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CHARACTERISTICS OF SEVERE ANEMIA AND ITS ASSOCIATION WITH MALARIA IN YOUNG CHILDREN OF THE KASSENA-NANKANA DISTRICT OF NORTHERN GHANA

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Abstract. Severe anemia is thought to be the principal underlying cause of malaria death in areas of intense seasonal malaria transmission such as the Kassena-Nankana District of northern Ghana. Factors associated with severe anemia in young children, 6–24 months old, were elucidated by analyzing results of 2 malaria-associated anemia surveys (1996, 2000), separated by 4 years, but conducted in the same community and at the same seasonal time point. Age-adjusted comparison confirmed that the proportion of severely anemic children and overall mean hemoglobin (Hb) levels in the November 2000 sample were significantly improved over those of the 1996 sample (17.5 versus 26.4%, $P = 0.03$; Hb 7.5 versus 6.9 g/dL, $P = 0.002$). Weight-for-age Z-scores also indicated a significant improvement in the 2000 sample (−1.93 versus −2.20, $P < 0.05$). Independently, each survey identified statistically significant associations between severe anemia and age, parasite rate, fever, and sex. Relative to children with Hb ≥ 6.0 g/dL, those with severe anemia (Hb < 6.0 g/dL) were older, more frequently parasitemic (odds ratio [OR], 1.60; 95% confidence interval [CI], 1.08–2.35), more often febrile (OR, 2.44; 95% CI, 1.71–3.48), and predominantly male (OR, 1.50; 95% CI, 1.05–2.13). An association was identified in both surveys between severe anemia and residence in the northern part of the district, but no clear link was observed in relation to irrigation. Blood transfusions, a likely surrogate index of severe anemia in young children, followed a distinct seasonal pattern. Evidence suggests that dramatic peaks and troughs of severe anemia are regular and possibly predictable events that may be used to gauge the health and survival of young children in this area.

INTRODUCTION

Severe anemia may be the principal underlying cause of malaria death in areas of intense seasonal malaria transmission such as the holoendemic Kassena-Nankana District (KND) of northern Ghana.[1,2] A recent study of malaria-associated anemia there of young children 6–24 months old revealed that 22% of those sampled at the end of the wet season (November 1996), a time corresponding to agricultural and nutritional abundance, had hemoglobin (Hb) concentrations < 6.0 g/dL. In contrast, a survey of the same age cohort 6 months later at the end of the dry season, and at a time of dwindling food supply, found that only 1% of the children fell into this category of severe anemia.[2] With entomological inoculation rates in nonirrigated and irrigated sectors calculated to be, respectively, 72 and 800 infective bites per person-year (Binka FNB, unpublished data), and a clear pattern of malaria deaths that mirrored rainfall,[1] it was reasoned that anemia trends in this vulnerable age group were primarily influenced by the intensity of malaria transmission and that dramatic troughs and peaks of severe anemia are regular seasonal events.

The findings presented by Koram and others[2] suggest that naturally declining levels of malaria transmission, seen during 6 months of dry season, augmented only by their own progressive malaria immunity, enable most young Ghanaian children to stabilize and improve their Hb status. This reversal appears to occur without any recourse to improved diet, nutrient supplement, or anti-infective therapy. If this is the case, then proportions of young children with severe anemia, rather than proportions dying, might serve as a more conservative and accessible measure of malaria vaccine effect.

Toward this objective, we sought to elucidate factors associated with or influencing severe anemia in young children of this district by reexamining the previously collected data and by expanding the database with newly acquired results. We hypothesized that a repeat study of malaria-associated anemia of the same age groups and locations as previously studied, but at a time corresponding to the end of the 2000 wet season, would again show large numbers of young children with severe anemia. Relative to the cohort with noncritical Hb, we also hypothesized that severe anemia would be associated with parasitemia, higher parasite density, more febrile illness, and residence proximal to perennial breeding sites of anopheline mosquitoes. Owing to natural decline, by 6 months of maternally transferred protection,[3] and the greater vulnerability to infection that malnutrition, low birth weight, and stunting impart, we further expected that severe anemia might be more prevalent at the lower end of the 6–24-month range studied and would be associated with higher rates of parasitemia, greater parasite densities, more febrile illness, female sex, and low body weight for age.

