

The impact of population level deworming on the haemoglobin levels of schoolchildren in Tanga, Tanzania

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Summary

The impact of albendazole (400 mg) and praziquantel (40 mg/kg body weight) treatment of schoolchildren was compared with placebo according to the presence of anaemia (haemoglobin concentration < 11.0 g/dl) and heavy (> 5000 epg) or light (< 5000 epg) hookworm egg load. The study was conducted in rural Tanga. Medication was administered in September 1994 and children were followed-up in January 1995. Overall, anthelmintic treatment reduced the fall in haemoglobin concentration compared with that observed in the placebo group (- 0.11 g/dl vs. - 0.35 g/dl; $P = 0.02$). Anthelmintic treatment was of greatest benefit to the 9% of children with both anaemia and heavy hookworm egg load (+ 0.67 g/dl vs. - 0.67 g/dl) and was also of significant benefit to the 38% of children with anaemia and light hookworm egg load (+ 0.07 g/dl vs. - 0.21 g/dl). It was of no significant benefit to children who were not anaemic. This study suggests that single-dose anthelmintic treatment distributed in schools in this area achieves haematological benefits in nearly half of children infected with *S. haematobium* and geohelminths (37% of total population).

keywords deworming, anaemia, Tanzania, schoolchildren, gut helminths, hookworm, *Schistosoma haematobium*, *Ascaris lumbricoides*, *Trichuris trichiura*

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Introduction

It is increasingly recognized that intestinal helminths may have a harmful impact on haemoglobin, growth and cognitive function of school age children. Previous studies have demonstrated this for heavy infection with hookworm, *Schistosoma haematobium*, *Trichuris trichiura*, and to a lesser degree, *Ascaris lumbricoides* (Layrisse & Roche 1964; Layrisse *et al.* 1967; Stephenson *et al.* 1985; Nokes *et al.* 1992; Prual *et al.* 1992; Stoltzfus *et al.* 1997a). Conventional approaches to helminth control have relied on public health measures including education and environmental improvement aimed at behavioural change, together with identification and treatment of individuals with particularly heavy burdens of infection.

With growing recognition of the enormous scale of micronutrient malnutrition, growth retardation and cognitive impairment that can be attributed to intestinal helminths,

this approach is no longer considered adequate or appropriate. Instead, population-based approaches in which all children in high risk communities are treated have been proposed and are increasingly being implemented (WHO 1992; Stoltzfus *et al.* 1997b). However, with limited resources, it is necessary to define the proportion of children who benefit from a populationwide intervention to enable policy makers to make informed decisions about which populations should have priority for control programmes.

The use of single-dose treatments for schistosomiasis (praziquantel) and intestinal helminths (benzimidazoles) once a year, for instance, has been proposed as a potential disease control strategy, particularly now that such drugs have become considerably cheaper (Savioli *et al.* 1992; PCD 1998a). Even so, if governments, donors, community groups or parents are to pay for treatment without prior diagnosis, it is important to know the proportion of children who will benefit from such population-based approaches. The purpose

of this study was to estimate the benefit to schoolchildren, in terms of anaemia reduction, of using a two-drug regimen proposed for schoolchildren living in areas with a high burden of intestinal helminths and schistosomiasis, and a high prevalence of anaemia.

Methods

Study area and population

This study was conducted by Ushirikiano wa Kumwendeleza Mtoto Tanzania (UKUMTA – Tanzania Partnership for Child Development), a group of collaborating government agencies, scientific institutions and donor agencies which aims to improve the health of school-age children in Tanzania and is part of an international research consortium (PCD 1997). UKUMTA's work began in Tanga Region and the study took place in a rural area of Muheza District in the villages of Misongeni, Ubembe and Kilometa Saba, from September 1994 with follow-up in January 1995. After a house-to-house survey to record the number of 7–12 year-old children living in the villages, all children in this age range were invited to participate irrespective of school attendance.

Study design and randomization

Children included in the intervention study were assigned to one of six categories on the basis of prevalence and intensity of helminth infection. Randomization within each category was achieved using random number tables. Children included in the treatment group were given single doses of 400 mg albendazole (Zentel, Smithkline Beecham, UK) and praziquantel (Biltricide; Bayer Pharmaceutical, Germany) given at a dose of 40 mg/kg body weight. The other group received placebos (magnesium sulphate and cellulose). The design was single-blind only: measurement staff did not know the treatment group. The health status of the children was assessed at baseline and some four months after treatment.

