RANDOMIZED INTERVENTION STUDY COMPARING SEVERAL REGIMENS FOR THE TREATMENT OF MODERATE ANEMIA AMONG REFUGEE CHILDREN IN KIGOMA REGION, TANZANIA

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Abstract. Anemia-specific mortality was markedly elevated among refugee children < 5 years of age in Tanzania. In a randomized, double-blind study, 215 anemic children were initially treated for malaria and helminth infection and then received 12 weeks of thrice-weekly oral iron and folic acid. Group I received placebo and chloroquine treatment for symptomatic malaria infection (i.e., no presumptive anti-malarial treatment given). Group II received placebo and monthly presumptive treatment with sulfamethoxazole-pyrimethamine (SP). Group III also received monthly SP and thrice-weekly vitamins A and C (VAC). Mean hemoglobin concentration increased from 6.6 to 10.2 g/dL, with no significant differences among groups. Group II had lower mean serum transferrin receptor levels (TfR) than group I [P = 0.023]. A greater proportion of participants in group III had normal iron stores (TfR < 8.5 µg/ ml.) than in group II [P = 0.012]. Initial helminth and malaria treatment, followed by thrice-weekly iron and folic acid supplements resulted in increased hemoglobin levels. Monthly SP and thrice-weekly VAC contributed to improve iron stores. Monthly SP may have a role in situations where asymptomatic disease is prevalent or where access to care is limited. Because administration of VAC also hastened recovery of iron stores over administration of monthly SP alone, health care personnel could add VAC to the treatment for moderate anemia if maximum recovery of iron stores is desired.

INTRODUCTION

Anemia is a public health problem worldwide, and has long been recognized as a major cause of pediatric morbidity and mortality in Africa.1-4 The World Health Organization estimates that the prevalence of anemia, defined by a hemoglobin concentration of less than 11.0 g/dL in African children less than five years of age, is approximately 33%.5 Individual studies have estimated the prevalence of anemia to be from 24% in western Africa to almost 80% in western Kenya.6-8 The etiology of anemia in sub-Saharan Africa is complex and frequently multifactorial.6 However, in areas where malaria is endemic, infection with Plasmodium falciparum, both clinical and sub-clinical, and underlying iron deficiency are the major causes of anemia in young children.9-11 Malaria-associated anemia was a significant cause of morbidity and mortality in Burundian refugee children less than five years of age in western Tanzanian refugee camps. In Nduta refugee camp, anemia-specific mortality rates in children less than 5 years of age peaked at 2.51 deaths per 10,000 per day in May 1997, exceeding the usual mortality rate in this age group from all causes in stable developing country populations (0.5/10,000/day) (Tomashek K and others, unpublished data). Burundian children in these refugee camps were at risk for anemia due to high rates of malaria infection, hookworm infestation, and iron deficiency due to an inadequate diet of maize meal, beans, corn-soy blend, salt, and vegetable oil. The treatment of malaria-associated anemia in Nduta, as in other areas of intense malaria transmission, has focused on preventing and treating malaria in addition to treating underlying nutritional deficiencies.12-13

The standard treatment for anemia in Nduta refugee camp consisted of daily iron supplementation and treatment with chloroquine for children who presented to the health clinic with symptomatic malaria infection. Weekly malaria prophylaxis with chloroquine for children less than five years of age was instituted during the peak malaria transmission season in the year prior to our study. These treatment and prevention measures were ineffective due to poor compliance with daily iron supplementation, failure of anemic children to return for follow-up, a diet containing substances that inhibit iron absorption, chloroquine resistant malaria, and the high prevalence of asymptomatic malaria infections.

This study’s objective was to determine an effective, safe, and feasible treatment protocol for moderate anemia (i.e., hemoglobin 5.0 to 8.0 g/dL) in children less than five years of age in Nduta refugee camp. Because of the high prevalence of anemia and the relative lack of resources, treatment of all cases of mild anemia (i.e., hemoglobin 8.1 to 10.9 g/dL) was not considered feasible. Intermittent iron supplementation, which has been shown to be as effective as daily supplementation in improving iron status, may be a promising alternative in such settings where daily supplementation is logistically difficult.14-16 Concurrent administration of vitamins A and C may enhance iron absorption in this population which consumes dietary inhibitors of iron absorption. In addition, monthly presumptive treatment with the long acting, effective antimalarial sulfadoxine-pyrimethamine (SP) may be an alternative to standard case management of symptomatic malaria infection with chloroquine, or weekly chloroquine chemoprophylaxis. This approach would induce extended periods of aparasitemia during which anemic children can rebuild hematologic reserves.

