

Sickle cell disease and malaria morbidity: a tale with two tails

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More than 230 000 children are born in Africa with sickle cell disease (SCD) each year: approximately 85% of all affected births worldwide. Although malaria is commonly viewed as a major problem for African patients with this condition, questions still remain about its relative importance as a cause of ill health and death. In the absence of definitive studies investigating the contribution of malaria to morbidity and mortality in African children with SCD, policy makers will continue to lack the evidence on which to base appropriate management guidelines.

Sickle cell disease is a common problem in Africa

The gene for haemoglobin S (HbS), a structural variant of normal haemoglobin (HbA), is widely distributed in the developing world, having been selected to high frequencies by the protection afforded to carriers (HbAS; sickle cell trait) against malaria [1,2]. HbS is the classic example of a balancing polymorphism, its frequency in populations reflecting the equilibrium between the historic degree of positive selection for heterozygotes (HbAS) and negative selection for homozygotes (HbSS), who suffer from a chronic form of haemolytic anaemia known as sickle cell disease (SCD) [3]. HbS results from an amino acid substitution at position 6 of the β -globin subunit [4]. Under conditions of low oxygen tension, HbS polymerizes and results in the sickling (Figure 1) that underlies much of the pathology associated with the condition [4]. Although HbSS is the most common genetic variant of SCD, accounting for around 70% of cases worldwide, the term SCD encapsulates any condition in which pathological consequences result from HbS production [4] (Table 1).

Globally, around 280 000 children are born with SCD every year [5]. Large family sizes coupled with the correlation between allele frequencies for HbS and the historic incidence of malaria [2], mean that 85% of affected children (approximately 230 000 cases/year) are born in sub-Saharan Africa. Nevertheless, the prognosis for these children remains poor, the majority dying undiagnosed in early childhood from diseases that are poorly character-

ized. Although malaria is widely cited as a major cause for these deaths [6–8] the evidence is somewhat scanty. Here we review the available data and suggest that definitive studies are long overdue.

Sickle cell disease and malaria

The relation between SCD and malaria is intriguing. When the protective effect of HbS was first suspected more than 60 years ago [9] the genetic basis for HbS had not yet been described and tests were not available that could reliably differentiate heterozygotes from homozygotes. Although the strong protective effect of heterozygosity has subsequently been confirmed in multiple studies conducted in various countries [10,11], far fewer have focused on homozygotes. Virtually nothing is known about malaria in patients with other forms of SCD, hence this review is limited to a discussion of HbSS.

Theoretical considerations

Although not completely understood, the mechanisms by which HbAS protects against malaria probably include reduced parasite growth and enhanced removal of parasitized cells through innate or acquired immunological processes [10]. Moreover, it has been suggested that the degree of this protection might be correlated with the intracellular concentration of HbS [12] and, as such, it might be expected that subjects with SCD, whose erythrocytes contain the highest concentrations of HbS, might be even more protected than carriers. Equally, however, there are numerous theoretical reasons why malaria might be more dangerous in patients with SCD than normal subjects. First, the chronic haemolysis experienced by patients with SCD is associated with a marked reticulocytosis, commonly exceeding 10%. As a consequence, it is possible that increased efficiency of infection by both *Plasmodium falciparum*, which appears to show some preference for the youngest, most metabolically active red blood cells [13], and *Plasmodium vivax*, which only invades reticulocytes, might render patients with SCD more susceptible to malaria attacks. Second, another central feature of SCD is early deterioration in splenic function through auto-infarction, and because the spleen

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Figure 1. Peripheral blood smear showing sickled red blood cells. The figure shows a peripheral blood film from a patient with sickle cell disease. The arrows mark red blood cells that have become misshapen in the classical sickled shape because of the polymerization of the abnormal haemoglobin S molecules at low ambient oxygen concentrations.

plays such an important role in malaria immunity, this could well be associated with a reduction in the ability of patients to clear infected red cells. Third, subjects with SCD are chronically anaemic with haemoglobin concentrations roughly half of normal, at only 6–8 g/dl. A rapid fall from such a low base line level because of the haemolysis or ineffective erythropoiesis that normally accompany malaria infections [14] could easily be catastrophic. Finally, it is also probable that the tissue hypoxia and inflammatory processes that typically accompany malaria infection are potent triggers of ‘sequestration crises,’ in which red cells sequester in the spleen, lungs and other deep organs, resulting in sudden declines in peripheral haemoglobin concentrations. In theory, therefore, the balance of probabilities is that subjects with SCD are at increased risk from malaria infections. But what clinical evidence is there to support this hypothesis?

