

# Effects Of Sickle Cell Traits on Malaria

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**Abstract.** Background: Malaria continues to be a significant public health concern in Africa, posing a threat to the population. Malaria causes damage to various body systems, including the gastrointestinal and nervous systems, as well as metabolic abnormalities. However, effective treatments for malaria are currently lacking, and the clinical application of sickle cell traits remains unexplored. Objective: To establish the correlation between malaria and sickle cells and comprehensively understand the mechanisms through which sickle cells influence malaria. Method: This study was conducted by searching PubMed and CNKI for studies published within the last decade concerning the impact of sickle cell trait on malaria incidence, mortality, and morbidity in Africa. Data were meticulously extracted, analyzed, and synthesized to assess the protective role of SCT against malaria. Results: A total of 509 studies were found in the literature, of which 11 met the inclusion criteria and were selected for detailed analysis. The findings from these studies consistently indicate that sickle cell trait is associated with reduced incidence of malaria, as well as lower mortality and morbidity rates among affected individuals. These protective effects suggest potential new targets for malaria intervention and control strategies. Conclusion: Malaria threatens the population in Africa, causing substantial harm to individuals and communities. A comprehensive understanding of the effects of sickle cells on malaria and their mechanisms is necessary for the development of effective treatment and prevention programs.

**Keywords:** Malaria; Mortality; Incidence; Morbidity; Sickle cell.

## 1. Introduction

### 1.1. Malaria and its effects

Malaria was a globally endemic disease just 100 years ago, and it is the main cause of mortality and morbidity all over the world. All human malaria is caused by parasites in the genus *Plasmodium*, infecting red blood cells, the liver, spleen and bone marrow. And all of them are transmitted by mosquitoes, and malaria has a highly complex life cycle involving only mosquitoes and human hosts. The primary factors contributing to the resurgence of malaria are the appearance of drug-resistant strains of the parasite, the spread of insecticide-resistant strains of the mosquitos, and the lack of licensed malaria vaccines of proven efficacy [1].

Malaria profoundly affects the individual, manifesting in several painful symptoms across various bodily systems. Initially, the disease impacts the gastrointestinal tract; following infection, patients typically experience weakened gastrointestinal function. This often results in uncomfortable symptoms such as nausea, vomiting, and diarrhea. In severe cases, these symptoms can lead to significant dehydration and electrolyte imbalances, posing serious health risks. The disease also compromises the nervous system. Common neurological symptoms following malaria infection include dizziness, headaches, and a general feeling of malaise. In more severe instances, patients may experience life-threatening conditions such as coma, highlighting the critical nature of the disease. Moreover, malaria can disrupt normal metabolic processes. It may cause renal failure, which interferes with the kidneys' ability to manage waste and balance fluids and electrolytes. This disruption can lead to edema—swelling caused by excess fluid trapped in the body's tissues. Accompanying these symptoms are fever, hypoglycemia, and severe anemia, each of which can further complicate the patient's condition and potentially become life-threatening.

## 1.2. Anti-malarial measures

The sweet wormwood plant was used as early as the second century BC to treat malaria fever in China. Much later, quinine started being used as an anti-malaria drug. A global battle against malaria started in 1955, and Croatia declared 1964 to be the year of malaria eradication. The World Health Organization carries out a malaria control program on a global scale, focusing on local strengthening of primary health care, early diagnosis of the disease, timely treatment, and disease prevention. Globally, the burden of malaria is lower than ten years ago. However, in the last few years, there has been an increase in the number of malaria cases around the world. It is moving towards targets established by the WHO, but that progress has slowed down [2]. In the 1960s, when chloroquine failed to fight malaria and humans were suffering from malaria, Tu Youyou, who worked as a study intern in the Institute of Traditional Chinese Medicine of the Chinese Academy of Traditional Chinese Medicine, accepted the arduous antimalarial study task of the Office of “523” of the National Malaria Control Program in 1969. Tu Youyou, as the head of the Chinese medicine anti-malaria team, has an indissoluble bond with Chinese medicine anti-malaria. Artemisinin-combined treatments are primary weapons against malaria and were discovered by a Chinese scientist, Tu Youyou. The treatments are highly effective. Besides, the methods of preventing malaria include using insecticide-treated bed nets, Indoor spraying of residual insecticides, and modifying the environment against vector mosquito species, and so on.