MATERIALS AND METHODS

Subjects and informed consent process. The study site and population have been described in previously published reports.[1,2,4–7] As with previous studies, use was made of the Navrongo Demographic Surveillance System, a continually updated database that records virtually all births, deaths, and movements in the district's population of 140,000. An accurate name, age, and home location listing was made from this database of children aged 6–24 months on the first of November, 1996, and again in November 2000. Respective parents and community leaders were identified, contacted, and given a detailed explanation of the study plan. Informed parents wishing to have their children tested for malaria and Hb gave

their assent in writing or provided a thumbprint, then brought their infants to a central location for registration and testing.

Sample collection and screening. Children were assigned a study number on the basis of their consecutive order of appearance, and they were given a brief physical examination. Axillary temperature was recorded and temperatures ≥ 37.5°C were designated febrile. A sterile lancet was used to prick the heel or toe sufficient to make thick and thin blood films on a clean labeled slide. Approximately 5 μL additional blood was obtained for Hb determination by means of the Hemocue photometer (Leo Diagnostics, Helsinborg, Sweden). Hemoglobin readouts were transcribed into the child's record. Parents were informed when their child's Hb readout was < 6.0 g/dL, and treatment was initiated. On the bases of physical condition and Hb level, children were either administered daily treatment with orally administered ferrous sulfate solution or typed in preparation for transfusion by a malaria-free family member. In accordance with national health policy, orally administered chloroquine (25 mg/kg) was provided as first-line treatment for cases of uncomplicated clinical malaria. Malaria slides were stained with Giemsa and examined via high-power ×1,000 oil immersion microscopy for the presence of malaria parasites. Parasite species were identified by morphology, and parasite density per microliter of blood was estimated from counts per 200 white blood cells and an assumption of 8,000 leukocytes/μL. Three hundred thick-film fields were examined before assigning a negative malaria diagnosis.

Blood transfusion records. Daily record of blood transfusions performed in the single district hospital during the 18-month period October 1999 to March 2001 were evaluated as a complementary index of severe anemia in the district population. This activity recorded each recipient's name, address, age, sex, blood type, malaria status, and Hb level, as well as the identity and results of laboratory screening performed on donors.

RESULTS

Full data set comparisons between times and cohorts. Parental consent was provided nearly universally in both surveys. Severe anemia was significantly more prevalent at the time of the 1996 survey than in 2000 (22 versus 12.5%; $P < 0.0002$) (Table 1). The ages of children in both the Hb < 6.0 and Hb ≥ 6.0 cohorts of the 1996 survey were significantly greater than those of their respective 2000 cohorts ($P < 0.0001$), and mean Hb levels in these two 1996 cohorts were significantly lower ($P = 0.005$) than their 2000 counterparts. Moreover, significantly greater numbers of children overall (69.2 versus 57.1%, $P < 0.001$), as well as in the two Hb cohorts, were parasitemic in the 1996 survey. Analysis of each sample population subdivided into severely anemic (Hb < 6.0 g/dL), moderately anemic (Hb 6.0–7.9 g/dL), and normal (Hb ≥ 8.0 g/dL) groups, revealed that severely anemic children in both surveys were older (1996: 16.0 months versus 14.3 months, $P = 0.03$; 2000: 12.6 months versus 11.4 months, $P = 0.02$) and contained fewer girls than normal Hb groups (1996: 39.5 versus 53%, $P = 0.0002$; 2000: 38.7 versus 54%, $P = 0.01$). Relative to the normal Hb group, point prevalence of parasitemia was significantly higher in both the moderately ($P < 0.001$) and severely anemic ($P = 0.05$) children.