Clinical studies of SCD and malaria

A lower prevalence and/or a lower density of malaria parasitaemia among subjects with SCD compared to non-SCD controls has been reported in several studies [15–22]. On the face of it, this appears to support the conclusion that SCD subjects enjoy an even greater degree of resistance to malaria infection than heterozygotes. Nevertheless, whether or not patients with SCD are relatively resistant to malaria infections, it is clear from numerous reports that malaria can result in serious consequences

when patients do get infected. Although malaria did not feature strongly in early descriptions of the natural history of SCD [23,24], the infection has been implicated as a significant problem in several later reports. The description of a SCD patient admitted to the hospital with severe malaria infection in Ibadan [25] prompted a flurry of letters stating the clinical impression that malaria is a frequent and significant cause of ill health and death among patients with SCD [26–28]. This impression is supported by many subsequent reports describing the experience of clinicians in a range of situations [21,29,30]. Nevertheless, in regions where a large proportion of children carry malaria parasites throughout their early life, it is difficult to interpret the relevance of a positive blood film in the absence of data regarding parasite carriage in either controls or in children with SCD at steady state, data that are missing from virtually all such studies.

Natural history studies

Although cohort studies offer one approach to addressing the causal relation between malaria infections, morbidity and mortality in patients with SCD, surprisingly few reports have been published that have used this study design. A major problem of this approach relates to ethical considerations: given the wide-spread perception that malaria can be dangerous in patients with SCD it would generally be considered unethical to withhold prophylaxis from malaria-exposed patients once a diagnosis of SCD has been made. However, this treatment bias has been minimized in two published studies. First, in a birth cohort study conducted in Western Kenya, a retrospective approach was used to test participants for SCD on completion of the study using archived samples collected at the time of recruitment [31]. Although all-cause mortality was significantly higher among SCD than control children, on the basis of data collected during monthly cross-sectional blood sampling surveys, significantly lower incidence rates were reported for both severe malaria anaemia and high density *P. falciparum* infections in those with SCD [31]. Again, although this study suggests that children with SCD might enjoy a degree of resistance to *P. falciparum* infections, the possibility that malaria infections might have been a precipitating event in some or all of those who died cannot be excluded. In a more recent study, a cohort of patients attending a SCD clinic at a major teaching hospital in Tanzania was followed [20]. Although at the time of the study, guidelines recommended routine prophylaxis with chloroquine, the drug was not routinely available, effectively meaning that study patients were receiving no preventive treatment. Two potentially important findings

Table 1. The most common genetic causes of sickle cell disease found in Africa

Genotype	Comments
HbS/S	Sickle cell anaemia: accounts for ~70% of cases of SCD.
HbS/C	Less severe form of SCD. Accounts for 25–30% cases of SCD in Africa. Largely confined to West Africa.
HbS/ β -thalassaemia ^a	Rare in Africa; most prevalent in the Eastern Mediterranean and India.
HbS/O Arab ^b	A rare form of SCD found in North Africa, the Middle East and the Balkans.
HbS/D Punjab ^c	Occurs throughout the world but is most commonly found in Northern India.

^a β -thalassaemia = an inherited condition characterized by the reduced production of normal beta-globin chains because of mutations at the beta-globin gene locus.

^{b,c}Haemoglobins O Arab and D Punjab result from mutations of the beta globin gene locus that lead to the production of structurally abnormal forms of haemoglobin.

were reported. First the prevalence of *P. falciparum* parasites was significantly lower among patients with SCD than in those without SCD both at routine hospital visits and during episodes of hospitalization. However, second, the prevalence of parasites was considerably higher among hospitalized than non-hospitalized patients with SCD, an observation that was particularly marked for patients with severe anaemia, and malaria was strongly associated with a fatal inpatient outcome [20]. This study suggests that although patients with SCD might be relatively resistant to malaria infection when compared to non-SCD subjects, when they do become infected the disease can have serious, and sometimes fatal, consequences. In another recent study, conducted on the coast of Kenya, a similar conclusion was reached. A surveillance study of children admitted to Kilifi District Hospital was used as a sampling framework for a case-control analysis investigating the odds of SCD among patients admitted with a range of specific diagnoses. Although SCD was a significant risk factor for admission to the hospital, both with non-malaria diagnoses in general and with invasive bacterial diseases in particular, it was not associated with admission to the hospital with malaria [32]. Nevertheless, both severe anaemia and mortality were considerably higher in SCD than non-SCD children who were hospitalized with malaria, suggesting that any resistance to malaria infections might be offset by the massively increased risk of death when such children do develop the disease.

