MAJOR ARTICLE

Sickle Cell Trait and the Risk of *Plasmodium falciparum* Malaria and Other Childhood Diseases

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Background. The gene for sickle hemoglobin (HbS) is a prime example of natural selection. It is generally believed that its current prevalence in many tropical populations reflects selection for the carrier form (sickle cell trait [HbAS]) through a survival advantage against death from malaria. Nevertheless, >50 years after this hypothesis was first proposed, the epidemiological description of the relationships between HbAS, malaria, and other common causes of child mortality remains incomplete.

Methods. We studied the incidence of falciparum malaria and other childhood diseases in 2 cohorts of children living on the coast of Kenya.

Results. The protective effect of HbAS was remarkably specific for falciparum malaria, having no significant impact on any other disease. HbAS had no effect on the prevalence of symptomless parasitemia but was 50% protective against mild clinical malaria, 75% protective against admission to the hospital for malaria, and almost 90% protective against severe or complicated malaria. The effect of HbAS on episodes of clinical malaria was mirrored in its effect on parasite densities during such episodes.

Conclusions. The present data are useful in that they confirm the mechanisms by which HbAS confers protection against malaria and shed light on the relationships between HbAS, malaria, and other childhood diseases.

Malaria causes >200 million episodes of febrile illness and >1 million deaths every year in young children living in sub-Saharan Africa [1, 2]. The factors determining which children die and which survive are complex, but they are likely related to both the host and the parasite. Of the host-specific factors, the sickle cell trait (HbAS) remains the best described [3], having been shown to confer strong protection against *Plasmodium falciparum* malaria in numerous studies conducted in various countries over the course of >50 years [4–10]; nevertheless, the protective mechanisms at work remain incompletely understood. A number have been proposed, including reduced parasite growth [11, 12] and enhanced removal of parasitized cells through innate [13, 14] or acquired [15–18] immune processes; however, which are relevant in vivo and whether *P. falciparum* is the only selective agent remain unknown.

Of the many epidemiological studies conducted to date, most have had shortcomings; the majority have been small or cross-sectional and have provided only limited data on the prevalence of *P. falciparum* [19]. Case-control studies have focused on malaria and have provided few data on other diseases [4–7]. In addition, of the few cohort studies that have been conducted, none have provided data on falciparum malaria over its full range of clinical manifestations, and few have provided data on nonmalarial diseases [7, 15, 16, 20]. Therefore, with a view to filling in some of these gaps, we conducted 2 large cohort studies involving a total of >3000 children. These studies show the absence of any significant effect of HbAS on a wide range of childhood diseases and illustrate the specificity of protection against falciparum malaria.

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PARTICIPANTS, MATERIALS, AND METHODS

Study design. As outlined below, we conducted 2 studies that investigated the effect of HbAS on falciparum malaria and other childhood diseases, on the basis of clinical observations made in 2 cohorts of children living on the coast of Kenya.

Mild-disease cohort study. The design of this study has been described in detail elsewhere [21, 22]. In brief, in September 1998, a cohort of 800 children and adults was recruited in the Ngerenya area of Kilifi District. This cohort was followed for clinical events by weekly active surveillance until August 2001. In addition, we tracked intercurrent clinical events at a dedicated research outpatient clinic. Children born into study households were recruited at birth. Participants exited the study if informed consent was withdrawn, if they moved out of the study area for >2 months, or if they died. During this interval, we conducted 4 cross-sectional surveys to assess the prevalence of *P. falciparum*. For the purpose of the present analysis, children were censored on their fifth birthday; this analysis includes 323 children who were <5 years old for >1 week during the study period.

Birth cohort study. This study, which formed the basis of a randomized, controlled community trial of insecticide-impregnated bed nets, was conducted as described elsewhere [23–25]. In brief, all children born within a defined rural study area (to the north of Kilifi District Hospital [KDH]) between May 1992 and April 1995 were recruited into a fixed birth cohort through a system of demographic surveillance involving visits every 6 weeks, by which all births, deaths, and migration events were recorded. Between May 1992 and December 1997, members of this cohort were identified on admission to the pediatric ward at KDH, the hospital facility closest to the study area. Routine collection of blood samples was not part of the original study; however, between May and October 2000, 2695 resident surviving members of the cohort were identified and were invited to provide a blood sample for hemoglobin genotyping. Genotyping was successfully completed for 2655 children.

