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Short communication

Iron status, malaria parasite loads and food policies: Evidence from sub-Saharan Africa

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ABSTRACT

This brief article investigates the consequences of improving children's iron status for malaria parasite loads by analyzing data from Cote d'Ivoire, Zambia, and Tanzania; the treatment of iron deficiencies has been argued to flare up malaria in under-nourished populations. The data from a randomized controlled trial in Cote d'Ivoire showed statistically insignificant effects of the consumption of iron-fortified biscuits on children's malaria parasite loads. Second, nutrient intakes data from Zambia showed insignificant correlations and associations between children's iron and folate intakes and malaria parasite loads. Third, malaria parasite loads did not change significantly for Tanzanian children receiving anthelmintic treatment; malaria loads were lower for older children and for those using bed nets. Overall, the evidence from sub-Saharan African countries suggests that small improvements in iron status achieved via suitable food policies are unlikely to have detrimental effects for children's malaria parasite loads.

1. Introduction

Iron deficiencies are widely prevalent in developing countries (UNICEF/WHO, 1999) and many individuals suffer from their consequences such as lower cognitive development among children (Pollitt, 1993), and reduced physical work capacity of adults (Basta et al., 1979). Treatment against iron deficiency, however, has been argued to exacerbate malaria infections in severely under-nourished populations (Murray et al., 1975). It is therefore important to further investigate such aspects by analyzing the data from studies in malaria endemic countries.

While "non-heme" iron is present in ample quantities in staple foods such as rice and wheat, iron absorption rates are low due to phytates and other inhibitors in the meal (Monsen and Balintfy, 1982). By contrast, "heme" iron from meat, fish and poultry iron is easily absorbed though the costs of diets may be prohibitive for the poor. In addition, helminth infections such as hookworm and Schistosomiasis are widely prevalent in developing countries due to poor sewage disposal and exacerbate iron loss. Because malarial morbidity is common especially in sub-Saharan Africa and claims the lives of millions of children, it is important to reappraise the conceptual and empirical issues surrounding iron supplementation and malaria parasite loads for facilitating the formulation of food policies.

There are several strategies for combating iron deficiencies in developing countries such as supplementing

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populations via iron tablets (Ekstrom et al., 2002), increasing iron content of staple foods (Harvest Plus, 2010), and higher intakes of enhancers of iron absorption (Garcia-Casal et al., 1998). While the deleterious effects of iron repletion for pulmonary tuberculosis were noted in the nineteenth century by Trousseau (1872), the recent literature has emphasized possible adverse effects of iron supplementation for malaria parasite loads. For example, Murray et al. (1975) reported that severely undernourished populations in drought-stricken Niger had attacks of malaria after their food intakes improved during hospital stay. Furthermore, a study in Pemba, Zanzibar daily supplementing infants between ages of 1 and 35 months with 12.5 mg of iron and 50 μg of folic acid was terminated because of increased malarial morbidity (Sazawal et al., 2006).

2. Some conceptual aspects

There are at least four sets of conceptual issues that merit discussion for analyzing the links between iron status and malaria parasite loads in developing countries. First, iron tablets typically contain between 10 and 90 mg of iron that may be more easily available to parasites infecting the host (Fontaine, 2007). By contrast, iron intakes via fortified foods such as rice entail increases of less than 1 mg per meal that are accompanied by phytate intakes inhibiting absorption. Thus, despite the evidence from Niger where the subjects were on the verge of starvation, it is likely that small increases in iron intakes via fortified foods do not promote malaria parasite growth among typical sub-Saharan African populations (see below).

Second, the median requirements of absorbable iron for children under the age of 12 years are estimated to be less than 1 mg per day (FAO/WHO, 1988); requirements for adult men and non-menstruating women are approximately 1 mg. A critical aspect not sufficiently emphasized in the iron supplementation literature is the likely absorption rates. While some researchers estimate non-heme iron absorption rates from mixed diets to be 1–3% (Bhargava et al., 2001), others have suggested that they may be around 17% (Haas et al., 2005) which seems rather high in view of iron deficiencies in developing countries. Because iron absorption rates from tablets may also be high (Ekstrom et al., 2002), and iron absorption may be affected by malaria parasite loads (Fontaine, 2007), it is important not to supplement children with excessively high iron doses especially in malaria endemic regions.