Age-stratified analysis. Figure 1, which plots the frequency distribution of ages sampled and proportions of severely anemic children by age, shows uniformity in sampling over age groups in 1996, and no indication of declining rates of severe anemia in the 18–24 month age range. The 2000 survey, in

TABLE 1

Characteristics of severe anemia (hemoglobin [Hb] < 6.0) and noncritical anemia (Hb > 6.0) among 2 populations of Ghanaian children, 6–24 months old, surveyed November 1996–November 2000†

Characteristic	November 1996		November 2000	
	Hb < 6.0 g/dL	Hb ≥ 6.0 g/dL	Hb < 6.0 g /dL	Hb ≥ 6.0 g/dL
Number (%)	75 (22.0)**	266	87 (12.5)**	608
Sex				
Male	45 (25.4)	132	51 (14.6)	299
Female	30 (18.3)	134	36 (10.4)	309
Age (mo) (mean ± SD)	16.0 ± 1.9**	15.0 ± 0.7**	12.8 ± 0.7**	12.0 ± 0.3**
Male	16.4 ± 1.5	15.3 ± 0.2	12.5 ± 1.0	12.1 ± 0.5
Female	15.4 ± 0.4	14.6 ± 0.9	13.8 ± 1.2	11.8 ± 0.5
Hemoglobin (g/dL) (mean ± SD)	4.8 ± 0.2**	7.8 ± 0.2**	5.2 ± 0.1**	8.2 ± 0.1**
Male	4.9 ± 0.3	7.8 ± 0.2	5.3 ± 0.2	8.1 ± 0.1
Female	4.8 ± 0.2	7.9 ± 0.2	5.1 ± 0.2	8.3 ± 0.1
Parasitemia, n (%)	55 (76.0)**	181 (68.0)**	49 (65.3)**	296 (55.9)**
Male	32/45 (71.1)	90/132 (68.2)	30/47 (63.8)	141/256 (55.1)
Female	23/30 (83.3)	91/134 (67.9)	19/28 (67.8)	155/273 (56.8)
GM parasitemia/μL (95% CI)	1288 (860–1928)	1106 (842–1452)	1644 (1062–2547)	1312 (1066–1614)
Male	1248 (737–2115)	904 (614–1330)	2203 (1202–4036)	1306 (955–1977)
Female	1345 (709–2551)	1349 (920–1977)	1037 (601–1791)	1315 (984–1758)
Febrile, n (%)	16/76 (21.0)*	22/265 (8.3)*	18/74 (24.3)*	62/528 (11.7)*
Febrile and parasitemic, n (%)	12/55 (21.8)*	15/181 (8.3)*	12/48 (25.0)*	39/295 (13.2)*
Male	7/32 (21.9)*	7/90 (7.8)*	7/30 (23.3)*	20/141 (14.2)*
Female	5/23 (21.7)*	8/91 (8.8)*	5/18 (27.8)*	19/154 (12.3)*
Weight (kg) (mean ± SD)	7.9 ± 0.3	8.0 ± 0.2	7.7 ± 0.3	7.6 ± 0.1
Male	8.2 ± 0.5*	8.3 ± 0.3	8.1 ± 0.4*	7.9 ± 0.1*
Female	7.4 ± 0.4*	7.6 ± 0.3	7.1 ± 0.4*	7.3 ± 0.1*

* Statistically significant differences between groups or cohorts within a survey.
** Statistically significant differences between surveys for a group or cohort.
† 95% CI = 95% confidence interval; GM = geometric mean parasitemia; Hb = hemoglobin.
SD = standard deviation.

