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Review Article

Exploring the Potential of CRISPR-Cas9 Gene Editing for Sickle Cell Disease and Malaria Resistance: A Systematic Review

Comfort Ohunene Matthew[1], Bassey Atte Inyang[2], Verity Ghansah[3], Blessing Chinonye Nwadike[4], Obinna Hilary Tony-Okpalaobi[5], Anthony Kosisochukwu Anyabuoke[6]

[1]*Department of Clinical Pharmacy, Faculty of Pharmacy, University of Benin, Benin City, Nigeria*
[2]*Department of Medical Biochemistry, College of Health Sciences, University of Abuja, FCT, Nigeria*
[3]*Department of Biology, New Mexico Institute of Mining and Technology, Socorro, NM, USA*
[4]*Department of Medical Laboratory Science, Faculty of Health Science, Imo State University, Owerri, Imo state, Nigeria*
[5]*Department of Internal Medicine, Federal Medical Center Jabi, Abuja, Nigeria*
[6]*Department of Biology, Columbus State University, Columbus, GA, USA*

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Corresponding author's email:
matthewcot94@gmail.com

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ABSTRACT

Background: Sickle cell disease (SCD) and malaria remain major health challenges in sub-Saharan Africa. CRISPR-Cas9 has enabled advances in SCD gene therapy and malaria-related experimental research, but these applications represent distinct biological and translational pathways. This systematic review evaluated CRISPR-Cas9 applications in SCD and malaria research while distinguishing clinical therapeutic evidence from experimental malaria-related findings.

Methods: A systematic review was conducted following PRISMA 2020 and Joanna Briggs Institute guidance. PubMed, ScienceDirect and Google Scholar were searched on 12 August 2026. Studies investigating CRISPR-Cas9 applications related to SCD or malaria, including *HBB* correction, fetal haemoglobin induction, host-cell modification, parasite genome editing and mosquito-vector modification, were included. Data were synthesised narratively due to substantial heterogeneity among study designs and outcomes.

Results: Thirteen studies were included, comprising six SCD-related and seven malaria-related studies. SCD studies demonstrated progression from experimental genome correction and haemoglobin regulation strategies to clinical application of CRISPR-edited autologous haematopoietic stem and progenitor cells. Malaria-related studies primarily investigated parasite functional genomics, erythrocyte invasion mechanisms and mosquito genetic modification. No included study evaluated a single CRISPR-Cas9 intervention that simultaneously treated SCD and enhanced malaria resistance.

Conclusion: CRISPR-Cas9 represents an advancing therapeutic platform for selected SCD applications and an important experimental tool in malaria research. Current evidence supports separate translational pathways, with clinical progress established in SCD and malaria applications remaining predominantly preclinical.

Keywords: CRISPR-Cas9; Sickle Cell Disease; Malaria Resistance; Gene Editing; Genetic Therapies

Introduction

Sickle cell disease (SCD) and malaria remain major causes of illness and premature mortality in sub-Saharan Africa, where their geographical distributions substantially overlap. SCD is an inherited haemoglobin disorder caused by pathogenic variants in HBB, most commonly the β-globin substitution that produces haemoglobin S (HbS), leading to haemolysis, vaso-occlusion and progressive organ injury. The World Health Organization [WHO], (2025) [1] estimated that 7.74 million people were living with SCD in 2021 and that almost 80% of the global burden occurred in sub-Saharan Africa. Malaria also remains concentrated in this region: an estimated 282 million cases and 610,000 deaths occurred globally in 2024, with the WHO African Region accounting for most cases and deaths [2]. Their geographical overlap has an evolutionary basis. Heterozygous carriage of HbS can protect against severe consequences of *Plasmodium falciparum* infection, although the relationship varies by age and outcome and does not imply complete resistance to infection [3]. This biological relationship provides a strong context for examining genome-editing research across both disease areas.