Evidence from intervention studies

Although valuable data have been derived from observational studies such as those described above, in many ways, intervention studies comprise a more robust approach to investigating the role of malaria in the health of subjects with SCD. As discussed already, in light of the general belief that malaria is dangerous in subjects with SCD, withholding prophylaxis from malaria-exposed subjects with an existing diagnosis is ethically contentious. Nevertheless, several intervention studies have been undertaken and have yielded important data. The Garki study, conducted in the Sudan savanna of Nigeria during the 1970 s, is one example [16]. During the course of initial cross-sectional surveys of the study population, the investigators noticed that although the prevalence of SCD among newborns was as expected on the basis of the Hardy Weinberg equilibrium, there was a deficit of subjects with SCD among older age groups, suggesting a high mortality in early childhood. Although the improved survival of children with SCD that followed the random assignment of malaria control to half of the study population has often been cited in support of a role for malaria in these early deaths, these data are inconclusive for two reasons. First, the study was small; there were four children with SCD in the population at the beginning of the study and seven at its conclusion, and the observed increase did not reach statistical significance. Second, the chosen intervention, a combination of sulfalene and pyrimethamine could also have influenced the incidence of other parasitic and bacterial diseases.

Several placebo-controlled trials of antimalarial prophylaxis have been conducted in patients with an existing diagnosis of SCD, including two considered sufficiently

robust to inform the recommendations of a recent Cochrane review [33]. In the first, a range of health outcomes were compared in two groups of SCD children attending a Ugandan outpatient clinic during the 1960 s: a treatment group receiving chemoprophylaxis with both oral chloroquine and intramuscular long-acting penicillin, and a placebo group receiving intramuscular sterile water [34]. Several important observations were made. First, the treatment group experienced a significantly lower incidence of dactylitis (a common complication of SCD in younger children) and of falls in haemoglobin to less than 6.0 g/dl (normal 7.3 g/dl (standard deviation 1.3 g/dl) [19]). Although, as in the Garki project [16], it is impossible to ascribe these benefits to one or other component of the prophylactic regime, the treated group experienced both a lower prevalence of slide-positive malaria and a higher mean haemoglobin concentration at routine clinic visits. Moreover, it was noted that 'almost every positive finding of malaria was either preceded or followed by a fall of up to 2 g Hb/100 ml blood.' [34] This study, therefore, provides compelling support for a causal link between malaria and anaemia in patients with SCD. A second small trial, involving a total of 97 Nigerian patients, included three groups of children with SCD: two groups received active oral malaria prophylaxis with either proguanil or pyrimethamine and the third received oral placebo (vitamin C) [35]. Although no significant differences were found in the incidence of malaria between the three groups, patients in the placebo group were admitted to the hospital more frequently, received more blood transfusions and experienced lower steady-state haemoglobin concentrations [35]. Proguanil appeared more effective than pyrimethamine, possibly because of the prevalence of resistance to the latter. Subsequently, a third randomized controlled trial, conducted in Senegal, found that, compared to those receiving placebo, patients with SCD receiving monthly intermittent presumptive treatment with sulphadoxine-pyrimethamine during the malaria transmission season experienced significant benefits in terms of the incidence of malaria, SCD crises and the need for blood transfusions [36].