Clinical definitions. For both studies, at the time of presentation, a trained clinician who had access to appropriate clinical and laboratory tests obtained a detailed clinical history, conducted an examination, and recorded the results. Comorbid presentations were common in both studies, and the clinician could record up to 3 diagnoses for each child; however, for the purpose of the present analysis, we considered only the primary diagnoses leading to consultation or admission. We defined malaria in a number of ways. For the mild-disease cohort study, we defined symptomless parasitemia as a slide positive for *P. falciparum* in the absence of fever or other symptoms of clinical illness. For mild clinical malaria, we used 3 different definitions. Definition 1 was based on the diagnosis made by the trained clinician without the constraint of specific clinical or laboratory features; definition 2 was based on fever (axillary temperature of >37.50°C) in conjunction with a slide positive for blood-stage asexual *P. falciparum* at any parasite density (regardless of the age of the child); and definition 3 was based on fever in conjunction with a slide positive for blood-stage asexual *P. falciparum* at any parasite density for children <1 year old and at a parasite density of >2500 parasites/μL for children $\geqslant$1 year old. Definition 3 was derived by multiple logistic regression methods, as described elsewhere [26], and accords with both a sensitivity and a specificity for clinical malaria of >85% in both subjects with HbAA and those with HbAS (T.W.M., unpublished data). On admission to the hospital, malaria was considered to be the primary diagnosis if *P. falciparum* was found in the peripheral blood and if other likely causes of clinical presentation could be excluded. The following definitions (which are modifications of those described elsewhere [27]) were used for severe malaria: (1) coma—the inability to localize a painful stimulus, assessed >1 h after a seizure or the administration of anticonvulsants and after correction of hypoglycemia; (2) prostration—the inability to breast-feed or sit without assistance; (3) multiple seizures—2 or more seizures within 24 h of admission; (4) severe malarial anemia—hemoglobin level of <5.0 g/dL in association with a parasite density of >10,000 parasites/μL; and (5) hyperparasitemia—an episode of malaria in which >20% of red blood cells are infected with *P. falciparum*. Upper respiratory tract infection was diagnosed in children whose principal symptoms were characterized by choryza or pharyngitis and who had no other features of malaria. Acute lower respiratory tract infection was diagnosed in children who fulfilled the World Health Organization clinical criteria for pneumonia [28] if tests and the subsequent clinical course of disease supported this diagnosis. Gastroenteritis was defined as diarrhea (3 or more watery stools/day) with or without vomiting (3 or more episodes/day). In the mild-disease cohort study, slide-negative fever was defined as an axillary temperature of >37.50°C in a child whose slide was negative for *P. falciparum* and who had not received treatment with an antimalarial drug within the preceding 21 days; this definition took no account of the primary or secondary diagnosis and, therefore, encapsulated febrile episodes of a range of nonmalarial causes. Fever of unknown cause was a diagnosis of exclusion and was allocated to children whose slide was negative for *P. falciparum* and whose fever had no obvious etiology. Helminth infection was diagnosed in children who had a history of passing worms of any species, and skin infection was diagnosed in children who presented with a range of dermatological conditions, including scabies, boils, and impetigo. In the birth cohort study, malnutrition was diagnosed in children whose weight-for-height or weight-for-age was <70% or <60%, respectively, of the US National Center for Health Statistics reference medians or who had signs of marasmus or kwashiorkor. Nonmalarial anemia was

Table 1. Incidence of mild clinical malaria and other diseases, by hemoglobin genotype.

