MAJOR ARTICLE

Decreased Prevalence of Anemia in Highland Areas of Low Malaria Transmission After a 1-Year Interruption of Transmission

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Background. Malaria control campaigns have reduced malaria transmission to very low levels in many areas of Africa. Yet the extent to which malaria interruption or elimination might decrease the prevalence of anemia in areas of low malaria transmission is unknown.

Methods. Kapsisiywa and Kipsamoite, highland areas of Kenya with low, unstable malaria transmission, experienced a 12-month interruption in malaria transmission from April 2007 to May 2008, following high-level coverage (>70% of households) with indoor residual insecticide spraying in 2007. Hemoglobin levels were tested in 1697 randomly selected asymptomatic residents of Kapsisiywa (n = 910) and Kipsamoite (n = 787) at the beginning of a 12-month period of interrupted transmission (in May 2007) and 14 months later (in July 2008).

Results. From May 2007 to July 2008, only 1 of 1697 study cohort members developed clinical malaria. In this period, the prevalence of anemia decreased in Kapsisiywa in all age groups (from 57.5% to 37.9% in children aged <5 years [$P < .001$], from 21.7% to 10.5% in children aged 5–14 years [$P < .001$], and from 22.7% to 16.6% in individuals aged ≥15 years [$P = .004$]). The prevalence of anemia in Kipsamoite also decreased in children aged <5 years (from 47.2% to 31.3%; $P = .001$) but was unchanged in children aged 5–14 years and in individuals aged ≥15 years. Among children <5 years, anemia prevalence was reduced by 34% in both Kapsisiywa (95% confidence interval [CI], 21%–45%) and Kipsamoite (95% CI, 16%–48%).

Conclusions. Successful malaria elimination or interruption may lead to substantial reductions in anemia prevalence even in areas of very low transmission.

Anemia is a significant health complication for approximately two-thirds of preschool-aged children in sub-Saharan Africa and for more than half of pregnant women [1]. Severe anemia leads to increased risk of death in children [2] and pregnant women [3], while chronic anemia can impair cognition, school performance, and motor and behavioral development [4]. Multiple factors contribute to anemia, including nutritional deficiencies, red blood cell polymorphisms, and infectious etiologies, such as human immunodeficiency virus type 1 infection, helminth infection, and malaria. Studies suggest that malaria alone may account for nearly half of all severe anemia cases in areas of high malaria endemicity [5, 6]. However, the effect of malaria reduction on anemia in areas of very low transmission has not been evaluated. In light of recent successes in reducing malaria incidence [7–10] and the call for malaria elimination and eventual eradication [11], assessing the effect of malaria interruption or elimination on clinical end points, such as anemia, in areas of low transmission is particularly relevant.

We have conducted malaria epidemiology studies since 2003 in 2 highland areas of Kenya with low, unstable malaria transmission. Following widespread indoor residual insecticide spraying (IRS) coverage in March–April 2007 and the introduction of coartemether as

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first-line treatment for uncomplicated malaria in late 2006/early 2007, a 12-month period of interrupted transmission occurred from April 2007 to March 2008 [12]. To evaluate the effect of a sustained absence of malaria transmission on anemia prevalence in this population, we assessed hemoglobin levels, *Plasmodium* parasitemia, and malaria incidence in a cohort of asymptomatic individuals during and 14 months after the 2007 spraying campaign.

METHODS

Study Sites

This study was conducted in the adjacent highland areas (elevation, 1829–2132 m) of Kapsisiywa (2007 population, 3787) and Kipsamoite (2007 population, 4180) in Nandi North District, Kenya. Climate and geospatial characteristics of the study areas have been described previously [13]. Both areas experience low-level, unstable, highly seasonal malaria transmission and have an estimated entomological inoculation rate of <1 infectious bite per person per year (C. C. J., unpublished data). The area has low frequencies of hemoglobin S carriage (3%) and glucose-6-phosphate dehydrogenase deficiency (1%) [14].