Community and institutional approval

The study was approved by the Tanzania Commission for Science and Technology, the Muhimbili Medical Centre, Dar es Salaam and local officials of the Ministries of Health and Education in Tanga. After obtaining their agreement, meetings were held in all villages before the start of the trial to explain both its aims and procedures, and to gain community consent. The entry of children into the study was achieved after fully explaining to parents and children that they could decline to enter the study or remove themselves at any time without prejudice to their treatment. In the event, none declined.

Baseline measurements

Stool, urine and blood samples were collected from each child. Stool samples were examined microscopically once for the eggs of species of intestinal worms using the rapid Kato-Katz technique (WHO 1992) and the concentration of eggs was expressed as eggs/gram of faeces (epg). Ten ml of urine was filtered through 13 mm diameter polycarbonate membranes with a 12 µm pore size (Costar UK, High Wycombe, UK) held in pop top membrane holders (Costar UK). The presence of *S. haematobium* eggs was noted and the concentration expressed as eggs/10 ml of urine. Venous blood was collected using a closed collection system (Vacutainer Ltd, Oxford, UK) and the haemoglobin concentration estimated using a photometer (Hemocue Ltd, Sheffield, UK) which was regularly calibrated with standards. Thick and thin blood films were prepared and stained using Giemsa stain and then examined for the presence of *Plasmodium* spp. The concentration of infected red blood corpuscles was expressed as parasites per 200 white blood cells. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, using a stadiometer ('Leicester' Model, Children's Growth Foundation) and electronic scales (Soehnle, London, UK). Z scores of height for age and weight for age were calculated using NCHS reference values using EpiInfo version 6.0 software. A socioeconomic score was developed for reported possession (1) or lack (0) of the following household items: flush toilet, concrete house construction, owner occupation, bed, bicycle, sewing machine and radio. The socioeconomic score was formed by summing the scores (maximum 7, minimum 0).

Inclusion and exclusion criteria

Children were invited to participate in the study if they were infected with both *S. haematobium* and at least one species of geohelminth. The criteria for excluding children from the study were a haemoglobin concentration < 7.0 g/dl, hookworm egg count > 20000 epg, *S. haematobium* egg count > 2000 eggs/10 ml urine or *A. lumbricoides* egg count > 200000 epg. Children excluded from the study were given immediate treatment as necessary (hookworm infection: 400 mg albendazole; *S. haematobium* infection: praziquantel 40 mg/kg body weight; haemoglobin < 7.0 g/dl: 200 mg ferrous sulphate per day for 4 weeks). Children with symptomatic malaria were offered 25 mg chloroquine base/kg body weight given over 3 days.

Follow-up

Fourteen to 15 weeks after treatments, children were asked to provide stool and urine samples again for parasitological examination and 16 weeks after treatment were weighed,

Table 1 Mean age of children in years \pm s.e

	Boys		<i>P</i>	Girls		<i>P</i>
	Treatment (<i>n</i> = 63)	Placebo (<i>n</i> = 66)		Treatment (<i>n</i> = 64)	Placebo (<i>n</i> = 57)	
Age	9.9 \pm 0.2	9.5 \pm 0.2	0.26	9.8 \pm 0.2	9.5 \pm 0.2	0.31

measured for height and asked to give a venous blood sample to estimate the concentration of haemoglobin and intensity of infection with *Plasmodium* spp. The children then received anthelmintic treatment as necessary and all those with < 12.0 g/dl haemoglobin were given 28 tablets of 200 mg ferrous sulphate.

Data entry and statistical methods

Data were double-entered using FoxPro (Microsoft) and analysed using SAS software. Because most variables were not normally distributed, Mantel-Haenszel tests were used to compare prevalence and Kruskal-Wallis tests to compare differences between continuous variables. Tables show arithmetic means of variables with standard errors.

The effect of anthelmintic treatment on changes in haemoglobin concentration was estimated with respect to initial haemoglobin concentration and hookworm egg count. Children with a haemoglobin concentration < 11.0 g/dl were defined as anaemic (Stoltzfus *et al.* 1996).

