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FACTORS ASSOCIATED WITH HEMOGLOBIN CONCENTRATIONS IN PRE-SCHOOL CHILDREN IN WESTERN KENYA: CROSS-SECTIONAL STUDIES

MEGHNA R. DESAI, DIANNE J. TERLOUW, ARTHUR M. KWENA, PENELOPE A. PHILLIPS-HOWARD, SIMON K. KARIUKI, KATHLEEN A. WANNEMUEHLER, AMOS ODHACHA, WILLIAM A. HAWLEY, YA PING SHI, BERNARD L. NAHLEN, AND FEIKO O. TER KUILE

Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; Center for Vector Biology and Control Research, Kenya Medical Research Institute, Kisumu, Kenya; Department of Infectious Diseases, Tropical Medicine & AIDS, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Department of Medical Biochemistry, Faculty of Health Sciences, Moi University, Eldoret, Kenya; Office of Preventive Health, Kenyan Ministry of Health, Kisumu, Kenya; Roll Back Malaria, World Health Organization, Geneva, Switzerland

Abstract. In sub-Saharan Africa, the etiology of anemia in early childhood is complex and multifactorial. Three community-based cross-sectional surveys were used to determine the prevalence and severity of anemia. Regression methods were used to compare mean hemoglobin (Hb) concentrations across covariate levels to identify children at risk of low Hb levels in an area with intense malaria transmission. In a random sample of 2,774 children < 36 months old, the prevalence of anemia (Hb < 11g/dL) was 76.1% and 71%, respectively, in villages without and with insecticide-treated bed nets (ITNs); severe-moderate anemia (Hb < 7 g/dL) was observed in 11% (non-ITN) and 8.3% (ITN). The prevalence of anemia, high-density malaria parasitemia (21.7%), microcytosis (34.9%), underweight (21.9%), and diarrhea (54.8%) increased rapidly from age three months onwards and remained high until 35 months of age. Multivariate analyses showed that family size, history of fever, pale body, general body weakness, diarrhea, soil-eating, concurrent fever, stunting, and malaria parasitemia were associated with mean Hb levels. Prevention of severe anemia should start early in infancy and include a combination of micronutrient supplementation, malaria control, and possibly interventions against diarrheal illness.

INTRODUCTION

Approximately three-fourths of pre-school children in sub-Saharan Africa have anemia, rendering it a common direct and indirect cause of pediatric morbidity and mortality in this region.[1] The complex etiology of anemia involves the interaction between multiple factors including nutritional deficiencies, genetic red blood cell disorders, and infectious diseases, particularly malaria and hookworm infections. Human immunodeficiency virus/acquired immunodeficiency syndrome should also increasingly be considered as a direct and indirect contributor to anemia in this young age group.[2,3]

In areas with intense malaria transmission, malaria is likely the predominant cause of anemia in young children. Insecticide-treated bed nets (ITNs) have proven to be very efficacious in reducing moderate to severe anemia and increasing mean hemoglobin (Hb) concentrations in young children.[4–6] Following several ITN trials, heads of state from 44 malaria-afflicted countries in Africa signed the Abuja declaration, affirming their commitment to provide ITNs to at least 60% of those at risk of malaria, especially pregnant women and children less than five years of age by 2005.[7]

The Roll Back Malaria Initiative has recently proposed using anemia in pre-school children as one of its indicators of malaria control in areas with stable malaria transmission in sub-Saharan Africa.[8] Anemia is measurable and quantifiable in the field with the portable HemoCue® (HemoCue AB, Angelholm, Sweden) hemoglobinometer using small volumes of capillary blood. The prevalence of anemia has also been shown to be a more sensitive indicator to changes in malaria exposure than parasite prevalence in areas with stable malaria transmission[6,9,10] and may respond more timely to malaria control measures than existing indicators such as all-cause mortality that require large surveys and are often assessed retrospectively. Currently, cost-effective strategies are being designed that combine malaria control interventions (such as ITNs) with other disease control programs that may also reduce the burden of anemia.[11]

We conducted a series of cross-sectional surveys involving a random selection of 2,774 children less than three years old as part of a larger controlled study of the impact of ITNs on childhood morbidity and mortality.[12–14] These community-based household surveys provided an opportunity to determine the prevalence and severity of anemia, and to the best of our knowledge, for the first time in this area, present descriptive statistics of factors associated with Hb concentrations in asymptomatic pre-school children living in a setting with intense malaria transmission. These results may assist in identifying children at risk for anemia, and in the design and packaging of anemia control interventions.

MATERIALS AND METHODS

Study area and population. The study area was Asembo, located in the Bondo District (until 1999 part of the Siaya District) northeast of Lake Victoria in the Nyanza Province in western Kenya. The study site has been described in detail elsewhere.[13,15,16] Briefly, approximately 55,000 people live in Asembo (14% of whom are less than five years of age), a rural area covering 200 km^2. The population is ethnically homogeneous: more than 95% are members of the Luo tribe. Families in this polygamous society live in compounds constituting a main house surrounded by several houses for women and children. The houses are dispersed and surrounded by fields, and people earn their living primarily through subsistence farming and fishing. Malaria is holoendemic with year round transmission, and a mean entomologic inoculation rate ranging between 60 and 300 bites per person a year.[17] Sulfadoxine-pyrimethamine (SP) replaced chloroquine as the first-line drug for the treatment of uncomplicated malaria in this area in January 1999.[18] Cholera and bacillary

dysentery are endemic in this area.[19,20] Malnutrition is also an important health problem: more than 30% of the children 6–59 months old are stunted.[21] This area has high infant and under-five-year mortality rates (176/1,000 and 257/1,000 live births).[22]

Bed net study design. Following randomization, permethrin-treated bed nets (Siam Dutch, Bangkok, Thailand), pre-impregnated with a target dose of 0.5 grams of permethrin per meter^2 of netting, were distributed to half of the villages in Asembo by January 1997 (ITN villages). The control villages received ITNs in early 1999 after the two-year intervention period.[12] The ITNs were re-treated biannually by project personnel. The coverage was 1.46 persons per ITN.

Participant recruitment and study design. Between February 1998 and July 1999, three independent cross-sectional surveys (henceforth referred to as survey 1, survey2, and survey 3) were conducted to determine the impact of ITNs on all-cause morbidity in pre-school children, as described in more detail elsewhere.[6,21] Briefly, each household was randomized to cross-sectional survey 1, 2, or 3 such that one household and their occupants could only contribute once. Caregivers were invited to bring all children less than three years old (survey 1) or those less than five years old (surveys 2 and 3) living in their household to a central location in the village on a preset day. They were asked to bring fresh stool samples of the children on the day of the survey.

Household characteristics. A structured questionnaire was used to record details of the socioeconomic status for each household, the main income-generating activities, and the education and age of the caretaker and head of household. The choice of indicators for the assessment of the household socioeconomic status was based on a previous study conducted as part of the ITN study.[23]

Clinical data. The age of each child was copied from census records (collected on a six-month basis as part of the ITN study) and vaccination cards (if available) after verbal verification with the caregiver. Caretakers were asked open-ended and prompted questions (yes/no/don't know) regarding signs and symptoms of illness observed in their children in the last two weeks. These included questions on treatment seeking behavior and history of signs or symptoms: fever, general body weakness (*del monyosore*), body rash, ear pain/pus, eye infection, coughing or difficulty breathing, gastrointestinal complaints including diarrhea, a specific question on soil-eating (to determine its relationship with microcytosis and helminth infection), and the presence of *del maraton'g*, a local term for pale body/skin. Anthropometric measurements were recorded,[21] and each child was examined by a village health worker for signs and symptoms of anemia. In surveys 2 and 3, palpable spleen and signs of kwashiorkor were also determined. A finger prick blood sample was collected in 200–500-μL tubes (Eppendorf, Hamburg, Germany). Finally each child was seen by a clinical officer and treated free of charge if indicated. All children with an HB concentration < 11 g/dL received a treatment dose of SP or amodiaquine and iron supplementation. Children with severe illness were referred for further evaluation and treated free of charge at the local mission hospital.