## 1.3. Sickle cell anemia

When hemoglobin is exposed to a variety of environments, it distorts and becomes sickle, which allows red blood cells to pass between cells, causing tissue damage, it is dysfunctional, but it has some resistance to malaria parasites. Sickle cell anemia, also known as hemoglobin S(HbS) disease, occurs predominantly in Africa and is an autosomal dominant disease. Sickle cell anemia is not completely immune to malaria, but it is relatively resistant to malaria. Besides, sickle cell anemia is related to the special red cell morphology, can weaken the oxygen-carrying capacity of red cells, and can change the growth and reproduction of malaria parasites. And sickle cell anemia is relatively insensitive to Plasmodium falciparum because of the decreased potassium concentration in erythrocytes during hypoxia, which can cause Plasmodium falciparum death. Because sickle cell hemoglobin is insoluble in water, it hinders the phagocytosis and pinocytosis of Plasmodium falciparum. When oxygen is depressed, hemoglobin can form microcrystals, which can puncture the surface membrane of Plasmodium, thus affecting its survival. Sickle cells can reduce the adhesion of certain proteins, thereby reducing the expression of certain genes, such as PfEMP1 (Plasmodium falciparum erythrocyte membrane protein 1), which in turn protects against the malaria parasite.

Malaria can take a huge toll on individuals, families and even the world, and humans do not have a powerful weapon against malaria. Many scientists have shown that sickle cells can reduce malaria infection, but this conclusion has not been applied in clinical practice. So, the study’s main objectives are to further confirm the association between sickle cell and malaria, show that sickle cells can reduce the incidence and risks of malaria, and mention the potential protective measures. Afterward, morbidity and mortality are reduced.

## 2. Methods

### 2.1. Search strategy

A systematic search was conducted in the PubMed and CNKI databases to identify relevant study studies. The search terms “malaria” and “sickle cell” were used to retrieve potential studies. The search was limited to publications in recently 10 years to ensure the relevance and recency of the data.

## 2.2. Inclusion and exclusion Criteria

The inclusion criteria for study selection were as follows: (1) studies published within the past 10 years, (2) studies specifically addressing malaria and sickle cell, (3) studies containing data analysis related to the mortality and morbidity of malaria. Non-English-language studies were excluded. Additionally, studies with redundant information were excluded from the review.

## 2.3. Data extraction and synthesis

Information from a total of 11 studies was included in this review. The following data were collected from each study: authors, year of publication, countries, sickle cell characteristics, mean age, gender, control, sample size, experimental method, measurements of outcome, credibility and main findings. To synthesize the extracted data, a narrative synthesis approach was used, focusing on thematic analysis to identify patterns and draw conclusions about the relationship between sickle cell traits and malaria outcomes.

