Hookworm Control as a Strategy to Prevent Iron Deficiency

Rebecca J. Stoltzfus, Ph.D., Michele L. Dreyfuss, M.P.H., Hababuu M. Chwaya, M.D., and Marco Albonico, M.D.

The hookworms Necator americanus and Ancylostoma duodenale infect approximately 1 billion people worldwide. The prevalence of hookworm infection increases with age in children, typically reaching a plateau in late adolescence, whereas the intensity of infection may continue to increase throughout adulthood. Hookworms cause intestinal blood loss in amounts proportional to the number of adult worms in the gut. The relationship between hookworm infection intensity and hemoglobin concentration is evident in epidemiologic studies, but may be apparent only above a threshold worm burden that is related to the iron stores of the population. Current hookworm control efforts are focused on reducing infection load and transmission potential through periodic anthelminthic chemotherapy. Several controlled trials have demonstrated a positive impact of anthelminthic treatment on hemoglobin levels, with best results obtained in settings where iron intakes were also increased. Evidence suggests that anthelminthic programs will modest impacts on iron deficiency anemia in the short term, with greater impacts on more severe anemia. Hookworms are an important cause of anemia in women, who are often overlooked by current helminth control programs. Current WHO recommendations for use of anthelminthics in schoolchildren and women are reviewed. There is a need to clarify whether hookworms are an important etiology of iron deficiency anemia in preschool children.

Introduction

For decades it has been beyond doubt that hookworms cause blood loss, yet there are few modern examples of hookworm control programs that have been designed with the measured objective of reducing iron deficiency. Nor are there outstanding examples of anemia control programs that have integrated hookworm control as a part of the control strategy. In part this is due to the difficulty of eradicating hookworm infection in populations and the disenchantment with interventions that can reduce the problem but cannot get rid of it. We suspect it is also because scientists are trained to focus within their own discipline, and effective integration of hookworm control and programs to prevent iron deficiency requires collaboration between parasitologists and nutritionists. However, if we are serious about meeting the current global objective of reducing anemia by one-third, hookworm-related blood loss cannot be ignored.

This paper focuses on hookworms and their relation to iron status. However, let us remember that hookworms are not the only helminth—often Ascaris lumbricoides and Trichuris trichiura are more prevalent than hookworm—and that helminths have other adverse effects in addition to causing iron loss. These effects may include growth retardation, vitamin A deficiency, and cognitive deficits.

We address the following objectives: to review the evidence that hookworm infection is an important etiology of iron deficiency in most populations where hookworms are endemic; to present recent data showing that current anthelminthic therapies can improve iron status, and to summarize current public health recommendations for hookworm control and suggest some ways they could be advanced. Throughout the paper we will draw attention to the importance of hookworms as a cause of iron deficiency in women, a group who have been neglected until recently in most discussions of these issues.

Prevalence and Epidemiology of Hookworm Infection

Hookworms infect approximately 1 billion people worldwide. Prevalence rates range from 10% to 20% in relatively dry, unsanitary areas such as Iran and parts of Pakistan to greater than 80% in rural, unsanitary conditions in the wet, humid tropics. Two species of hookworm, Ancylostoma duodenale and Necator americanus, are endemic in human populations. Ancylostoma duodenale is usually found...
in cooler, drier regions, such as Europe, the Middle East, the Mediterranean, North Africa, Pakistan, and northern India. Necator americanus predominates in the Americas, Central Africa, eastern and southern India, Indonesia, and the South Pacific. However, mixed infections are found in many areas of the world, including parts of Latin America.4

Both species of hookworm require an infective stage in the human host to complete their life cycles. The transmission of hookworm infection in human populations depends on three factors: the extent of fecal pollution of the soil, the suitability of environmental conditions for egg hatching and larval development, and the extent of contact of contaminated soil with human skin.3 Contamination of soil occurs when sanitary facilities are not available and community members defecate directly in the soil or when human feces is used as fertilizer for agricultural activities. In warm, humid environments, hookworm eggs in feces hatch and develop into infective larvae, which can live for a period of several days to 1 month4 before needing to enter a human host to continue their development. The larvae enter the host through the skin, migrate through the circulatory system to the lungs, pass through the alveolar system up the trachea, are swallowed, and finally take up residence in the intestines where they mature into adult worms with a life span of 2–3 years. Adult female worms lay eggs, which pass in the feces and continue the transmission cycle. The presence and number of eggs in the feces also serve as the most practical indicators of hookworm infection in population studies.