Laboratory methods. Hemoglobin concentrations were measured in the field using a portable battery powered Hemocue® machine. A full blood count, including repeat Hb measurement, was determined the same afternoon using a Coulter Counter® (Coulter Corporation, Miami, FL). Blood slides were stained using Giemsa and examined for the presence of malaria parasites. Parasites and leukocytes were counted in the same fields until 500 leukocytes were counted. Parasite densities are expressed per microliter of blood using the Coulter counter leukocyte count or assuming a leukocyte count of 8000/μL if Coulter counter readings were missing. Slides were considered negative if no asexual parasites were found in 200 high-power ocular fields of the thick smear. Species diagnosis was made using a thin blood film. A stool sample was microscopically examined for helminth infection using a modification of the formol-ether and ethyl acetate concentration technique and by Kato-Katz methods.[24,25]

Data analyses. Because survey 1 only included children less than 36 months old, all analyses have been restricted to this age group. Since all villages had been given ITNs by the time survey 3 was conducted, and because ITNs were previously found to have a profound impact on Hb levels in survey 1 and survey 2,[6] it was neither necessary nor appropriate to make a direct comparison in the current analysis between ITN and control villages. Thus, all data have been analyzed and described separately for children from households with one or more ITNs at the time of survey (intervention villages in surveys 1 and 2 and all villages in survey 3) and without an ITN (control villages of surveys 1 and 2).

Variables of interest have been categorized into sociodemographic indicators, history of illness and health care–seeking indicators, findings from the basic clinical examination, and laboratory results. The data was initially described and summarized using univariate statistics to document their distribution among children (Table 1). Regression methods were used to compare mean Hb levels across covariate levels, controlling for survey number (Table 2). Continuous variables were categorized using either known cut-off values based on previous analyses (e.g., distance to nearest ITN household)[26] or by division into five equal categories based on ranking (e.g., wealth index). To avoid assessment of the significance of all the potential factors associated with Hb levels in one model, we implemented a strategy to first narrow down the list of covariates that were most significantly associated with Hb levels within each of the four predictor variable categories before they were entered into a multivariate model. Thus, in non-ITN households, within each of the four predictor variable categories, factors that were associated with mean Hb levels in univariate analyses (Table 2, at alpha = 0.1) were entered into a multivariate linear regression model and assessed for significance at alpha = 0.05 after adjustment for survey number and age (using global mean for non-ITN households, Table 3, columns 2 and 3). These same factors were then tested for their association with Hb levels in children from households with an ITN (using global mean for ITN households, Table 3, columns 4 and 5). In an effort to identify one final model for the non-ITN households, the four multivariate models (from Table 3, non-ITN columns) were consolidated into a single model (Table 4). Factors found to be no longer significant were removed. A logistic regression model was also fit to assess the association between severe-moderate anemia and malaria parasitemia. Standard errors are adjusted for clustering at the compound level. Only vari-

TABLE 1
Characteristics of 2,774 children less than 36 months old enrolled in three cross-sectional surveys in western Kenya*

Characteristic	Non-ITN (n = 912)	ITN (n = 1,862)	Total (n = 2,774)
Cross-sectional survey			
1. Feb–Mar 1998, no. (%)	479 (52.5)	501 (26.9)	980 (35.3)
2. Nov–Dec 1998, no. (%)	433 (47.5)	477 (25.6)	910 (32.8)
3. Jun–Jul 1999, no. (%)	0 (0)	884 (47.5)	884 (31.9)
Age (months), mean (95% CI)	18.1 (17.5, 18.7)	17.0 (16.5, 17.4)	17.4 (17.0, 17.7)
Sex (male, no. (%)	450 (49.3)	906 (48.7)	1,356 (48.9)
Received complete set of childhood vaccinations	240 (31.5)	560 (41.7)	800 (38.0)
Education, housing, and socioeconomics†			
Head of household level of education			
Primary school completed	443 (65.4)	874 (63.2)	1,317 (63.9)
Primary school not completed	234 (34.6)	510 (36.8)	744 (36.10)
Head of household's most common income generating activities			
Farmer	303 (42.6)	762 (53.0)	1,065 (49.6)
Salaried work	119 (16.7)	258 (18.0)	377 (17.6)
Other (fisher, labor, business, etc.)	289 (40.6)	417 (29.0)	706 (32.9)
Distance to nearest clinic < 500 meters	76 (10.0)	58 (3.9)	134 (6.0)
Distance to nearest control/ITN compound < 300 meters	171 (22.4)	582 (39.4)	753 (33.7)
Number of children < 5 years old			
1	335 (47.1)	756 (52.6)	1,091 (50.8)
2–3	370 (52.0)	677 (47.1)	1,047 (48.7)
> 3	6 (0.84)	4 (0.28)	10 (0.47)
Mother's age (years)‡, no. (%)			
< 21	56 (13.8)	161 (18.5)	217 (17.0)
21–30	226 (55.7)	451 (51.7)	677 (53.0)
> 30	124 (30.5)	260 (29.8)	384 (30.1)
History of illness, treatment, or soil eating in previous two weeks			
Fever	802 (87.9)	1,612 (86.6)	2,414 (87.0)
Gastrointestinal problems	629 (69.0)	1,276 (68.5)	1,905 (68.7)
Body pallor, no. (%)	398 (43.8)	741 (40.1)	1,139 (41.3)
Weak body, no. (%)	237 (26.1)	436 (23.4)	673 (24.3)
Respiratory tract problems, no. (%)	113 (12.4)	367 (19.8)	480 (17.4)
Diarrhea, no. (%)	521 (57.4)	996 (53.6)	1,517 (54.8)
Soil eating, no. (%)	247 (27.1)	409 (22.0)	656 (23.7)
Sought healthcare, no. (%)	770 (84.5)	1,521 (81.7)	2,291 (82.6)
Clinical examination			
Axillary temp ≥ 37.5°C, no. (%)	92 (10.1)	138 (7.5)	230 (8.4)
Weight-for-height Z-score			
Mean (95% CI)	−0.38 (−0.46, −0.30)	−0.31 (−0.36, −0.26)	−0.33 (−0.38, −0.29)
< −2 Z-score, no. (%)	54 (6.1)	101 (5.6)	155 (5.8)
Weight-for-age Z-score			
Mean (95% CI)	−1.02 (−1.11, −0.92)	−0.96 (−1.02, −0.89)	−0.98 (−1.03, −0.92)
< −2 Z-score, no. (%)	203 (22.7)	395 (21.5)	598 (21.9)
Height-for-age Z-score			
Mean (95% CI)	−1.11 (−1.21, −1.01)	−1.12 (−1.19, −1.05)	−1.12 (−1.17, −1.06)
< −2 Z-score, no. (%)	213 (24.4)	445 (25.0)	658 (24.8)
Mid-upper-arm-circumgerence for age Z-score§			
Mean (95% CI)	−1.24 (−1.32, −1.15)	−1.15 (−1.20, −1.09)	−1.18 (−1.23, −1.13)
< −2 Z-score, no. (%)	169 (22.3)	287 (19.4)	456 (20.4)
Laboratory examination			
Malaria smear positive, no. (%)	601 (66.6)	949 (52.1)	1,550 (56.9)
Geometric mean (95% CI) parasitemia/mm^3	159.2 (119.9, 213.3)	51.9 (42.2, 63.4)	75.2 (63.4, 89.2)
High-density parasitemia, no. (%)	236 (25.9)	365 (19.6)	601 (21.7)
Gametocytemic, no. (%)	274 (30.5)	1,070 (58.8)	1,344 (49.5)
Clinical malaria	53 (5.9)	56 (3.1)	109 (4.0)
Mean corpuscular volume‡, mean (95% CI)	75.2 (74.3, 76.1)	74.7 (74.1, 75.3)	74.8 (74.3, 75.3)
Microcytosis‡, no. (%)	143 (33.6)	429 (35.4)	572 (34.9)
Hemoglobin (g/dL), mean (95% CI)	9.52 (9.38, 9.67)	9.87 (9.77, 9.97)	9.76 (9.67, 9.84)
Hemoglobin S phenotype‡, no. (%)			
HbAS	90 (21.5)	284 (22.2)	374 (22.0)
HbSS	3 (0.7)	7 (0.5)	10 (0.59)
HbAA	325 (77.8)	991 (77.3)	1,316 (77.4)
Any helminth in stool¶, no. (%)	151 (25.2)	299 (23.0)	450 (23.7)
Hookworm, no. (%)	52 (8.7)	99 (7.6)	151 (8.0)
Density; median (range)	33 (17, 1,333)	67 (17, 800)	50 (17, 1,333)
Count > 100 per gram of stool, no. (%)	5/52 (9.62)	21/99 (21.2)	26/151 (17.2)
Ascaris lumbricoides, no. (%)	117 (19.5)	250 (19.2)	367 (19.3)
Trichuris trichiura, no. (%)	19 (3.2)	32 (2.5)	51 (2.7)
Strongyloides stercoralis, no. (%)	0 (0)	5 (0.4)	5 (0.26)
Schistosoma mansoni, no. (%)	0 (0)	1 (0.1)	1 (0.05)

* ITN = insecticide-treated bed net; CI = confidence interval; Hb = hemoglobin.
† Data based on number of households (2,238), not number of children.
‡ Measured only in surveys 2 and 3.
§ World Health Organization reference used for 6–59-month-old children.
¶ For all helminthes, n = 1,299 in ITN villages and n = 600 in non-ITN villages.

