

Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants

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Summary

Background Malaria and anaemia, especially that due to iron deficiency, are two leading causes of morbidity worldwide. Little is known about the relative contribution of *Plasmodium falciparum* infection and iron deficiency to the aetiology of anaemia in malaria-endemic areas. We undertook a randomised comparison of different strategies for control of anaemia and malaria in infants, including an assessment of the effect of iron supplementation on malaria susceptibility.

Methods 832 infants born at one hospital in a malaria-hyperendemic area of Tanzania between January and October, 1995, were randomly assigned to group DI, receiving daily oral iron (2 mg/kg daily) plus weekly Deltaprim (3-125 mg pyrimethamine plus 25 mg dapsone); group IP, receiving iron plus weekly placebo; group DP, receiving daily placebo plus weekly Deltaprim; or group PP, receiving daily placebo plus weekly placebo. Daily supplementation was given from 8 to 24 weeks of age, and the weekly chemoprophylaxis from 8 to 48 weeks. The frequency of severe anaemia (packed-cell volume <25%) and malaria episodes was assessed through a combination of passive case detection and cross-sectional surveys.

Findings The groups that received iron supplementation had a lower frequency of severe anaemia than those that did not receive iron (0.62 vs 0.87 cases per person-year; protective efficacy 28.8% [95% CI 6.3-45.8]). Iron supplementation had no effect on the frequency of malaria (0.87 vs 1.00 cases per person-year; protective efficacy 12.8% [-12.8 to 32.5]). The groups that received malaria prophylaxis had lower frequencies of both severe anaemia (0.45 vs 1.04 episodes per person-year; protective efficacy 57.3% [43.0-67.9]) and malaria (0.53 vs 1.34 episodes per person-year; protective efficacy 60.5% [48.2-69.9]) than the groups that did not receive prophylaxis. After the end of the intervention period, children who had received malaria chemoprophylaxis had higher rates of severe

anaemia and malaria than non-chemoprophylaxis groups (relative risks 2.2 [1.3-3.7] and 1.8 [1.3-2.6]).

Interpretation Malaria chemoprophylaxis during the first year of life was effective in prevention of malaria and anaemia but apparently impaired the development of natural immunity. Iron supplementation was effective in preventing severe anaemia without increasing susceptibility to malaria. Our findings support iron supplementation of infants to prevent iron-deficiency anaemia, even in malaria-endemic areas.

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Introduction

Anaemia, especially that due to iron deficiency, is a leading cause of morbidity and mortality worldwide.¹ Iron deficiency is associated with a wide variety of abnormalities, including depression of cell-mediated immune responses² and impairment of normal motor and cognitive development.³ Because the adverse effects of iron deficiency are preventable, there have long been recommendations for its prevention, in both developed and developing countries.⁴ WHO and UNICEF have included the reduction of iron deficiency⁵ among their goals. Most countries recommend routine oral iron supplementation for pregnant women and young children. However, iron supplementation of young children is rare in developing areas, where the burden of iron deficiency among this age-group is high.⁶

The adequacy of the recommendations is often questioned, particularly as regards iron supplementation to infants and children living in malaria-endemic areas. There is conflicting evidence on the effects of iron deficiency or overload in determining the severity of infectious diseases.^{7,8} Hypoferraemia is one of the most constant features of infectious disease. Iron deprivation in bacterial cultures is associated with growth inhibition,⁹ so there have been suggestions that hypoferraemia is an important host defence mechanism. Several studies have raised the possibility of increased susceptibility to malaria in individuals receiving iron,¹⁰⁻¹⁴ whereas others have found no such an association.¹⁵⁻¹⁷ These apparent discrepancies may be explained by differences in dose, duration, and route of administration, as well as in the degree of malaria immunity of the study individuals.

Plasmodium falciparum infection contributes to the aetiology and severity of anaemia through several mechanisms, including the direct destruction of parasitised red blood cells, immune mechanisms (including the destruction of unparasitised red cells), and dyserythropoiesis.¹⁸ Malaria may also contribute to iron deficiency, and thus anaemia, by reducing iron absorption during acute episodes¹⁹ and through sequestration of iron in malaria pigment.²⁰ The role of malaria in the aetiology

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of anaemia is supported by the observations that in malaria-endemic areas, the incidence and age pattern of severe anaemia are strongly dependent on the intensity of *P falciparum* transmission.²¹ Malaria-control trials have been associated with improvements in haematological indices in both children and pregnant women.^{22,23}

Severe anaemia is one of the most common causes of hospital admission and death among infants in the malaria-hyperendemic areas, such as the Kilombero Valley in southern Tanzania. At St Francis Designated District Hospital (SFDDH), Ifakara, Tanzania, severe anaemia (packed-cell volume [PCV] less than 25%), malaria, and the two disorders together account for 20%, 23%, and 36% of all infant admissions, and 27%, 13%, and 23% of infant deaths in hospital, respectively (unpublished). We report the results of a randomised, double-blind, placebo-controlled trial of iron supplementation, malaria chemoprophylaxis, or both. We assessed several community-based strategies for the prevention of severe anaemia in infants exposed to intense and perennial *P falciparum* malaria transmission.

