

# HOW SICKLE CELL TRAIT PROTECTS AGAINST MALARIA

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## Abstract

PubMed was searched for research articles describing the sickle cell trait, defined as red blood cells being heterozygous for normal hemoglobin (HbA) and sickle cell hemoglobin (HbS). The search resulted in finding articles that supported the belief that sickle cell trait protects against malaria in 1 population, 3 epidemiological, and 4 biochemical studies.

**Pierce EC. How Sickle Cell Trait Protects Against Malaria. Med J Therapeut Africa. 2007;1:61-62.**

Keywords: malaria sickle cell anemia HbA HbS sub-Saharan Africa

## Introduction

Sickle cell anemia is an autosomal recessive genetic disorder. In sickle cell anemia a single amino acid substitution in HbA results in HbS, and red blood cells are hard, sticky, and crescent-shaped. Sickle red blood cells tend to stick together and block narrow blood vessels. Such blockages prevent oxygen from reaching all parts of the body, causing tissue damage, anemia, and painful episodes (crises) in a patient's joints and bones.(1)

The goal of this report was to explain how the sickle cell trait, which results from red blood cells hav-

ing both HbA and HbS, protects against malaria.

## Methods

After an initial internet search engine search on the sickle cell trait and malaria, the PubMed database was searched for the terms: "sickle cell anemia", "sickle cell trait", "malaria", and "sickle cell trait protection".

## Results

A total of 8 studies were found which gave evidence of protection against malaria in humans with the sickle cell trait, HbA-HbS. These were 1 population, 3 epidemiological, and 4 biochemical studies.

Williams and colleagues studied the effects of age on malaria infection in children living on the coast of Kenya and reported that children with HbA-HbS had a 40% protective advantage against mild cases of malaria. This protection increased with age from 20% to nearly 60% over the first 10 years of life. After the age of 10, protection returned to around 30%.(2)

The effect of HbA-HbS on childhood diseases and malaria was studied in over 3,000 children living on the coast of Kenya. No significant effect of having HbA-HbS on other childhood diseases was observed. The study demonstrated that HbA-HbS protects against malaria caused by Plasmodium falciparum, (P falciparum) Table 1. The incidences of mild cases of malaria (93 versus 1,195) and the incidences of hospital admission for severe cases of malaria (6 versus 191) were significantly lower in children with HbA-HbS. Parasite densities during both mild and severe malaria episodes were significantly lower in children with HbA-HbS. Children with HbA-HbS admitted to the hospital for falciparum malaria had a 4-fold lower parasitic density.(3)

Epidemiological studies in Nigeria measured the number of P falciparum parasites in blood samples of children with the sickle cell trait who had lowered frequency of parasites and less malarial infections. The report's conclusions were that the lower frequency of parasites was mostly likely due to the destruction of infected red blood cells.(4)

Aidoo and colleagues reported that children under 5 with HbA-HbS had fewer episodes of severe malaria anemia (2 versus 4 crude incidence per 1,000 person-months). Because severe malarial anemia is a major cause of death, a decreased number of

	Children with HbA-HbS	Children with HbA-HbA
Incidences of mild clinical malaria	93	1195
Incidences of hospitalization for severe malaria	6	191
Incidences of cerebral malaria	1	34
Incidences of severe malarial anemia	1	48

**Table 1. Children living on the coast of Kenya, adapted from Ref 3.**

episodes is evidence for the sickle cell trait protection against malaria-related deaths. Children with HbA-HbS had reduced risks of high-density parasitemia (over 10,000 parasites. $\mu\text{mL}^{-1}$ ) (17.3 versus 20.0 crude incidence per 1,000 person-months).(5)

In vitro studies by Roth and colleagues demonstrated that under conditions of both total and partial deoxygenation, red blood cells infected with *Plasmodium falciparum* sickled faster than non-infected red blood cells. Red blood cells infected with ring forms of the *Plasmodium* parasites sickled nearly 8 times faster than non-infected cells. At every oxygen saturation, red blood cells infected with small parasites sickled more than non-infected red blood cells.(6)

When a parasite invades a red blood cell, the parasite's metabolism reduces the oxygen in the cell. The decrease in oxygen causes the red blood cell to sickle; those sickle cells, and the pathogens infecting those cells, are then removed by the spleen or destroyed by phagocytes. This clearance of infected sickled red blood cells by the body's immune system reduces and prevents malarial infections.(7)

Phagocytosis is enhanced in sickle cell trait red blood cells infected with parasitic ring forms. These ring forms are an early stage of development in the malarial parasite's life cycle. The removal of these early parasite forms is advantageous to the host because the enhanced phagocytosis of these infected red blood cells reduces parasitic invasion and growth. The parasitic ring forms are more rapidly digested by monocytes than the more mature parasitic forms. The phagocytosis of more mature forms of the parasite has been shown to affect the ability of monocytes to repeat the phagocytic process.(8)

Malarial parasites cannot live in sickle cells because the cell membrane of those distorted red blood cells becomes porous. Nutrients that the parasite needs to live escape through the permeable membrane of the sickle red blood cells. Red blood cells of humans with the sickle cell trait produce more superoxide anion and hydrogen peroxide, which are toxic to malarial parasites.(4)

## Discussion

A benefit in having HbA-HbS to protect against malaria was first suggested because of the high frequency of HbA-HbS in areas with high incidences of malaria. The frequency of sickle cell disease is higher in Africa (16%) compared to the frequency in the United States (4%), particularly in western Africa.(6) Support for the concept that HbA-HbS is beneficial came from research that concluded that humans native to the highland regions of Africa did not have

as high a frequency of the HbS gene as did humans in the lowland regions.

Neither malaria, nor the gene for sickle hemoglobin occurs in the cooler, drier climates of the African highlands.(4)

Humans with normal hemoglobin have a greater risk of dying from malaria.(6) The premature death of individuals homozygous for HbA results in a lower frequency of normal Hb genes within the population. Humans with 2 sickle cell genes develop sickle cell anemia, and also die at an early age. Heterozygous humans are more likely to survive malarial infections than humans homozygous for HbA. Carriers of the genes for HbA-HbS are able to reproduce and pass the sickle cell gene to their offspring. As a result, HbA-HbS is sustained in the population at a relatively high frequency.(4)

## Conclusion

The sickle cell trait, which results from having blood heterozygous for HbA and HbS, protects against malaria. Consequently, humans with the trait are more likely to survive malarial infections and reproduce than humans homozygous for HbA or HbS. The protective advantage also explains why the frequency of the sickle cell trait is higher in malaria-endemic areas found in sub-Saharan Africa.

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