People of all ages are susceptible to hookworm infection. However, the prevalence of infection increases with age in children, typically reaching maximum levels at 15–20 years and leveling off in adulthood.5 Infection intensity follows a similar pattern of increasing with age, but does not necessarily level off during adulthood, often continuing to increase in older adults. Hookworm infection is different in this regard than A. lumbricoides and T. trichiura infections, which reach maximal prevalence and intensity in the school-age years and then decline in adulthood.

Men often have higher levels of hookworm infection than women, and this is most likely related to gender differences in exposure to contaminated soil.3 For example, in western and northern Nigeria, women do not do agricultural work in the field, so infection is heavier and more prevalent among men.14 However, in eastern Africa and other areas where women participate in agricultural work, there is no significant difference in prevalence rates between the sexes.7

Where hookworm infection is endemic, it is common in pregnant and lactating women. Infection in pregnancy is particularly disastrous to iron status because iron demand is already very high in pregnancy. It is possible that changes in the immune response during pregnancy and lactation may modulate the susceptibility of pregnant and lactating women to hookworm infection, but this has not been adequately investigated.

A characteristic of hookworm and other helminth infections is that a small proportion of individuals carry the majority of the hookworms in the community. For example, a study in West Bengal found that greater than 60% of the hookworms were harbored by less than 10% of the population sampled.9 This clearly identified distribution pattern of infection in populations has led some to hypothesize that certain "wormy people" are predisposed to heavy infections because of undefined genetic, ecological, behavioral, and social factors. Numerous studies conducted to test this hypothesis have found that the infection intensity prior to anthelmintic treatment is significantly correlated with the infection intensity from reinfection after treatment.6-12 The causes of this predisposition to hookworm infection have yet to be fully elucidated and could be either behavioral or biological in nature. This epidemiologic characteristic of the disease has led some to suggest that an efficient, economic, and effective hookworm control program would target those individuals predisposed to heavy infection for chemotherapy treatment.9 However, such a strategy would not address the fact that light or moderate hookworm infection is sufficient to cause anemia in people with low iron stores and intakes. Furthermore, for such a strategy to work in practice, a simple method for accurately identifying "wormy people" within treatment programs would need to be developed.

Effects of Hookworm Infection on Iron Status

Relationship of Hookworm Infection to Iron Loss
The mechanism by which hookworm infection leads to iron deficiency anemia is chronic intestinal blood loss.13 Adult hookworms attach to mucosa in the upper small intestine, ingesting tissue and blood and changing their feeding site every 4–6 hours.14,15 Blood is primarily lost when it passes through the hookworm's intestinal tract and is subsequently expelled during feeding, but secondary loss also occurs from bleeding of the damaged mucosa.4

Numerous studies have shown that both the worm load and the fecal egg count are strongly correlated with the amount of blood loss.13,16-19 We measured this relationship in Zanzibari schoolchildren20 from a sample of 200 chosen to represent the range of hookworm infection intensity in the population (Figure 1). Hookworm infection intensity was measured using fecal egg counts, and gastrointestinal blood loss was measured by determining the concentration of heme in the feces, using the Hemoquant method.21 This method determines the amount of porphyrins contained in the feces before and after digestion that degrades heme to its porphyrin constituents. The concentration of porphyrin after digestion is used to calculate the total fecal heme concentration, and the ratio of the porphy
from this and other studies, the iron loss from a moderate hookworm infection can be compared with other iron requirements (Table 1). A moderate hookworm infection approximately doubles the iron requirement of a woman. Two other parasitic infections are also included in this table for comparison with hookworms. *Trichuris trichiura* is believed to cause a loss of iron about one-tenth of that of hookworms, although much less evidence supports this estimate than supports the hookworm figures. *Schistosoma haematobium* infections cause significant urinary iron loss when the infection is severe. However, this parasite is limited to Africa and the Middle East. Malaria, especially *Plasmodium falciparum* malaria, is commonly associated with anemia, but there is no good evidence that malarial infection brings about iron loss. Rather, body iron is dramatically redistributed toward storage forms. Thus, malaria is not a cause of iron deficiency in the same sense as these parasites.