Methods

Study area and population

The study was carried out in the town of Ifakara, Kilombero District, Morogoro Region, in south-eastern Tanzania (08° 9' S; 36° 40' E). The town lies south of the Udzungwa Mountains in the flood plain of the Kilombero river. There are two rainy seasons, from March to June and from December to January, and a cool dry season from July to September. Rainfall in 1995 was 1439 mm. The population of Ifakara town is estimated to be about 50 000. Most villagers are subsistence farmers, growing rice and maize, and increasing numbers are small traders. Houses are typically made of thatched roofs and mud walls.

P falciparum malaria transmission is intense and perennial, with an average entomological inoculation rate in adults in a nearby village of about one infectious bite per person per night.²⁴ Malaria control in the area is based on prompt diagnosis and treatment of suspected cases with chloroquine. Chloroquine consumption is high, and about 70% of parasites are not cleared by day 7 after treatment (Hatz C, et al, unpublished). Government health facilities in Ifakara are limited to the SFDDH and the adjacent maternal and child health clinic. The SFDDH is a well-staffed 375-bed hospital, with 70 paediatric beds. In addition, there are increasing numbers of private health-care workers and pharmacies.

Study design

The primary objectives of this trial were to assess the efficacy of daily iron supplementation, weekly malaria chemoprophylaxis, or both in reducing the frequency of severe anaemia and malaria among infants. A sample size of 800 infants was estimated to give the study at least 90% power at 5% significance to detect a 15% difference in the frequency of clinical malaria and an 18% difference in the frequency of severe anaemia between any of the intervention groups and the control group. This calculation assumed that 75% and 60% of infants would have had an episode of malaria or severe anaemia, respectively, by age 1 year.

Informed consent, recruitment, and randomisation

Ethical approval for the trial was given by the Medical Research Coordinating Committee of the National Institute for Medical Research through the Tanzanian Commission for Science and Technology. Women who gave birth at SFDDH and who reported being permanent residents of Ifakara town were invited to participate in the study. On admission to the hospital for delivery, an eligible woman was given a copy of the consent letter (in Kiswahili); it included detailed information on procedures and the potential risks and benefits of the study. Maternal and cord blood samples were collected into tubes containing edetic acid, and the infants' birthweight was recorded. Within 24 h, a paediatrician

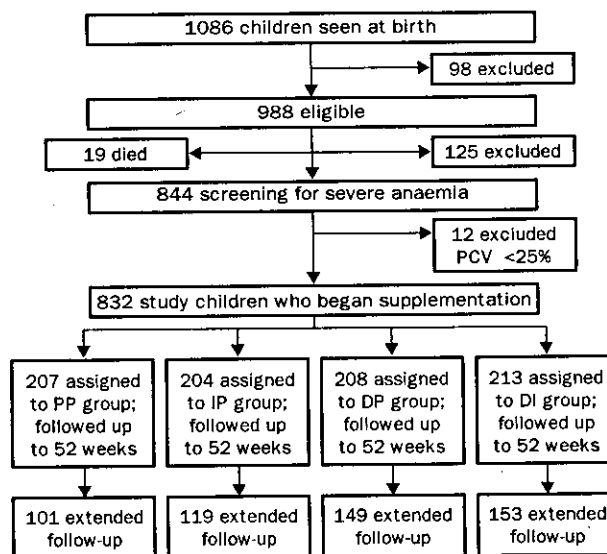


Figure 1: Trial profile

examined the baby. Infants who had birthweight greater than 1.5 kg, no obvious congenital malformations, and no signs of cerebral asphyxia or congenital or neonatal infections were issued with a unique personal number and a provisional identity card.

4 weeks after birth, study infants were visited by field assistants who confirmed the residence details and status, recorded the full name of the child, and invited mothers to attend a survey when the child would be 8 weeks old. At that survey, confirmation of the informed consent was sought, and the axillary temperature was recorded by means of an electronic thermometer (Becton-Dickinson, UK). A fingerprick blood sample was collected into microtainers (Beckton Dickinson), and thin and thick blood films were prepared. A photograph of the infant and mother was taken and a laminated identity card produced. A duplicate copy of this card was kept by the investigators to ensure adequate identification of study children at all contacts.