TABLE 2
Factors univariately associated with hemoglobin (Hb) among children less than 36 months old in western Kenya*

Risk factor	Non-ITN (n = 908)			ITN (n = 1,862)		
	Hb mean (95% CI)	Difference in Hb mean (95% CI)	*P*	Hb mean (95% CI)	Difference in Hb mean (95% CI)	*P*
Sociodemographics						
Sex						
Male	9.39 (9.19, 9.59)	**−0.29 (−0.57, −0.01)**	0.04	9.73 (9.59, 9.88)	**−0.37 (−0.57, −0.17)**	0.0004
Female	9.68 (9.48, 9.87)	Reference		10.1 (9.96, 10.24)	Reference	
Received complete set of childhood vaccinations						
Yes	9.39 (9.11, 9.67)	−0.10 (−0.47, 0.27)	0.59	9.66 (9.49, 9.83)	**−0.36 (−0.63, −0.10)**	0.008
No	9.49 (9.28, 9.71)	Reference		10.01 (9.83, 10.21)	Reference	
Head of household (HH) level of education						
Primary school completed	9.67 (9.49, 9.86)	**0.34 (0.04, 0.64)**	0.03	9.94 (9.81, 10.08)	0.058 (−0.16, 0.28)	0.60
Primary school not completed	9.34 (9.10, 9.57)	Reference		9.88 (9.71, 10.06)	Reference	
HH's most common income generating activities			0.45			0.50
Farmer	9.53 (9.32, 9.74)	−0.21 (−0.62, 0.21)	0.32	9.98 (9.83, 10.13)	0.13 (−0.15, 0.40)	0.36
Other	9.46 (9.23, 9.70)	−0.28 (−0.71, 0.16)	0.21	9.86 (0.67, 10.05)	0.004 (−0.29, 0.30)	0.98
Salaried work	9.74 (9.38, 10.1)	Reference		9.85 (9.62, 10.09)	Reference	
Wealth below 60% percentile						
Yes	9.42 (9.25, 9.60)	−0.28 (−0.57, 0.01)	0.06	9.96 (9.82, 10.10)	0.10 (−0.10, 0.31)	0.32
No	9.70 (9.46, 9.94)	Reference		9.86 (9.69, 10.02)	Reference	
Distance to nearest clinic < 500 meters						
Yes	10.05 (9.57, 10.52)	**0.57 (0.08, 1.07)**	0.02	10.40 (9.89, 10.92)	0.50 (−0.02, 1.03)	0.06
No	9.48 (9.34, 9.62)	Reference		9.90 (9.80, 10.01)	Reference	
Distance to nearest clinic/ITN compound < 300 meters						
Yes	9.91 (9.64, 10.17)	**0.48 (0.17, 0.78)**	0.002	9.86 (9.68, 10.04)	−0.09 (−0.32, 0.14)	0.43
No	9.43 (9.27, 9.59)	Reference		9.95 (9.82, 10.08)	Reference	
Number of children < 5 years old			0.003			0.10
1	9.32 (9.10, 9.54)	Reference		9.83 (9.68, 9.98)	Reference	
2–3	9.73 (9.54, 9.92)	**0.41 (0.12, 0.70)**	0.007	9.98 (9.84, 10.13)	0.16 (−0.05, 0.36)	0.14
>3	8.44 (7.48, 9.40)	−0.88 (−1.87, 0.10)	0.08	10.83 (9.65, 12.01)	1.00 (−0.19, 2.19)	0.10
Mother's age (years)†			0.13			0.97
< 21	9.38 (8.68, 10.08)	−0.70 (−1.48, 0.09)	0.08	10.07 (9.70, 10.44)	0.01 (−0.43, 0.46)	0.95
21–30	10.14 (9.83, 10.45)	0.07 (−0.39, 0.52)	0.76	10.03 (9.81, 10.24)	−0.03 (−0.36, 0.30)	0.86
> 30	10.07 (9.72, 10.43)	Reference		10.06 (9.81, 10.31)	Reference	
History of illness, treatment, or soil eating in previous two weeks						
Fever						
Yes	9.40 (9.25, 9.54)	**−1.19 (−1.69, −0.70)**	< 0.0001	9.76 (9.65, 9.86)	**−1.14 (−1.49, −0.79)**	< 0.0001
No	10.59 (10.11, 11.06)	Reference		10.90 (10.57, 11.23)	Reference	
Gastrointestinal problems						
Yes	9.29 (9.13, 9.46)	**−0.78 (−1.07, −0.49)**	< 0.0001	9.65 (9.52, 9.77)	**−0.82 (−1.05, −0.66)**	< 0.0001
No	10.07 (9.83, 10.32)	Reference		10.47 (10.28, 10.66)	Reference	
Body pallor						
Yes	9.00 (8.79, 9.21)	**−0.95 (−1.21, −0.70)**	< 0.0001	9.38 (9.22, 9.54)	**−0.87 (−1.07, −0.66)**	< 0.0001
No	9.95 (9.78, 10.12)	Reference		10.24 (10.11, 10.38)	Reference	
Weak body						
Yes	8.74 (8.48, 9.00)	**−1.06 (−1.36, −0.75)**	< 0.0001	9.11 (8.91, 9.30)	**−1.05 (−1.28, −0.83)**	< 0.0001
No	9.80 (9.64, 9.95)	Reference		10.16 (10.04, 10.28)	Reference	
Respiratory tract problems						
Yes	9.21 (8.84, 9.57)	−0.39 (−0.87, 0.01)	0.05	9.74 (9.52, 9.96)	−0.21 (−0.46, 0.03)	0.09
No	9.59 (9.44 (9.74)	Reference		9.96 (9.84, 10.08)	Reference	
Diarrhea						
Yes	9.21 (9.04, 9.38)	**−0.79 (−1.05, −0.52)**	< 0.0001	9.61 (9.48, 9.75)	**−0.65, (−0.85, −0.44)**	< 0.0001
No	10.00 (9.79, 10.20)	Reference		10.26 (10.10, 10.42)	Reference	
Soil eating						
Yes	8.83 (8.59, 9.06)	**−0.97 (−1.25, −0.69)**	< 0.0001	9.16 (8.97, 9.36)	**−0.97 (−1.20, −0.75)**	< 0.0001
No	9.80 (9.63, 9.96)	Reference		10.14 (10.02, 10.26)	Reference	
Sought health care						
Yes	9.41 (9.26, 9.55)	**−0.83 (−1.23, −0.43)**	0.0001	9.73 (9.62, 9.84)	**−1.03 (−1.34, −0.71)**	< 0.0001
No	10.24 (9.86, 10.61)	Reference		10.75 (10.46, 11.05)	Reference	
Clinical examination						
Axillary temperature ≥ 37.5°C						
Yes	8.37 (7.98, 8.76)	**−1.30 (−1.72, −0.89)**	< 0.0001	9.25 (8.89, 9.61)	**−0.73 (−1.10, −0.35)**	0.0002
No	9.67 (9.53, 9.82)	Reference		9.97 (9.86, 10.08)	Reference	
Palpable spleen†						
Yes	9.38 (9.15, 9.61)	**−1.63 (−2.03, −1.24)**	< 0.0001	8.99 (8.77, 9.21)	**−1.41 (−1.67, −1.14)**	< 0.0001
No	11.01 (10.68, 11.35)	Reference		10.40 (10.25, 10.54)	Reference	
Weight-for-height Z-score < −2						
Yes	8.74 (8.18, 9.30)	**−0.85 (−1.43, −0.27)**	0.007	9.33 (8.94, 9.72)	**−0.63 (−1.03, −0.23)**	< 0.0001
No	9.59 (9.43, 9.74)	Reference		9.96 (9.85, 10.07)	Reference	
Weight-for-age Z-score < −2						
Yes	8.71 (8.44, 8.99)	**−1.05 (−1.37, −0.73)**	< 0.0001	9.10 (8.89, 9.32)	**−1.05 (−1.28, −0.81)**	< 0.0001
No	9.76 (9.61, 9.92)	Reference		10.15 (10.04, 10.27)	Reference	
Height-for-age Z-score < −2						
Yes	8.97 (8.70, 9.24)	**−0.75 (−1.07, −0.44)**	< 0.0001	9.20 (9.02, 9.39)	**−0.98 (−1.19, −0.77)**	< 0.0001
No	9.72 (9.56, 9.88)	Reference		10.18 (10.06, 10.30)	Reference	
MUAC-for-age Z-score < −2						
Yes	8.66 (8.37, 8.96)	**−0.92 (−1.25, −0.60)**	< 0.0001	8.88 (8.63, 9.14)	**−0.92 (−1.19, −0.65)**	< 0.0001
No	9.58 (9.43, 9.74)	Reference		9.80 (9.69, 9.91)	Reference	