Diagnosis,[a] hemoglobin genotype	No. of episodes	Incidence (no. of episodes/cyfu)	IRR (95% CI)	*P*
All diagnoses				
AA	3782	9.68	1	
AS	482	7.70	0.79 (0.60–1.04)	.097
Nonmalaria				
Upper respiratory tract infection				
AA	1027	2.63	1	
AS	139	2.27	0.84 (0.63–1.13)	.243
Lower respiratory tract infection				
AA	424	1.09	1	
AS	66	1.08	0.99 (0.67–1.46)	.953
Gastroenteritis				
AA	406	1.04	1	
AS	72	1.17	1.19 (0.77–1.82)	.431
Skin infection				
AA	418	1.07	1	
AS	66	1.08	0.96 (0.63–1.47)	.850
Fever of unknown cause				
AA	197	0.50	1	
AS	21	0.34	0.70 (0.41–1.19)	.185
Helminth infection				
AA	115	0.29	1	
AS	15	0.24	0.81 (0.44–1.48)	.489
Slide-negative fever[b]				
AA	558	1.42	1	
AS	81	1.32	1.02 (0.84–1.26)	.780
Malaria				
Definition 1				
AA	1195	3.06	1	
AS	93	1.52	0.49 (0.33–0.74)	<.001
Definition 2[c]				
AA	872	2.22	1	
AS	79	1.28	0.55 (0.37–0.81)	.003
Definition 3[c]				
AA	531	1.35	1	
AS	43	0.70	0.49 (0.32–0.75)	.001

NOTE. Episodes of mild clinical malaria were identified at the study outpatient clinic during the mild-disease cohort study. Diagnoses represent those recorded as either the primary or secondary diagnoses at each visit by the consulting clinician. The data on sickle cell trait (HbAS) were collected from 40 children during 61.3 child-years of follow-up (cyfu), and the data on HbAA were collected from 283 children during 390.6 cyfu. The incidence rate ratios (IRRs) were calculated using Poisson regression models that included each diagnosis separately as the dependent variables and the explanatory variables hemoglobin genotype, age (as a continuous variable), sex, season (defined in 3-month blocks), and ethnic group. The 95% confidence intervals (CIs) and *P* values were adjusted to account for the potential clustering of events within individual study children by use of the sandwich estimator [29].

[a] See Participants, Materials, and Methods for clinical definitions of the diseases.
[b] Children may be represented under other nonmalarial diagnostic categories.
[c] Children may be represented under other malaria-specific diagnostic categories.

diagnosed in children who presented with a hemoglobin level of <5.0 g/dL and without evidence of malarial infection.

Laboratory procedures. Blood films were stained and examined for *P. falciparum* by standard methods. Parasite densities were recorded as a ratio of parasites to white blood cells or, for heavier infections, to red blood cells. Densities (number of parasites per microliter of whole blood) were calculated with data from full hematological assessments, if available, or, if not, on the assumption of a white blood cell count of 8×10^3 cells/μL or a red blood cell count of 5×10^6 cells/μL. Hemoglobin genotypes were characterized by electrophoresis.

Statistical analysis. Odds ratios (ORs) for the prevalence of symptomless parasitemia in children with HbAS versus children with HbAA were derived by both univariate and multivariate logistic regression analysis. Multivariate analyses included age and season (defined in 3-month blocks). We accounted for

the potential clustering of symptomless-parasitemia events within individual study children by using the sandwich estimator (as described by Armitage et al. [29]), which inflates confidence intervals (CIs) and adjusts *P* values as appropriate. Log-transformed parasite densities in *P. falciparum*–positive children with HbAA and those with HbAS were compared within each clinical classification by linear regression analysis, with adjustment for within-participant clustering of events and both with and without adjustment for the confounding variables age, proximity to the nearest health center, and season. We derived incidence rate ratios (IRRs) for malaria and other diseases in children with HbAS versus those with HbAA within each cohort separately, using Poisson regression. For both cohort studies, our final models included the following explanatory variables: hemoglobin genotype, age (as a continuous variable), sex, season, and ethnic group. For the birth cohort study, we also adjusted for bed-net usage (by randomization arm), proximity to the nearest health center, and access to the hospital by bus. We used the likelihood ratio test to assess interactions between explanatory variables, as appropriate; no significant interactions were found. For the purpose of the present analysis, children in the mild-disease cohort were considered not to be at risk for malaria (and were omitted from both the numerator and denominator populations) for 21 days after receiving treatment with an antimalarial drug. All children were censored on their fifth birthday. In all of our analyses, we controlled for the duration of follow-up of study children. All analyses were conducted by use of STATA (version 8.0; Timberlake).

Permission with respect to ethics was granted for both studies by the Kenya Medical Research Institute National Ethical Review Committee. Written, informed consent was provided by all study participants or their parents.