Infants who had a PCV of 25% or more at 8 weeks of age started receiving one of the four study supplement/prophylaxis schemes. Individual allocation to one of the four groups was by block randomisation in groups of 20 according to sequential identity numbers, to ensure that of every 20 infants, five would be assigned to each of the four intervention groups, to reduce the risk of seasonal imbalances. The randomisation code was prepared before the trial started and kept by an independent monitor (Prof M Corachan) until the end of the study.

Study treatments

The target dose of iron was 2 mg/kg daily. We assumed an average bodyweight of 6 kg for the iron supplementation period; children therefore received 2.4 mL daily of ferrous glycine sulphate (Plesmet syrup, Link Pharmaceuticals Ltd, UK, containing 25 mg ferrous iron per 5 mL). Malaria prophylaxis was given weekly and consisted of 2.5 mL oral Deltaprim syrup (Wellcome, South Africa, containing 3.125 mg pyrimethamine and 25 mg dapsone per 5 mL). The combination of pyrimethamine and dapsone was chosen because it has been safe and effective malaria prophylaxis in children elsewhere.²⁵ A preliminary in-vivo efficacy study in schoolchildren in a nearby village showed that even at prophylactic doses the combination was more effective than chloroquine in clearing *P falciparum* parasitaemia.²⁵

The four schemes were as follows. Group IP received oral iron syrup daily plus placebo syrup weekly. Group DP received Deltaprim syrup weekly plus placebo syrup daily. Group DI received Deltaprim syrup weekly plus oral iron syrup daily. Group PP received two types of placebo syrup (daily and weekly). To ensure masking, placebo and treatments were undistinguishable in terms of colour, taste, and appearance, and were provided in identical 100 mL or 50 mL amber bottles.

	PP group (n=207)	IP group (n=204)	DP group (n=208)	DI group (n=213)
Mothers at delivery				
Age (years)	24.7 (6.4)	24.5 (6.1)	24.3 (6.0)	24.7 (6.4)
Parity	3.2 (2.4)	3.1 (2.2)	3.0 (2.0)	3.1 (2.2)
PCV (%)	33.3 (5.6)	33.4 (5.0)	33.4 (6.4)	33.0 (5.3)
Prevalence of <i>P. falciparum</i>	43/197 (22%)	42/190 (22%)	53/200 (26%)	51/201 (25%)
Parasite density*	1217	1641	1215	1318
Child				
Male	125/207 (60%)	91/204 (45%)	95/208 (46%)	107/213 (50%)
Birthweight	2860 (411)	2820 (396)	2838 (424)	2787 (478)
Number with birthweight <2500 g	30/207 (14%)	34/204 (17%)	34/208 (16%)	41/213 (19%)
Haemoglobin genotype†				
AA	68/166 (41%)	52/174 (30%)	61/184 (33%)	59/186 (32%)
AF	79/166 (48%)	96/174 (55%)	98/184 (53%)	105/186 (56%)
AS	19/166 (11%)	25/174 (14%)	24/184 (13%)	22/186 (12%)
FS		1/174	1/184	

Data are mean (SD) or number/total (%) of participants. *Geometric mean parasite density in parasites per μL . †Assessed at age 5 months; three children with FAS were included in the AS group.

Table 1: Baseline characteristics of study cohorts

Daily supplementation (iron or placebo) was given by the mother starting on the day of the visit (infant aged 8 weeks) and continued until the child was 24 weeks old. Weekly prophylactic treatment (Deltaprim or placebo), administered at the child's home by a project field assistant, started the week after this visit and continued until the child was 48 weeks old. At each visit, compliance with supplementation was assessed by measuring the amount of syrup left in the bottle.

Follow-up

Information on death and residence status of study children was obtained through monthly home visits. Clinical and parasitological follow-up consisted of passive case detection, as well as cross-sectional surveys when the infants were 20, 32, and 48 weeks old. All study infants who presented sick at the maternal and child health clinic or the SFDDH were seen by project medical personnel, who provided 24 h cover. Standard procedures included identification of the infant, measurement of axillary temperature, completion of a morbidity questionnaire, and physical examination. If the temperature was 37.5°C or higher, or if the parents reported that the child had been febrile during the previous night, a fingerprick blood sample was collected into an edetic-acid microtainer for measurement of PCV, and two thick blood films were prepared. For children who required admission to the paediatric ward, a more detailed questionnaire and physical examination were undertaken.