**Relationship of Hookworm Infection to Iron Deficiency Anemia**

From what we know about hookworms, this parasitic infection should be strongly associated with iron deficiency anemia. Have population studies found this to be the case?

Numerous studies dating back to 1920 have found a significant correlation between hemoglobin levels and worm load and/or fecal egg counts. A review of the evidence for the relationship between hookworm infection and iron deficiency anemia also identified some studies where the relationship was not significant. Roche and Layrisse described four conditions necessary to identify this relationship in population studies: a large sample size to account for individual variation, quantitative measurement of hemoglobin levels and worm loads (or egg counts), a wide range of infection levels, and no more than a minimal presence of other anemia-producing deficiencies. In

---

**Table 1. Iron Losses and Requirements for a Typical Woman**

<table>
<thead>
<tr>
<th>Source</th>
<th>Iron Cost (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal requirement</td>
<td>0.72</td>
</tr>
<tr>
<td>Menstruation</td>
<td>0.44</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>2.14</td>
</tr>
<tr>
<td>Lactation</td>
<td>0.23</td>
</tr>
<tr>
<td>Hookworm infection (moderate intensity)</td>
<td></td>
</tr>
<tr>
<td><em>N. americanus</em></td>
<td>1.10</td>
</tr>
<tr>
<td><em>A. duodenale</em></td>
<td>2.30</td>
</tr>
<tr>
<td>Other parasitic infections</td>
<td></td>
</tr>
<tr>
<td><em>T. trichiura</em> (moderate intensity)</td>
<td>0.16</td>
</tr>
<tr>
<td><em>S. haematobium</em> (severe infection)</td>
<td>2.10</td>
</tr>
</tbody>
</table>

*Normal requirements from reference 22. Losses from parasites from reference 3.

---

Figure 1. Fecal heme content and hookworm infection intensity in Zanzibari schoolchildren. Bars represent SEM. Increasing trend in fecal hemoglobin is significant (*p* < 0.001). Numbers of children at each ascending level of hookworm eggs per gram of feces are 45, 83, 19, 22, 18, and 16. Reprinted with permission from reference 20.
Table 2. Relation Between Hookworm Infection Intensity and Hemoglobin Concentration in Nepal and Zanzibar

<table>
<thead>
<tr>
<th>Hookworm Infection Intensity (eggs/g feces)</th>
<th>Nepalese Pregnant Women*</th>
<th>Hemoglobin Concentrations (g/L)</th>
<th>Zanzibari Schoolchildren*</th>
<th>Zanzibari Adult Men</th>
<th>Zanzibari Nonpregnant Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>105 ± 12 (97)*</td>
<td>110 ± 13 (215)</td>
<td>129 ± 19 (24)</td>
<td>115 ± 16 (53)</td>
<td></td>
</tr>
<tr>
<td>1–1999</td>
<td>102 ± 14 (256)</td>
<td>105 ± 13 (2562)</td>
<td>121 ± 22 (351)</td>
<td>109 ± 18 (375)</td>
<td></td>
</tr>
<tr>
<td>2000–3999</td>
<td>100 ± 18 (39)</td>
<td>100 ± 17 (456)</td>
<td>113 ± 28 (72)</td>
<td>105 ± 22 (97)</td>
<td></td>
</tr>
<tr>
<td>4000–5999</td>
<td>86 ± 21 (24)</td>
<td>96 ± 19 (128)</td>
<td>104 ± 23 (34)</td>
<td>105 ± 24 (42)</td>
<td></td>
</tr>
<tr>
<td>≥ 6000</td>
<td>89 ± 20 (18)</td>
<td>93 ± 23 (67)</td>
<td>96 ± 38 (14)</td>
<td>98 ± 20 (15)</td>
<td></td>
</tr>
</tbody>
</table>