Results

The survey revealed that 722 children aged 7–12 years lived in the three villages. The number of children who volunteered to participate in the baseline survey was 541, and of these 357 met the inclusion criteria. Of the 184 children who were not recruited to the study, 21 (11%) were excluded because of a haemoglobin concentration < 7.0 g/dl or an extremely heavy helminth infection. Thirty (16%) were excluded because they did not complete all baseline measurements and 133 (72%) because they were not infected with both *S. haematobium* and at least one species of geohelminth; of these 50% were anaemic (Hb < 11.0 g/dl). Complete follow-up measurements were taken of 250 (70%) children with 107 (30%) children dropping out of the study despite visits to encourage compliance. Of these, 56 were in the placebo group and 51 in the treatment group. Children who completed the study did not differ from those who dropped out with respect to any of the

	Prevalence			Mean intensity \pm SE		
	Treatment (<i>n</i> = 127)	Placebo (<i>n</i> = 123)	<i>P</i>	Treatment (<i>n</i> = 127)	Placebo (<i>n</i> = 123)	<i>P</i>
Hookworm						
Baseline	94	92	0.31	2247 \pm 31.2	1837 \pm 226	0.59
Follow-up	54	86	0.0001	430 \pm 115	1994 \pm 306	0.0001
% Change	-43	-6	0.0001	-81	+7	0.0001
<i>T. trichiura</i>						
Baseline	69	67	0.76	449 \pm 89	393 \pm 65	0.91
Follow-up	52	69	0.0007	290 \pm 72	415 \pm 61	0.0006
% Change	-24	+4	0.0001	-35	+5	0.0011
<i>A. lumbricoides</i>						
Baseline	47	51	0.54	9124 \pm 1695	12376 \pm 2319	0.30
Follow-up	12	47	0.0001	1094 \pm 445	8317 \pm 1343	0.0001
% Change	-75	-6	0.0001	88	-33	0.01

Table 2 Prevalence (%) and intensity (epg) of infection with intestinal helminths

	Prevalence			Mean intensity \pm SE		
	Treatment (<i>n</i> = 127)	Placebo (<i>n</i> = 123)	<i>P</i>	Treatment (<i>n</i> = 127)	Placebo (<i>n</i> = 123)	<i>P</i>
Baseline	100	100	1	254 \pm 32	227 \pm 27	0.98
Follow-up	41	-85	0.0001	3 \pm 1	255 \pm 34	0.0001
% Change	-60	-14	0.0001	-99	+12	0.0001

Table 3 Prevalence (%) and intensity (eggs/10 ml urine) of infection with *S. haematobium*

Table 4 Prevalence (%) and parasitaemia (parasites/200 wbc) of infection with *P. falciparum*

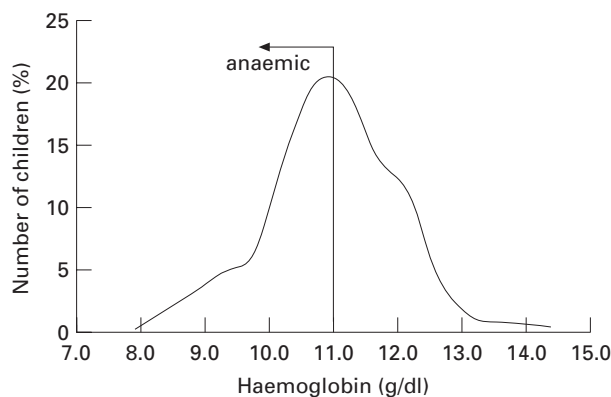
	Prevalence			Mean parasitaemia \pm SE		
	Treatment (<i>n</i> = 127)	Placebo (<i>n</i> = 123)	<i>P</i>	Treatment (<i>n</i> = 127)	Placebo (<i>n</i> = 123)	<i>P</i>
Baseline	78	70	0.15	27 \pm 7	29 \pm 7	0.13
Follow-up	72	67	0.33	36 \pm 13	46 \pm 13	0.86
% change	-8	-5	0.66	+33	+59	0.44