Infants found to have a PCV of less than 25% were withdrawn from the study. They were treated according to hospital guidelines with 2 weeks of oral iron (6 mg/kg daily) and a course of chloroquine (25 mg/kg over 3 days). Children with clinical malaria were treated and remained in the study, continuing to receive the interventions.

Haematological side-effects associated with the administration of Deltaprim were excluded by full blood counts at each of the cross-sectional surveys, as well as in all study children admitted to the paediatric ward. Other potential side-effects associated with this drug combination, such as severe skin reactions, were also monitored through morbidity questionnaires.

Laboratory methods

Thick and thin blood films were air-dried, stained with giemsa or May-Grünwald, respectively, and read on a light microscope (Wild-Heerbrug, Switzerland) with a $\times 50$ oil immersion lens and $\times 10$ eyepieces, following standard procedures.²⁶ PCV, haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, and counts of white blood cells, red blood cells, platelets, monocytes, and granulocytes were measured in whole blood collected into edetic-acid microtainers, with a semiautomatic cell counter (Sysmex F800 microcell counter, TOA Medical Electronics, Kobe, Japan). The PCV was also measured in heparinised microcapillary tubes by means of a microhaematocrit centrifuge. Haemoglobin electrophoresis on cellulose acetate strip

was done to assess sickle-cell status on samples collected when the infants were 20 weeks old.

Case definitions and statistical methods

Data were double-entered in a menu-driven system written in FoxPro 2.6 (Microsoft Corporation). Databases were cleaned and locked before they were provided to the clinical monitor, who then handed over the randomisation code. Before the code was broken, an analytical plan was written. The analysis was done by S-plus v3.3 (MathSoft, Seattle, USA) and Stata version 5.0 (StataCorp, Texas, USA) software.

A clinical malaria episode was defined as a documented axillary temperature of 37.5°C or higher plus asexual *P. falciparum* parasitaemia of any density at the time of contact with the health services. We chose this definition after assessing its sensitivity and specificity through logistic regression models.²⁷ The sensitivity and specificity obtained throughout the first year of life were 100% and 88%. A severe anaemia episode was defined as a PCV less than 25% at the time of contact with the health services. This cut-off for anaemia was chosen because it has been associated with increased mortality.²⁸

Two follow-up periods are analysed in the study. The main follow-up period ran from when infants started to receive supplements at 8 weeks of age to age 52 weeks (ie, 4 weeks after the last study drugs were given). A second follow-up period was for study children aged 53–92 weeks who had not been withdrawn from the study, and had therefore completed the supplementation scheme (ie, had not been diagnosed as having severe anaemia and remained resident in the study area).

The primary analysis for each of the two endpoints includes all children eligible to receive study drugs and is based on time at risk, up to the first or only malaria or severe anaemia episode, respectively, withdrawal, or end of the main follow-up period. The relative risks for the first or only episode were estimated by Poisson regression models for each of the outcomes. Protective efficacies were calculated from the standard formula $(1 - \text{relative risk}) \times 100\%$. With these models, the frequencies in each of the treatment groups (IP, DP, and DI) were compared with that in the PP group. We also estimated the effect of iron by comparing the groups that received iron (IP, DI) with the groups that did not receive it (PP, DP), after adjustment for the effect of

	PP group (n=207)	IP group (n=204)	DP group (n=208)	DI group (n=213)	p*
Withdrawals					
Severe anaemia	81 (39.1%)	58 (28.4%)	39 (18.8%)	31 (14.6%)	<0.001
Migration	14 (6.8%)	13 (6.4%)	8 (3.8%)	12 (5.6%)	0.58
Refusal	1 (0.5%)	1 (0.5%)	0	2 (0.9%)	0.81
Other	0	1 (0.5%)	3 (1.4%)	4 (1.9%)	0.16
Deaths					
	10 (4.8%)	12 (5.9%)	9 (4.3%)	11 (5.2%)	0.91

*By χ^2 test except for refusals and other withdrawals (Fisher's exact test).