*From reference 27.
*From reference 28.
*Mean ± SD; sample size in parentheses.

most studies finding no significant correlation between hookworm infection and iron deficiency anemia, at least one of these conditions was not met.13

Layrisse and Roche's seminal population-based study of hookworm infection in Venezuela23 documented a highly significant relationship between hemoglobin levels and fecal egg counts. However, a threshold effect was also observed, demonstrating the dependency of this relationship on a minimum level of infection. Hemoglobin levels were significantly lower in women and children with more than 2000 eggs per gram (epg) of feces and in men with more than 5000 epg compared with those with light infections. Some other studies have found the same phenomenon, although the threshold worm load varied from 1000 to 5000 epg.24–27

The threshold worm load associated with anemia does not derive from the characteristics of hookworm infection—we have seen that the relationship between hookworm infection intensity and iron loss has no threshold—but rather from the characteristics of anemia as an indicator of iron status. Hemoglobin concentration falls only when iron stores are depleted. The development of iron deficiency anemia from hookworm infection thus depends on three factors: iron intake, iron stores, and the intensity and duration of infection.7 Iron intake and stores differ significantly between communities and population subgroups. Thus, a light infection might be sufficient to cause negative iron balance in someone with a low iron-bioavailable diet, but another person with a more iron-rich diet would have negative iron balance only if more heavily infected. Women and young children usually have the lowest iron stores, making them particularly vulnerable to developing iron deficiency anemia from chronic blood loss due to hookworm. This is illustrated in the work of Layrisse and Roche23 in Venezuela, where low hemoglobin levels occurred at a lower threshold worm load in women and children than in men. At the opposite extreme, in a Nigerian population where average iron intake is 21–30 mg/day, iron deficiency anemia was not apparent unless subjects were infected with more than 800 worms.5

We have studied the association between hookworm infection intensity and iron deficiency anemia in two regions that have iron-poor diets: Pemba Island, Zanzibar, in East Africa, and the Terai region of Nepal, just across the border from northern India. In Zanzibar, the Ministry of Health has conducted a representative survey of schoolchildren on Pemba Island and a community-based survey of adult men and nonpregnant women. In Nepal, we are continuing to evaluate the iron status and risk factors for iron deficiency in pregnant women in Sarlahi district. In each of these studies, hemoglobin and erythrocyte protoporphyrin concentrations have been determined from venous blood samples, and hookworm infection intensity was assessed by the Kato-Katz method of counting eggs per gram feces.

In each of these population subgroups the relationship between hookworm infection intensity and hemoglobin concentration is very strong (Table 2). In Zanzibari women and children and pregnant Nepalese women, the hemoglobin concentration falls about 5 g/L per 2000 hookworm epg. In Zanzibari men the decline is even steeper, about 8 g/L per 2000 hookworm epg. The iron status of these populations is very poor. Even among the groups with no hookworm infection, mean hemoglobin levels are below normative definitions of anemia. Therefore, the decline in hemoglobin is apparent even at the lowest levels of hookworm infection intensity. In populations like these, individuals have no iron stores to buffer the losses caused by hookworms, and thus the linear intensity-dependent relationship between hookworm infection and iron status
Table 3. Proportions of Anemia Attributable to Hookworm Infection in Different Population Groups

<table>
<thead>
<tr>
<th>Population Group</th>
<th>Iron Deficiency Anemia</th>
<th>Moderate to Severe Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zanzibari schoolchildren</td>
<td>41%</td>
<td>57%</td>
</tr>
<tr>
<td>Zanzibari men</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>Zanzibari nonpregnant women</td>
<td>19%</td>
<td>56%</td>
</tr>
<tr>
<td>Nepalese pregnant women&lt;sup&gt;b&lt;/sup&gt;</td>
<td>29%</td>
<td>41%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Iron deficiency anemia is defined as protoporphyrin > 80 μmol/mol heme and hemoglobin < 110 g/L in pregnant women and schoolchildren or < 120 g/L in nonpregnant women or < 130 g/L in men. Moderate to severe anemia is defined for all groups as hemoglobin < 90 g/L.