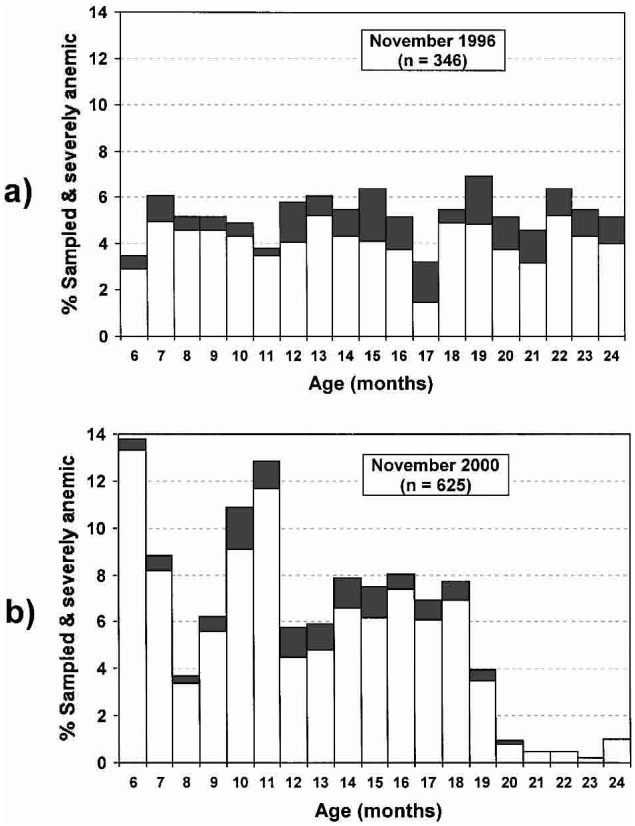

FIGURE 1. Comparative frequency distributions of ages sampled and the proportions of severely anemic (hemoglobin < 6.0 g/dL) children detected by age group in 2 community-wide surveys of malaria-associated anemia **(a)** November 1996 and **(b)** November 2000.

contrast, preferentially sampled the 6–11-month age range. Children aged 20–24 months, who comprised 27% of the 1996 sample and 29% of its severely anemic cohort, comprised only 3% of the 2000 survey. To determine whether this bias may have been responsible for differences between survey times, analysis was reapplied, but only to children 12–18 months of age in the 2 survey populations. This age-adjusted comparison confirmed that the proportion of severely anemic children and overall mean Hb levels in the November 2000 sample were significantly improved over those of the 1996 sample (26.4 versus 17.5%, $P = 0.03$; 6.9 versus 7.5 g/dL, $P = 0.002$). Differences between survey times for rates of parasitemia in children 12–18 months old (69.2 versus 57.1%) and the geometric mean (GM) parasitemia of those with patent infections were not statistically significant.

Comparisons between sexes. Despite uneven age-group sampling, nearly equal numbers of boys and girls were screened in the 2 surveys. Girls in both noncritical and severely anemic cohorts weighed significantly less ($P < 0.02$) than their male counterparts. Interestingly, boys accounted for the majority of severely anemic children in both surveys, a difference that attained statistical significance when each survey population was subdivided into severely anemic, moderately anemic, and normal cohorts or when the 2 study populations were combined (boys, 18.2% versus girls, 12.9%, $P = 0.02$). Figure 2, a paired frequency histogram of this combined population comparing proportions by age of severely anemic boys and girls, shows similar profiles and the suggestion of age relatedness; lowest proportions of severe anemia in boys and girls were measured in the younger, < 12-month age groups. A positive correlation between age and proportion with Hb < 6.0 g/dL in the combined 1996 and 2000 population of 6–19-month-olds attests to a stronger relationship in girls (boys, $r^2 = 0.04$; girls, $r^2 = 0.53$).

Effect of irrigation and sector of residence. Analysis of the 1996 and 2000 survey populations was stratified according to whether children lived in irrigated or nonirrigated communities of the KND. Children residing in irrigated communities accounted for 57% of the 1996 survey population but comprised only 29% of the 2000 sample ($P < 0.0001$). Unexpectedly, no statistically significant differences were seen between survey years in malaria point prevalence (66.2 versus 62.2%), frequency of severe anemia (19.9 versus 10.9%, $P = 0.11$), mean Hb levels (7.3 versus 7.7 g/dL), or GM parasitemia (891