Table 2: Withdrawals and deaths during main follow-up (to 52 weeks)

	Rate per person-year at risk (total number)				Iron effect		Deltaprim effect	
	PP group	IP group	DP group	DI group	RR (95% CI)	p	RR (95% CI)	p
Main follow-up period								
Admission rate	0.98 (203)	0.75 (154)	0.48 (100)	0.59 (126)	0.94 (0.78-1.13)	0.48	0.61 (0.51-0.75)	<0.001
Outpatient visits rate	7.00 (1450)	6.67 (1360)	6.05 (1259)	6.27 (1335)	0.99 (0.94-1.04)	0.74	0.90 (0.83-0.97)	0.01
Second follow-up period								
Admission rate	1.03 (78)	1.14 (84)	1.28 (95)	1.15 (89)	0.99 (0.78-1.25)	0.93	1.12 (0.88-1.42)	0.34
Outpatient visits rate	5.28 (401)	5.86 (433)	5.51 (409)	6.00 (464)	1.10 (0.97-1.24)	0.16	1.03 (0.90-1.17)	0.68

RR=relative risk.

Table 3: Rates of admissions and outpatients visits by group and by follow-up period in all children who started supplementation, including those withdrawn during study

chemoprophylaxis administration. Similarly, we estimated the effect of Deltaprim by comparing the groups that received it (DP, DI) with those that did not (PP, IP), with adjustment for the effect of iron supplementation. The interaction between iron and Deltaprim was tested by the likelihood ratio test.

In further analysis, we looked at multiple malaria episodes. In this analysis, children with an episode were taken not to be at risk for the next 28 days. For multiple malaria episodes, the relative risks were estimated by means of Poisson regression models with random effects to account for heterogeneity between individuals. These models were also used to calculate the rates of admissions and outpatient visits by group and follow-up period, which included children withdrawn during the study (STATA routine supplied by D Clayton and M Hills).

Kaplan-Meier survival curves were used to present the time until the first episode of anaemia or malaria in each of the follow-up periods. Kruskal-Wallis tests were used to compare compliance in the four groups, measured by the amount of supplement received.

Results

Infants were recruited to the study from 1086 born at SFDDH between January and October, 1995. 98 were excluded at birth—two infants were stillborn, three had severe congenital malformations, 21 cerebral asphyxia, six neonatal infection, nine birthweight below 1.5 kg, and nine were twins; 41 mothers left the hospital before enrolment, 12 were judged unreliable, and one refused. A further 125 were excluded before screening started because they had moved away (48), refused (four), or had severe anaemia (seven), or the house could not be found (66). The composition of the study cohorts is shown in figure 1 and their baseline characteristics in table 1. The study groups were similar except for an imbalance in the sex ratio; however, this variable was not associated with the risk of the two main outcomes (data not shown).

There were no differences among the four groups in the mean number of either daily or weekly doses taken. 75% of the children in each group took more than 72% of the expected weekly doses and more than 67% of the expected daily doses. Side-effects were rare and mild. Vomiting was reported for seven infants (three DP group, three DI group, one PP group). Only one child (DI group) had repeated vomiting and was withdrawn from the study. Monitoring of potential haematological toxic effects from Deltaprim was carried out throughout the study. No differences were found among the four groups in any of the haematological indices measured. In particular, the frequencies of leucopenia (leucocyte counts less than $5 \times 10^9/L$), thrombocytopenia (platelet count less than $50 \times 10^9/L$), or granulocytopenia (granulocyte count less than $1.5 \times 10^9/L$) were similar in all groups (data not shown). No clinical mucocutaneous reactions or cases of methaemoglobinemia were seen.

42 infants died and 268 were withdrawn during the main follow-up period (table 2). During the second follow-up period (up to Oct 13, 1996) there were a

further three deaths (two IP group, one DP group).

During the main follow-up period, infants who received malaria chemoprophylaxis had a significantly lower rate of attendance to the outpatient clinic (relative risk 0.90, $p=0.01$) or of being admitted (relative risk 0.61, $p<0.001$) than did children who received placebo (table 3). There were no differences in risk of hospital admission or outpatient attendance between children who did and did not receive iron. During the second follow-up period, the rates of admission and outpatient attendance were similar in all four groups (table 3).

22% (45/209) of all cases of severe anaemia were detected through cross-sectional surveys (table 4). There was no evidence of an interaction between the iron and Deltaprim treatment (likelihood ratio test for interaction, $p=0.624$). Malaria chemoprophylaxis reduced the rate of severe anaemia by 57.3% (95% CI 43.0-67.9, $p<0.001$), whereas iron supplementation reduced the rate by 28.8% (6.3-45.8, $p=0.015$).

All but two (0.9%) episodes of clinical malaria were detected through passive case detection. Deltaprim prevented 60.5% (48.2-69.9%, $p<0.001$) of first or only episodes of clinical malaria and 64.4% (53.3-73.0, $p<0.001$) of multiple episodes, whereas iron supplementation had little effect on the rate of clinical malaria (protective efficacy 12.8% [-12.8 to 32.5], $p=0.30$). Again, there was no significant interaction between Deltaprim and iron on the frequency of clinical malaria ($p=0.834$, likelihood ratio test).