TABLE 2
Continued

Risk factor	Non-ITN (n = 980)			ITN (n = 1,862)		
	Hb mean (95% CI)	Difference in Hb mean (95% CI)	*P*	Hb mean (95% CI)	Difference in Hb mean (95% CI)	*P*
Signs of kwashiorkor (thin and light hair)†						
Yes	9.37 (8.74, 10.00)	**−0.71 (−1.39, −0.03)**	0.04	9.18 (8.67, 9.69)	**−0.87 (−1.41, −0.34)**	0.002
No	10.08 (9.82, 10.33)	Reference		10.05 (9.92, 10.18)	Reference	
Laboratory examination						
Malaria smear						
Positive	9.09 (8.93, 9.25)	**−1.33 (−1.60, −1.07)**	< 0.0001	9.13 (8.99, 9.27)	**−1.60 (−1.80, −1.40)**	< 0.0001
Negative	10.42 (10.21, 10.64)	Reference		10.73 (10.58, 10.88)	Reference	
Gametocytemic						
Yes	8.88 (8.66, 9.09)	**−0.93 (−1.20, −0.67)**	< 0.0001	9.33 (9.16, 9.50)	**−1.11 (−1.39, −0.82)**	< 0.0001
No	9.81 (9.65, 9.98)	Reference		10.44 (10.26, 10.62)	Reference	
Clinical malaria						
Yes	8.31 (7.81, 8.81)	**−1.30 (−1.81, −0.79)**	< 0.0001	8.29 (7.75, 8.83)	**−1.67 (−2.22, −1.11)**	< 0.0001
No	9.61 (9.46, 9.76)	Reference		9.96 (9.85, 10.07)	Reference	
Microcytosis†						
Yes	9.67 (9.39, 9.95)	**−0.51 (−0.89, −0.13)**	0.01	9.28 (9.11, 9.45)	**−1.04 (−1.27, −0.81)**	< 0.0001
No	10.18 (9.90, 10.46)	Reference		10.32 (10.16, 10.48)	Reference	
HbS phenotype†			0.04			< 0.0001
HbAS	10.30 (9.94, 10.67)	0.42 (0.001, 0.84)	0.05	10.16 (9.93, 10.39)	0.18 (−0.09, 0.45)	0.19
HbSS	9.27 (8.39, 10.15)	−0.16 (−1.53, 0.31)	0.18	7.10 (5.93 8.27)	**−2.88 (−4.06, −1.71)**	< 0.0001
HbAA	9.88 (9.63, 10.13)	Reference		9.98 (9.83, 10.13)	Reference	
Any helminth in stool‡						
Yes	9.50 (9.05, 9.95)	0.02 (−0.45, 0.49)	0.95	9.06 (8.50, 9.63)	−0.13 (−0.42, 0.16)	0.38
No	9.48 (9.25, 9.71)	Reference		9.19 (8.69, 9.68)	Reference	
Hookworm						
Yes	9.55 (8.66, 10.44)	0.06 (−0.77, 0.89)	0.86	9.21 (8.41, 10.02)	0.05 (−0.50, 0.60)	0.85
No	9.49 (9.23, 9.75)	Reference		9.17 (8.65, 9.68)	Reference	
Hookworm: count > 100 per gram of stool						
Yes	9.73 (8.18, 11.27)	0.24 (−1.30, 1.79)	0.57	8.41 (5.87, 10.95)	−0.75 (−2.73, 1.22)	0.24
No	9.48 (9.02, 9.94)	Reference		9.16 (8.06, 10.26)	Reference	
Ascaris lumbricoides						
Yes	9.46 (8.98, 9.93)	−0.04 (−0.56, 0.49)	0.89	9.05 (8.47, 9.63)	−0.13 (−0.43, 0.17)	0.37
No	9.49 (9.25, 9.74)	Reference		9.19 (8.69, 9.68)	Reference	
Trichuris trichiura						
Yes	9.59 (8.22, 10.96)	0.10 (−1.28, 1.48)	0.85	8.41 (7.30, 9.51)	−0.77 (−1.73, 0.19)	0.10
No	9.48 (9.19, 9.78)	Reference		9.18 (8.60, 9.76)	Reference	

* ITN = insecticide-treated bed nets; Hb = hemoglobin; CI = confidence interval; MUAC = mid-upper-arm-circumference. All analyses adjusted for clustering at the compound level, and controlling for survey number; **bold** estimates were statistically significant at alpha = 0.05.
† Measured only in surveys 2 and 3.
‡ Analyses restricted to surveys 2 and 3 (for ITN) and survey 2 (for non-ITN) and estimates also control for hemoglobin S phenotype due to confounding. There were too few cases of *Strongyloides stercoralis* and *Schistosoma mansoni* for inclusion in further analyses.

ables that were available from all three surveys were included in the multi-variate models (e.g., palpable spleen was excluded because it was not assessed in survey 1).

Anemia. Anemia was defined as an HB level < 11.0 g/dL and categorized as severe (Hb ≤ 5 g/dL), moderate (Hb = 5.1–6.9 g/dL), and mild (Hb = 7.0–10.9 g/dL) anemia.

Microcytic anemia. This was a surrogate marker of iron deficiency. The mean corpuscular volume value below an age-specific cut-off was measured in femtoliters: 0–5 months old = 70 fl; 6–11 months old = 73 fl; and > 12 months old = 75 fl.[27]

Malaria. Malaria infection was defined as any parasitemia (any species) detected in the blood smear. Clinical malaria was defined as a documented axillary temperature ≥ 37.5°C in the presence of malaria parasitemia (any species) above an age-dependent fever threshold parasite density (0–5 months = 1,500/mm^3; 6–11 months = 6,000/mm^3; and 12–35 months = 7,000/mm^3).[28] High-density parasitemia was defined as a parasite density greater than 5,000/mm^3, irrespective of the presence of fever.

Nutritional parameters. Height-for-age (HAZ), weight-for-age (WAZ), weight-for-height (WHZ), and mid-upper-arm-circumference (MUAC)–for age Z-scores were calculated using Epi-Info version 2000 (Centers for Disease Control and Prevention [CDC], Atlanta, GA) based on reference data developed by the National Centers for Health Statistics (NCHS) and CDC, which use data from the Fels Health Institute and U.S. Health Examination Surveys.[29] The growth curves are recommended by the World Health Organization (WHO) for international use.[30] Infants were classified as stunted, underweight, or wasted if the HAZ, WAZ, and WHZ scores were < 2 SD of the NCHS reference median, respectively. A low MUAC for age score was defined as a MUAC for age Z-score < 2 SD of the NCHS/WHO reference (which was only available for children more than six months of age). The presence of both thin and light hair were used as indicators of kwashiorkor.

Upper gastrointestinal problem. This was defined as a history of a loss of appetite or vomiting in the previous two weeks.

Hookworm infection. The cut-off value for assessing hookworm infection was set at the 80th percentile of the frequency of egg count distributions, which equated to > 100 eggs per gram of stool.

Vaccination. Children in each age group were considered to have completed their age-specific vaccinations if they had received immunizations with the following vaccines: 1 day–7.9 weeks old: anti-tuberculosis vaccine (Bacillus Calmette-Guerin [BCG]) and one dose of the oral polio vaccine (OPV); 8–11.9 weeks old: the above plus one additional dose of OPV and the first immunization with anti-diphtheria, pertussis, and tetanus (DPT) vaccine; 12–15.9 weeks old: the above plus one additional dose of OPV, and the second DPT immuniza-

TABLE 3
Multivariate analyses by sociodemographics, history of illness, and clinical and laboratory examination*