MATERIALS AND METHODS

Study population. The study was conducted in Nduta, a refugee camp with a population of approximately 30,000 Burundians, located in Kigoma Region in western Tanzania. The study began in March 1998. The study protocol was reviewed and approved by the ethics committees of the Tan-
zanian National Institute of Medical Research, the Office for Protection from Research Risks at the U.S. National Institutes of Health, and the Institutional Review Board at the U.S. Centers for Disease Control and Prevention. Research permits were obtained from the Tanzanian Commission for Science and Technology.

**Enrollment procedure.** All refugee children 6 to 59 months of age living in Nduta camp who were clinically diagnosed with anemia were referred by health care workers to be screened for study eligibility. After parental consent was obtained, 526 children underwent screening, which included examining children and obtaining capillary blood samples by finger stick. Screening laboratory tests consisted of hemoglobin concentration and testing for sickle cell disease or trait. Hemoglobin concentration was measured by HemoCue B-Hemoglobin Photometer® (HemoCue AB, Angelholm, Sweden). The accuracy of the photometer was checked each morning with a control cuvette provided by the manufacturer. Sickle cell disease or trait was defined by the presence of sickle cells on 2% sodium metabisulphite testing.24

Children were offered study admission if they had a hemoglobin concentration of 5.0 to 8.0 g/dL. For the purposes of this study, severe anemia was defined by a hemoglobin concentration of less than 5.0 g/dL, moderate anemia by 5.0 to 8.0 g/dL and mild anemia by 8.1 to 10.9 g/dL.4,7 In Nduta camp, criteria for blood transfusion included having either a hemoglobin concentration less than or equal to 4.0 g/dL or symptoms of congestive heart failure and a hemoglobin of 7.0 g/dL or less. Children were excluded from study admission if they had signs or symptoms of heart failure, severe malaria infection, splenomegaly, or sickle cell disease or trait. Participants who met the entrance criteria were enrolled if parental informed consent was obtained. Children were then stratified by age (6.0–24.0 and 24.1–59.9 months of age) and initial hemoglobin concentration (5.0 to 6.5 g/dL and 6.6 to 8.0 g/dL), and were randomly assigned to one of three treatment groups using a computer-generated randomization list. Stratification was done to assure that potential confounders, age and enrollment hemoglobin, would not bias the comparison among treatment groups. The stratification was accounted for in all analyses presented in this paper. The study coordinator and the study nurse, who were responsible for distributing medications, were the only team members with access to the register containing participants’ names and group assignment. All other research team members were blinded to participants’ treatment group assignment.

**Enrollment evaluation and treatment.** At the time of enrollment, all children received a baseline evaluation including stool testing for *Ascaris lumbricoides*, *Trichuris tri- chiura*, and *Nector americanus* by gravity sedimentation.20 Urine samples from children 36 to 59 months of age were tested for *Schistosoma haematobium* by membrane filter technique.21 Each child was screened for malaria infection by microscopic inspection of a Giemsa-stained thin and thick blood smear. Malaria parasite counts were done against 200 leukocytes, then converted into parasite densities assuming 8000 leukocytes/mm³ blood.22,23 Five mL blood were collected by venipuncture from each participant, and serum was separated by centrifugation and kept frozen until analyzed. Serum transferrin receptor (TfR) was measured using the TIR® enzyme-linked immunosorbent assay (Ramco Laboratories, Inc., Houston, TX).