Children who had received Deltaprim during the first year of life had significantly higher rates of first or only and multiple malaria episodes during the second year of follow-up than those who had received placebo (relative risk 1.8 [95% CI 1.3-2.6], $p<0.001$) and 1.8 [1.3-2.5], $p<0.001$, respectively). In the analysis of all children in the cohorts, including those withdrawn during the main follow-up period, there was still a significantly higher rate of clinical malaria among children who had received Deltaprim (relative risk 1.4 [1.1-1.7, $p=0.02$). Previous Deltaprim prophylaxis was also associated with a higher rate of severe anaemia during the second follow-up period

Group	Number of episodes	Person-years at risk	Incidence per person-year	Protective efficacy (95% CI)
Severe anaemia				
PP	81	129.8	0.62	
IP	58	136.9	0.42	32.1% (4.9-51.6)
DP	39	155.5	0.25	59.8% (41.1-72.6)
DI	31	157.6	0.20	68.5% (52.3-79.2)
First or only episode of clinical malaria				
PP	81	113.8	0.71	
IP	75	118.4	0.63	11.0% (-21.8 to 35.0)
DP	42	145.4	0.29	59.4% (41.1 to 72.0)
DI	36	148.5	0.24	65.9% (49.6 to 77.0)

Table 4: Incidence of severe anaemia (PCV <25%) and malaria during main follow-up period

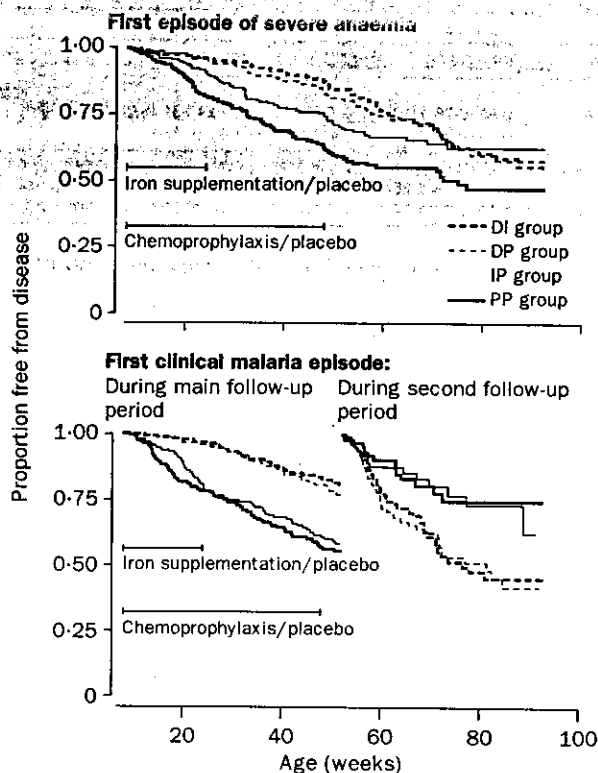


Figure 2: Kaplan-Meier survival curves of proportion of children who had not yet had an episode of malaria or an episode of severe anaemia by intervention group and follow-up period

(2.2 [1.3–2.7], $p < 0.01$). So that we could assess possible differences in the severity of malaria episodes between the groups during the second follow-up period, mean parasite density, PCV, axillary temperature, proportion of severe anaemia cases, proportion of admissions, and duration of admission were compared. No significant differences in any of these variables were found (data not shown).

There was no evidence of increased risk of malaria or severe anaemia episodes associated with having taken iron during the first year of life (1.0 [0.7–1.3] and 0.9 [0.7–1.2], for first or only and multiple malaria episodes, respectively, and 1.0 [0.6–1.6] for severe anaemia). Figure 2 shows the proportion of children who had not yet had an episode of severe anaemia or malaria by follow-up time, during the two follow-up periods.

Discussion

The burden of disease in infants and use of health services is high in this area of Tanzania, with intense malaria transmission. On average, each infant has attended outpatient clinics seven times and has been admitted to hospital once during the first year of life. During that period, severe anaemia has been diagnosed in more than 40% of infants, and each infant has on average had at least 0.7 episodes of malaria. In this setting, malaria chemoprophylaxis with Deltaprim from 8 to 48 weeks of age was safe and effective in preventing clinical malaria episodes and severe anaemia. Oral iron supplementation in prophylactic doses from 8 to 24 weeks of age prevented about 30% of severe anaemia episodes throughout the first year of life, and was not associated with an increased risk of malaria. There was no evidence of interaction between the two treatments in the prevention of either anaemia or clinical malaria.