## 3. Results

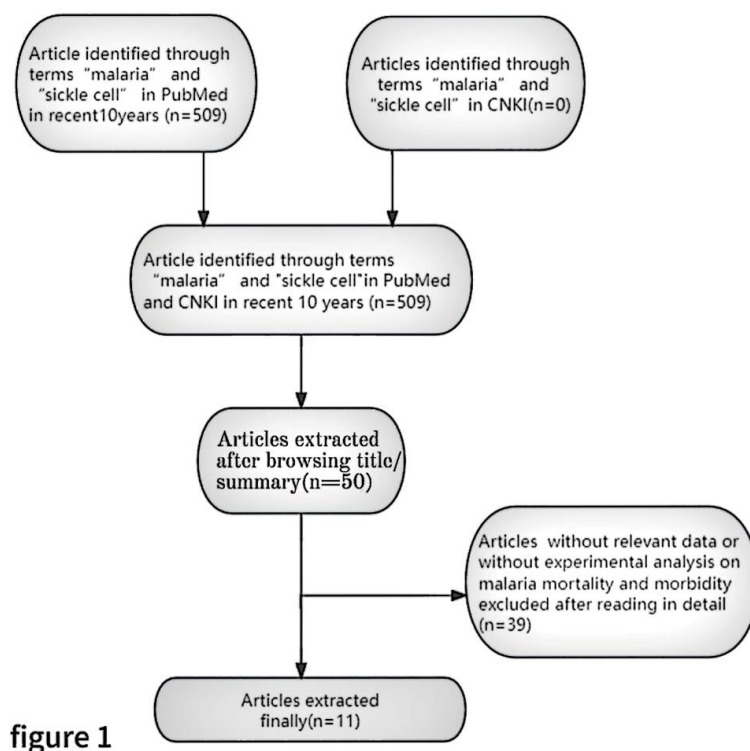


figure 1

Fig. 1 The study selection process

**Table 1** The characteristics of included studies

Author/year	Country	Sickle cell	Mean age	Gender	Control	Sample size	Experimental method	Measurements of outcomes	Credibility	Main findings
Saibu D Oumbia, et al., 2016	Mali	inborn	6 months to 17 years old	NA	The children with sickle cells were compared to the children without sickle cells	1586	Incidence rate ratios (IRRs) were modeled with quasi-Poisson regression; parasite densities were analyzed with Generalized Estimating Equations	malaria incidence was reduced 34% in HbAS vs HbAA children. Parasite density was reduced in HbAS vs HbAA children (median 10, 550 vs 15, 150 parasites/ $\mu$ L; p=0.0004)	NA	sickle cells could protect people from malaria
Valentina D Mangan, et al., 2015	Burkina Faso	inborn	NA	NA	The people with sickle cells were compared to the people without sickle cells	NA	NA	association between a 70% reduction of harboring P. falciparum parasite and sickle cell	odds ratio [OR] for AS vs AA, 0.27 95% confidence interval [CI], .11-.66; P = .004	HbS is associated with a 70% reduction of harboring falciparum parasite

Author/year	Country	Sickle cell	Mean age	Gender	Control	Sample size	Experimental method	Measurements of outcomes	Credibility	Main findings
Kwaku Poku Asante, et al., 2014	the middle belt of Ghana	inborn	under 5 years old	NA	The children with sickle cells were compared to the children without sickle cells	341	Multivariate regression analysis	proportion of risk of malaria decreased by 79%	(OR = 0.21, 95% CI: 0.06–0.73, p = 0.01)	a protective effect of sickle cell trait on clinical malaria infection
Michael A Krause, et al., 2014	in three villages (Keni eroba, Fourda, and Bozokin) located 75 km south west of Bamako, Mali	inborn	aged 0.5–17 years	NA	The children with sickle cells were compared to the children without sickle cells	1514	31 adhesion comparison	adhesion change rate of HbAS compared with HbAA: 1.46 and that of HbAC: 1.99	fold-change = 1.46, 95% CI 0.97–2.19, n=16, p=0.07	Increased binding to MVECs means the expression of PfEMP1 decreasing, malaria are resisted
Mtebe Majigo, et al., 2019	Salalam	inborn	NA	NA	The children with sickle cells were compared to the children	children with measured plasma IgG concentrations (110HbAA and 110 HbSS)	ELISA	the median IgG concentration to PfEBA-175, Pfg27, yPfs28C antigens were HbSS; 20.7 ng/ml	NA	level of IgG corresponding children with HbSS>1 level of IgG corresponding children with HbAA

Author/year	Country	Sickle cell	Mean age	Gender	Control	Sample size	Experimental method	Measurements of outcomes	Credibility	Main findings
					with out sickle cells			(IQR; 18. 1–25. 6) vs. HbAA; 2. 3 ng/ml (IQR; 1. 21–3. 04), HbSS; 2. 76 ng/ml (IQR : 2. 08–5. 69) vs. HbAA; 1. 36 ng/ml (IQR : 1. 28–1. 76), and HbSS; 26, 592 ng/ml (IQR : 10817–41, 462) vs. HbAA; 14, 164 ng/ml (IQR; 3069–24, 302)		Children with sickle cells have stronger immunity
Chukwu di A. Ekechi, 2019	Galabwr, Nigeria	inborn	NA	NA	The people with sickle cells were compared to the people	60		the parasite density of the HbAS (3100 ± 1828. 48 µL) and HbSS (2400 ± 1687. 06 µL) were significa		sickle cell gene reduces the severity of malaria parasite infection and hence protects against