Additionally, at enrollment all children were given a thorough physical examination, and height and weight measurements were taken using standard methodology.22 Parents were interviewed to collect information about the child participant’s past medical history, and basic household and demographic data including time spent as a refugee, mother’s years of formal education, and number of siblings less than five years. All enrolled children received presumptive treatment for malaria with SP and for helminths with mebendazole. No praziquantel was given because no *S. haematobium* were detected in urine specimens. Children 48 months and older received one SP tablet containing 500 mg sulfadoxine and 25 mg pyrimethamine. Children 12 to 47 months received one-half tablet, and children 6 to 12 months received one-quarter tablet. Children 24 to 59 months of age received one 500 mg Mebendazole tablet, while children 12 to 23 months of age received one-half tablet (250 mg). Mebendazole was not given to children less than 12 months of age.

**Study interventions.** All study participants were treated with iron and folic acid supplements for the entire twelve-week intervention. Twelve weeks was chosen as the length of the study because it was felt to be a sufficient amount of time for hemoglobin recovery given that the maximum rate of recovery from severe anemia in a child is 0.25 to 0.4 g/dL per day.25 Children 18 months of age and older received one tablet containing 200 mg ferrous sulphate (60 mg of elemental iron) and 250 μg folic acid three times per week. Children younger than 18 months of age received one-half tablet three times per week. In addition, participants in group I received a vitamin placebo three times per week and treatment with chloroquine for those who presented to the health clinic with symptomatic malaria infection. Unlike groups II and III, group I did not receive weekly or monthly presumptive treatment for malaria. Chloroquine was the first line therapy for laboratory-confirmed malaria infection recommended by a Tanzanian Ministry of Health at the time of this investigation. Participants in group II received the thrice-weekly vitamin placebo and monthly presumptive malaria treatment with SP. Participants in group III received a multivitamin containing vitamins A and C (VAC) three times per week, and monthly presumptive malaria treatment with SP. Monthly presumptive malaria treatment with SP was given at week four, eight and 12 follow-up visits in the same way it was given at enrollment (i.e., as described above). Children 18 months of age and older were given a chewable tablet containing 400 μg vitamin A and 75 mg vitamin C; children less than 18 months of age were given a chewable tablet containing 400 μg vitamin A and 30 mg vitamin C. All drugs and supplements were obtained locally.

For each study participant, a home health visitor administered one dose of iron and placebo or iron and VAC at weekly home visits. At these visits, parents were given two additional doses of the appropriate treatment to be given every second day for that week. Home health visitors measured compliance by asking the parent to show them the plastic bag that contained the medicines from the previous week. Parents were also educated about anemia. In addition to the weekly visits, each study participant visited the clinic
monthly (i.e., at week four and 12) for a physical examination, height and weight measurements, hemoglobin measurement, and a malaria blood smear. Venous blood was obtained at week 12 for comparison testing as stated above. Participants in groups II and III were given monthly presumptive malaria treatment with SP at monthly clinic visits.

**Study design and analysis.** The sample size was calculated based on the ability to detect a 1.0 g/dL difference in mean hemoglobin concentration among groups (α = 0.05; power = 80%) at the end of three months. An additional 20% was added to the sample to adjust for anticipated study drop-out. The standard deviation of hemoglobin concentration in the study population was assumed to be 1.5 g/dL, based on hemoglobin measurements in other refugee populations. Therefore, a sample of 225 children, 75 per intervention arm, was needed to conduct the study.

The overall efficacy of the interventions was determined by evaluating the outcomes of mean hemoglobin, prevalence of anemia (defined as a hemoglobin < 11.0 g/dL), mean TfR level, and prevalence of iron deficiency (defined as a TfR level ≤ 8.5 μg/mL) among treatment groups. Hemoglobin concentration results were analyzed at study enrollment and at clinic visits at weeks four, eight and 12. Transferrin receptor levels were evaluated at enrollment and week 12. The effect of VAC on these outcomes was evaluated by comparing groups II and III, which differed only by vitamin intervention. The effect of monthly SP on these outcomes was evaluated by comparing groups I and II, which differed only by SP intervention.

The diagnosis of iron deficiency in settings with high prevalence of infection is difficult because traditional laboratory measures, such as serum ferritin, are affected by infection and inflammation independent of a person’s iron status. However, TfR levels, which measure tissue iron depletion, are generally thought to be unaffected by infection. While the value of TfR as a sensitive indicator of iron deficiency has been established, its ability to assess iron status has only been evaluated in individuals with mild acute infection and the effect of hemolysis associated with malarial infection on TfR levels is unknown. Children enrolled in the study did not have serious acute illness at enrollment or week 12 when TfR levels were drawn.