RESULTS

In the mild-disease cohort study, 4254 clinic visits were made by 323 children during 451.9 child-years of follow-up (cyfu). The following 7 diagnoses accounted for >90% of the consultations: mild clinical malaria (definition 1) (1288/4254 [30%]), upper respiratory tract infection (1168/4254 [27%]), skin infection (571/4254 [13%]), lower respiratory tract infection (539/4254 [13%]), gastroenteritis (478/4254 [11%]), fever of unknown cause (244/4254 [6%]), and helminth infection (170/4254 [4%]). The numbers of children who received other diagnoses were too few to permit meaningful comparisons. Only 1 child died, a participant with HbAA who had been suffering from malnutrition. In the birth cohort study, a total of 1145 hospital admissions were recorded among 2655 children during 10,381 cyfu. Malaria (561/1145 [49%]), lower respiratory tract infection (310/1145 [27%]), and gastroenteritis (91/1145 [8%]) accounted for 84% of all admissions. Of the 561 children with malaria, 197 (35%) showed 1 or more signs of severity. Of the 197 episodes, 182 (92%) could be defined according to 1 of 3 categories: cerebral malaria, severe malarial anemia with >10,000 parasites/μL, and malaria with convulsions (2 or more seizures during the previous 24 h). The numbers of children admitted with other diagnoses or malarial syndromes were too few to permit meaningful comparisons. Because the hemoglobin genotyping for this cohort was conducted at the end of the study, it was not possible to investigate the contribution of genotype to death. No children with sickle cell disease (HbSS) were detected in the mild-disease cohort, but 3 children with HbSS were detected in the birth cohort. None of these children were admitted to the hospital during the study period.

HbAS and the risk of malaria. We found no evidence for any effect of HbAS on the prevalence of symptomless parasitemia: the prevalence during the 4 cross-sectional surveys combined was 95 (14.8%) of 643 in children with HbAA and 13 (14.4%) of 90 in children with HbAS (adjusted OR, 0.96 [95% CI, 0.44–2.07]); $P = .91$). However, both the incidence of mild clinical malaria in the community and of hospital admission for severe malaria were significantly lower in children with HbAS than in children with HbAA, the degree of protection being roughly twice as great for the latter than the former (tables 1 and 2). HbAS was associated with a similar degree of protection against mild clinical malaria for each of the 3 definitions considered (table 1). Conversely, in the case of hospital admissions for malaria, HbAS was in general associated with increasing protection against episodes of increasing severity: although the incidence of all admissions for malaria was reduced by 75%, the incidence of admissions for cerebral malaria was reduced by 86%, and the incidence of admissions for severe malarial anemia was reduced by almost 90% (table 2).

Parasite densities during incident events. We found no significant effect of HbAS on geometric mean densities of *P. falciparum* parasites during episodes of symptomless parasitemia, either before or after adjustment for the effects of age, proximity to the nearest health center, and season (ratio, 1.27 [95% CI, 0.28–5.89]; $P = .747$). However, parasite densities were significantly lower during episodes of both mild clinical malaria (ratio, 0.49 [95% CI, 0.29–0.83]; $P = .009$) and severe malaria that required a child to be admitted to the hospital (ratio, 0.23 [95% CI, 0.10–0.52]; $P < .0001$) (figure 1).

Nonmalarial diseases. We found no significant associations between HbAS and the incidence of any other diseases, whether detected at the outpatient clinic or on hospital admission (tables 1 and 2). Of particular note, in the mild-disease cohort study, we saw no effect of HbAS on the incidence of documented febrile episodes (of any cause) in the absence of malaria (IRR, 1.02 [95% CI, 0.84–1.26]; $P = .78$) or on the incidence of upper or lower respiratory tract infections. The low IRRs for admission to the hospital for gastroenteritis (IRR,

Table 2. Incidence of hospitalization for malaria and other diseases, by hemoglobin genotype.