Third, while adequate iron intakes are critical for child development (Pollitt, 1993; Bhargava and Fox-Kean, 2003), it is important to delineate the biological, food policy, and economic aspects of interventions. For example, nutritional interventions offering iron tablets to children in a short time frame such as for a few months cheaply provide high amounts of iron; end-points in such studies are biomarkers such as hemoglobin and ferritin concentrations. By contrast, food policies ensuring adequate intakes of absorbable iron throughout childhood are costly and gradually supply low quantities of iron. While iron supplementation via tablets may seem a cost-effective short-term strategy, policies improving diet quality facilitate long-term development without the risks (see Section 6). Such factors were recognized in the early nutrition interventions such as in Guatemala that provided children with a nutritious food supplement (Martorell and Scrimshaw, 1995). From this viewpoint, it would be of interest to investigate if higher iron intakes predict greater malaria parasite loads in sub-Saharan African populations.

Finally, iron status often improves following anthelmintic treatment in developing countries (Smith and Brooker, 2010). With an increase in iron stores, greater quantities of iron can be mobilized and may remain in the plasma for longer periods so that in theory iron can facilitate malaria parasite growth. However, malaria loads fluctuate with seasons and individuals with light loads often remain asymptomatic; it would be of interest to investigate if anthelmintic treatment improving iron status can inadvertently increase malaria parasite loads. Moreover, data on malaria loads can be analyzed to assess the role played by seasonal and socioeconomic factors. Because iron status and malaria loads have not been the main focus of interventions, the next three sections investigate these issues using different approaches (Bhargava, 2008a) by analyzing available data sets from Cote d'Ivoire, Zambia, and Tanzania.

3. The effects of iron-fortified biscuits on children's malaria parasite loads in Cote d'Ivoire

A randomized controlled trial in Cote d'Ivoire in 2006–07 conducted by Rohner et al. (2010) offered iron fortified biscuits containing 20 mg of iron four times per week to 75 children ages 6–14 years in the Treatment Group 1. Another 75 children in Treatment Group 2 received the biscuits along with treatment against malaria at the baseline and after 3 months. Children in the Control Group received biscuits without the iron. Approximately 58% of the children were infected with *Plasmodium* species at the baseline so that malaria was prevalent in this population. However, the effects of consuming higher quantities of iron via fortified biscuits on malaria parasite loads were not investigated by Rohner et al. (2010). Since the data on malaria parasite loads were made available to the author, further comparisons for the malaria parasite loads of children in the Control and Treatment Groups can provide useful insights.

Table 1 presents the sample means of malaria parasite loads in the Control and Treatment Groups 1 and 2, and independent *t*-tests for comparing differences in changes between baseline and 6 months in the Control and Treatment Groups. While malaria parasite loads declined slightly at 6 months in the Control Group, there was an increase in the Treatment Groups. However, the standard deviations were large and null hypotheses that differences between changes in Control and Treatment Groups were zero were accepted in both cases. In fact, both the *t*-statistics were 1.16 with *p*-values 0.25.

Further, because malaria parasite loads were high for certain children, malaria loads were transformed into natural logarithms with the zero values set to unity prior to the transformations; the logarithmic transformation

Table 1
Sample means and standard deviations of malaria parasite loads for children in Cote d'Ivoire at baseline and 6 months.[a]

	Group					
	Control Group		Treatment Group 1: iron[b]		Treatment Group 2: (iron + malaria)[c]	
	Mean	SD	Mean	SD	Mean	SD
Baseline	597.08	1120.4	475.18	894.5	333.23	751.6
At 6 months	439.35	1079.9	812.05	3243.9	2132.31	14482.5
t-Tests (*p*-values)[d]	–		1.16 (0.248)		1.16 (0.249)	

[a] There were 74 children in each group and malaria load was measured as parasites/μL blood.
[b] Treatment Group 1 received iron fortified biscuits containing 20 mg of iron four times per week.
[c] Treatment Group 2 received the iron fortified biscuits and children were treated at baseline and after 3 months with 500 mg sulfadoxine plus 25 mg pyrimethamine.
[d] Independent *t*-tests for the null hypothesis of no difference between changes from baseline to 6 months in the treatment and control groups.

greatly reduced outliers in the data. The independent *t*-statistics for comparing differences between changes in Control Group and Treatment Group 1 and for comparing differences between changes in Control Group and Treatment Group 2 were 0.44 and 0.97, respectively. Thus, the *t*-tests again accepted the null hypothesis of no differences in the changes between baseline and 6 months in the Control and Treatment Groups. Note that it was not necessary to estimate "difference-in-differences" type regressions models for changes in malaria parasite loads for Control and Treatment Groups since the *t*-tests showed that overall differences between the two groups were statistically not different from zero.