Table 5 Prevalence (%) of anaemia (hb < 11.0 g/dl) and mean haemoglobin concentrations (g/dl)

	Prevalence			Mean haemoglobin (g/dl) \pm SE		
	Treatment (<i>n</i> = 127)	Placebo (<i>n</i> = 123)	<i>P</i>	Treatment (<i>n</i> = 127)	Placebo (<i>n</i> = 123)	<i>P</i>
Baseline	46	51	0.38	11.0 \pm 0.09	11.0 \pm 0.09	0.80
Follow-up	53	62	0.12	10.9 \pm 0.08	10.7 \pm 0.10	0.06
% change	+7	+11	0.45	-0.11 \pm 0.07	-0.35 \pm 0.07	0.02

variables measured except that they were more heavily infected with *T. trichiura* (422 epg *vs.* 411 epg) ($P = 0.03$) and more lightly infected with *A. lumbricoides* (10724 epg *vs.* 17996 epg) ($P = 0.01$).

Review of the characteristics of the subjects in treatment and placebo groups after randomization showed that there were no differences between the groups with respect to age, sex, estimated prevalence and intensity of infection with parasites and haemoglobin concentration (Tables 1,2,3,4,5). The distribution at baseline of haemoglobin concentration and of hookworm egg counts are given in Figures 1 and 2, respectively. The two groups had almost identical mean socioeconomic status scores (treatment score = 2.67, placebo score = 2.72 $P = 0.94$).

**Figure 1** Baseline distribution of haemoglobin levels in all children. Anaemia is defined as < 11.0 g/dl.

Fourteen to 15 weeks after treatment, the prevalence and intensity of infection with helminths of children given anthelmintics were significantly lower than those of children given placebos (Tables 2 and 3). Sixteen weeks after treatment, the prevalence and intensity of infection with *P. falciparum* did not differ significantly between groups (Table 4).

The mean haemoglobin concentration of both treatment and placebo group decreased. At follow-up, the concentration in children given anthelmintics was greater than that of the placebo group, but the benefit was statistically significant only when the change in haemoglobin was compared between baseline and follow-up. Prevalence of anaemia increased during the study but did not differ significantly between groups (Table 5). The impact of treatment on severe anaemia

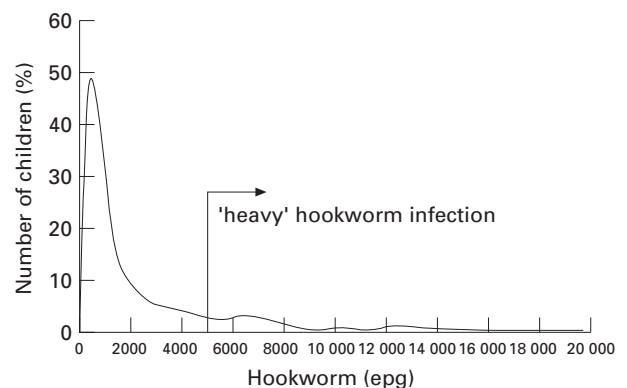
**Figure 2** Baseline distribution of hookworm infection in all children. Heavy hookworm infection is defined as >5000 epg.

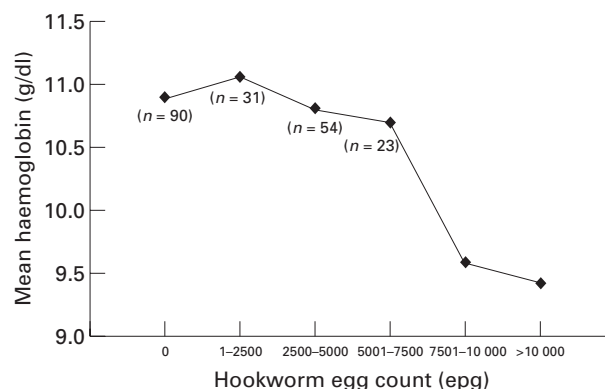
Table 6 Stepwise multiple linear regression analysis of haemoglobin levels at follow-up

Selected variables	Standardized b	P	Adjusted R ²
Initial haemoglobin	0.73	0.0001	0.55
Treatment/placebo	0.11	0.0082	

(Hb < 8.0 g/dl) could not be measured since due to exclusion criteria, only one child was so affected at baseline and follow-up.