The balance of evidence

From the literature reviewed above, it can be seen that the relation between malaria and SCD remains somewhat confusing. A summary of what we consider to be the most probable relation between these two conditions is illustrated in Figure 2. On the basis of evidence collected during cross-sectional studies in multiple countries [15–22], SCD appears to be associated with reductions in both the prevalence and density of asymptomatic parasitaemia. In many cases, this effect is considerably greater than that seen in heterozygotes with HbAS, suggesting a dose-dependent effect of the gene for HbS with regard to protection from infection with malaria parasites. Nevertheless, this protection is certainly not complete, and there is plenty of evidence to show that when patients with SCD do become infected the consequences can be grave. The strongest evidence relates to anaemia, where sudden and catastrophic falls in haemoglobin concentration can follow the onset of malaria infection [20,32,33,36], but it is possible that malaria infections in patients with SCD might also

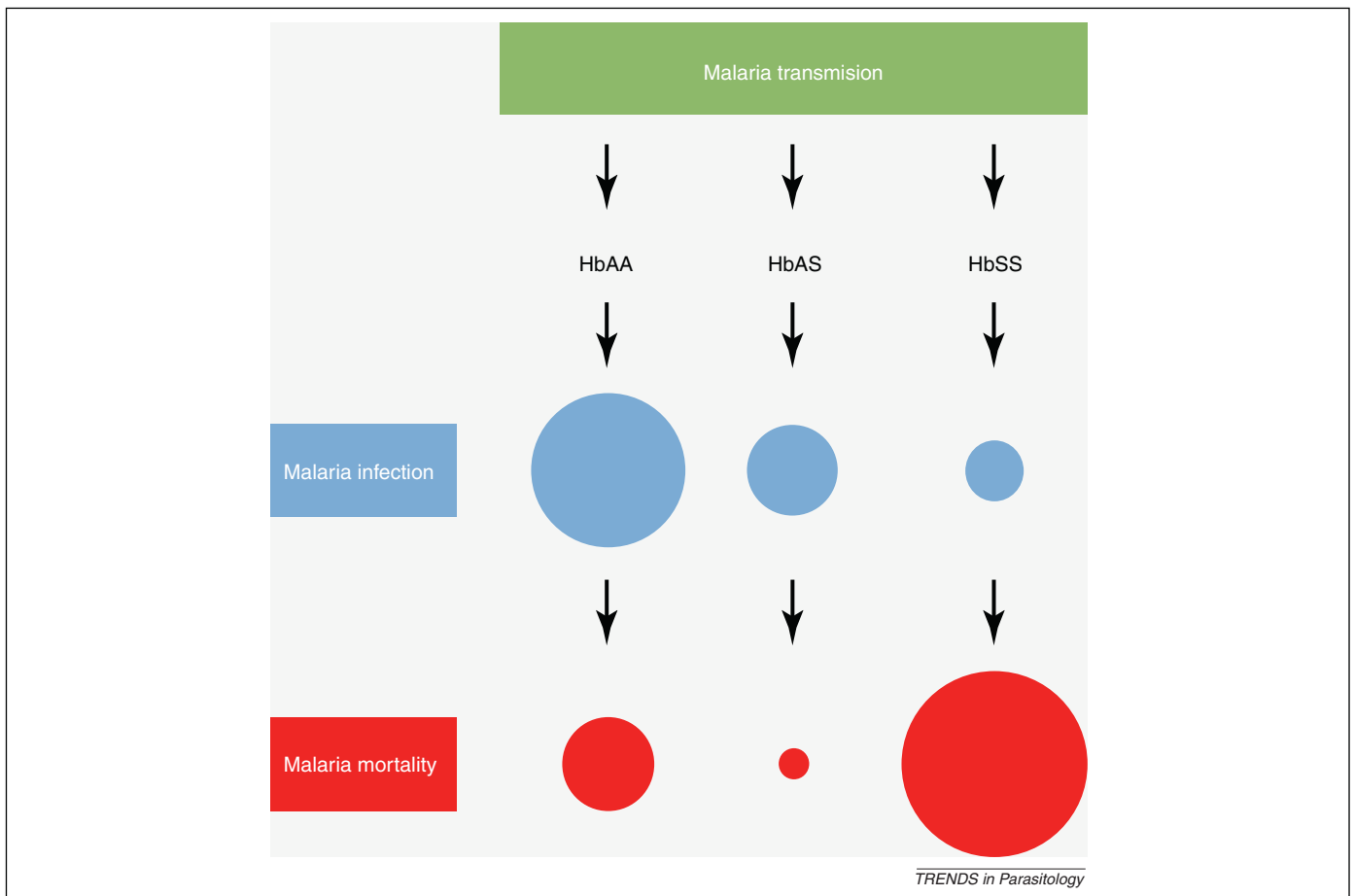


Figure 2. A model of the relative risks of malaria infection and malaria-specific mortality in subjects of different HbS genotype. The cartoon illustrates one interpretation of the available epidemiological data regarding the relation between HbS and malaria. The size of the circles represents the genotype-specific risk of each event under conditions of equivalent malaria exposure. Subjects with HbAS are at lower risk of malaria infection than subjects with HbAA and even if infected are at lower risk of progression to severe and fatal disease. Subjects with HbSS (SCD) are at lower risk still of malaria infection but if infected are at substantial risk of subsequent mortality meaning that overall, despite the reduced risk of infection, malaria-specific mortality is greater than in normal subjects (HbAA). Although available data suggest that malaria mortality is > 90% lower in HbAS than in normal subjects [10], insufficient data are available from which to estimate the relative risks of infection and death in subjects with SCD. Without considerable further research it is impossible to scale the illustration with any degree of accuracy.

have other downstream effects. Moreover, it is possible that the risk from malaria in any individual patient might be influenced by their wider genetic makeup. For example, α -thalassaemia, a condition affecting the production of the α -globin subunits of haemoglobin, is well recognized as an ameliorating factor in patients with SCD [37] and can also influence malaria risk [12,38].

Policy implications and research priorities

Although there are few firm data on which to estimate current survival rates, the balance of evidence suggests that between 50% and 90% of children born with SCD in Africa will die before their fifth birthday [39]. There can be little doubt that, as in the developed world, the early diagnosis of SCD through screening, followed by the provision of a limited number of essential interventions (including parental education [40,41] and vaccination or prophylaxis against common bacterial infections [34]) would have a major impact on the survival of children born with SCD in sub-Saharan Africa. Nevertheless, our formulation of the relation between SCD and malaria raises several questions regarding the relative contribution that malaria prevention might make to this improved survival.

