feld 324, 69120 Heidelberg, Germany. E-mail: olaf.muller@urz.uni-heidelberg.de; heiko.becher@urz.uni-heidelberg.de

Michel Garenne, Institut Pasteur, 28 rue du Docteur Roux, 75724 Paris Cedex 15, France. E-mail: mgarenne@bhdc.jussien.fr

Bocar Kouyaté, Centre de Recherche en Santé de Nouna, B.P. 34, Nouna, Burkinu Faso E-mail: bocar.crsn@fasonet.bf