In addition, monthly SP intervention was evaluated by analyzing the proportion of participants in group I compared to group II with positive smears and high density smears (defined by > 2,000 asexual malaria parasites per mm³ blood) at weeks eight and 12. Smear results at week four were not included in this analysis because they may have been influenced by the SP treatment received by all participants upon enrollment. The effect of malaria infection on hemoglobin recovery and iron stores was assessed by evaluating hemoglobin concentration and TfR levels at twelve weeks from all participants, regardless of group assignment, among participants with differing numbers of positive monthly blood smears during the 12 week intervention. All laboratory testing for hemoglobin, TfR levels and malaria infection was done on coded specimens. Laboratory workers were not aware of participants’ group assignment.

The statistical significance of differences among the treatment groups was assessed by multiple logistic regression for dichotomous variables and multiple linear regression for comparison of means. In addition, F-tests from linear regression analysis were used to evaluate the effect of repeated positive blood smears on mean hemoglobin concentration and TfR level at week 12. All regression analyses accounted for the stratified study design, and were adjusted by sex. The P-values presented in this paper are adjusted. Data was analyzed using Epi Info 6.0 and SAS© (SAS Institute, Cary, NC).

**RESULTS**

**Enrollment and follow-up.** Among the 526 children screened for study admission (Figure 1), the mean age was 27.1 months, and 48.5% were female. The hemoglobin concentration of children screened ranged from 2.8 to 13.0 g/dL with a mean of 7.9 g/dL. Nearly half (48.3%) of those screened had a hemoglobin of 5.0 to 8.0 g/dL; however, because 14 children were sickle cell positive, only 240 children were eligible for study admission. Two children failed to return to the study clinic and were not enrolled. In total, 45.2% of children screened were enrolled. No parent refused study admission. There was no significant difference in age and sex distribution between enrolled children and children screened but not enrolled. After stratification and random allocation to treatment groups there were 82 children in group I, 81 in group II and 75 in group III.

Among enrolled children 215 (90%) completed the twelve-week intervention, including all follow-up visits. Of the 23 children who did not complete the twelve-week intervention, eight (35%) children left Nduta camp with their families. Six (26%) children died, two from anemia, one from malaria, two from pneumonia, and one from dehydration. Causes of death among study participants were determined clinically by hospital staff. Because such diagnoses were often made in the absence of diagnostic testing, their accuracy is unknown. Three (13%) children were excluded from the study because their hemoglobin concentration dropped below 4 g/dL, and they were given blood transfusions. (Two of these three children received transfusions within one week of enrollment.) Three (13%) children were lost to follow-up because of incorrect addresses. The moth-
Of two (9%) children requested removal from study for unknown reasons. One (4%) child was lost to follow-up for unknown reasons. In total, group I lost five children to follow-up, group II lost eight, and group III lost ten. The remainder of the results and conclusions are based on the 215 children who participated in the entire 12-week intervention.

Description of the study population. There was no significant difference among the treatment groups in terms of age, breastfeeding status, mother’s years of formal education, number of siblings less than five years of age, total number of people in the participant’s household, or time since arrival in Nduta (Table 1). Treatment groups differed significantly by sex.

There was no significant difference in enrollment laboratory test results among treatment groups (Tables 1 and 2). By definition, all study participants had moderate anemia at enrollment. Of the 214 who had their blood drawn, 203 (94.8%) had TfR levels ≥ 8.5 μg/mL indicating iron deficiency. Nearly half (47.5%) of the 122 children who had malaria infection at enrollment had a blood smear with