Clustered regularly interspaced short palindromic repeats-associated protein 9 (CRISPR-Cas9) has accelerated targeted genomic modification in experimental and therapeutic research. In SCD, CRISPR-Cas9 strategies broadly follow two mechanistically distinct routes. One directly corrects the pathogenic *HBB* sequence in patient-derived haematopoietic stem and progenitor cells (HSPCs), with preclinical studies demonstrating restoration of normal β-globin production and improved erythropoiesis after editing [4]. The other does not repair HBB; instead, it reactivates fetal haemoglobin (HbF) by disrupting regulatory sequences that suppress γ-globin expression. Clinical studies targeting the erythroid-specific *BCL11A* enhancer or the HBG1/*HBG2* promoters have produced sustained HbF induction and substantial reductions in SCD manifestations [5, 6]. This pathway has advanced to phase 3 evidence, where exagamglogene autotemcel, an autologous CRISPR-Cas9-edited HSPC product targeting the *BCL11A* enhancer, produced sustained freedom from severe vaso-occlusive crises in most evaluable participants [7].

CRISPR-Cas9 applications in malaria research occupy different biological and translational domains. Host-directed studies use gene editing to identify erythrocyte determinants required for parasite invasion. Knockout of BSG and CD44 in an experimentally tractable erythroid model altered P. falciparum invasion, demonstrating how CRISPR can clarify host factors involved in parasite entry [8]. More recent work has similarly expanded host-directed investigation of erythrocyte factors involved in parasite invasion. A separate stream edits the parasite genome itself. High-throughput CRISPR systems in *Plasmodium* berghei provide tools for functional genomics and identification of genes relevant to parasite biology and therapeutic development [9]. Vector-directed research forms another distinct stream, with CRISPR-Cas9 gene-drive systems developed to spread antiparasitic traits through Anopheles mosquito populations under laboratory conditions [10].

These developments show that CRISPR-Cas9 has relevance to both SCD and malaria, but the evidence does not demonstrate a single intervention that simultaneously treats SCD and confers malaria resistance. SCD studies largely concern somatic ex vivo editing of autologous HSPCs and include human clinical outcomes, whereas malaria-related studies span erythroid cell models, parasite functional genomics and genetically modified mosquito vectors. Their biological targets, experimental systems, measured outcomes and stages of translation differ substantially. No assumption should therefore be made that correction of an SCD-related genomic target reduces malaria susceptibility, or that parasite or vector editing constitutes evidence of malaria resistance in treated humans. A rigorous synthesis should distinguish direct *HBB* correction, HbF-inducing regulatory editing, host-cell determinants of parasite invasion, parasite genome editing and vector modification while considering their broader relevance to two co-endemic diseases.

This distinction is particularly important for sub-Saharan Africa. The region bears a large proportion of the global burden of both diseases, but clinically advanced CRISPR interventions for SCD require stem-cell collection, ex vivo manufacturing, myeloablative conditioning, reinfusion and prolonged follow-up. These requirements raise questions about affordability, specialist infrastructure, workforce capacity and equitable access even where efficacy has been demonstrated. Malaria-related CRISPR applications face different translational questions because most remain experimental and require evaluation of biological effectiveness, ecological safety, population acceptability and governance before population-level health benefits can be inferred. Thus, reviewing both fields together is most useful as comparative evidence synthesis and translational mapping, instead of as evidence for one established dual-purpose therapeutic strategy.

Accordingly, this systematic review aims to synthesise and critically evaluate CRISPR-Cas9 applications in SCD and malaria research as distinct but

biologically related evidence streams. Specifically, it seeks to examine the effectiveness, safety and developmental status of CRISPR-Cas9 approaches for SCD while distinguishing direct *HBB* correction from HbF-inducing regulatory editing; characterise malaria-related applications as host-cell editing, parasite genome editing or mosquito-vector modification and identify the outcomes directly demonstrated by each; compare the maturity and evidentiary strength of clinical, preclinical and experimental findings across these domains; and identify methodological, safety, ethical, accessibility and implementation gaps for future research. By maintaining these distinctions, the review provides a clearer basis for assessing the present and future relevance of CRISPR-Cas9 to populations affected by SCD and malaria.