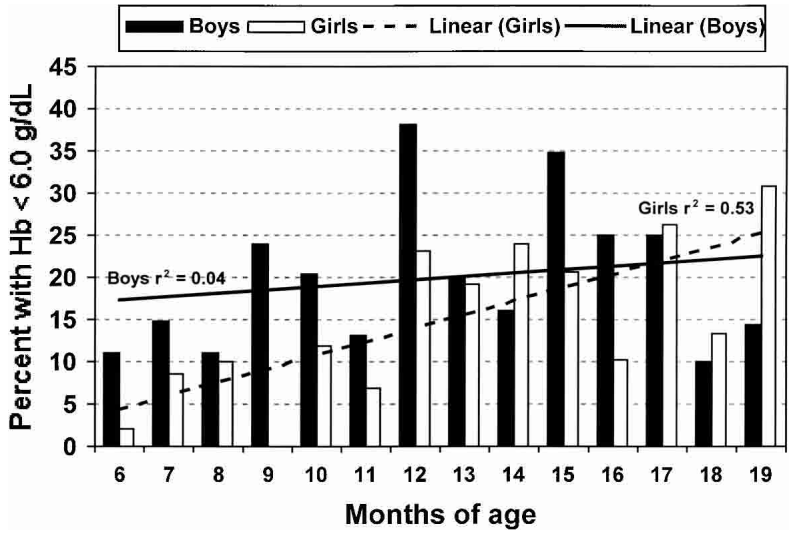

FIGURE 2. Paired frequency histogram of the combined 1996 and 2000 survey populations comparing proportions by age of severely anemic (hemoglobin < 6.0 g/dL) boys and girls 6–19 months old.

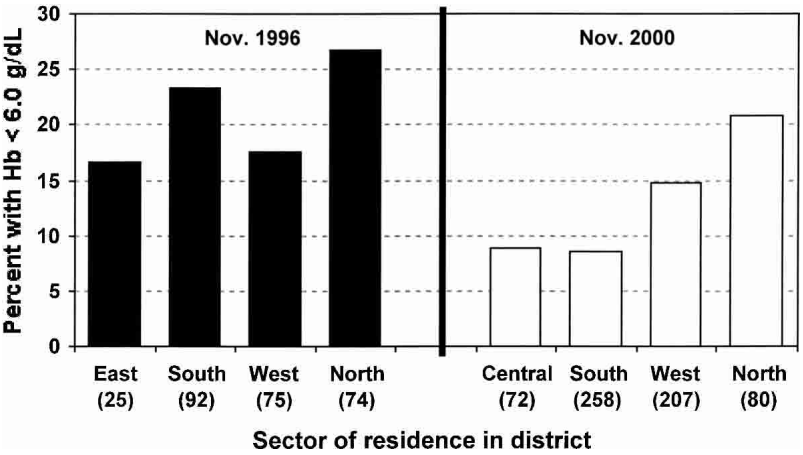

FIGURE 3. Point prevalence of severe anemia (hemoglobin < 6.0 g/dL) in young children according to geographic sector of residence within the Kassena-Nankana District, northern Ghana: comparison of 1996 and 2000 survey results.

versus 1,349/μL) of children living in irrigated communities. Significant differences were seen in comparing between 1996 and 2000 "nonirrigated" cohorts of children; the expected higher frequencies in 1996 of parasitemia (72 versus 54.5%, $P = 0.0003$) and severe anemia (25.3 versus 13.8%, $P = 0.05$), and the overall mean Hb level (7.0 versus 7.8 g/dL, $P < 0.05$). Analysis between the 1996 irrigated and nonirrigated cohorts revealed a significantly lower mean Hb level among severely anemic children of the irrigated cohort (4.6 versus 5.0 g/dL, $P = 0.03$) and significantly greater GM parasitemia among those of the nonirrigated cohort (1,549 versus 891/μL, $P = 0.02$). Measured characteristics of children in the November 2000 irrigated and nonirrigated cohorts were comparable.

Analysis by sector was performed to determine whether severe anemia and malaria infection in these children might be associated with residence in a particular geographic zone within the district (north, south, east, west, central). Consistent differences were seen between sectors in the prevalence of severe anemia, with highest levels in both surveys associated with residence in the north (Figure 3). Differences between zones in the prevalence of severe anemia were most pronounced and statistically significant in the 2000 survey. Mean Hb levels of severely anemic children did not differ appreciably among zones, but in both surveys, Hb levels for the larger cohorts of noncritical (Hb ≥ 6.0 g/dL) children followed the same zonal pattern seen with the severely anemic cohorts (Figure 4).

Blood transfusions as plausible marker of severe anemia. Figure 5, which plots the monthly numbers of transfusions in young children (age < 60 months) and rainfall, shows that most transfusions were to infants < 25 months old (381 of 485, 78.6%), and there was a distinctly seasonal pattern in the frequency of occurrence. The monthly transfusion profile during 2000 for children ≤ 2 years old appears to follow the very sharply demarcated period of rains, with transfusions peaking 1 month after the month of greatest rainfall. As with severe anemia, boys accounted for the majority of young children receiving transfusions (57.5%); the frequency of transfusion for young girls was significantly lower than that expected under conditions of equality (50 versus 42.5%, $P = 0.01$). There was no difference between sexes in the age and Hb levels of those receiving blood. Pairwise comparison by age between boys and girls (Figure 6) shows that the majority of transfusion recipients in both sexes were 5–12 months old and that relatively few children > 36 months old underwent transfusion.