Diagnosis,[a] hemoglobin genotype	No. of episodes	Incidence (no. of episodes/1000 cyfu)	IRR (95% CI)	*P*
Nonmalaria				
All nonmalaria				
AA	512	57.83	1	
AS	72	47.72	0.84 (0.60–1.17)	.289
Lower respiratory tract infection				
AA	271	30.55	1	
AS	43	28.50	0.96 (0.63–1.46)	.857
Gastroenteritis				
AA	83	9.36	1	
AS	8	5.30	0.59 (0.28–1.21)	.150
Malnutrition				
AA	11	1.24	1	
AS	2	1.33	1.14 (0.17–7.56)	.895
Accidents				
AA	24	2.70	1	
AS	4	2.65	0.94 (0.31–2.88)	.916
Severe anemia without malarial parasites				
AA	18	2.01	1	
AS	1	0.66	0.35 (0.05–2.59)	.302
Malaria				
All malaria				
AA	536	60.42	1	
AS	25	16.57	0.25 (0.16–0.39)	<.0001
All severe malaria				
AA	191	21.53	1	
AS	6	3.98	0.17 (0.07–0.40)	<.0001
Cerebral malaria[b]				
AA	34	3.83	1	
AS	1	0.66	0.14 (0.02–1.17)	.070
Severe malarial anemia with >10,000 parasites/μL[b]				
AA	48	5.41	1	
AS	1	0.66	0.11 (0.01–0.97)	.047
Malaria with convulsions (2 or more seizures during the previous 24 h)[b]				
AA	94	10.60	1	
AS	4	2.65	0.23 (0.08–0.67)	.007

NOTE. Admissions to the pediatric ward at Kilifi District Hospital were identified through the birth cohort study. The data on sickle cell trait (HbAS) were collected from 384 children during 1509.9 child-years of follow-up (cyfu), and the data on HbAA were collected from 2271 children during 8871.4 cyfu. Incidence rate ratios (IRRs) were calculated by Poisson regression analysis as described in table 1 but with the additional explanatory variables bed-net usage (by randomization arm), proximity to the nearest health center, and access to the hospital by bus.

[a] See Participants, Materials, and Methods for clinical definitions of the diseases.

[b] These 3 categories are mutually exclusive; the hierarchy for classification was cerebral malaria, severe malarial anemia, and then malaria with convulsions.

0.59) and severe anemia without malarial parasites (IRR, 0.35) were based on very few observations, and neither reached statistical significance (table 2).

DISCUSSION

The protective effect of HbAS against falciparum malaria has been the subject of speculation and debate for >50 years. After early scepticism [30, 31, 32], it is now widely accepted that the most likely explanation for the current frequencies of HbAS in many tropical populations is selection by *P. falciparum;* however, the epidemiological evidence supporting this conclusion remains incomplete. For example, although the available data suggest that HbAS confers greater protection against severe forms of malaria than against mild forms, these data are difficult to interpret, because they originate from many studies that investigated limited aspects of falciparum malaria and that were conducted in areas of varying transmission (reviewed in Roberts et al. [19]). Moreover, very few studies have investigated the degree to which the protection conferred by HbAS is specific to malaria. These issues are important, not only because they may be informative