Author/year	Country	Sickle cell	Mean age	Gender	Control	Sample size	Experimental method	Measurements of outcomes	Credibility	Main findings
					without sickle cells			ntly lower than that of HbAA (4040 ± 1529.44 µL).		severe acute malaria while having less effect on infection
Bryan Greenhouse, et al., 2020	Uganda	inborn	A total of 1010 (76.4%) participants were children 0.5–10 years of age and 312 (23.6%) were adult	approximately half the children and 94% of adults were female	The people with sickle cells were compared to the people without sickle cells	1322	a longitudinal cohort study was used to quantify association	HbAS was associated, compared to wild type, with a lower incidence of malaria, lower parasite density upon infection	(PR = 0.66, 95% CI 0.51–0.85, p = 0.001) (IRR = 0.78, 95% CI 0.66–0.92, p = 0.003)	Sickle cells are more strongly associated with a lower incidence of malaria
Doumbo, et al., 2020		inborn	NA	NA	The children with sickle cells were compared to the children without sickle cells	NA	pair samples	cellular commune profiles were more enriched in HbAS than in HbAA, with a distinct NK subset	NA	Children with sickle cells have stronger resistance to malaria
Joseph W	NA	inborn	NA	NA	The peop	NA	static adhesi	sickle-trait		This provide

Author/year	Country	Sickle cell	Mean age	Gender	Control	Sample size	Experimental method	Measurements of outcomes	Credibility	Main findings
Saelens, et al., 2021					le with sickle cells were compared to the people without sickle cells		on assays	reduced adhesion by 73-86% to CD36 and 83% to EPCR. Similarly, sickle-trait reduced the surface expression of EPCR-binding PfEMP1.		s a direct mechanism for protection against severe malaria conferred by sickle-trait hemoglobin
Sophie Uyoga, PhD et al., 2022	Uganda	inborn	NA	NA	The children with sickle cells were compared to the children without sickle cells	3359		1815 (78%) of 2321 children without SCA (HbAA) tested positive, children with SCA (347 [33%] of 1038 tested positive	(p<0.0001)	children with SCA are innately protected against classic severe malaria
Keri Oxendine Harp, et al., 2023		inborn	NA	NA	The people with sickle cells were compared to	24				sickle cell hemoglobin genotypes affect malaria parasite growth and

Author/year	Country	Sickle cell	Mean age	Gender	Control	Sample size	Experimental method	Measurements of outcomes	Credibility	Main findings
					the people with out sickle cells					correlate with Exosomal miR-451a and let-7i-5p Levels

Note:1.“NA” is “Not applicable”.

2.HbAA: normal haemoglobin (haemoglobin A)

3.HbS: sickle cell anaemia (haemoglobin S)

4.HbC: sickle cell anaemia (haemoglobin C)

5.HbAC: heterozygous for HbA and HbC

6.HbAS: heterozygous for HbA and HbS

7.HbSC: heterozygous for HbB and HbS

### 3.1. Study selection and characteristics

PubMed and CNKI yielded 509 studys across the recent 10 years. Preliminary screening by title and summary resulted in the identification of 50 possibly suitable publications. The author discovered 11 acceptable studys for inclusion in our study after rejecting 39 studies during the final full-text screening (Figure 1).

The following are specific features included in the study : the region is Africa, the population is dominated by children, the variable is the presence or absence of sickle cells, the observed result is the risk of death from malaria, incidence, mortality, and association of sickle cells with a low incidence of malaria (Table 1).