In summary, despite malaria prevalence in Cote d'Ivoire, iron supplementation via fortified biscuits did not significantly affect children's parasite loads, though the sample sizes were modest. This was also true for children receiving intermittent treatment against malaria that was not very effective. Although 20 mg of iron per day did not significantly affect malaria loads, the results might have been different for younger children with lower iron requirements. Such issues are important for iron supplementation studies though the fortification of staple foods typically entails small increases in iron intakes.

4. Correlations and associations between iron intakes and malaria parasite loads in Zambia

A recent cross-sectional survey in Zambia conducted by Palaniappan et al. (2010) assessed the dietary intakes of 387 children ages 1–5 years via the 24-h recall method; food intakes were converted into nutrient intakes using conversion tables. Children's malaria parasite loads were measured. Because malaria parasites can benefit from higher iron intakes, it is conceivable that children with high intakes of iron and possibly of folate may have higher malaria loads. A subset of variables that were relevant for investigating these links was made available to the author for further analyses. The bivariate correlations between iron and folate intakes and malaria parasite loads were computed to be −0.015 and −0.025, respectively and were not statistically significant; *p*-values were 0.778 and 0.625, respectively. While such correlations have not been estimated previously from dietary surveys, they might in fact be *negative* in some analyses because children from better off households typically consume higher quantities of absorbable iron and have lower exposure to mosquitoes due to bed net use.

Further, while the survey in Zambia was cross-sectional, we estimated regression models for children's malaria parasite loads that were explained by gender, age in months, and the intakes of protein, iron, folic acid, and β-carotene. However, coefficients of the explanatory variables were statistically not different from zero at the five percent level; *R*-squared was 0.009 and was not significantly different from zero. While the results might have been different if greater number of children were longitudinally observed, the next section presents evidence from Tanzania where longitudinal data were available on children's malaria parasite loads.

5. Anthelmintic treatment, socioeconomic variables and malaria parasite loads in Tanzania

A randomized controlled trial was conducted in 1997–98 in 10 schools in the coastal regions of Tanzania (Bhargava et al., 2003). Children ages 9–15 years in the Treatment Group infected with hookworm and Schistosomiasis received treatment at 3 and 15 months after the baseline, and their hemoglobin and ferritin concentration increased significantly. For the present analysis, the mean malaria parasite loads were computed for children in Control and Treatment Groups at baseline, 3 and 15 months. These new analyses are presented in Table 2 along with *t*-tests. While mean malaria loads were higher at 3 months, they showed a decline at 15 months. However, differences between changes between baseline and 3 months in the Control and Treatment Groups were not statistically significant using *t*-tests; differences in changes between baseline and 15 months were also insignificant. Thus, despite an increase in ferritin concentrations that reflect iron stores in individuals without inflammations, there were no significant effects of anthelmintic treatment on children's malaria parasite loads. Note that *t*-tests do not require a detailed understanding of the underlying mechanisms through which malaria parasite loads might have changed. By contrast, application of "difference-in differences" type estimators for malaria parasite loads entail regressing changes in malaria parasite loads on changes in indicators of iron status such as children's hemoglobin and ferritin concentrations. In fact, the underlying relationship is likely to run in the opposite

Table 2
Sample means and standard deviations of malaria parasite loads for Tanzanian children baseline, and 3 and 15 months.[a]

	Group			
	Control Group		Treatment Group[b]	
	Mean	SD	Mean	SD
Baseline	15.99	43.24	20.14	47.76
At 3 months	37.58	108.58	37.13	106.18
At 15 months	28.72	192.47	27.71	55.62
t-Tests (*p*-values)	−0.669 (0.504)[c]		−0.488 (0.626)[d]	

[a] There were 662 children in the Control group; malaria load expressed as merozoites per 200 white blood cells.
[b] There were 380 children in the Treatment Group; infected children received treatment against hookworm (albendazole 400 mg) and/or Schistosomiasis (praziquantel 40 mg/kg body weight).
[c] Independent *t*-tests for the null hypothesis of no difference between changes from baseline to 3 months in the treatment and control groups.
[d] Independent *t*-test for changes from baseline to 15 months in the treatment and control groups.