Our findings suggest that even the moderate efficacy

against clinical malaria afforded by chemoprophylaxis during the first year of life was sufficient to impair the development of naturally acquired immunity. First, there was a significantly higher risk of clinical malaria and anaemia after withdrawal of chemoprophylaxis in the Deltaprim groups than in the placebo groups. The possible explanation is that the cohorts were not strictly comparable at the outset of the second follow-up period, because they do not include the children withdrawn during the first year because of severe anaemia. However, when the analysis included these withdrawn children the results were similar. Second, the frequency of clinical malaria in the 8 weeks after prophylaxis stopped was about twice as high as that seen in the placebo (PP) group at any time during the main follow-up period (figure 2). This rate probably represents an estimate of the risk of malaria among children who are essentially non-immune, since they are likely to have lost all maternally transferred immunity without having developed a significant degree of naturally acquired immunity themselves. Furthermore, it allows us to estimate the efficacy and duration of passively acquired immunity in an area of high transmission.

These results accord with those of a trial in The Gambia, in which fortnightly malaria chemoprophylaxis was given to children aged 3 months to 5 years. There was a rebound in malaria morbidity once the intervention was discontinued, but no evidence of increased mortality.²⁹ Our results differ from the findings of the Garki project, in which malaria chemoprophylaxis was combined with insecticide spraying,³⁰ and those from Nigeria, in which weekly chloroquine prophylaxis for 1–2 years was not followed by an increase in mortality or morbidity.³¹ Differences in the age at which prophylaxis is started, the dose, frequency, and duration of administration, the intensity of malaria transmission, and methods of clinical surveillance used may all contribute to the apparent discrepancies between these studies.

Although malaria control strategies rely on the use of chemotherapy, most national control programmes in Africa still advocate (but rarely implement) the use of chemoprophylaxis for high-risk groups, including pregnant women and young children. Do our results imply that malaria chemoprophylaxis should not be further recommended? Furthermore, do they caution against the use of effective short-term malaria control tools, especially those that may be associated with reduced exposure to asexual blood stage *P. falciparum* antigens, and therefore delay the acquisition of naturally acquired clinical immunity? Despite the enormous and growing problem of drug resistance and the cost and complexity of routine delivery, it is possible that malaria prophylaxis during infancy is just delaying the risk of malaria to older children. Such a shift in the age pattern of disease is likely to change the clinical presentation of malaria, with an increase in the proportion of cerebral malaria.^{32,33} This alarming and visible form of clinical malaria is associated with a high case-fatality rate and is probably a major contributor to direct malaria mortality. A shift in the age pattern of disease and clinical presentation, which could also arise from reduced intensity of transmission or exposure, may imply a lack of an effect of such interventions in survival by age 5, and in the worse scenarios, even a net increase in overall mortality.^{32,33} Our study was not designed to assess these questions, but long-term follow-up of the cohorts may allow us to find out absolute risks of malaria and to estimate survival by age 5.

The study shows that partly effective malaria control has modified the rate at which naturally acquired immunity develops and changed the age pattern of disease. However, there was no evidence of an increase in the severity of disease among children previously chemosuppressed. The rates of all-cause and malaria-specific hospital admissions during the second follow-up period were similar in all treatment groups, as were the mean body temperature, parasite density, PCV, and duration of admission among malaria cases in the previously chemosuppressed and placebo groups. Although there are few data on the relation between age and severity of disease in non-immune children, some evidence suggests that the severity of malaria decreases with age.³⁴ The implication of this evidence is that the older the person at the time of the first malaria encounter, the lower the risk of a poor outcome. This effect may be further reinforced in young children by a decreasing risk of severe anaemia, a less visible form of clinical malaria. Indeed, 22% of all severe anaemias were ascertained through cross-sectional surveys and not through passive case detection, whereas nearly all clinical episodes were detected in that way. Anaemia is likely to be a large and silent contributor to overall mortality, especially in the presence of cofactors such as other infectious diseases. A decreasing incidence of these diseases as children grow older, may imply a reduced risk of indirect malaria mortality, and therefore of overall malaria-related mortality.³⁵ Our findings argue against the withholding of effective control methods from anybody at risk of malaria, even if this treatment leads to a delay in the acquisition of clinical immunity.