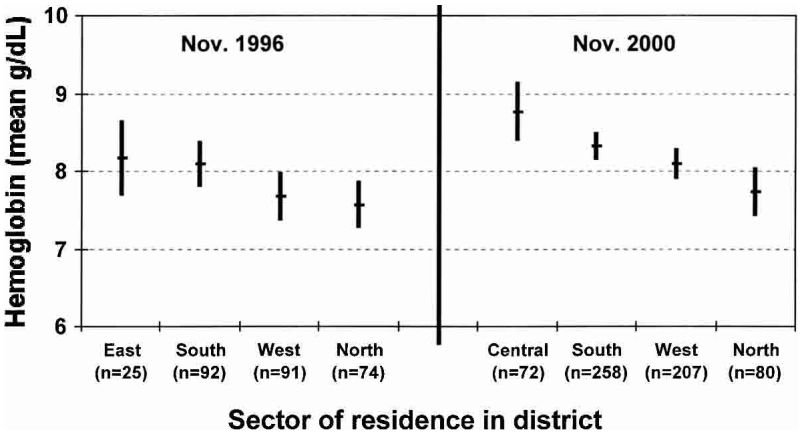

FIGURE 4. Mean hemoglobin levels in young, noncritically anemic (hemoglobin ≥ 6.0 g/dL) children according to geographic sector of residence within the Kassena-Nankana District, northern Ghana: comparison of 1996 and 2000 survey results.

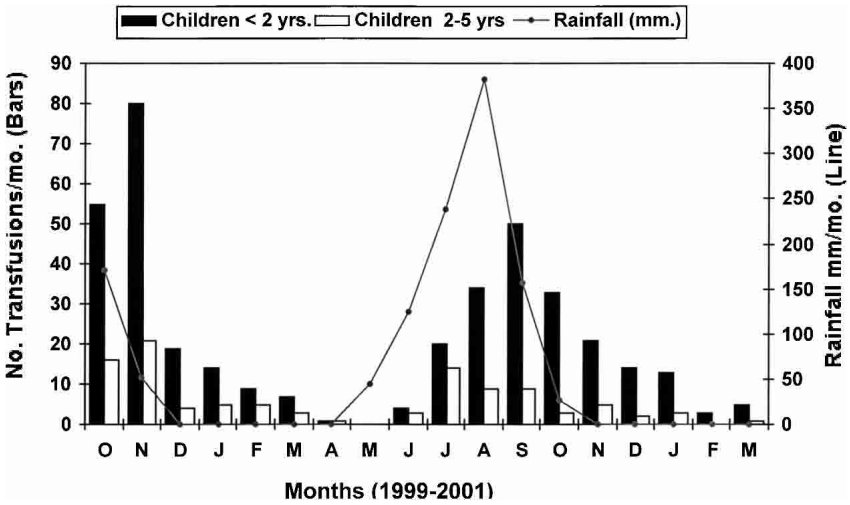

FIGURE 5. Monthly distribution of transfusions in children (0–5 years old) during October 1999–March 2001, separated by age ≤ 24 months **(shaded bars)** and 25–60 months **(open bars)**.

DISCUSSION

Two malaria-associated anemia surveys, separated by 4 years but conducted in the same community and at the same November time point corresponding to early dry season in the northern Ghana sahel, both document alarmingly high rates and levels of anemia in young children 6–24 months old. Independently, each survey identified associations between severe anemia and age, parasite rate, fever, and sex. Relative to children with Hb ≥ 6.0 g/dL, those with severe anemia were older, more frequently parasitemic, more often febrile, and predominantly male. Our initial hypotheses that severe anemia was associated with higher parasitemias was not borne out by analysis, nor was evidence obtained to suggest that severe anemia was associated with being younger, lower weight, or female.