### 3.2. Results of individual studies

In these 11 studies, a total of 3,100 children aged 0. 5 to 17 years, 341 children under 5 years, and 1,010 children aged 0. 5 to 10 years and 312 adults were known (assuming a mean age of 45 years), so the estimated mean age is 9. 93 years.

A survey published by Tatiana M Lopera-Mesa, et al., in 2016 showed parasite density in children with sickle cells and in normal children and showed the proportion of incidence decreasing [3]. A survey published by Valentina D Mangano, et al., in 2015 showed the association of Hobbs (hemoglobin S) and a 70% reduction of harboring falciparum parasitemia [4]. A study published by Nicholas Amoako, et al., in 2014 suggested how much the risk of malaria decreases under the influence of sickle cells [5]. A study published by Michael A Krause, et al., in 2014 adhesion change rate of HbAS and HbAC [6]. A study published by George Msema Bwire, et al., in 2019 showed level of IgG corresponding children with HbSS and level of IgG corresponding children with HbAA [7]. A study published by Ifeyinwa M. Okafor, Henshaw U. Okoroiwu, and Chukwudi A. Ekechi in 2019 showed the parasite density of the HbAS and HbSS [8]. A study published by Bryan Greenhouse, et al., in 2020 showed IRR and PR of HbAS and IRR and PR of HbSS [9]. A study published by Claire Loiseau, et al., in 2020 showed that normal children who have relatively less cellular commune profiles and children with sickle cells, who have more cellular commune profiles [10]. A study published by Jens E V Petersen, et al., in 2021 suggested how much sickle-trait hemoglobin reduces adhesion to both CD36 and EPCR by Plasmodium falciparum-infected erythrocytes [11]. A study published by Sophie Uyoga, PhD et al., in 2022 suggested that prevalence of malaria in children with

sickle cell disease and normal children [12]. A study published by Keri Oxendine Harp, et al., in 2023 showed that sickle cell Hemoglobin Genotypes affect malaria parasite growth and correlate with exosomal miR-451a and let-7i-5p levels [13].

The study in Mali, including 1586 children in the age of 6 months to 17 years old offers evidence for the finding that sickle cells could protect people from malaria by showing a series of data: malaria incidence was reduced 34% in HbAS vs HbAA children, parasite density was reduced in HbAS vs HbAA children [3]. The study in Burkina Faso could suggest that HbS is more associated with a 70% reduction of harboring falciparum parasitemia by data and odds ratio [4]. The study in the middle belt of Ghana, including 341 children under 5 years old, shows the result, compared with the children with HbAA, risks of malaria which the children with HbAs have, have decrease by 79% [5]. The study thirty hemoglobin SS (HbSS), 30 hemoglobin AS (HbAS) individuals and 30 hemoglobin AA (HbAA) individuals recruited as control in Galabwr, Nigeria, showed that the parasite density of the HbAS and HbSS were significantly lower than that of HbAA [8]. The study in Uganda 1322 were included in the analyse showed that HbAS was associated, compared to the wild type, with a lower incidence of malaria, lower parasite density upon infection [9]. The study in which 1038 of 3483 Ugandan children had sickle cells, showed that prevalence was significantly lower in children with sickle cells [12]. All six studies suggest that sickle cells could protect people against malaria parasites to a certain extent.

Those two studies including adhesion comparison showed that direct mechanism for protection against malaria by inhibiting the expression of certain genes.

The study in Salaam including 220 children with measured plasma IgG concentrations by ELISA, showed children with sickle cells have the higher IgG concentrations [7]. The study in Boubacar Traore cross children showed that cellular commune profiles were more enriched in HbAS than in HbAA, with a distinct NK subset [10]. The all two studies showed children with sickle cells are more resistant to malaria because of stronger immunity.