	Non-ITN		ITN	
	Hb mean (95% CI)	Difference in Hb mean (95% CI)	Hb mean (95% CI)	Differences in Hb mean (95% CI)
Model I: Sociodemographics†				
Head of household level of education				
Primary school completed	9.45 (9.11, 9.79)	**0.33 (0.04, 0.63)**	10.21 (9.80, 10.63)	0.06 (–0.16, 0.27)
Primary school not completed	9.12 (8.75, 9.48)	Reference	10.16 (9.71, 10.60)	Reference
Wealth below 60% percentile				
Yes	9.13 (8.79, 9.47)	**–0.30 (–0.59, –0.02)**	10.24 (9.81, 10.67)	0.11 (–0.10, 0.33)
No	9.43 (9.08, 9.79)	Reference	10.13 (9.70, 10.56)	Reference
Distance to nearest ITN/control compound < 300 meters				
Yes	9.52 (9.12, 9.91)	**0.47 (0.16, 0.78)**	10.12 (9.69, 10.56)	–0.12 (–0.35, 0.12)
No	9.05 (8.75, 9.34)	Reference	10.24 (9.83, 10.66)	Reference
Number of children < 5 years old				
1	9.48 (9.23, 9.73)	Reference	9.79 (9.63, 9.95)	Reference
2–3	9.82 (9.62, 10.02)	**0.34 (0.05, 0.63)**	9.94 (9.79, 10.10)	0.15 (–0.06, 0.36)
> 3	8.55 (7.69, 9.41)	**–0.93 (–1.81, –0.05)**	10.82 (9.61, 12.03)	1.03 (–0.19, 2.24)
Model 2: History of illness or soil eating in previous two weeks†				
Fever				
Yes	9.13 (8.96, 9.30)	**–0.72 (–1.20, –0.25)**	9.41 (9.27, 9.54)	**–0.74 (–1.08, –0.40)**
No	9.85 (9.39, 10.32)	Reference	10.15 (9.81, 10.49)	Reference
Body pallor				
Yes	9.32 (9.01, 9.62)	**–0.35 (–0.62, –0.08)**	9.57 (9.35, 9.80)	**–0.42 (–0.63, –0.20)**
No	9.67 (9.40, 9.94)	Reference	9.99 (9.77, 10.20)	Reference
Weak body				
Yes	9.18 (8.84, 9.51)	**–0.63 (–0.96, –0.31)**	9.50 (9.24, 9.76)	**–0.57 (–0.81, –0.32)**
No	9.81 (9.55, 10.07)	Reference	10.06 (9.88, 10.25)	Reference
Diarrhea				
Yes	9.34 (9.07, 9.60)	**–0.31 (–0.58, –0.05)**	9.64 (9.44, 9.85)	**–0.27 (–0.47, –0.07)**
No	9.65 (9.34, 9.96)	Reference	9.92 (9.69, 10.14)	Reference
Soil eating				
Yes	9.13 (8.82, 9.44)	**–0.73 (–1.00, –0.45)**	9.41 (9.16, 9.66)	**–0.74 (–0.96, –0.52)**
No	9.86 (9.59, 10.12)	Reference	10.15 (9.96, 10.34)	Reference
Model 3: Clinical examination†				
Axillary temperature ≥ 37.5°C				
Yes	8.18 (7.76, 9.59)	**–1.29 (–1.71, –0.86)**	9.18 (8.81, 9.55)	**–0.57 (–0.94, –0.20)**
No	9.46 (9.29, 9.63)	Reference	9.75 (9.63, 9.87)	Reference
Height-for-age Z-score < –2				
Yes	8.41 (8.09, 8.73)	**–0.82 (–1.13, –0.51)**	9.00 (8.75, 9.26)	**–0.92 (–1.13, –0.71)**
No	9.23 (9.00, 9.45)	Reference	9.93 (9.73, 10.12)	Reference
Model 4: Laboratory examination†‡				
Malaria smear				
Positive	8.68 (8.43, 8.92)	**–1.21 (–1.51, –0.91)**	8.70 (8.44, 8.97)	**–1.56 (–1.78, –1.34)**
Negative	9.89 (9.54, 10.25)	Reference	10.26 (9.96, 10.56)	Reference
Gametocytemia				
Yes	9.04 (8.71, 9.36)	**–0.49 (–0.76, –0.22)**	9.29 (8.99, 9.59)	**–0.38 (–0.67, –0.09)**
No	9.53 (9.27, 9.80)	Reference	9.67 (9.37, 9.97)	Reference
Clinical malaria				
Yes	8.88 (8.38, 9.39)	**–0.81 (–1.31, –0.30)**	9.01 (8.48, 9.55)	**–0.93 (–1.48, –0.39)**
No	9.69 (9.53, 9.84)	Reference	9.95 (9.84, 10.05)	Reference

* ITN = insecticide-treated bed net; Hb = hemoglobin; CI = confidence interval. Factors that were independently associated ($P < 0.1$) with mean hemoglobin in univariate analyses for non-ITN households (Table 2, column 2–4) were entered into four separate multivariate models for each of the categories of sociodemographics (model 1), history of illness (model 2), clinical examination (model 3), and laboratory examination (model 4) using backward selection. The same covariates that were found to be statistically significant ($P < 0.05$) in these multivariate models for non-ITN households (Table 3, columns 2 and 3) were then forced into a model using children from ITN households and assessed for their significance (Table 3, columns 4 and 5).
† Adjusted for survey number and age (non-ITN: global mean = 18.1 months, ITN: global mean = 17.0 months). **Bold** estimates were statistically significant at alpha = 0.05.
‡ Since microcytosis and HbS genotype were measured only in surveys 2 and 3, they were not included in the multivariate analysis.

tion; 16–51.9 weeks old: BCG and all the OPV and DPT vaccinations. Children ≥ 12 months old were considered fully immunized if they had received BCG, OPV (4×), DPT (3×), and the anti-measles vaccination. Attendance at either the 1997 or 1998 polio eradication campaigns was considered to be a satisfactory substitute to fulfill the polio immunization criteria.

Ethical clearance and informed consent. This study was reviewed and approved by the institutional review boards of the Kenya Medical Research Institute (Nairobi, Kenya) and the CDC (Atlanta, GA). Written informed consent was obtained from caretakers for each individual participant.

RESULTS

Prevalence of anemia. The overall prevalence of anemia was 76.1% and 71% in villages without ITNs (surveys 1 and 2) and with ITNs (surveys 1, 2, and 3), respectively. The prevalence of severe to moderate anemia (Hb <7 g/dL) was 11% in non-ITN villages and 8.3% in villages with ITNs.

The association between age and anemia was similar in non-ITN and ITN villages (Figures 1 and 2). Data of mean Hb by age show that children born in households without ITNs have considerably lower Hb concentrations in the first two months of life than a normal Caucasian American reference

TABLE 4
Overall multivariate model for non-ITN households*

	Hb (95% CI)	Difference in Hb mean (95% CI)	*P*
Number of children < 5 years old			0.04
1	9.09 (8.73, 9.44)	Reference	
2–3	9.41 (9.06, 9.76)	0.33 (0.07, 0.58)	0.01
> 3	9.04 (8.20, 9.87)	–0.05 (–0.86, 0.77)	0.90
Fever			0.009
Yes	8.86 (8.51, 9.21)	–0.64 (–1.11, –0.17)	
No	9.50 (9.84, 10.05)		
Body pallor			0.009
Yes	8.99 (8.56, 9.43)	–0.37 (–0.64, –0.10)	
No	9.36 (8.96, 9.76)		
Weak body			0.01
Yes	8.96 (8.52, 9.40)	–0.43 (–0.76, –0.10)	
No	9.39 (8.98, 9.81)		
Diarrhea			0.02
Yes	9.02 (8.62, 9.42)	–0.31 (–0.58, –0.05)	
No	9.33 (8.90, 9.77)		
Soil eating			< 0.0001
Yes	8.85 (8.41, 9.28)	–0.66 (–0.94, –0.39)	
No	9.51 (9.11, 9.91)		
Axillary temperature ≥ 37.5°C			0.001
Yes	8.79 (8.25, 9.32)	–0.79 (1.23, 0.34)	
No	9.57 (9.20, 9.95)		
Height-for-age Z-score < –2			0.001
Yes	8.92 (8.46, 9.37)	–0.52 (–0.83, –0.21)	
No	9.44 (9.05, 9.83)		
Malaria smear			< 0.0001
Positive	8.61 (8.23, 8.99)	–1.14 (–1.14, –0.87)	
Negative	9.75 (9.30, 10.20)		

* Controlling for survey number and continuous age (global mean = 18.1 months). ITN = insecticide-treated bed net; Hb = hemoglobin; CI = confidence interval.

population.[27] Children less than two months of age were found to have Hb levels in the normal range, though 41.3% and 34.9% were anemic (Hb < 11 g/dL) in the non-ITN and ITN households, respectively. Data show that children in this study area experience the normal physiologic decrease in the first 2–3 months of age; however, they do not exhibit the subsequent increase in Hb concentrations as is seen in healthy reference infants. Instead, the Hb concentrations continued to decrease until they reached a nadir at the age of 9–10 months, after which concentrations increased slightly but remained well below 2 SD from the reference mean (Figure 1).

Other characteristics. The characteristics of 2,774 children less than 36 months of age enrolled in the three cross-sectional surveys stratified by household ITN status are shown in Table 1.