<sup>b</sup>From reference 27.

is readily observed.

Because these data are representative of their respective communities, we can calculate the proportion of anemia in the population group that is attributable to hookworm infection, i.e., the attributable fraction (Table 3). This is analogous to attributable risk, but anemia prevalence rather than incidence is used. These proportions can be thought of as the maximum fraction of anemia that would be prevented if hookworms were removed from the population. Reduction of hookworm burdens will make a sizable impact on the prevalence of iron deficiency anemia, especially moderate to severe anemia, in these groups.

**Treatment and Prevention of Hookworm Infection**

Surely the eradication of hookworm infection is an appropriate long-term goal for countries and regions where the parasite is now endemic. However, the inability to permanently rid communities of hookworm due to frequent reinfection has contributed to a loss of support for eradication efforts. More recently, the programmatic focus has shifted from eradication to control. The intensity-dependent relationship between hookworm infection and iron deficiency means that reduction of infection intensity alone will help control iron deficiency anemia in communities. Thus, current hookworm control efforts are focused on reducing infection load and transmission potential to reduce morbidity associated with the disease. Periodic anthelmintic chemotherapy, ideally in the context of ongoing sanitation efforts, is the key intervention in current hookworm control strategies.

**Anthelmintic Drugs**

Several safe and effective anthelmintic drugs are available to treat hookworm infection. The benzimidazoles (albendazole and mebendazole) are broad-spectrum anthelmintics that are increasingly popular for individual and communitywide treatment of hookworm infection. They are effective at substantially reducing the intensity and somewhat reducing the prevalence of infection with either hookworm species. The benzimidazoles reduce prevalence and intensity of *A. lumbricoides* infections with >90% effectiveness but are much less effective against *T. trichiura* infections, usually reducing only the infection intensity.

The two benzimidazole drugs, albendazole and mebendazole, differ in terms of dose and cost. The recommended dose of albendazole is 400 mg whereas mebendazole can be taken as a single 500-mg dose or as 200 mg daily for 3 days. Although treatment trials indicate that mebendazole’s 3-day dosing schedule is most efficacious, a single-dose treatment is clearly preferable for public health control programs. A recent trial compared the efficacy of single doses of albendazole and mebendazole and found mebendazole to be almost as efficacious as albendazole in the treatment of hookworms.

Two other drugs may also be used to treat hookworm infections. Pyrantel is effective in reducing the prevalence and intensity of hookworm infections. The dosage is 10 mg/kg body weight for 3 days. The requirement for multiple doses presents logistical problems in public health settings. Levamisole is generally considered to be less effective at curing hookworm infection. However, it does reduce the intensity of infection as measured by egg counts. The recommended dose is 3 mg/kg body weight.

Concern about the safety of anthelmintic drugs for the fetus and pregnant mother has limited efforts to control hookworm infection as a cause of iron deficiency anemia in women. However, the World Health Organization (WHO) recently convened a meeting to address this issue, and it was concluded that “single-dose, oral anthelmintic treatment can also be given to pregnant and lactating women. However, as a general rule, no drug should be given in the first trimester.” This statement should allow for new avenues of research on hookworm infection and the importance of its control in women.