Study Population and Recruitment

Individuals living in these areas are predominantly Nandi, a Kalenjin subtribe. Written informed consent for study participation was obtained from consenting heads of households, for demographic surveys, and from individuals or their parents/guardians, for sample collection and evaluation. Ethical approval for the study was obtained from the Kenya Medical Research Institute National Ethical Review Committee and the institutional review boards for human studies at Case Western Reserve University and the University of Minnesota.

Demographic Data and Clinical Malaria Surveillance

Demographic information for all households was collected in April 2003 and every 4–6 months thereafter. Starting in 2005, these surveys included assessments of travel, insecticide-treated bed net (ITN) use, and IRS treatment of houses. Clinical malaria surveillance was initiated in 2003 for the entire population at Ministry of Health dispensaries, which are the only healthcare facilities within the study sites. Free malaria diagnosis and treatment were available to all study participants. Individuals with symptoms of malaria (ie, fever, chills, severe malaise, and headache) and no clear alternative diagnosis were assessed for malaria by blood smear microscopy. Clinical malaria was defined as symptoms of malaria and a blood smear positive for any *Plasmodium* species. Consenting individuals also provided blood spots on filter paper for detection of *Plasmodium falciparum* by polymerase chain reaction (PCR). Primary treatment for uncomplicated malaria was given according to Kenya Ministry of Health provisions for the clinics: sulfadoxine-pyrimethamine (2003–2004), amodiaquine (2004–2006), or coartemether (2007–2008). Because of changes in studies, forms, and clinic personnel, clinic surveillance was not conducted in the months of July–December 2005 and January, March, and June–November 2006 in Kapsisiywa and January and July–November 2006 in Kipsamoite.

Hemoglobin Testing and Surveillance for Asymptomatic Parasitemia

Samples for hemoglobin testing were collected during 2 sitewide household surveys of asymptomatic individuals done in May 2007 and July 2008. In May 2007, samples were collected from all consenting area residents (2813 in Kapsisiywa and 2940 in Kipsamoite) during the time of collection. In July 2008, samples were collected from a randomly selected subset of approximately one-third of these individuals. This gave a study cohort of 1697 individuals (age range, 1 month–97 years; median age, 12.8 years) who had samples collected at both times (910 in Kapsisiywa, of whom 50.8% were female, and 787 in Kipsamoite, of whom 49.7% were female). Finger-prick blood samples were collected for detection of *Plasmodium* species infection by microscopy and for hemoglobin testing. Hemoglobin level was determined by photometry (HemoControl; EKF Diagnostics). Hemoglobin values were adjusted by −0.8 g/dL for altitude and by +1.0 g/dL if the individual was pregnant, per World Health Organization recommendations [15]. Cutoffs for anemia were defined as follows: age 0.5–4.9 years, 11.0 g/dL; age 5–11.9 years, 11.5 g/dL; age 12–14.9 years, 12 g/dL; nonpregnant females ≥15 years, 12.0 g/dL; and males ≥15 years, 13.0 g/dL [15]. Individuals found to be anemic were referred to the local dispensary for evaluation and treatment.

Blood spots for PCR diagnosis of *P. falciparum* infection were collected on Whatman 903 filter paper (Whatman Corp) and stored with desiccant in a −20°C freezer until testing. PCR testing was done on all samples from individuals with symptomatic malaria, on 400 randomly selected asymptomatic individuals from each of the May 2007 and July 2008 sample collections, and from any individual in these sample collections who had a microscopy-positive blood smear.

Microscopy and PCR Testing for *P. falciparum* Parasitemia

Microscopy for detection of *Plasmodium* species was performed using thick and thin blood smears [16], with 2 independent readings and a third reading for slides with discordant results. Genomic DNA was isolated with a QIAamp 96 DNA blood kit (Qiagen) from dried filter paper blood spots, and *P. falciparum* infection was determined by nested PCR targeting the small subunit RNA gene [17]. In previous surveys in these areas, we documented low frequencies of *Plasmodium malariae* infection (<1%) and no *Plasmodium vivax* or *Plasmodium ovale* infections

by microscopy and PCR [16, 18], so these infections were only diagnosed by microscopy.