The mean (95% confidence interval [CI]) age of children was 17.4 (17.0, 17.7) months and 48.9% were males. Eight hundred (38%) of the children ≥ 12 months old were fully immunized (including anti-measles vaccine). There was a very high cumulative prevalence of morbidity reported by the caretakers. Perceived febrile episodes in the previous two weeks were the most common illness reported by the caretaker (six of every seven children). One in two children were reported to have had diarrhea in the previous two weeks, with the prevalence being highest among children 3–24 months old (Figure 3). Among these, 7.3%, 82.4%, and 35.4% were reported to have bloody, non-bloody, and watery diarrhea, respectively. Health care was sought for more than three-fourths of the children (2,291 of 2,774); of them, 47.0% visited a traditional healer, 25.0% visited a formal clinic, 36% visited a shop that also sells drugs, and 11% visited a market vendor/hawker. The prevalence of wasting, underweight, and stunting was 5.8%, 21.9%, and 24.8%, respectively, in all children and 6.6%, 25.7% and 29.5%, respectively, in children 6–35 months of age. Eight percent had a documented fever at the time of the survey. A palpable spleen was evident in 61.4% and 25.1% of the children in non-ITN and ITN households, respectively. The presence of thin and light hair (indicative of kwashiorkor) was observed in 7% of all children, and only 1% of all children had bipedal edema.

The overall prevalence of malaria parasitemia was 56.9% with the following species distribution: *Plasmodium falciparum* = 82.8%, *P. malariae* = 1.03%, *P. ovale* = 0.13%, and mixed species = 15.7%. Overall, only 4.0% had concomitant fever (a non-specific indicator of acute clinical malaria). Microcytemia was detected in 34.9% of the children; exploration of age pattern in non-ITN villages showed that microcytosis was most common in children 6–18 months old (Figure 3) and overlapped with the high prevalence of malaria parasitemia and reported diarrheal illness in this age period. Hemoglobin electrophoresis (assessed only in surveys 2 and 3) indicated that 22.0% of the children had the sickle cell trait, and 0.6% had the HbSS phenotype. The prevalence of helminth infections was low in infants (8.4%), but increased rapidly with age: more than 40% of the children ≥ 30 months old were infected with one or more helminthes (Figure 4). *Ascaris lumbricoides* was the most common geohelminth identified (19.3%), followed by hookworm (8.0%) and *Trichuris trichiura* (2.7%). Schistosome infection (*Schistosoma mansoni* or *S. hematobium*) was virtually absent (0.1%).

Factors associated with mean Hb concentrations. *Sociodemographic indicators.* The levels of education of the caretaker and the head of the household were strongly correlated (r = 0.86); therefore, only the results of the head of the household level of education are presented. Three household indicators and two geographic variables were significantly associated (alpha = 0.10) with mean Hb levels in the non-ITN villages (Table 2): level of education of the head of household; wealth; number of children less than five years old in the household; distance to the nearest ITN compound; and distance to the nearest clinic. Of these, all but distance to the clinic remained significant when entered into a multivariate model containing all the other variables, as well as survey number and age (Table 3, model 1, non-ITN column).

Estimates of adjusted means from the multivariate model indicate significantly lower Hb levels in children from households where the head of the household did not complete primary school compared with those with the head of the household who did complete primary school (mean difference [95% CI] = –0.33 [–0.63, –0.04]); in children from poorer households (< 60th percentile) compared with wealthier households (–0.3 [–0.59, –0.02]); and in children who came from households with ≥ 4 pre-school children compared with those with only 1 (–0.93 [–1.81, –0.05]). Children from households with two or three pre-school children had higher mean Hb levels than those with only one child (0.34 [0.05, 0.63]). Residing within 300 meters of an ITN compound resulted in children having significantly higher mean Hb levels compared with those who lived further away (0.47 [0.16, 0.78]). Of note is that none of these indicators were associated with Hb levels in the villages with ITNs (Table 3, model 1, ITN column).

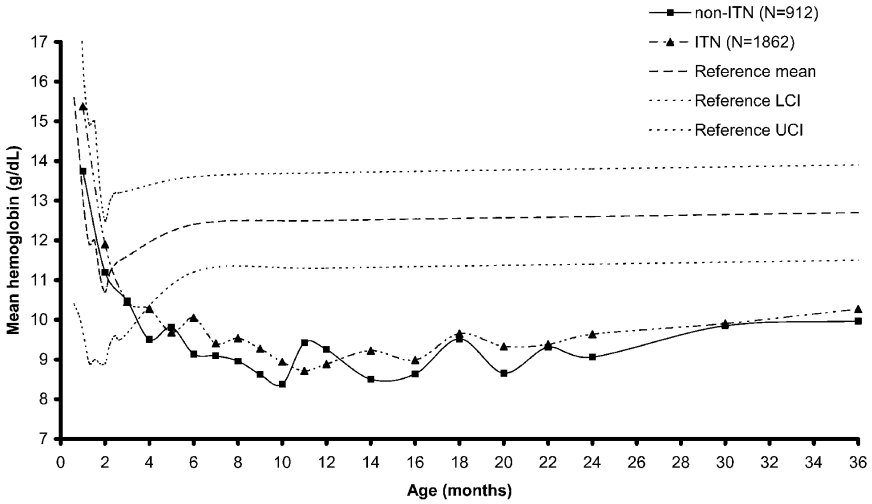

FIGURE 1. Mean hemoglobin concentrations by age and presence of an insecticide-treated bed net (ITN) in the household in western Kenya. Reference values use capillary blood samples from a healthy western population.[27] ITN = villages using an ITN (50% of the 60 villages in survey 1 and 2, and all 60 villages in survey 3), non-ITN = control villages in survey 1 and 2. LCI = lower 95% confidence limit, UCI = upper 95% confidence limit.

Health care–seeking behavior and morbidity. Seeking health care, including visiting a traditional healer, a health center/dispensary, or a market vendor in the last two weeks was strongly associated with lower mean Hb levels, regardless of whether treatment was received (Table 2). All of the reported signs and symptoms of illness were significantly associated with lower mean Hb levels. In multivariate analyses for households without ITNs, history of fever, pale body, weak body, diarrhea, and soil eating were all associated with lower mean Hb levels, but upper gastrointestinal symptoms were not (Table 3, model 2, non-ITN column). These parameters were also statistically significant in the multivariate model for ITN households (Table 3, model 2, ITN column). Further stratification of diarrheal illness showed that a history of bloody diarrhea was not significantly associated with Hb concentrations (mean Hb [95% CI] = −0.35 [−1.00, 0.30]), but there was a significant association with non-bloody diarrhea (−0.73 [−1.00, −0.47]) and watery diarrhea (−0.73 [−1.06, −0.39]). In addition, children who ate soil were more likely to be microcytemic (45.6%) than those who were not reported as eating soil (31.9%).

Clinical examination. Univariate models showed that documented fever, palpable spleen, WHZ, WAZ, HAZ, and MUAC for age Z-scores, and signs of kwashiorkor were all associated with mean Hb levels in both non-ITN and ITN households (Table 2). Of the four measured indicators of malnutrition, only HAZ and WHZ were considered in the multivariate modeling. Results from the multivariate models indicate that children who had concurrent fever and/or stunting had significantly lower mean Hb levels than children who did not exhibit these symptoms, for both non-ITN and ITN households (Table 3, model 3).

Laboratory results. Children with evidence of asexual malaria parasitemia had considerably lower mean Hb concentrations in both non-ITN and ITN villages (Table 2). Similarly, children with gametocytemia had lower mean Hb values than

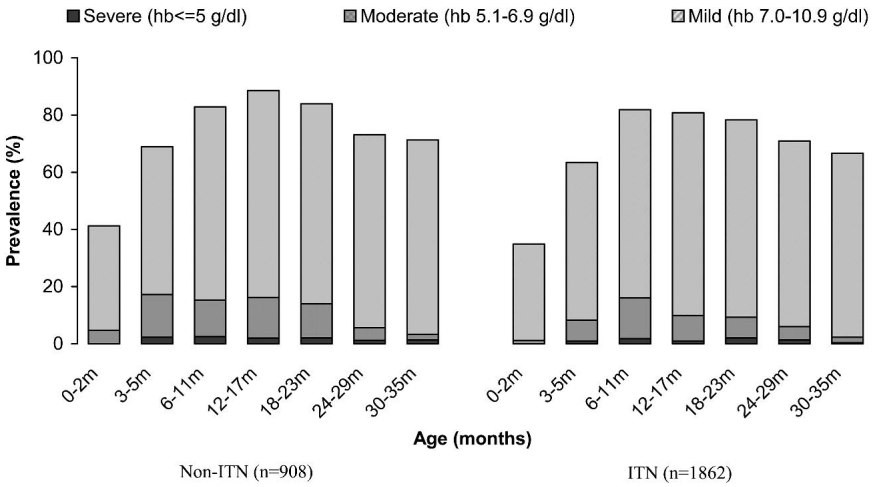

FIGURE 2. Prevalence of anemia by age and insecticide-treated bed net (ITN) status among 2,770 children < 36 months old enrolled in three cross-sectional surveys (February 1998–July 1999) in western Kenya. Hb = hemoglobin.