<table>
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<th>Table 1</th>
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<td>Characteristics of all study participants and participants in the three anemia treatment groups at enrollment</td>
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<tr>
<th>Demographic variables</th>
<th>All study participants (n = 215)</th>
<th>Group I (n = 77)</th>
<th>Group II (n = 73)</th>
<th>Group III (n = 65)</th>
<th>P-value</th>
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<tr>
<td>Mean age, mo.</td>
<td>26.8</td>
<td>26.1</td>
<td>27.9</td>
<td>26.4</td>
<td>NS§</td>
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<tr>
<td>Female, no. (%)</td>
<td>100 (46.5)</td>
<td>41 (53.2)</td>
<td>38 (52.1)</td>
<td>21 (32.3)</td>
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<td>Current breast-fed. no. (%)</td>
<td>104 (48.4)</td>
<td>37 (48.1)</td>
<td>38 (52.1)</td>
<td>29 (46.4)</td>
<td>NS£</td>
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<tr>
<td>Mean yr of mother's total formal education</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.1</td>
<td>NS§</td>
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<tr>
<td>Mean no. of siblings &lt; 5 yr of age</td>
<td>1.0</td>
<td>1.0</td>
<td>1.1</td>
<td>0.9</td>
<td>NS§</td>
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<tr>
<td>Mean no. in household</td>
<td>5.6</td>
<td>5.8</td>
<td>5.8</td>
<td>5.1</td>
<td>NS§</td>
</tr>
<tr>
<td>Mean time since arrival in Nduta camp, mo.</td>
<td>6.4</td>
<td>6.6</td>
<td>6.0</td>
<td>6.8</td>
<td>NS§</td>
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<td>Laboratory results, no. (%) positive</td>
<td></td>
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<td></td>
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<tr>
<td>Malaria blood smear</td>
<td>122 (56.7)</td>
<td>45 (58.4)</td>
<td>40 (54.8)</td>
<td>37 (56.9)</td>
<td>NS£</td>
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<tr>
<td>Stool</td>
<td>O and P</td>
<td>24 (11.3)</td>
<td>11 (14.5)</td>
<td>9 (12.5)</td>
<td>4 (6.2)</td>
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<tr>
<td>Hookworm</td>
<td>14 (6.5)</td>
<td>6 (2.3)</td>
<td>6 (2.3)</td>
<td>2 (0.9)</td>
<td>NS£</td>
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<tr>
<td>Urine</td>
<td>O and P</td>
<td>0</td>
<td>0</td>
<td>0</td>
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* Group I = thrice-weekly oral iron and chloroquine treatment for symptomatic malaria infection.
† Group II = thrice-weekly oral iron and monthly presumptive treatment with sulfamethoxazole-pyrimethamine (SP).
‡ Group III = thrice-weekly oral iron and vitamins A and C, and monthly SP.
§ P-value for comparison among groups.
¶ ANOVA, P-values.
£ Chi-square, P-values.
NS = not significant; O = ova; P = parasite.

<table>
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<th>Table 2</th>
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<tr>
<td>Laboratory outcome measures of all study participants and participants in treatment Groups I, II and III† at enrollment and at week 12</td>
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<tr>
<th>Enrollment</th>
<th>All study participants (n = 215)</th>
<th>Group I (n = 77)</th>
<th>Group II (n = 73)</th>
<th>Group III (n = 65)</th>
<th>Adjusted P-values‡</th>
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<tbody>
<tr>
<td>Anemia prevalence</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>NS§</td>
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<tr>
<td>Mean hemoglobin, g/dL</td>
<td>6.6 (6.5–6.7)</td>
<td>6.6 (6.4–6.8)</td>
<td>6.7 (6.5–6.9)</td>
<td>6.6 (6.4–6.8)</td>
<td>NS#</td>
</tr>
<tr>
<td>Iron deficiency prevalence</td>
<td>94.9% (92.0–97.8)</td>
<td>96.1% (91.8–100.4)</td>
<td>95.9% (87.0–104.8)</td>
<td>92.2% (85.7–98.7)</td>
<td>NS§</td>
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<tr>
<td>Mean transferrin receptor, g/mL</td>
<td>18.4 (17.3–19.5)</td>
<td>18.5 (16.8–20.2)</td>
<td>18.6 (16.7–20.5)</td>
<td>18.0 (16.2–19.8)</td>
<td>NS#</td>
</tr>
<tr>
<td>Week 12</td>
<td>Anemia prevalence</td>
<td>66.0% (59.7–72.3)</td>
<td>68.8% (58.5–79.1)</td>
<td>65.8% (55.0–76.7)</td>
<td>63.1% (51.4–75.0)</td>
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<td>Mean hemoglobin, g/dL</td>
<td>10.2 (10.0–10.4)</td>
<td>10.2 (9.9–10.5)</td>
<td>10.2 (9.8–10.6)</td>
<td>10.1 (9.7–10.5)</td>
<td>NS#</td>
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<tr>
<td>Iron deficiency prevalence</td>
<td>72.6% (66.6–78.6)</td>
<td>79.2% (70.0–88.4)</td>
<td>72.6% (62.4–82.8)</td>
<td>64.6% (53.0–76.2)</td>
<td>0.012‡</td>
</tr>
<tr>
<td>Mean transferrin receptor, g/mL</td>
<td>11.1 (10.5–11.6)</td>
<td>12.0 (11.1–12.9)</td>
<td>10.5 (9.6–11.4)</td>
<td>10.6 (9.7–11.5)</td>
<td>NS§</td>
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</table>