Statistical Methods

Unadjusted comparisons of hemoglobin level and anemia prevalence between May 2007 and July 2008 used paired *t* tests and exact 2-tailed McNemar tests, respectively. Adjusted analyses of the change in hemoglobin level between surveys used multiple linear regression. Adjusted analyses of the change in anemia prevalence used generalized estimating equations with the form of a logistic regression, treating a person as a cluster. Predictive factors of interest included site, age group, survey time, ITN use, sex, and pregnancy status. Interactions of survey time with pairs of other factors were tested. For anemia, the interaction between pregnancy and survey time was significant ($P < .05$), and for hemoglobin, the interaction between pregnancy, ITN use, and survey time was significant, so final analyses considered pregnant and nonpregnant persons separately. In the final analyses for nonpregnant persons, sex (hemoglobin analysis) and sex and ITN use (anemia analysis) were not significant ($P > .10$) and were not included. Confidence intervals (CIs) for relative risks were computed using the bootstrap method, sampling persons with replacement (1000 bootstrap samples; the 95% CI is the 2.5th and 97.5th percentiles of the relative risks in the bootstrap draws).

RESULTS

IRS and ITN Coverage

Ministry of Health–organized annual IRS campaigns began in the study areas on a limited scale in 2005 but did not reach high-level coverage (>70% of households) in both sites until 2007 (Table 1). ITNs treated with short-lasting α-cypermethrin were offered to pregnant women and their children ≤5 years of age at antenatal care clinic visits, usually for a small copay fee, beginning in 2005. From 2006 on, ITNs treated with long-lasting deltamethrin or permethrin were offered. In July 2008, ITN use was reported in Kapsisiywa by 11.3% of cohort individuals (ITNs were used by 13.2% of children age <5 years, and by 30% of pregnant women), and in Kipsamoite by 16.8% of cohort individuals (children aged <5 years, 22.7%; pregnant women, 33.3%).

Prevalence of Asymptomatic *P. falciparum* Parasitemia

In May 2007, 5 of 1697 asymptomatic persons (0.3%) were microscopy positive for *P. falciparum* in the study cohort; all were from Kipsamoite. In July 2008, 3 of 1697 persons (0.2%) were microscopy positive for *P. falciparum*; all were from Kapsisiywa. All microscopy-positive samples and 400 randomly selected samples from each time were PCR negative for *P. falciparum*. Among a separate cohort of asymptomatic area residents tested in August 2007, November 2007, and April 2008, *P. falciparum* infection was detected by microscopy in 0%, 0%, and 0.19% of individuals, respectively, and by PCR in 0.25%, 0%, and 0%, respectively [12].

Table 1. Indoor Residual Spraying of Insecticide Coverage in 2 Highland Areas, by Household (Entire Site) and Individuals (Study Cohort)

Year and Area	Months of Spraying	Households Sprayed, Proportion (%)[a]	Individuals Residing in Sprayed Household, Proportion (%)
2005			
Kapsisiywa	Apr–Jun	354/642 (55.1)	447/795 (56.2)
Kipsamoite	Apr–May	39/679 (5.7)	54/673 (8.0)
2006			
Kapsisiywa	Feb–May	324/683 (47.4)	504/891 (56.6)
Kipsamoite	Feb–May	116/730 (15.9)	104/762 (13.6)
2007			
Kapsisiywa	Apr–Jun	656/702 (93.4)	853/910 (93.7)
Kipsamoite	Apr–Jul	534/761 (70.2)	615/787 (78.1)
2008			
Kapsisiywa	Jul–Aug	637/709 (89.8)	865/910 (95.1)
Kipsamoite	Jul–Aug	285/770 (37.0)	376/787 (47.8)