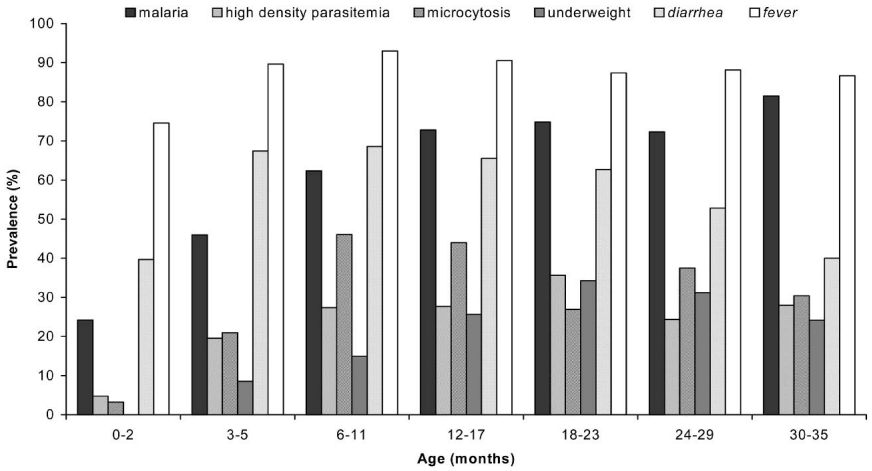

FIGURE 3. Prevalence of malaria parasitemia (any species and density), high-density parasitemia (>5,000/mm^3), microcytosis, underweight, history of diarrhea, and history of fever by age, among children in non-ITN villages in western Kenya. ITN = insecticide-treated bed net.

children without gametocytemia, even if there were no asexual parasites seen on the thick blood smear. Microcytosis was also associated with lower mean Hb levels.

The overall *P* value for the relationship between asexual parasite density and severe-to-moderate anemia was 0.27 and < 0.0001 in non-ITN and ITN villages, respectively. The odds of severe-to-moderate anemia increased with increasing parasite densities. This relationship was similar in ITN and non-ITN households. Of note was that even low parasite densities (between the 10th and 20th percentiles, or 65–352 parasites/mm^3) were associated with significantly increased odds of severe-to-moderate anemia (Figure 5) compared with those without parasitemia. This relationship was maintained when analysis was restricted to children less than 24 months old or 6–24 months old.

A previous study in eastern Kenya found that stunting increased the detrimental effect of malaria on Hb levels.[31] In our study, stunting (but not underweight status or wasting) was associated with a 1.87 greater odds of having malaria (95% CI = 1.25, 2.79), adjusting for survey number and age. However, our data did not confirm findings from eastern Kenya and showed that the malaria-associated decrease in mean Hb level was slightly greater in the non-stunted children (mean difference [95% CI] = –1.39g/dL [–1.70, –1.08]) than the stunted children (–0.76g/dL [–1.47, –0.05]; *P* = 0.12 in non-ITN villages). The malaria-associated decrease in mean Hb level was also greater in children who were not underweight (–1.45 [–1.75, –1.14]) than in underweight children (–0.60 [–1.27, 0.06]; *P* = 0.03). In ITN households, however, the malaria-associated decrease in Hb level was very similar between stunted and non-stunted children (*P* = 0.69) and underweight and non-underweight children (*P* for WAZ malaria = 0.90).

As expected, those with the HbAS phenotype had higher Hb levels than those with HbAA, and children with the HbSS phenotype had the lowest Hb concentrations (Table 2). Helminths were not associated with Hb levels at any density detected and in any age group. Previous studies have suggested that helminth infection may modify the severity of malaria-associated anemia.[32] Multivariate analysis indicated that the effect of malaria on mean Hb levels was not influenced by the presence of helminth infections (*P* for non-IT*N*

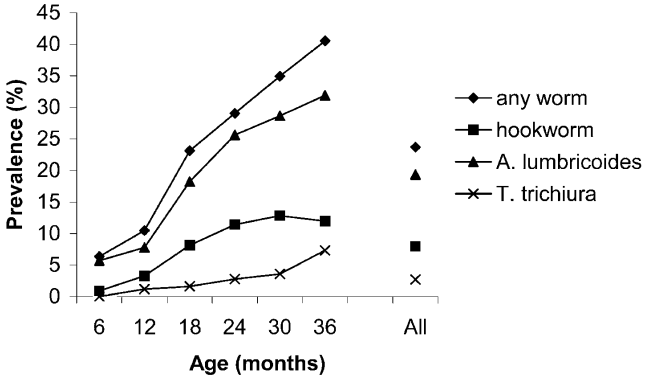

FIGURE 4. Prevalence of helminth infection by age in western Kenya. Data are for all children less than 36 months old (with or without an insecticide-treated bed net [ITN]) with a stool examination (n = 1,899). *Schistosoma mansoni* or *S. hematobium* were absent. Results did not differ by ITN status. A. = *Ascaris*; T. *Trichuris*.

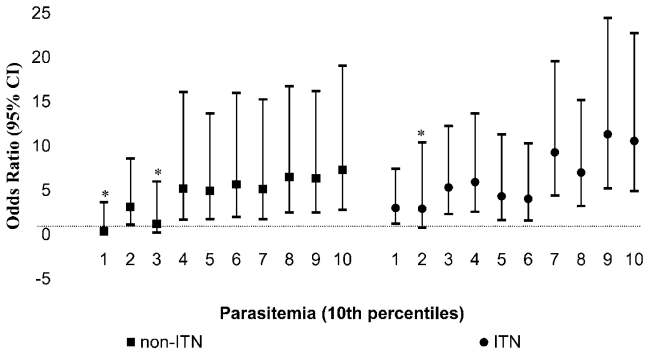

FIGURE 5. Odds ratios and 95% confidence limits (adjusted for survey number and age) for the association between parasite densities and severe to moderate anemia among children less than 36 months old in western Kenya. N = 898 for non-ITN and 1,818 for ITN households using negative parasitemia as the reference group. *n < 5, 10th percentiles: 1 (0–64); 2 (65–352); 3 (353–880); 4 (881–1,488); 5 (1,489–2,768), 6 (2,769–4,656), 7 (4,657–7,920), 8 (7,921–13,840), 9 (13,841–25,280), 10 (> 25,280). ITN = insecticide-treated bed net; CI = confidence interval.

= 0.23 and for ITN = 0.24, adjusted for age and HbS phenotype).

Overall model. The final linear regression model began with all factors that were shown to be significantly associated with Hb levels in the four multivariate models of the sociodemographic, history of illness and healthcare seeking, clinical examination, and laboratory classifications in non-ITN households (from Table 3, non-ITN column). The final model contains those variables that remained significant when all other variables, including age and survey number, were in the model. These were number of children less than five years old, history of fever, pale body, weak body, diarrhea, soil eating, axillary temperature ≥37.5°C, stunting, and presence of malaria parasitemia (Table 4).

DISCUSSION

Childhood anemia is a significant public health problem in this area of intense malaria transmission and high prevalence of malnutrition: 76.1% and 71% of children < 36 months old were anemic in households without ITNs and with ITNs, respectively, which is consistent with other published reports from sub-Saharan Africa[1,33] and a recent survey of anemia conducted among pre-school children in Kenya.[34] Our final model for parameters that were significantly associated with Hb concentrations contained a combination of direct indicators that could be assessed relatively easily during cross-sectional surveys, such as the cumulative history of illness in the previous two weeks (e.g., fever, diarrhea, soil eating) and the presence of malaria parasitemia, concurrent fever, and stunting. It also identified *del monyosore* and *del maraton'g*, two local terms for signs of general body weakness and the presence of body pallor as factors strongly associated with Hb concentrations, suggesting that caretakers were able to recognize severe-to-moderate anemia in their children.