* See Table 1 for treatments. Values in this table are reported as the unadjusted point estimates (95% confidence interval) within each group.
† P-values for comparison between Groups I and II that differ only by monthly presumptive anti-malarial treatment.
‡ P-values for comparison between Groups II and III that differ only by tri-weekly multivitamin supplementation.
§ ANOVA, P-value.
# Chi-square, P-value.
2000 asexual malaria parasites per mm$^3$ blood. Stool and urine helminth infections were not common.

**Prevalence of anemia and mean hemoglobin concentration.** There was no statistically significant difference in the prevalence of anemia or mean hemoglobin concentration at enrollment, week four, week eight, or week 12 among treatment groups. While there was no statistically significant difference among groups, at all follow-up visits, a smaller proportion of participants in groups II and III had anemia than participants in group I (Figure 2).

By week 12, the prevalence of anemia among all participants decreased to 66.0%, and the overall mean hemoglobin concentration was 10.2 ± 1.5 g/dL (Table 2). Nearly two-thirds (131) of all participants had a ≥ 3 g/dL rise in hemoglobin concentration between enrollment and week 12 and the mean hemoglobin rise was 3.5 g/dL. The most dramatic increase in hemoglobin concentration occurred in the first four weeks of the intervention when 71.1% of the total hemoglobin recovery occurred.

**Prevalence of iron deficiency and mean TfR levels.** Overall, there was no significant difference among groups in the prevalence of iron deficiency at enrollment. By week 12, the prevalence of iron deficiency among participants in group III was significantly lower than in group II ($P = 0.012$), while the difference between groups I and II was not statistically significant (Table 2). The proportion of participants with iron deficiency decreased from 94.9% at enrollment to 72.6% at week 12.

Mean TfR levels at enrollment did not differ among treatment groups. The overall mean TfR level decreased from 18.3 μg/mL at enrollment to 11.1 μg/mL at week 12. At week 12, group I had a significantly higher mean TfR level than groups II and III, indicating poorer recovery of iron stores in group I ($P = 0.023$) (Table 2).

**Malaria blood smear positivity and density.** Although groups I and II differed somewhat in the proportion of participants with positive blood smears at week eight (55.8% versus 47.9% respectively) and week 12 (53.2% versus 47.9%), these differences were not statistically significant. In addition, the proportion of participants with high density blood smears at weeks eight and 12 was similar, and did not differ substantially between groups I and II (13.0% in group I versus 11.0% in group II at both weeks eight and 12).

There was a significant inverse linear relationship between the number of positive blood smears during the 12 week follow-up period and the mean hemoglobin concentration at twelve weeks (Figure 3) [$P < 0.01$]. There was also a significant positive linear relationship between number of positive blood smears and mean TfR levels, indicating poorer iron stores, at week 12 (Figure 4) [$P < 0.001$].

**DISCUSSION**

The treatment of moderate anemia in areas like Nduta where malaria is holoendemic may be problematic because of the high prevalence of asymptomatic malaria infections that go untreated. The investigators hypothesized that SP, with its long half-life, would induce prolonged periods of apasitemia when given monthly. While monthly presumptive treatment with SP does not replace the identification and treatment of children with malaria infection, prophylaxis can
help prevent malaria infection from occurring, and allow an anemic child to recover hematologically.