Incidence of Clinical Malaria

Malaria incidence in the study cohort showed seasonal variation before high-level IRS coverage in 2007, with an annual incidence in 2003, 2004, 2005, and 2006 (from April of each year to March of the following year) of 118, 89, 10, and 12 cases per 1000 persons per year, respectively, for Kapsisiywa and of 23, 33, 18, and 3 cases per 1000 persons per year, respectively, for Kipsamoite (Figure 1). From April 2007 to July 2008, only 1 symptomatic study cohort individual from Kipsamoite had microscopy-confirmed *P. falciparum* parasitemia (malaria incidence, 0 cases per 1000 persons per year in Kapsisiywa and 0.6 cases per 1000 persons per year in Kipsamoite), and 1 symptomatic cohort individual from Kapsisiywa and 4 from Kipsamoite had PCR-confirmed *P. falciparum* parasitemia (incidence, 1.1 and 5.1 cases per 1000 persons per year, respectively).

Hemoglobin Levels and Anemia Prevalence

In May 2007 at both study sites, anemia was present in 26.9% (456 of 1697) of all individuals and in 52.5% (177 of 337) of children <5 years of age (Table 2). In July 2008, after a 1-year absence of malaria transmission, significant increases in hemoglobin levels and concordant decreases in anemia prevalence were seen in all age groups in Kapsisiywa and in children aged <5 years in Kipsamoite (Table 2). Assessment in a separate randomly selected cohort of 45 children aged <5 years from the 2 sites in 2009 showed that the increased hemoglobin levels were sustained with continued absent or extremely low transmission

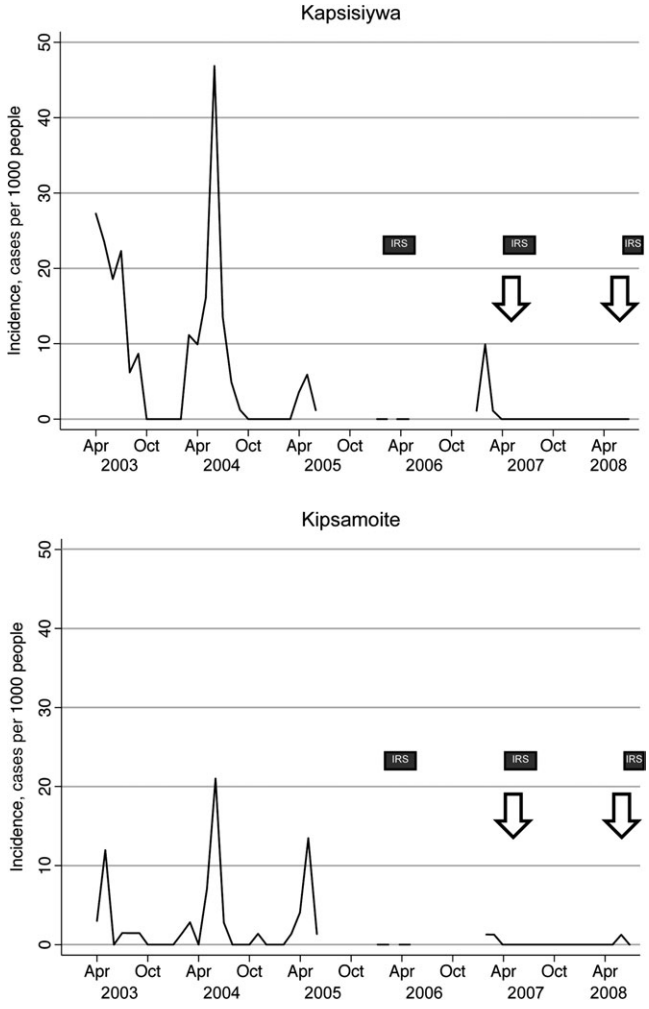

Figure 1. Monthly malaria incidence, 2003–2008, in the study cohort of individuals from Kapsisiywa (top; n = 910) and Kipsamoite (bottom; n = 787), 2 villages in highland Kenya. Boxes indicate periods of indoor residual spraying campaigns in the areas. Arrows indicate the 2 sample collection time points for hemoglobin evaluation, May 2007 and July 2008.