Infants 0–2 months old had similar Hb concentrations as healthy reference children from developed countries,[27] but unlike in reference populations, Hb levels continued to decrease until the age of 9–10 months with little subsequent improvement. Approximately two-thirds of the infants 3–5 months old had become anemic, and 83% were anemic between 6 and 18 months of age. Thus, in this area most anemia is acquired from the age of two months onwards. Similar findings have been reported from cohort studies in this and other malaria-endemic areas.[16,35,36]

Although our cross-sectional design limits the interpretation of our findings, our previous studies implicate malaria and iron deficiency as the main causes of anemia in these young children.[5,6,37–39] Of note was that, in households without ITNs, almost half of infants 3–5 months old were infected with malaria. Infants in the first few months of life are partially protected against clinical malaria through a combination of reduced exposure to mosquito bites and physiologic (e.g., fetal HB), and immunologic factors such as the *in utero* transfer of maternal IgG antibodies and possibly sensitization of the fetus.[40,41] Our results and that from a concomitant birth cohort[5] indicate that this period of protection is short lived in this area with intense malaria transmission. Thus, malaria plays an important role in the etiology of childhood anemia from very early infancy onwards.

In addition, the contribution of iron deficiency is likely to increase from three months of age onwards. In non-ITN households, the prevalence of microcytosis was 3.2% in 0–2-month-old infants and increased to 21% and 45% among 3–5- and 6–18-month old children, respectively. More recent studies point to evidence that exclusively breastfed children in less developed countries are not protected from developing iron deficiency anemia within 4–6 months,[42–46] which is in contrast to earlier findings from observational studies suggesting that healthy term infants are usually born with adequate iron stores that last approximately six months, irrespective of the iron status of the mother.[47] The maternofetal unit is dependent on exogenous iron, and the level of iron stores is related to maternal iron status during pregnancy. This is consistent with observations from previous placebo controlled studies in children 2–36 months old, which indicate even 2–6-month-old infants with anemia benefited considerably from iron supplementation.[38,48]

As reported in more detail elsewhere, few children less than three months of age in these surveys were stunted or underweight, but the prevalence increased rapidly between 3 and 18 months of age and was highest among children who are 18–23 months old.[21] Stunting and underweight children had markedly lower Hb levels than their well-nourished counterparts. In addition, our data showed that stunted children were at greater risk of having malaria parasitemia than non-stunted children, similar to findings reported in a recent review.[49] Some studies have shown that anemia associated with malaria[31] or febrile/diarrheal illness[50] is more severe among stunted than non-stunted children, suggesting that stunting modifies the association between some infectious diseases and Hb concentrations. We, however, were unable to confirm this in the current study; the malaria-associated decrease in Hb in our study was slightly greater among non-stunted and non-underweight children than in stunted and underweight children, respectively, but only in the control villages and not in the ITN villages.

There was a clear relationship between parasite densities and Hb levels in all age groups. Among children living in households without ITNs, the odds of severe-to-moderate anemia were increased seven-fold in the highest parasite density group compared with children without parasitemia. However, we also found that even the very low density infections (10th–20th percentiles) were significantly associated with severe-to-moderate anemia (odds ratio [95% CI] = 3.11 [1.12, 8.61]). Low-density infections are very common in these areas of intense malaria transmission,[28] and either reflect chronic low-grade infections or the tail-end of what may have started as an acute high-density infection. Previous studies with longitudinal follow-up have also shown a significant impact of asymptomatic, chronic, low-density parasitemia on anemia,[35,37] implying that interventions limited to treatment of symptomatic, and often high-density malaria infections, are not sufficient. The significance of both low- and high-density parasitemia suggests that malaria control interventions that combine interventions that prevent infections, albeit incompletely, such as ITNs,[5,51,52] with interventions that treat and clear stealthy asymptomatic infections, such as intermittent preventive treatment, may have a greater impact on anemia than any of these interventions alone.

Of the long list of symptoms and signs collected in the morbidity questionnaire, a history of perceived fever was the most common symptom reported, and this was also strongly

associated with Hb levels. Similarly, more than half the children had a history of diarrheal episodes requiring treatment in the two weeks before the surveys, and this was also independently associated with lower Hb concentrations. Approximately one-third of children in the first three months of life had a history of diarrhea; the prevalence increased rapidly thereafter and remained high in 3–24-month-old children. We are not able to discern what proportion of diarrheal illness was a result of chronic versus acute episodes. Diarrheal illness is frequently reported among young children in developing settings such as western Kenya[53–55]; however, it is often viewed as an outcome on its own and not in association with anemia. Diarrheal illness is associated with loss of iron and decreased absorption of nutrients needed to maintain normal Hb status,[50] and chronic inflammation could possibly lead to a cytokine-mediated suppression of erythropoetin synthesis. In addition, when severe enough, diarrheal illness may result in wasting.[56] While specific pathogens were not determined in the current study, clinic-based surveillance conducted in this area between May 1997 and April 2001 implicated *Shigella*, *Campylobacter*, *Salmonella*, and *Vibrio cholera* species as predominant bacterial causes of diarrheal episodes in young children.[53,54] These studies did not test for non-bacterial pathogens, but noroviruses and rotaviruses are likely a common cause of diarrheal illness among young children in this area (Brooks J, unpublished data).

A recent survey conducted among 1,246 children 10–12 years old in 32 primary schools in this area reported a high prevalence of geohelminths (63%) and *S. mansoni* infection (16%).[57] Contrary to our expectations, our study found a low prevalence of helminth infections among pre-school children in this area: 8%, 2.7%, and 0.05% of the children had hookworm, *T. trichiuria*, and *S. mansoni*, respectively. Infection with *A. lumbricoides* was more prevalent (19.3%). However, in contrast to the significant association between helminth infection and anemia reported in other areas of Africa with a higher prevalence of helminths in pre-school children,[58,59] none of the helminth infections in our study were associated with anemia. Of interest in this respect is the high prevalence of soil-eating among pre-school children in our study sample (24%). Geophagy is very common among Luo women and children in western Kenya,[60–62] and a likely source of ascariasis and possibly trichuriasis, as well as dietary iron and zinc.[60,63] Geophageous children had considerably lower Hb concentrations and were more likely to be microcytemic than non-geophageous children, consistent with a previous longitudinal study in school age children in this area.[60] In our study, however, we did not find a significant association between infection with *A. lumbricoides* and soil eating.

As reported by others, several of the sociodemographic factors were associated with Hb levels, including educational level of the head of household and caretaker, socioeconomic status, and family size.[45,50,64–66] Of note, however, was that the variation in socioeconomic status was small in this community, where essentially every one is poor[23] and the observed differences in Hb levels were small, and not consistent between the surveys conducted in households with ITNs and those who did not yet receive ITNs.[23]

We have clearly not assessed all factors that could potentially be associated with Hb levels (and anemia), or interactions among them. For example, since all villages had been given ITNs by the time survey 3 was conducted, we were not able to directly assess the effect of ITNs on Hb levels. A myriad of studies, however, indicate the association of ITNs with anemia through reduction in the incidence of malaria parasitemia and fever.[4–6] In addition, we found a significant effect of malaria parasitemia even in the ITN villages, suggesting the occurrence of malaria-associated anemia even in the presence of ITNs. Furthermore, we were not able to assess biochemical markers of iron deficiency and thus provide a true prevalence of iron deficiency anemia in our study sample. Finally, some factors (e.g., palpable spleen) were not considered in the final multivariate model because they were not measured in all three surveys.

No inference about causality can be made from these cross-sectional survey data, and this study provides at best descriptive statistics of anemia as a public health problem in this area. Despite these limitations this study demonstrates that infants in this area have Hb concentrations similar to that of healthy reference populations in the first two months of life, but are at high risk of becoming severely anemic thereafter. The age of peak prevalence of malaria,[28,67] malnutrition,[21] and diarrhea overlap, placing children between 3 and 24 months of age at a particularly high risk of developing severe anemia. Human immunodeficiency virus status was not assessed in these surveys, but it is also known to contribute to anemia in infants in this area.[3] While malaria control in this population is well under its way, prevention of severe anemia will require prioritization of interventions that begin early in infancy and include a combination of malaria control, micronutrient supplementation, and possibly interventions, such as the Safe Water System,[55,68] to reduce diarrheal illness in these young children. Helminth control is not as important in this young age group.

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Authors' addresses: Meghna R. Desai, Penelope A. Phillips-Howard, Kathleen A. Wannemuehler, William A. Hawley, and Feiko O. ter Kuile, Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, 4770 Buford Highway NE, Mailstop F-22, Atlanta, GA 30341, E-mail: mdesai@cdc.gov. Dianne J. Terlouw, Department of Infectious Diseases, Tropical Medicine & AIDS, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands. Arthur M. Kwena, Department of Medical Biochemistry, Faculty of Health Sciences, Moi University, Eldoret, Kenya. Simon K. Kariuki, Amos Odhacha, and Ya Ping Shi, Center for Vector Biology and Control Research, Kenya Medical Research Institute, PO Box 1578, Kisumu, Kenya. Bernard L. Nahlen, Roll Back Malaria, World Health Organization, 1211 Geneva 27, Switzerland.

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