Table 3
Efficient parameter estimates from static random effects models for malaria parasite loads of Tanzanian children in Control and Treatment groups.[a]

Explanatory variable	Control group		Treatment group	
	Coefficient	SE	Coefficient	SE
Constant	9.300	2.281	8.686	3.061
ln (Age in months)	−1.544*	0.436	−1.267*	0.585
Household possessions index	−0.102	0.064	0.131	0.097
Socioeconomic status index	−0.001	0.009	−0.017	0.012
Child using bed-nets (0–1)	−0.065	0.095	−0.251*	0.128

[a] There were 644 and 367 children, respectively, in the Control and Treatment Groups; slope coefficients and asymptotic standard errors are reported. Malaria parasite loads were expressed as merozoites per 200 white blood cells.
* $p < 0.05$.

direction, that is, children with higher malaria parasite loads may eventually turn anemic (Crawley, 2004).

Further, for investigating the proximate determinants of malaria parasite loads, Table 3 presents the results using three time observations on 644 children in the Control Group and on 367 children in the Treatment group computed for this article. Because the data were available at unequal intervals (baseline, 3 and 15 months), static random effects models were estimated (Bhargava, 1991) allowing for unobserved between-children differences in malaria loads. The main findings in Table 3 were that older children had significantly lower parasite loads in both groups; estimated elasticities of malaria loads with respect to children's ages in the Control and Treatment groups were −1.54 and −1.27, respectively. Thus, children's malaria parasite loads declined rapidly with age and older children were less susceptible to malaria infections. The only other significant coefficient in Table 3 was that of the indicator variable for children using bed nets in the Treatment Group; malaria loads were 25% lower for such children. Thus, iron supplementation studies could also provide bed nets for children from poor households. Finally, the within-child variances for malaria parasite loads were high for both Control and Treatment Groups indicating that seasonal factors strongly influenced the malaria loads.

6. Conclusion

We analyzed data from three malaria endemic countries in sub-Saharan Africa, that is, Cote d'Ivoire, Zambia and Tanzania, for investigating the possible links between children's iron status and the malaria parasite loads. The evidence-based approach and new data analyses conducted for this article provided useful insights for iron supplementation. First, fortification of staple foods entails very small increases in iron intakes that are unlikely to have noticeable effects on malaria parasite loads. Even for iron fortified biscuits containing 20 mg of iron in Cote d'Ivoire, the effects on malaria parasite loads were not significant in the treatment Groups though the sample sizes were modest. Second, it is important to assess the doses of iron that can be safely administered to children especially in malaria endemic regions. The design of the Pemba study (Sazawal et al., 2006) would have benefited from such considerations; lower than recommended iron doses seemed adequate for pregnant Bangladeshi women in a previous study (Ekstrom et al., 2002). Third, it is likely that children from households with higher socioeconomic status have better iron status and lower malaria parasite loads. While correlations between iron intakes and malaria parasite loads in Zambia were negative, they were not statistically significant. The Niger findings (Murray et al., 1975) indicating adverse effects of food intakes on malaria parasite loads were presumably due to the starvation-like conditions.

Finally, improving diet quality should be the long-term goal of food policies in developing countries (Bhargava, 2008b; Alderman and Linnemayr, 2009). Such policies require help from international donors especially in sub-Saharan Africa (e.g. Alderman et al., 2006) since they have several components including transfer of agricultural technologies, better irrigation and food storage methods, increased production of dairy products, poultry, fruits, and vegetables, reductions in nutrient loss via better sanitation and hygiene, and prevention of infectious diseases such as malaria. By contrast, the focus of studies providing iron tablets for a few months has been on improvements in hemoglobin and ferritin concentrations. If such interventions are unsustainable due to budget constraints and produce only temporary benefits, then it may be difficult to justify the studies from an ethical standpoint especially if they entail risks to subjects. Moreover, in view of the uncertainties in estimating iron absorption rates and requirements, iron supplementation via tablets in malaria endemic regions should mainly target vulnerable groups such as pregnant women while they are receiving antenatal care. Similarly, iron supplementation of children should be for specific periods under medical supervision. In the long-run, improvements in diet quality can be achieved via fortification of staple foods and by subsidizing the consumption of dairy products, poultry, fruits, and vegetables for enhancing population health. The evidence from sub-Saharan African countries presented in this article suggests that gradual improvements in children's iron status are unlikely to exacerbate malaria parasite loads.

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