**Sanitation**

Transmission of hookworm infection occurs primarily through physical contact with soil contaminated by human feces. Therefore, safe disposal of human feces is essential for the eradication of hookworm infection. Sanitation measures include the provision of latrines along with training in their use and the appropriate treatment of human waste before use in agriculture. Sanitation control pro-
Table 4. Results from Controlled Trials of Anthelmintic Treatment for Hookworm Infection: Impact on Hemoglobin Levels

<table>
<thead>
<tr>
<th>Country</th>
<th>Target Population</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>Impact on Hemoglobin(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya(^c)</td>
<td>Children</td>
<td>83</td>
<td>53</td>
<td>+ 3 g/L after 6 months</td>
</tr>
<tr>
<td>Kenya(^d)</td>
<td>Children</td>
<td>94</td>
<td>88</td>
<td>+ 3 g/L after 8 months</td>
</tr>
<tr>
<td>Kenya(^e)</td>
<td>Children</td>
<td>96</td>
<td>44</td>
<td>+ 4 g/L after 4 months</td>
</tr>
<tr>
<td>Papua New Guinea(^f)</td>
<td>Adult males</td>
<td>100</td>
<td>3</td>
<td>+ 6 g/L after 5 months</td>
</tr>
<tr>
<td>India(^g)</td>
<td>All</td>
<td>54</td>
<td>—</td>
<td>+ 5 g/L after 6 months</td>
</tr>
</tbody>
</table>

1. Prevalence rates of the treatment group at baseline and posttreatment.
2. Impact is defined as the pre-post difference in the treatment group minus the pre-post difference in the placebo group.
3. From reference 43.
4. From reference 44.
5. From reference 45.
7. All individuals in the deworming trial had received iron-fortified salt for 6 months prior to deworming and throughout the deworming trial. From reference 46.
8. Population prevalence from a previous study. From reference 47.

grams aim to reduce or interrupt transmission, prevent re-infection, and gradually reduce worm loads.

Footwear

Use of footwear to protect feet from contact with contaminated soil has been recognized as an important preventive measure against hookworm infection since the 1920s when Smillie documented the association between hookworm infection and plantation work.\(^{41}\) In a subsequent study in Alabama, Smillie found that the highest prevalence of hookworm in the community was among schoolchildren (99%) who commonly did not wear shoes, and he strongly advocated footwear use as protection from hookworm infection.\(^{42}\) This highly sensible recommendation is well accepted, although no real evaluations of its effectiveness have been done. Also, debate continues on whether promotion of footwear use is a feasible and effective hookworm control measure given the difficulties inherent in any behavior change strategy. However, this would seem to be a relatively simple behavior change compared with many other public health interventions such as condom use and dietary modification.

Efficacy Trials of Hookworm Control to Improve Iron Status

Several controlled trials have demonstrated a positive impact of anthelmintic treatment on hemoglobin levels (Table 4). Other trials that have not found a positive impact on hemoglobin concentration following deworming have not employed a control group\(^a\) or have had follow-up periods of less than 8 weeks.\(^{49,59}\) These controlled trials show that deworming can have a positive impact on hemoglobin concentration. It is also apparent that hookworm does not need to be cured in all individuals to benefit iron status. In the Kenyan studies,\(^{43,44}\) a positive impact on hemoglobin was observed even though the prevalence of hookworm infection was decreased at most by around half. In each of these studies the intensity of infection was significantly reduced among those individuals who remained infected. The results of the trials in Papua New Guinea and India are particularly impressive because the subjects were also provided with increased amounts of dietary iron. In Papua New Guinea\(^{39}\) the men were newly incarcerated prisoners provided with a nutritionally adequate prison diet, and all participants in the Indian trial were provided iron-fortified salt for 6 months prior to deworming and throughout the deworming trial.\(^{46}\)

Effectiveness of Hookworm Control Programs to Improve Iron Status

Several regional hookworm control programs have been evaluated for their impact on hookworm infections;\(^{51,52}\) however, evaluations of program effectiveness to improve iron status have been lacking. Until it has been demonstrated that large-scale anthelmintic programs actually do improve the iron status of communities, it will be difficult to garner support for their integration into strategies to control iron deficiency.