In our study, we found that groups II and III had significantly lower mean TfR levels compared to group I at week 12. This finding suggests that both monthly presumptive treatment with SP or monthly SP plus VAC lead to improved iron recovery compared to treatment with chloroquine for children presenting to health facilities with symptomatic malaria. Monthly presumptive treatment with SP plus VAC led to a significantly reduced proportion of participants with iron deficiency, suggesting that the addition of VAC to monthly SP was the most effective treatment for patients with an overlapping malaria- and iron deficiency-anemia in this environment. Regardless of treatment group, there was a significant positive association between the number of parasitemic episodes (i.e., number of positive blood smears during the 12 week intervention) and TfR level and a significant inverse relationship between number of parasitemic episodes and mean hemoglobin concentration at week 12. Our results support previous findings that prevention of parasitemia aids in iron recovery as well as hemoglobin recovery. We also saw a reduction in the number of positive blood smears among participants receiving monthly SP, suggesting that monthly presumptive treatment does have a protective effect. This difference, however, also did not reach statistical significance. Although differences in the prevalence of anemia and mean hemoglobin concentrations among groups did not reach statistical significance, at week 12 group III had a lower proportion of anemic participants than group II, and group II had a lower proportion than group I.

There are several potential explanations of why monthly SP did not produce as large an impact as expected on hemoglobin recovery. First, the period of observation may have been too limited. Because all participants were given treatment for malaria and helminth infection, regardless of group, none of the study interventions were complete at the end of the study, as demonstrated by the lower prevalence of iron deficiency among most study participants. In addition, all groups were given treatment for malaria and helminth infection, resulting in comparable rise in hemoglobin due to elimination of ongoing blood loss and red cell destruction. As a result, the addition of VAC, for which one of the mechanisms of action is enhancing iron absorption, did not result in any added observable benefit early in the intervention over effective treatment of parasites. Later in the intervention, when hemoglobin concentration was substantially higher and the rate of iron absorption decreased somewhat, VAC may have played a greater relative role in stimulating iron absorption as demonstrated by the lower prevalence of iron deficiency among group III participants. If the study interventions were continued for longer than 12 weeks, hemoglobin concentration, a late indicator of improved iron stores, may have increased leading to a greater difference in hemoglobin concentration between those receiving VAC and those not. Our results demonstrate that hemoglobin recovery in most subjects was not yet complete at the end of the study, as demonstrated by the majority of subjects who were still anemic, albeit mildly, at the end of the study interventions. Thus, the
manifestations of the full benefit of VAC administration on hemoglobin concentration may require more than 12 weeks of treatment. Refugee children with moderate anemia living in an area of intense malaria transmission had a significant increase in hemoglobin concentration after 12 weeks of treatment. All treatment groups under investigation were equally successful at increasing participants’ hemoglobin concentration. The majority of the hemoglobin recovery occurred during the first four weeks of the intervention due to the fact that iron absorption is maximally enhanced when anemia is most severe.48 In addition, all participants received effective treatment for both malaria and helminths at enrollment, thus eliminating further red blood cell destruction and blood loss. Neither monthly presumptive treatment with SP nor thrice-weekly administration of VAC contributed substantial benefit to hemoglobin recovery. Instead, our findings that anemic children with less frequent malaria infection had better hematologic recovery illustrates the importance of primary malaria prevention. Monthly presumptive treatment with SP did hasten the recovery of iron stores, presumably by preventing malaria infection, and may have a role in situations where asymptomatic disease is prevalent or where access to care is limited. Additionally, monthly SP would be a more effective alternative to standard malaria case management with chloroquine for symptomatic children or weekly chloroquine prophylaxis in areas with high chloroquine resistance as was the case in camp Nduta. Because administration of thrice-weekly VAC also hastened recovery of iron stores over administration of monthly SP alone, health care personnel could add VAC to the treatment for moderate anemia if maximum recovery of iron stores is desired. Although the cost of multivitamins may limit their long-term implementation in the treatment of moderate anemia in refugee settings, less expensive vitamin supplements, such as the UNICEF multivitamin or a vitamin C tablet, if made available, may make vitamin supplementation more feasible.

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