A number of factors which may have contributed to the level of haemoglobin at follow-up was analysed using multiple linear regression analysis. Variables included treatment (anthelmintic = 1; placebo = 0), initial haemoglobin concentration, the concentration of helminth eggs in stools and urine, Z scores of anthropometric indices, socioeconomic score and *P. falciparum* parasitaemia at both baseline and follow-up. The two factors found to be significant using a step-up multiple regression procedure were initial haemoglobin concentration and treatment/placebo (Table 6). The significant positive regression coefficient of the variable for treatment indicated that the improvement in haemoglobin concentration of children who received anthelmintics was significantly greater than that of those who received placebos. The model's value of standardized b for treatment/placebo indicated that when all subjects were included in the analysis, the impact of treatment upon the whole population was relatively minor.

At baseline, a significant correlation between helminth count and haemoglobin concentration existed for hookworm only (Spearman's Rank Correlation: hookworm $r = -0.1094$, $n = 511$, $P = 0.013$; *S. haematobium* $r = -0.0049$, $n = 516$, $P = 0.91$; *T. trichiura* $r = -0.0225$, $n = 511$, $P = 0.611$; *A. lumbricoides* $r = -0.0073$, $n = 511$, $P = 0.870$). Because hookworm anaemia is the result of locally variable interaction between infection intensity and iron intake (Fleming 1982), there is no universally agreed cut-off to define a 'heavy' hookworm egg count with respect to impact on haemoglobin. In this population, haemoglobin levels showed a marked decline in individuals with > 5000–7500 hookworm

**Figure 3** Mean haemoglobin concentration (g/dl) in relation to hookworm eggcount (epg) at baseline.

egg (Figure 3). Therefore 5000 epg was chosen as a locally suitable cut-off to define 'heavy' hookworm infection.

The benefits of anthelmintic treatment were investigated in relation to the initial presence or absence of anaemia (Stoltzfus *et al.* 1996) and initial intensity of infection with hookworm. The results of these analyses are shown in Tables 7 and 8. The mean haemoglobin of all anaemic children increased on anthelmintic treatment whilst that of children given placebos decreased. This was most pronounced in children who were both anaemic and heavily infected with hookworm. Children who were not anaemic derived no statistically significant benefit from anthelmintic treatment.

Discussion

Anthelmintic treatment had a beneficial impact on the haemoglobin levels of the treated population during a period of general decline in mean haemoglobin; treatment was associated with a significantly smaller fall in haemoglobin concentrations. The overall decline may have been caused by both malaria and low dietary iron intake, as the study occurred during the peak period of malaria transmission from October until February, encompassing unusually heavy short rains in November and December. Working with children aged under 7 in The Gambia, Greenwood *et al.* (1987) found that even

	Heavy hookworm load (> 5000 epg)			Light hookworm load (< 5000 epg)		
	Treatment (n = 14)	Placebo (n = 9)	P	Treatment (n = 44)	Placebo (n = 54)	P
Baseline	9.9 ± 0.24	10.2 ± 0.27	0.31	10.2 ± 0.09	10.2 ± 0.09	0.37
Follow-up	10.6 ± 0.33	9.5 ± 0.31	0.04	10.2 ± 0.1	10.0 ± 0.13	0.19
Change	+0.67 ± 0.25	-0.67 ± 0.30	0.003	+0.07 ± 0.09	-0.21 ± 0.1	0.03

Table 7 Change in mean haemoglobin (g/dl) ± SE of anaemic children (Hb < 11.0 g/dl) by hookworm egg load

Table 8 Change in mean haemoglobin (g/dl) \pm SE of nonanaemic children (Hb > 11.0) by hookworm egg load

	Heavy hookworm load (> 5000 epg)			Light hookworm load (< 5000epg)		
	Treatment (n = 6)	Placebo (n = 4)	P	Treatment (n = 63)	Placebo (n = 56)	P
Baseline	11.7 \pm 0.36	11.6 \pm 0.26	0.39	11.8 \pm 0.07	11.8 \pm 0.09	0.95
Follow-up	11.7 \pm 0.62	11.4 \pm 0.55	0.83	11.4 \pm 0.08	11.4 \pm 0.12	0.66
Change	-0.48 \pm 0.35	-0.23 \pm 0.55	0.83	-0.38 \pm 0.09	-0.44 \pm 0.09	0.73

when parasitaemia showed no seasonal variation, the clinical impact of malaria was highly seasonal, being mostly limited to a period at the end of the rainy season. Furthermore, our study took place during the season leading up to the harvest, a time when nutrient shortage, including iron, is known to occur. It is therefore likely that inadequate dietary iron was another factor contributing to the high rates of anaemia among these children and the decline in haemoglobin observed during the course of the study.