This study has confirmed the role of malaria as the largest contributor to the aetiology of severe anaemia in young infants in highly endemic areas, accounting for about 60% of all episodes. Iron deficiency, preventable by daily oral iron supplementation, accounts for about 30% of all severe anaemia episodes. This figure is similar to the estimated prevalence of iron deficiency (28%) defined by bone marrow iron stores, reported in a study among Gambian children with clinical malaria.³⁶

The potential of iron to increase the susceptibility to malaria and other infectious diseases has been a controversial issue.⁸ There is evidence that iron given in therapeutic doses increases the risk of malaria.¹⁰⁻¹⁴ Our results are straightforward—oral iron supplementation, given at doses and for a time adequate to replenish stores, does not increase susceptibility to clinical malaria in infants but lowers by a third the rate of severe anaemia. Supplementation through the mothers was satisfactory, and further research and development of improved formulations and delivery mechanisms with the aim of improving the cost-effectiveness are now required. Iron supplementation is safe and effective: this study firmly supports the large-scale provision of iron for the prevention of iron-deficiency anaemia in infants, including those living in malaria-endemic areas.

Contributors

Clara Mendez and Pedro Alonso coordinated the trial, as well as contributing to the rationale, design, execution, analysis, and writing. Elizeus Kahigwa contributed to the rationale, design, and analysis of the trial, and with Rosmarie Hirt, was responsible for the hospital-based surveillance system and field activities. Penelope Vounatsou and John Aponte were responsible for the analysis and contributed to interpretation and writing. Fidel Font, Camilo Acosta, David Schellenberg, and Claudia Galindo contributed to the field implementation of the trial, surveillance systems, and clinical care of patients. John Kimario and Tom Smith were responsible for programming, data management, and quality control.

Honorathy Urassa was responsible for the management and quality control of all laboratory procedures. Bernard Brabin and Andrew Kitua contributed to the rationale and design. Marcel Tanner also supported the implementation of activities, running of the Centre, and writing.

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Double-blind randomised trial of modest salt restriction in older people

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Summary

Background Stroke is directly related to blood pressure and treatment trials in older hypertensive individuals show a reduction in strokes. However, the majority of strokes occur in normotensive individuals in whom no attempt is made to lower blood pressure. We compared the effects of modest salt restriction on blood pressure in older hypertensive and normotensive people.

Methods 47 untreated elderly people (24 men, age range 60-78 years; blood-pressure range 123-205 mm Hg systolic and 64-112 mm Hg diastolic) completed a 2-month double-blind randomised placebo-controlled crossover study of modest salt restriction with slow sodium and placebo to give a salt intake of either 10 g (equivalent to the normal amount for the UK population) or 5 g.

Findings On the normal salt intake for the UK population, supine blood pressure was 163/90 (SD 21/10) mm Hg with urinary sodium excretion of 177 (49) mmol/day. With modest sodium restriction, blood pressure fell to 156/87 (22/9) mm Hg ($p < 0.001/0.004$) with a urinary sodium excretion of 94 (50) mmol/day. A reduction in sodium intake of 83 mmol/day was associated with a reduction of 7.2/3.2 mm Hg. There was no significant difference in the blood-pressure fall between 18 normotensive and 29 hypertensive participants (8.2/3.9 vs 6.6/2.7 mm Hg).

Interpretation A modest reduction in salt intake leads to a fall in blood pressure in both normotensive and

hypertensive older people similar to that in outcome trials of thiazide-based treatment. Since the majority of strokes in older people occur below the current definition of hypertension, our results have important implications for the prevention of stroke.

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See Commentary page 825

Introduction

Increasing blood pressure throughout its range is the major risk factor for the development of stroke. The absolute risk of a stroke is related not only to the height of blood pressure, but also to age.¹ Treatment trials, mainly diuretic based, in older people with high blood pressure, including isolated systolic hypertension, have shown a reduction in strokes, both fatal and non-fatal, with almost complete reversal of the calculated epidemiological risks.^{2,3}

Reductions in blood pressure in older hypertensive individuals similar to those in the treatment trials can be achieved by non-pharmacological intervention. For instance, a moderate reduction in salt intake alone,^{4,5} or combined with an increase in potassium intake,⁶ or with a reduction in bodyweight,^{5,7} lowers blood pressure in older hypertensive patients. However, no studies have been carried out in older people with blood pressure in the normal range, which is surprising given that the majority of strokes in older people occur at blood pressures in the upper range of normal where, at present, drug treatment is not considered and no attempt is made at prevention.

We thus decided to carry out a double-blind randomised trial of the effect on blood pressure of a modest reduction—5 g per day—in salt intake from the

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