(mean hemoglobin levels [SD], 11.6 [1.3] g/dL in 2008 and 11.6 [1.5] g/dL in 2009; $P = .89$, 2-sample t test).

To assess whether the increase in hemoglobin levels in children <5 years was age related, the change in hemoglobin level in these children was compared with the increase expected with age alone. The change in hemoglobin level expected with age was calculated from 2007 values by subtracting hemoglobin levels for children in each 1-year grouping (eg, 0–1 year) from hemoglobin levels in children in the 1-year-older interval (eg, 1–2 years). Increases in hemoglobin levels for children <3 years of age were far above those expected with age alone, while increases in children age 3–4 or 4–5 years were similar to those expected with age (Table 3). During the period of the study, there were no changes in rainfall or temperature compared with previous years [12], no differences in food supply or availability, and no nutrition programs or micronutrient supplementation conducted in the 2 areas.

Effect of Pregnancy and ITN Use on Change in Hemoglobin Levels

Interaction was seen between the effects of pregnancy and ITN use on hemoglobin levels, so separate analyses were conducted for pregnant and nonpregnant persons.

In nonpregnant persons, hemoglobin level changes did not differ according to sex (mean increases [SE], 0.38 [0.06] g/dL in women and 0.49 [0.06] g/dL in men; $P = .18$). The effect of ITN use on the change in hemoglobin level differed by age ($P = .01$ for age-by-ITN use interaction). Among children <5 years of age, those who used ITNs had a greater increase in hemoglobin level than those who did not, although this difference did not reach statistical significance (Table 4). In contrast, among persons ≥15 years of age in Kipsamoite, those who did not use ITNs had a larger increase in hemoglobin levels than those who used ITNs ($P = .01$; Table 4).

For women pregnant in May 2007, hemoglobin levels increased in the small number (n = 13) who slept under an ITN but was unchanged among those (n = 40) who did not (mean change [SE], 0.95 [0.44] vs −0.01 [0.25]; $P = .06$).

Reduction in Anemia Prevalence After Prolonged Absence of Transmission

In children <5 years of age, the risk of anemia was reduced by 34% in Kapsisiywa (95% CI, 21%–45%) and in Kipsamoite (95% CI, 16%–48%; Table 5). Anemia was also significantly reduced in nonpregnant persons 6–15 years of age and >15 years of age in Kapsisiywa but not among those in Kipsamoite (Table 5). Anemia risk did not differ significantly according to ITN use in nonpregnant individuals in any age group (data not shown). The reduction in the risk of moderate-to-severe anemia (hemoglobin level, <8 g/dL) in children <5 years of age (Kapsisiywa, 77% [95% CI, 43%–100%; $P = .013$, exact 2-tailed McNemar test]; Kipsamoite, 88% [95% CI, 60%–100%; $P = .001$, exact 2-tailed McNemar test) was even greater than the reduction in the risk of anemia using a standard hemoglobin level cutoff of 11 g/dL, consistent with findings from high-transmission areas [19].

Among individuals who were pregnant in May 2007, anemia prevalence was reduced by 50% (from 6 of 13 to 3 of 13) among those who used ITNs and by 33% (from 6 of 40 to 4 of 40) among those who did not use ITNs.

DISCUSSION

Malaria eradication is once again being promoted by the World Health Organization [11]. This renewed interest stems in part from the recent successes of malaria interventions including ITN [9, 10], IRS [7, 12], and artemisinin combination therapy

Table 2. Adjusted Hemoglobin Levels and Frequency of Anemia, by Age Group, After a 12-Month Interruption of Malaria Transmission in 2 Highland Areas of Kenya