On the basis of the available evidence it seems probable that malaria prevention would have a major impact on the survival of children living with SCD in areas of high malaria transmission. However, an increasing proportion of patients are now being born in areas where transmission is on the decline [42,43] or in cities where, in many cases, malaria transmission is relatively low. Should all malaria-exposed patients be prescribed prophylaxis throughout life, or is it possible that at lower levels of malaria transmission the risks of treatment might outweigh the risks of infection? An obvious issue in this context is the optimal anti-malarial regime. Although for many years chloroquine was considered standard, this drug is no longer effective in most of the continent and long-term prophylaxis is associated with a risk of ocular toxicity. Similarly, whereas Paludrine is recommended in some settings, it is expensive, almost certainly of limited efficacy, and is also associated with side effects in a proportion of users. Might alternative approaches, such as impregnated bed-nets, intermittent presumptive- or early diagnosis and treatment of malaria infections, be more appropriate in areas of lower transmission? Furthermore, should the same recommendations apply to both children and adults?

Whereas definitive answers to some of these questions are long overdue, what studies are needed and how would they be funded? Regardless of the indisputable benefits of malaria prevention in normal children, given the existing evidence from previous studies [33], placebo-controlled trials would be considered unethical in most endemic settings. Comparative trials of different approaches to antimalarial prophylaxis are probably the only ethically acceptable method of addressing this question but such studies come with different challenges. For example, the most appropriate target population would be very young children, and given the likelihood that most approaches to malaria prevention will be reasonably effective, such trials would need to be large. Such comparative studies would be predicated on the existence of large-scale, early-life screening programs, which remain uncommon throughout most of the continent. Nevertheless, recent years have seen promising developments. Successful pilot studies have been established in several centres [44–46] and with support from the government of Brazil, a national screening program is planned for Ghana, suggesting that with good advocacy and international will it is possible to raise the profile of sickle cell disease on national health agendas.

An improved understanding of both the role of malaria and of broader issues relating to the health of African children with SCD will be helped by several factors. Most importantly, African countries themselves must embrace the problem of SCD and develop a research agenda. Much could be gained by the strategic development of sustainable scientific partnerships with research centres in richer countries [47], an objective promoted by the recent establishment of a major collaborative network to advance this agenda [48] (<http://globalscd.ning.com/>). Finally, however, progress will remain slow without increased commitment from donor and development agencies and from major international research funders.

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