### 3.3. Synthetic of results

All the surveys were conducted in Africa; All the surveys were experimental studies; sickle cells were born with them, the average age of most of the surveys was under 18 years of age, some surveys did not mention age; most of the surveys did not mention gender, one survey showed that half of the children and 94% of adults were women, and all the controls compared people with sickle cells with and without sickle cells. These studies also considered that sickle cells reduce the incidence of malaria by increasing the cell's resistance to the parasite or by reducing the expression of certain genes. Measurements of outcomes are about the risk of death from malaria, incidence, mortality, immunity system and association of sickle cells with a low incidence of malaria. These studies also considered that sickle cells reduce the incidence of malaria by increasing the cell's resistance to the parasite or by reducing the expression of certain genes. Several studies had a statistical analysis of the results, including mortality, incidence, and the density of plasmodium.

## 4. Discussion

### 4.1. Summary of findings

This study focuses on the specific demographic most affected by malaria—children. Through the analysis of data collected from six different surveys conducted in Africa, it has been determined that children possessing the sickle cell trait exhibit significantly reduced vulnerability to malaria. Specifically, these children show approximately 40% lower incidence rates and a 79% reduced risk of contracting malaria compared to children without this genetic trait.

Malaria predominantly affects impoverished tropical and subtropical regions. The factors contributing to the prevalence of malaria in these areas include suitable climatic conditions for the parasite Plasmodium, which thrives in warm and humid environments, and socio-economic challenges that impede effective control measures [14]. A notable finding from a survey in Uganda

revealed emerging resistance to artemisinin among Plasmodium parasites, particularly in regions where malaria control is lax and transmission rates are highly variable [15].

Furthermore, an important observation is the role of environmental conditions, such as post-rainfall settings, which facilitate mosquito breeding and thus potentially increase the transmission of malaria. This study highlights the critical need for targeted malaria control strategies that address the specific vulnerabilities and conditions of the affected regions [16].

#### **4.2. Mechanisms and suggestions**

Combining two investigations involving adhesion comparisons, sickle cells and normal cells have different degrees of adhesion to certain proteins and therefore different expression of certain genes, which sickle cells can inhibit. This is one of the mechanisms by which sickle cells fight off malaria parasites. Combined with two investigations involving immune cells or immunoglobulins, sickle cells have a stronger immune function than normal cells against malaria parasites. This is also one of the mechanisms by which sickle cells fight off malaria parasites.

All the sickle cells investigated are innate in the human body, and sickle cells have been shown to be effective against malaria parasites, so it is possible to consider injecting sickle cells into the human body to fight malaria parasites.

Moreover, the WHO and medical institutions around the world should give Africa more medical supplies for diagnosis and preventive treatment. Local governments in Africa should put more money into the fight against malaria. Countries, governments and charities around the world should focus on Africa and give it more economic support.

The best way to prevent mosquito bites is to sleep in a mosquito net that has been treated with mosquito repellent. Usually, after rain, after a six-month interval, or after three washings, people should retreat the nets. Wearing long-glazed trousers immediately after dark is particularly important for children. Children are at great risk in malaria-endemic areas. Children with fever should go to a hospital for a check-up and, if diagnosed with malaria, should receive appropriate antimalarial treatment as soon as possible.

#### **4.3. limitations**

The limitations of this study encompass several key aspects. Firstly, the sample used in this study may not accurately represent all people all over the world. The data primarily derives from a specific region or country, potentially limiting the generalizability of the findings to malaria incidence and risks and plasmodium density in different regions and cultural contexts.

Second, there may be some small errors in the data analysis and experimental analysis involved in each investigation.

Third, the nutritional level of each person, the level of understanding of medical knowledge, and family economy, and so on cannot be ruled out as factors affecting the results of malaria incidence and the density of malaria parasites. However, these trials did not involve an investigation of these factors.

#### **4.4. Conclusions**

This study demonstrates the positive effects of sickle cells on malaria incidence, mortality risk, and mortality. The study delineates the role of sickle cells in regulating gene expression related to malaria and enhancing immune responses, providing a basis for future therapeutic strategies that could emulate these genetic defenses. The global challenge of malaria necessitates a concerted effort from international health organizations, governments, and the scientific community. By intensifying collaborations and focusing on genetic study, there is a feasible path toward controlling and eventually eradicating malaria. This objective is not merely a public health goal but a crucial step towards alleviating the impact of malaria on vulnerable populations worldwide.

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