Area and Age Group	Individuals, No.	Hemoglobin Level, g/dL, Mean SD[a]			Individuals With Anemia, %[b]		
		May 2007	Jul 2008	*P* Value[c]	May 2007	Jul 2008	*P* Value[d]
Kapsisiywa							
<5 y	174	10.5 (1.6)	11.3 (1.6)	<.001	57.5	37.9	<.0001
5–14 y	295	12.4 (1.5)	13.1 (1.4)	<.001	21.7	10.5	<.0001
≥15 y	441	13.6 (2.0)	14.1 (2.0)	<.001	22.7	16.6	.004
Kipsamoite							
<5 y	163	11.0 (1.7)[e]	11.8 (1.4)[e]	<.001	47.2	31.3	.001
5–14 y	316	12.7 (1.3)[e]	12.7 (1.3)[e]	.50	19.3	20.6[f]	.76
≥15 y	308	13.8 (1.9)	13.9 (1.9)	.24	17.5	15.6	.52

[a] Adjusted for altitude and pregnancy, according to World Health Organization (WHO) criteria (see Methods).

[b] Anemia is defined on the basis of WHO criteria (see Methods).

[c] By the paired *t* test.

[d] By the exact 2-tailed McNemar test.

[e] Significant difference ($P < .05$, by the Student *t* test) between areas for the same age groups.

[f] Significant difference ($P < .05$, by the χ^2 test) between areas for the same age group.

[7, 8, 12], which have reduced malaria incidence and mortality in areas of sub-Saharan Africa. Reducing malaria incidence in areas of high and moderate transmission leads to large decreases in the prevalence of anemia in these populations [19]. However, there are few data on whether the prevalence of anemia decreases in areas of very low transmission when malaria is eliminated or interrupted. The present study documents that reduction or interruption of malaria transmission leads to large, highly significant decreases in anemia prevalence even in areas of very low transmission. This reduction of anemia prevalence was most striking in the population at greatest risk, children <5 years of age, but it was present in older children and adults in 1 of the 2 areas studied. The study provides further impetus for malaria control and the move toward malaria elimination, as it demonstrates the potential for interventions that decrease or interrupt malaria transmission in these areas to significantly reduce the prevalence of anemia.

Table 3. Actual Versus Expected Change in Hemoglobin Level, April 2007–July 2008, for Children <5 Years of Age in 2 Highland Areas of Kenya

Age (y), 2007	Children, No.	Change in Hb Level, g/dL, Mean		
		Actual	Expected	Actual − Expected
<1	46	0.66	−0.30	0.96
1	59	1.34	0.57	0.77
2	73	0.88	0.55	0.33
3	80	0.62	0.64	−0.02
4	79	0.54	0.38	0.16

Abbreviations: Hb, Hemoglobin; y, years.

Previous evaluations of malaria control measures have shown similar effects in children in areas of high transmission. In studies in children <2 years of age, a randomized controlled trial of ITN use in a high-transmission area of Kenya found a 60% reduction in the incidence of moderate-to-severe anemia [20], and a survey of communitywide ITN distribution in Tanzania recorded a 47% decrease in anemia prevalence [21]. A meta-analysis of 29 malaria intervention studies including ITNs, IRS, and malaria chemoprophylaxis concluded that these measures led to a mean increase in hemoglobin level of 0.76 g/dL in areas

Table 4. Effect of Insecticide-Treated Bed Net Use on Change in Adjusted Hemoglobin Level in Nonpregnant Persons, by Age Group, After a 12-Month Interruption of Malaria Transmission in 2 Highland Areas of Kenya

Area and Age Group	Individuals, No.[a]		Change in Hb Level, g/dL, Mean (SE)[b]		
	ITN	No ITN	ITN	No ITN	*P* Value[c]
Kapsisiywa					
<5 years	23	145	0.92 (0.33)	0.73 (0.13)	.59
5–14 years	8	282	0.16 (0.56)	0.65 (0.10)	.39
≥15 years	58	325	0.27 (0.21)	0.52 (0.09)	.27
Kipsamoite					
<5 years	37	120	1.20 (0.26)	0.73 (0.15)	.12
5–14 years	24	283	0.49 (0.32)	0.01 (0.09)	.15
≥15 years	62	208	−0.29 (0.20)	0.29 (0.11)	.01

Abbreviations: ITN, insecticide-treated bed net; SE, standard error.