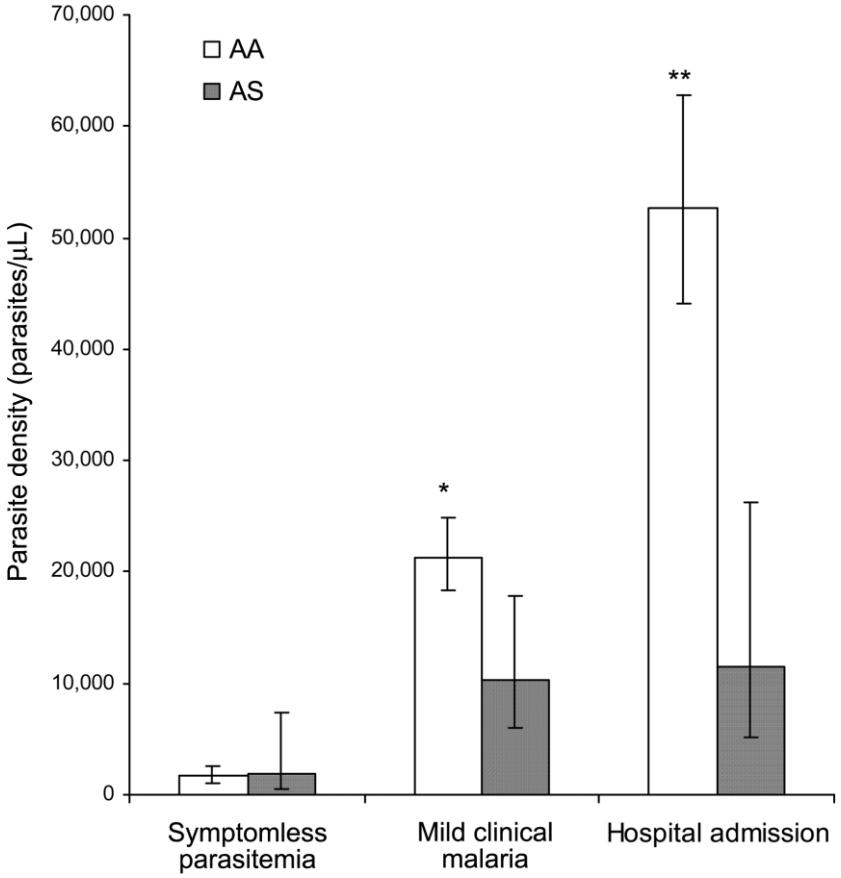

Figure 1. Geometric mean parasite densities, by clinical status and hemoglobin genotype (bars show 95% confidence intervals). The data on symptomless parasitemia derive from 4 cross-sectional surveys conducted in children participating in the mild-disease cohort study ($n = 13$ children with sickle cell trait [HbAS]; $n = 95$ children with HbAA). The data on mild clinical malaria derive from episodes of malaria detected during the same study (with mild clinical malaria defined as fever [axillary temperature of >37.50°C] in association with a slide positive for blood-stage asexual *Plasmodium falciparum* at any density [definition 2 as given in Participants, Materials, and Methods]); the data on HbAA reflect 872 episodes of malaria in 283 children, and the data on HbAS reflect 79 episodes of malaria in 40 children. The data on hospital admissions derive from participants in the birth cohort study who were admitted to the hospital with a primary diagnosis of malaria. The data on HbAA reflect 538 episodes of malaria in 424 children, and the data on HbAS reflect 25 episodes of malaria in 23 children. Comparisons were made by linear regression, with adjustment for the effects of age, season, and clustering of events within individual study children. In addition, the data on hospital admission were adjusted for bed-net usage (by randomization arm), proximity to the nearest health center, and access to the hospital by bus. $^{*}P = .009$; $^{**}P < .0001$.

with respect to the mechanisms by which HbAS confers protection against malaria, but because they may help us to better understand the relationships between HbAS, malaria, and other childhood diseases. It was for these reasons that we conducted the 2 large cohort studies described in this article.

In agreement with the findings of most other studies, we found no evidence that HbAS protects against symptomless parasitemia, in terms of either prevalence or parasite density. However, HbAS was 50% protective against mild clinical malaria, and parasite densities during such episodes were significantly lower in children with HbAS than in those with HbAA. Protection reached 75% against hospital admission for falciparum malaria and almost 90% against severe malarial episodes. Two observations were particularly striking: first, of the children admitted to the hospital for falciparum malaria, those with HbAS had parasite densities >4-fold lower than those with HbAA; and second, the protective effect of HbAS was equally strong against the 2 most common forms of severe malaria—cerebral malaria and severe malarial anemia. These observations support the concept that HbAS confers protection against severe malaria by limiting disease progression: infections less often progress to the point at which either symptoms are evident (mild disease) or complications ensue (severe disease). This could equally be mediated by the reduced ability of parasites to grow and multiply in HbAS cells [11, 12] or by their early removal from the circulation. A number of mechanisms have been proposed for the latter. First, parasite-infected HbAS erythrocytes have been shown to sickle 6 times more readily than nonparasitized HbAS cells [33, 34], a phenomenon that may lead to intracellular parasite death [35] and/or their enhanced removal

by the immune system. Although the latter may be largely the result of innate immunity [14, 36, 37], recent data have suggested that acquired immunity may also be involved [15–18]. Which of these processes are relevant in vivo and what their relative contributions to conferring protection against malaria might be remain to be determined.