Sampling bias was initially considered to be the major cause underlying differences between our studies. There was evidence from the 1996 study that severe anemia continued undiminished from 18 to 24 months, and beyond, but the 2000 population was not structured to sample these age groups and focused preferentially on children aged < 12 months, in whom severe anemia rates had been lower. The 1996 population had also been balanced in terms of children residing in irrigated and nonirrigated communities, whereas the 2000 population sampled predominantly children from nonirrigated compounds. However, even after correcting for age bias, differences remained highly significant, suggesting that rates of severe anemia, moderate anemia, and parasitemia may have improved from 1996. Monthly rainfall profiles for the KND show remarkable similarity over 20 years of recording, suggesting no aberrant pattern or volume as reasons for reduced malaria and anemia in 2000. In fact, total rainfall in 2000 exceeded that of 1996 and closely followed the classic profile of the 20-year average for the district. In this respect, the quality of rainfall, rather than its quantity, may have been decisive, because unusually heavy, infrequent rains may have disturbed anopheline populations in the KND far more than light, frequent rains. In addition, it is possible that widespread community participation in malaria research, such as the large vitamin A supplement trial[4] and bed net studies,[1,5–7] may have stimulated greater parental awareness and practice by November 2000. The 1996 Ghanaian Ministry of Health policy of free medical care and medicines for pregnant women and children < 5 years old also may have reduced malaria morbidity and mortality in children of the KND by November 2000.

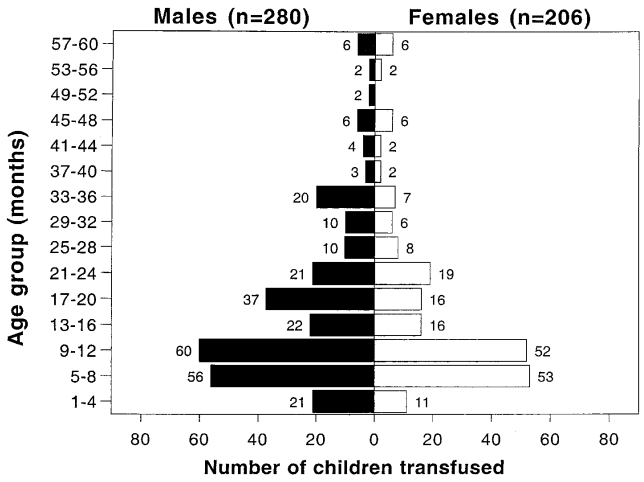

FIGURE 6. Pairwise comparison by age between boys and girls < 5 years old receiving at least one blood transfusion, for any reason, in the Kassena-Nankana District Hospital during October 1999–March 2001.

Twenty years of rainfall records show consistently that the July–August–September quarter is the high point of the KND wet season each year. Detailed studies in the KND have identified a corresponding pattern of child mortality in which rates increased 4-fold from April, the last month of dry season to August, the month of greatest rainfall. Rates of febrile illness and parasitemia, GM parasite densities, and mean Hb levels were similarly correlated with rainfall; infants 6–24 months old were most affected.[1] However, the regularity of the rainfall pattern does not translate over to an invariable pattern of malaria morbidity and death. Young children studied over a 3-year period in the KND experienced the highest death rates

in the first 2 years (1992 and 1993) during the July–September quarter. By contrast, the highest infant death rate during 1994 occurred in the early dry season quarter of October–December.[5] Blood transfusions performed on young children during 2 consecutive years appear to follow a pattern closely dictated by rainfall and malaria transmission. However, despite very comparable rainfall profiles in the 2 years, November stood out in 1999, as opposed to September in 2000, as the peak month for transfusions in children. We concede that other factors may account for a portion of the transfusions performed each month, but we believe that malaria-induced anemia is the dominant factor underlying transfusions in children. We further speculate that longitudinal profiling of infant deaths as well as rates of severe anemia would closely mirror the transfusion profile each year.