[a] Information on ITN use was missing for 18 persons in Kapsisiywa and 20 persons in Kipsamoite.

[b] Adjusted for altitude, according to World Health Organization criteria (see Methods).

[c] By multiple linear regression analysis.

Table 5. Relative Risk of Anemia in Nonpregnant Individuals After a 12-Month Interruption of Malaria Transmission in 2 Highland Areas of Kenya, According to Age

Area and Age Group	Individuals, No.	Relative Risk (95% CI)[a]	*P* Value[b]
Kapsisiywa			
>5 years	174	0.66 (.55–.79)	<.0001
5–14 years	294	0.48 (.31–.67)	<.0001
≥15 years	391	0.74 (.60–.92)	.011
Kipsamoite			
<5 years	163	0.66 (.52–.84)	.001
5–14 years	316	1.07 (.79–1.46)	.76
≥15 years	276	0.90 (.63–1.23)	.60

Abbreviation: CI, 95% confidence interval.

[a] Compares risk of anemia in the same individuals in July 2008 versus the risk in May 2007. The 95% confidence intervals were calculated using bootstrap sampling (see Methods).

[b] exact 2-tailed McNemar test.

where the level of malaria transmission is moderate to high [19]. We are not aware of any previous study that has evaluated the impact of malaria control measures on hemoglobin levels or the prevalence of anemia in low-transmission settings. The authors of the meta-analysis speculated that malaria control measures would have a small effect on anemia in areas of low, unstable transmission [19]. The present study's results indicate, in contrast, that reduction or interruption of malaria in areas of low malaria transmission may in fact lead to large decreases in the prevalence of anemia in children.

The present study further demonstrates that interruption of malaria may provide significant health improvements in older children and adults, populations often overlooked in malaria intervention studies. Anemia prevalence decreased in older children and adults only in Kapsisiywa, the site of historically higher malaria transmission, suggesting that a threshold malaria transmission level may be required for malaria to contribute to anemia in older children and adults. Future intervention studies in areas of higher transmission may consider assessing the benefits these interventions provide to adults as well as to children.

The present study was not designed as a controlled intervention trial. Changes in hemoglobin levels and anemia prevalence were associated with interruption of malaria transmission in the study areas, but it is impossible to determine definitively whether IRS and the consequent interruption of malaria transmission caused the decrease in anemia prevalence or whether other factors were involved. It is unlikely that the reduction in anemia was due to treatment of anemia, as <15% of anemic individuals chose to seek the recommended follow-up evaluation and treatment, or due to ITN use, which was infrequent and decreased during the study period [12]. ITN use was associated with increased hemoglobin levels for pregnant women and, to a lesser extent, young children in both sites, suggesting that ITN use combined with IRS may have additive effects [22]. Infection with helminth parasites such as hookworm or *Schistosoma* species can be significant contributors to childhood anemia in tropical areas [23, 24] and were not evaluated in this study. However, clinical signs of schistosomiasis in this highland population of study are rare, and a previous survey in a nearby highland area found that the prevalence of hookworm infection was generally ≤5% [25]. In addition, no interventions against either infection were conducted during the study period. Finally, while nutritional status was not evaluated, there were no changes in climate or food supply during the study period, nor were any nutritional or micronutrient programs conducted that might have led to the observed changes.

In summary, this study documents that anemia is a significant health problem for residents, particularly children <5 years of age, in areas of low and unstable transmission and that interventions leading to elimination or near elimination of malaria in these areas can produce a significant reduction in anemia. The results also suggest that older children and adults may also benefit from reductions in malaria transmission, although improvements were more modest in these groups. These findings strongly support the goal of malaria elimination in areas of low transmission, as they demonstrate that this may provide significant health benefits to individuals in these areas through reduction of anemia.

Notes

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