We recently completed an evaluation of the Zanzibar school-based deworming program, which is aimed at all primary school children in grades 1–5. The prevalence of hookworm infection in this population and age group is
more than 90%. So that the Ministry of Health of Zanzibar could obtain a valid estimate of program impact on children’s nutritional status, the program was phased in during its first year. In this way, children in schools receiving the program could be compared with children in schools not yet receiving the program. By the second year of the program, all schools received the full program regimen.

The program was implemented by the Zanzibar ministries of Health and Education, and the evaluation was implemented by the Pemba Island Helminth Control Team, Malaria Control Team, and the Nutrition Unit of the Ministry of Health. Out of 72 schools on Pemba Island, 12 were randomly selected for the evaluation. From these schools, 3605 children in grades 1–4 participated in the baseline survey, and 92% of these children were measured again at the 12-month follow-up survey. Of the 12 evaluation schools, 4 received deworming 3 times per year, 4 received deworming twice per year, and 4 received no deworming program. Deworming consisted of a single 500 mg dose of generic mebendazole. The cost of this drug was US$0.027 per dose.

In its first year, neither twice-yearly nor thrice-yearly deworming had a significant impact on average hemoglobin concentrations. However, thrice-yearly deworming reduced the incidence of severe anemia during the 1-year period by approximately one half. Deworming also improved children’s iron status as measured by serum ferritin and erythrocyte protoporphyrin. As expected from the linear relationship between hookworm infection intensity and intestinal blood loss, children with heavier hookworm infections at baseline benefited most from the intervention.

As these results demonstrate, even in populations where hookworms are highly endemic, the short-term impact of deworming alone on iron deficiency anemia will be modest. If one thinks of a person’s iron status as a bucket that needs filling, supplementation is like pouring iron into the bucket, food fortification is like trickling iron into the bucket, and deworming is like partially plugging a hole in the bucket. The impact from deworming alone might be compared to that of a food fortification program, because the impact is incremental and typically small in a 1-year time frame. However, these early results from the Zanzibar program coupled with the pattern of attributable risks of anemia in Table 3 suggest that deworming will have the greatest impact on the left tail of the hemoglobin distribution.

Certainly deworming alone will not solve the problem. The control of iron deficiency anemia in settings like Zanzibar will require integration of multiple interventions. However, deworming is low cost, feasible, and highly desired by communities, and it does improve children’s iron status. Deworming will be one essential component of an effective iron deficiency control program for Zanzibar and for other communities where hookworms are an important etiology of iron deficiency.

Recommended Approaches to Hookworm Control

We want to end by reviewing the two current policy recommendations made by WHO with regard to deworming and suggesting ways that they can be further advanced. The first addresses anthelmintic treatment in school health programs, and states: “Treatment without prior individual screening of the whole population is recommended where surveys of school-age children indicate the prevalence of intestinal helminths or schistosome infection exceeds 50%.” The stated objective of this policy recommendation is to prevent adverse effects of helminth infections on health, growth, and school performance of children. To date, the prevention of anemia in schoolchildren has not often been an explicit objective of school-based deworming programs. For those of us concerned with the control of iron deficiency, it would be helpful to refine this general recommendation to address the prevalence of hookworm for which treatment of the whole population is likely to bring about some impact on the prevalence of iron deficiency in schoolchildren. It would also be helpful to have some estimate of the benefit to children’s iron status that can be expected in a given time frame. One of our current collaborative research objectives is to begin to address these policy questions with the data from Zanzibar.

More recently, a recommendation was made to address the problem of hookworms in girls and women. This recommendation reads: “Since hookworm infections contribute to iron-deficiency anemia, it is recommended that, in areas where these infections are endemic (prevalence > 20–30%) and where anemia is prevalent, hookworm control ... be included in strategies designed to improve the health, development and nutritional status of girls and women.” It goes on to state that several anthelmintic drugs may be safely given to pregnant women beyond their first trimester. This policy statement, in contrast to the one for school-age children, was specifically motivated by the role of hookworms in causing anemia. The expectation is that anthelmintic treatment, especially combined with supplemental iron, will help prevent iron deficiency anemia and its consequences during pregnancy.