We obtained no evidence of positive or negative correlation between GM parasitemia and age, weight, or Hb in either individual or combined survey populations, but we did identify a weak negative correlation between age and Hb value and a statistically significant positive correlation between age and proportion of children with Hb < 6.0 g/dL. Previous study of children 0–5 years old at this location had reported a significant negative correlation between GM parasite density and Hb level.[5] This relationship was not apparent in our surveys and may have resulted from focusing on younger children of 6–24 months. Longitudinal study of Kenyan infants from birth also determined an association between concurrent parasitemia and lower mean Hb but required multiple slide readings over 90 days to show that significantly lower mean Hb levels were related to significantly higher mean parasite densities.[8]

We hypothesized that residence in an irrigated area would be a risk factor for malaria and severe anemia as a result of increased density of infective mosquitoes and perennial transmission, but no clear pattern of increased risk was apparent in our analysis. This result is suggestive of a uniform condition of malaria transmission over the entire KND, virtually equalizing irrigated and nonirrigated communities for a time—and hence our failure to detect any November differences between irrigated and nonirrigated cohorts. Alternatively, malaria transmission affecting young children in irrigated sectors may be so much more intense and regular as to induce an earlier, broader, and stronger immunity than that triggered only periodically by seasonal malaria in the nonirrigated sectors. Such an advantage in the irrigated cohort might originate from immediately protective higher titer maternal antibodies transferred during gestation and breast-feeding, fetal Hb, and subsequently from self-made cellular and humoral responses to a continuum of infections.[9–11] Although we failed to detect clear differences between irrigated and nonirrigated cohorts in either survey, we observed that anemia was more pronounced among children of the northern sector. Because this was seen in both surveys and manifested in multiple factors (proportions of severely anemic children, mean Hb levels among noncritical children), we consider these differences to be valid and suggestive of increased risk. Greater risk of severe anemia in the north may derive from 1) distance from medical treatment facility, 2) less effective or delayed protective immunity, or 3) nutritional and economic stress. On the bases of these initial observations, we hypothesize that differences between locations would be even more apparent during the truly dry months of December to March.

Although > 98% of our surveyed children fit the clinical definition of anemia (Hb < 11.0 g/dL) and 12.9% (75 of 581) of the parasitemias exceeded 10,000/μL, only 0.6% (6 of 945) fit the World Health Organization classification of severe malaria-associated anemia.[12] This low prevalence of severe malaria-associated anemia is in contrast with rates of 5.2% reported under conditions of fluctuating malaria in Malawi[13] and rates > 30% from areas of intense perennial transmission.[14,15] Notably, however, these high rates refer to predominantly male hospital admissions, whereas our rate is derived from a random cross-section of households with equal composition of boys and girls.

The unfortunate fact of household-level sex bias, which exists over much of the malarious world, is assumed to account for the reduced weight, health, and survival of infant girls and for the predominance of male hospital admissions for all causes.[13,16] For this reason, hospital-based studies are unsuited and unable to detect important natural differences between boys and girls. Following this rationale, we hypothesized a greater proportion and severity of anemia among infant girls and are impressed by random survey data indicating just the opposite. We speculate that the reduced nutritional state of girls renders them less capable or less suitable hosts for parasite superinfection and density-related pathology of these infections. The high nutritional demand that accompanies the faster growth of boys may disproportionately contribute to, or even worsen, their malaria-associated anemic condition over that of girls. Such protective mechanisms may compensate in a small way for the greatly increased risks of death that girls will later face from malaria in pregnancy.[17,18]

In summary, severe anemia in the northern Ghana sahel appears to be a regular and near-predictable seasonal event that is akin to a grim rite of passage for young children of rural Africa. Under starkly seasonal conditions that rigidly delimit malaria transmission, we identified high rates of severe anemia among boys and older children in the infant age group studied and obtained evidence associating anemia severity with residence in the northern sector of the KND. We believe that the daily record of blood transfusions performed at the district hospital is a simple, valuable index that reflects the intensity of malaria, malaria-associated anemia, and malaria death in this district. From recent demonstrations of success against the high level of severe malaria-associated anemia that occurs under conditions of continuous heavy transmission,[19–21] we advocate a similar attack against infant anemia as it occurs in the KND. This strategy, based on provision of orally administered iron syrup to mothers and simple presumptive treatment of young children with sulfadoxine-pyrimethamine therapy, both timed in accordance with childhood immunizations and given through the existing infrastructure of the World Health Organization Expanded Program of Immunization, could save and improve many young lives.

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