The lack of any measurable effect of HbAS on most other childhood diseases observed in the present analysis is interesting. Although HbAS has no appreciable impact on health in developed countries [38], we expected to find some impact on other childhood diseases in our cohorts, for a number of reasons. First, in many tropical settings, it can be difficult to differentiate among the common causes of childhood diseases on the basis of clinical criteria alone. For example, respiratory distress is a common feature in children with pneumonia, malaria, and other severe illnesses, and, therefore, differentiating among such diseases can be difficult in areas in which a large proportion of children are parasitemic [39, 40]. Even if the effect of HbAS were absolutely specific to malaria, we would still have expected a less clear-cut result simply because of some degree of misclassification. Second, we thought that HbAS might result in wider health benefits via a reduction in the sequelae of malarial infections. For example, malaria is a recognized cause of malnutrition [22, 41–43], which in turn is a major determinant of disease susceptibility [44, 45]. Similarly, malaria might enhance the severity of other comorbid infectious diseases via direct effects, such as immune suppression, or via enhancement of bacterial invasion [46]. Indeed, in a number of well-documented cases, effective malaria-control programs have lead to reductions in mortality several fold higher than what was expected on the basis of prior estimates of malaria-specific mortality [47–51], and estimates of the differential mortality required to explain the current prevalence of the HbS gene are also significantly greater than those attributed to malaria alone [46]. However, in both of these cases, it is impossible to determine the relative contributions of factors such as misclassification, potentiation of comorbid events, the nonspecificity of malaria control interventions, and genetic effects.

Despite these considerations, we found that the protection conferred by HbAS was strikingly specific to falciparum malaria. If endemic malaria really has a nonspecific impact on all-cause mortality, why was this not reflected by reductions in 1 or more categories of common nonmalarial events? Two explanations seem plausible. The first explanation is that the pathophysiological processes that result in death are largely silent and do not give rise to well-circumscribed clinical presentations. Two processes seem most likely in this regard: anemia and invasive bacterial disease.

Anemia is a common sequela of malarial infections but is often clinically silent [52, 53]. As such, it likely makes a large but hidden contribution to overall mortality due to malaria, especially in young children [52]. The pathogenesis of malaria-related anemia is multifactorial, involving both bone-marrow suppression and acute hemolysis [52, 54]. Mortality is greatest when anemia is severe (<5 g/dL hemoglobin) and is complicated by other signs of severity [55]. Two factors correlate best with the development of severe anemia: hemoglobin level preceding the malaria transmission season and the parasite density achieved during incident infection [56]. It seems likely that children with HbAS enjoy a double advantage in this regard: first, because they suffer fewer clinical attacks of malaria, their baseline hemoglobin levels may be higher; and second, they may be further protected by the lower parasite densities achieved during incident infection. This conclusion is supported by the protection conferred against severe anemia seen in both the present analysis and in previous studies [7]. Similarly, although it is probable that a high proportion of the deaths that occur during childhood involve invasive bacterial infections, these often present nonspecifically and can be rapidly fatal; therefore, they are difficult to quantify in facility-based studies [57]. Blood cultures were not done as part of our routine assessment of children during our 2 studies; as a result, we might well have failed to detect an effect of HbAS on bacteremia, even if one existed.

A second explanation for failing to detect a true effect of HbAS on nonmalarial disease relates to its lack of protection against symptomless parasitemia. It seems possible that symptomless malarial parasitemia, as opposed to symptomatic malarial infection, is the main predisposing factor for death due to other diseases. In areas of stable transmission, the bulk of the malarial disease pyramid lies in symptomless parasitemia in children <5 years old. Under these circumstances, it is hard to judge the relative effects of silent and symptomatic events on the risk of comorbid disease—even a small effect of symptomless parasitemia on the risk of other diseases in an individual could have a much greater effect at the population level, given the relative prevalence of these events. Under these circumstances, HbAS might not give rise to a visible effect on nonmalarial diseases, because it does not protect against symptomless parasitemia.

It can be seen from the above discussion that observational studies of the kind reported here can generate more questions than answers; nevertheless, we still believe that exploration of the relationships between genetic traits, malaria, and other morbid events is useful. In light of the results of the present analysis and other studies, it seems likely that the protection conferred by HbAS is remarkably specific to malaria. This does not appear to be true for α^+ thalassemia, in which homozygotes are equally protected against malaria and other infectious diseases [58]. Following some of nature's clues may yet yield rewards in terms of developing a better understanding the pathophysiological processes of malaria and their interactions with the processes of other diseases.

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