The high frequency of the gene for sickle cell haemoglobin (HbS) in malaria endemic regions, despite the high mortality rate among homozygotes, is thought to be due to a selective advantage conferred by HbAS against malaria mortality. The evidence in support of this hypothesis, however, is incomplete. First, although the protection against mortality conferred by HbAS has been indirectly estimated using HbS frequencies, the degree to which HbAS protects against mortality has not been determined using cohort studies. Second, although it has been suggested that HbAS would provide a protective advantage early in life before the acquisition of clinical immunity to malaria, definitive data to support this assumption, especially in high malaria transmission areas, are lacking.

We identified 1022 children from a birth cohort, the Asembo Bay Cohort Project, in Kisumu, Kenya, that had data on malaria morbidity and records of all-cause mortality from birth up to 3–5 years of life.2 Details of the Asembo Bay Cohort Project have been previously described. We did a survival analysis using sickle cell trait as a risk factor for all-cause mortality in a Cox regression model with time-dependent covariates. All-cause mortality was used because disease-specific mortality data were not available. Compared to HbAA, HbAS was significantly associated with a reduction in all-cause mortality only during the period from 2 to 16 months of age (risk ratio 0.45 [95% CI 0.24–0.84]; p=0.0001, figure). However, when compared with HbAA, HbAS was not associated with any survival advantage when compared with HbAA (figure).

A multivariate Poisson regression model controlling for birthweight was used to determine the relationship between haemoglobin genotype and morbidity. Children with genes for HbAS and HbSS had significantly fewer episodes of severe malarial anaemia (haemoglobin <6 g/dL plus 10 000 parasites/μL) than children with HbAA in the first 5 years of life (table). HbAS but not HbSS was associated...
with a reduced risk of severe anaemia episodes that occurred in the presence of any level of parasitaemia (table). Both HbAS and HbSS were significantly associated with reduced risks of high-density (>10,000 parasites/μL) parasitaemia when compared with HbAA (table). Furthermore, HbSS (risk ratio 0·83 [95% CI 0·70–0·97]; p=0·02), and not HbAS (0·96 [0·90–1·00]), was significantly associated with lower parasite rates than HbAA.

We show that HbAS is associated with protection against all-cause mortality among children during the period when they are most at risk of severe falciparum malaria (2–16 months). Although we did not have cause-specific mortality data, the finding that HbAS is associated with protection against severe malarial anaemia, a major cause of mortality, and high-density parasitaemia, supports the hypothesis that the lower mortality risk associated with HbAS is probably due to its protection against malaria-related mortality. Indeed, the association of HbAS with protection against severe anaemia in the presence of any level of parasitaemia was most evident from ages 2–16 months (risk ratio 0·52 [95% CI 0·31–0·86]; p<0·05), the period during which we noted a protective association against mortality. This result is consistent with the hypothesis that HbAS-mediated protection will be evident mainly before a significant level of clinical immunity is achieved. Unlike HbAS, the apparent lack of an association of HbSS with protection against mortality despite its association with protection against severe malarial anaemia most probably reflects the high mortality rate due to sickle cell disease.

The lack of an apparent protection against mortality among children with the HbAS gene in the first 2 months of life could be due to maternally transferred protective immunity or the presence, in the first few months, of high levels of fetal haemoglobin, which poorly supports the growth of P. falciparum. The lack of an association of HbAS with mortality after 16 months of age probably reflects a reduction in malaria-associated severe morbidity and mortality as a consequence of the development of clinical immunity rather than the absence of a protective effect. Alternatively, the apparent absence of a survival advantage after 16 months may be due to a reduction in the number of the susceptible HbAA population as a result of earlier malaria-related deaths.

We believe that the difference in the level of protection conferred by HbAS against severe malarial anaemia in our study and in The Gambia4 (60% vs 90%) can be explained by differences in the study design (longitudinal vs case control) and transmission intensity (high and perennial vs low and seasonal). Furthermore, in the Gambian study, the 90% protection from severe malaria included protection from cerebral malaria, which our study does not address. In this study, all fevers in the presence of a positive blood film were treated with the antimalarial drug sulfadoxine-pyrimethamine (25 mg pyrimethamine: 500 mg sulfadoxine per tablet). Therefore, the observed incidence of anaemia is likely to be an underestimate of what would be observed in a similar cohort without access to effective treatment.

This study confirms predictions from epidemiological observations that interventions to reduce malaria mortality and morbidity will probably be most effective when administered in the first years of life, especially in high perennial transmission areas such as western Kenya.

Contributors M Aidoo, F O ter Kuile, S Kariuki, B L Nahlen, A Lal, and V Udhayakumar designed the study. M Aidoo did the genotyping. D J Terlouw, M Kolczak, and P D McElroy did the statistical analysis. M Aidoo and V Udhayakumar wrote the paper.

Conflict of interest statement None declared.

Acknowledgments The US Agency for International Development (Grant HRN 6001-A-00-4010-00) funded the Asembo Bay Cohort Project. Dianne J Terlouw and Feiko O Ter Kuile received support from The Netherlands Foundation for the Development of Tropical Research (WOTRO), The Hague, Grant W93-323. Michael Aidoo was partly supported by the American Society For Microbiology/National Center for Infectious Diseases Postdoctoral Fellowship. The NCID/CDC Emerging Infectious Diseases Fund (V Udhayakumar, PI) supported the genotyping work. None of these funding agencies played a role in the study design, data collection, analyses and interpretation, or the writing of the report.