Anthelmintic treatment arrested the decline in haemoglobin concentration in anaemic children with helminth infection: the mean haemoglobin of all children with an initial haemoglobin concentration < 11.0 g/dl, 48% of the study population, increased on anthelmintic treatment. The fact that the benefits of treatment were so wide-reaching suggests that anthelmintic treatment was an extremely effective means of improving the haemoglobin levels of the population. The effect of treatment was most pronounced in the 9% of children recruited who were both anaemic and heavily infected with hookworm. In a population infected with helminths, mass treatment may remove one important cause of iron loss and thereby reduce the prevalence of anaemia. The absence of any significant effect of treatment in nonanaemic children with a haemoglobin concentration > 11.0 g/dl may reflect the better iron balance of this subpopulation (Fleming 1982).

It is important to recognize that 11% of exclusions from the study occurred either due to severe anaemia (haemoglobin concentration less than 7.0 g/dl) or extremely heavy helminth infection (hookworm egg count > 20000 epg, *S. haematobium* egg count > 2000 eggs/10 ml urine or *A. lumbricoides* egg count > 200000 epg). If this population were treated as a whole, without exclusion on the basis of screening for anaemia or extremely heavy infection, an additional 6% would benefit from deworming.

Previous studies have indicated the importance of heavy loads of hookworm infection in the development of anaemia (Gilles *et al.* 1964; Layrisse & Roche 1964). However, there are few data on the impact of deworming in subjects with differing initial levels of infection and haemoglobin. A study on the impact of hookworm infection amongst Zanzibari

schoolchildren, randomised by school, showed improved iron status after deworming as measured by protoporphyrin and prevention of moderate to severe anaemia in children with heavy hookworm infections > 2000 (epg) (Stoltzfus *et al.* 1998). However, no impact on haemoglobin concentration was discerned.

The results show that anthelmintic treatment was of significant haematological benefit to anaemic children, i.e. almost half the children included in the study. This demonstrates that anthelmintic treatment is an effective means of reducing the problem of low haemoglobin levels which are clinically associated with impaired cognition, decreased learning ability, impaired physical fitness and disadvantage during haemolytic episodes of malaria. The impact of deworming was comparable to other means of raising haemoglobin levels such as iron fortification (Gillespie & Johnston 1998). Treatment was shown to be of haematological benefit to children who were both anaemic and coinfecting with schistosomes and geohelminths, and in the total population would be expected to serve the 37% of children who are so affected. Children who were not coinfecting accounted for 25% of the total population of whom 50% were anaemic and 6% heavily infected with hookworm. If these children also profited from anthelmintic treatment, the proportion of the total population expected to benefit from mass anthelmintic treatment would be increased.

The results further show that simple summary statistics may not accurately capture the distribution of such a benefit within a population. The children helped by anthelmintic treatment were those who were already anaemic and in particular those who were simultaneously heavily infected with hookworm. This implies that anthelmintic treatment differentially benefits the most severely disadvantaged section of the population. This finding is welcome since the concern of any health programme is not primarily to aid those who are already comparatively healthy, but rather to help those who are most in need. Studies have now shown that anaemia is exceptionally common in schoolchildren in developing societies and that hookworm is often highly prevalent in the same age groups (PCD 1998b). Given the widespread nutritional benefit and low cost of mass anthelmintic treat-

ment, it is clear that mass treatment programmes offer a highly cost-effective strategy which can contribute to efforts to reduce iron deficiency. In the case of this population of Tanzanian schoolchildren, a mass deworming programme would offer haematological benefit to between one third and half the population.

Acknowledgements

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