Sri Lanka has made deworming, in addition to iron-folate supplementation, a routine part of its public health antenatal care program. In the program, pregnant women receive a single dose of mebendazole in the second trimester of pregnancy. The mebendazole is produced locally in Sri Lanka for less than US$0.03 per dose. A single evaluation of this intervention has been carried out in 195 pregnant tea plantation workers. The plantation community was chosen for the study because these women are at highest risk for hookworm infection. Women received interventions as they were delivered by the public health service; the study investigators did not control the interventions in any way. Thus, it happened that some women received iron-folate tablets and some did not, but all of the
women who received mebendazole also received iron-folate tablets. Receiving the combination of mebendazole with iron-folate supplementation was more effective in improving women’s iron status during pregnancy than receiving iron-folate supplementation alone.

This is a small study, but the results suggest that antenatal antihelmintic therapy could play an important role in preventing iron deficiency in women of reproductive age. Unfortunately, hookworm infections were not assessed in these women, so this impact cannot be related to the baseline prevalence and intensity of infection in the population. Additional research is needed to refine the recommendation with regard to the endemicity of hookworm infection in populations of women and whether a single treatment is the appropriate regimen in most circumstances.

From a nutrition perspective, it is noteworthy that there are no recommendations for the use of anthelmintic therapies for preschool children, in whom the problem of iron deficiency is particularly prevalent and severe. If anthelmintic therapy can improve the iron status of a 7-year-old schoolchild, can it also benefit a 5-year-old or a 3-year-old? The potential adverse effects of *Ascaris* infection on growth and vitamin A status have been the focus of the discussion of deworming in this age group. But where hookworm infection is endemic, it would be very useful to clarify whether hookworms are an important etiology of iron deficiency in young children and an additional motivation for preschool deworming programs.

Theoretical calculations suggest that hookworms could contribute to iron deficiency in preschoolers. Although hookworm infection intensities are light in young children compared with school-age children and women, a small blood loss in a small child is important. A light infection (1000 egp or 40 worms) of *N. americanus* causes a daily blood loss of around 0.55 mg, equal to the median iron requirement of 0.56 mg for children 2–6 years old. If children in many environments cannot meet this normal requirement, they certainly cannot offset a blood loss that doubles their requirement for absorbed iron. In many countries where targeted fortification efforts are not yet feasible, no interventions exist to address the problem of iron deficiency in young children. Where hookworms are endemic, anthelmintic therapy may be a feasible intervention.

In conclusion, it is important to reiterate that hookworms are not the only helminth and that hookworms may inhibit children’s growth and other aspects of development as well as induce iron deficiency. Helminth control programs must be designed to address a broader framework of health concerns than only iron deficiency. Yet at this moment, while there is a global commitment to the control of iron deficiency and a particular enthusiasm for deworming as a public health intervention, it is timely for nutritionists to clarify the importance of hookworms as an etiology of iron deficiency in different population contexts and to evaluate the role of antihelmintic therapy in strategies to control iron deficiency.

**Acknowledgment.** Our warm thanks to Lorenzo Savioli, Schistosomiasis and Intestinal Parasites Unit, Division of Control of Tropical Diseases, WHO, whose scientific excellence and dedication to the development of effective hookworm control programs have provided inspiration for this work, and whose collaboration enabled it.

17. Martinez-Torres C, Ojeda A, Roche M, Layrisse M.
26. Stoll NP, Tseng HW. The severity of hookworm disease in a Chinese group, as tested by hemoglobin readings for anemia and egg counts for the degree of infestation. Am J Hyg 1925;5:536–52
42. Smillie WG. Control of hookworm disease in south Alabama. South Med J 1924;17:494–9
53. Stolzflus RJ, Albionico M, Chwaya HM, et al. Impact of

54. Atukoral TMS, de Silva LDR, Dechering WHJC, et al. Evaluation of effectiveness of iron-folate supple-