Methodology

Study Design and Reporting Framework

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and informed by guidance from the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis [11, 12]. The review evaluated two related but distinct evidence streams: (1) CRISPR-Cas9 applications in sickle cell disease (SCD), including direct *HBB* correction and fetal haemoglobin induction strategies; and (2) CRISPR-Cas9 applications in malaria research, including host-cell modification, parasite functional genomics and mosquito vector modification. The review question was structured to include studies investigating either SCD-related or malaria-related CRISPR applications, as well as studies investigating both conditions where available.

Protocol Registration

A review protocol was developed before the final literature search; however, it was not prospectively registered in PROSPERO or another publicly accessible systematic review registry. This absence of prospective registration is acknowledged as a limitation of the review. The final review methods were documented according to PRISMA 2020 reporting requirements, including transparent reporting of information sources, search strategies, study selection and synthesis procedures [11].

Information Sources and Search Strategy

A comprehensive literature search was conducted in PubMed and ScienceDirect as the primary literature databases, while Google Scholar was used as a supplementary literature search platform for identifying additional relevant publications and citation-linked studies. The final search was performed on 12 August 2026. Searches covered publications from 2015 to 2026 because this period represents the major expansion of CRISPR-Cas9 applications in clinical and experimental biomedical research.

The search strategy was developed using two separate concept blocks to capture the distinct evidence streams.

For PubMed, the sickle cell disease focused search strategy was:

("CRISPR-Cas9" OR CRISPR OR "clustered regularly interspaced short palindromic repeats")

AND ("sickle cell disease" OR "sickle cell anemia" OR SCD OR "HbS" OR *HBB* OR "beta globin" OR "β-globin" OR *HBG1* OR *HBG2* OR *BCL11A*)

The malaria-focused PubMed strategy was:

("CRISPR-Cas9" OR CRISPR OR "clustered regularly interspaced short palindromic repeats")

AND (malaria OR *Plasmodium* OR "*Plasmodium falciparum*" OR "*Plasmodium* berghei" OR Anopheles OR "malaria vector" OR "gene drive" OR "erythrocyte invasion")

For ScienceDirect, equivalent keyword searches were applied:

("CRISPR-Cas9" OR CRISPR) AND ("sickle cell disease" OR SCD OR *HBB* OR *HBG1* OR *HBG2* OR *BCL11A*)

and

("CRISPR-Cas9" OR CRISPR) AND (malaria OR *Plasmodium* OR Anopheles OR "malaria resistance" OR "parasite invasion" OR "gene drive")

For Google Scholar, supplementary searches were performed using search strings as adopted in ScienceDirect. However, the yields were numerous to be screened, the first 100 yields of the searches were considered as they were relevant literature.

Reference lists of included studies and relevant reviews were also screened to identify additional eligible publications. Search results, screening decisions and extracted information were recorded to maintain transparency and reproducibility.

Eligibility Criteria

Studies were included if they investigated CRISPR-Cas9 applications related to either SCD or malaria. Eligible SCD studies included investigations involving correction of the *HBB* mutation, modification of haemoglobin regulatory pathways, or evaluation of CRISPR-edited haematopoietic stem and progenitor cells. Eligible malaria studies included CRISPR-based modification of parasite genes, host erythrocyte factors influencing parasite invasion, or mosquito genetic modification relevant to malaria transmission.

Studies were excluded if they were review articles, editorials, conference abstracts without sufficient data, non-English publications, or studies

unrelated to CRISPR-Cas9 applications in SCD or malaria research.

Study Selection

Two reviewers independently screened titles and abstracts, followed by full-text assessment of potentially eligible studies. Disagreements were resolved through discussion or consultation with a third reviewer.

The selection of studies for this review followed a rigorous screening process as outlined in Figure 1. Initially, a total of 6407 records were identified, and after applying the appropriate filters, and deduplication in Zotero, 4658 records were removed and the remaining 1749 records were subjected to title and abstract screening. Following title and abstract screening, 31 records were assessed for eligibility, with 13 studies ultimately meeting the inclusion criteria and included in the final review. The exclusion of studies were primarily due to irrelevance or failure to report the required outcomes.

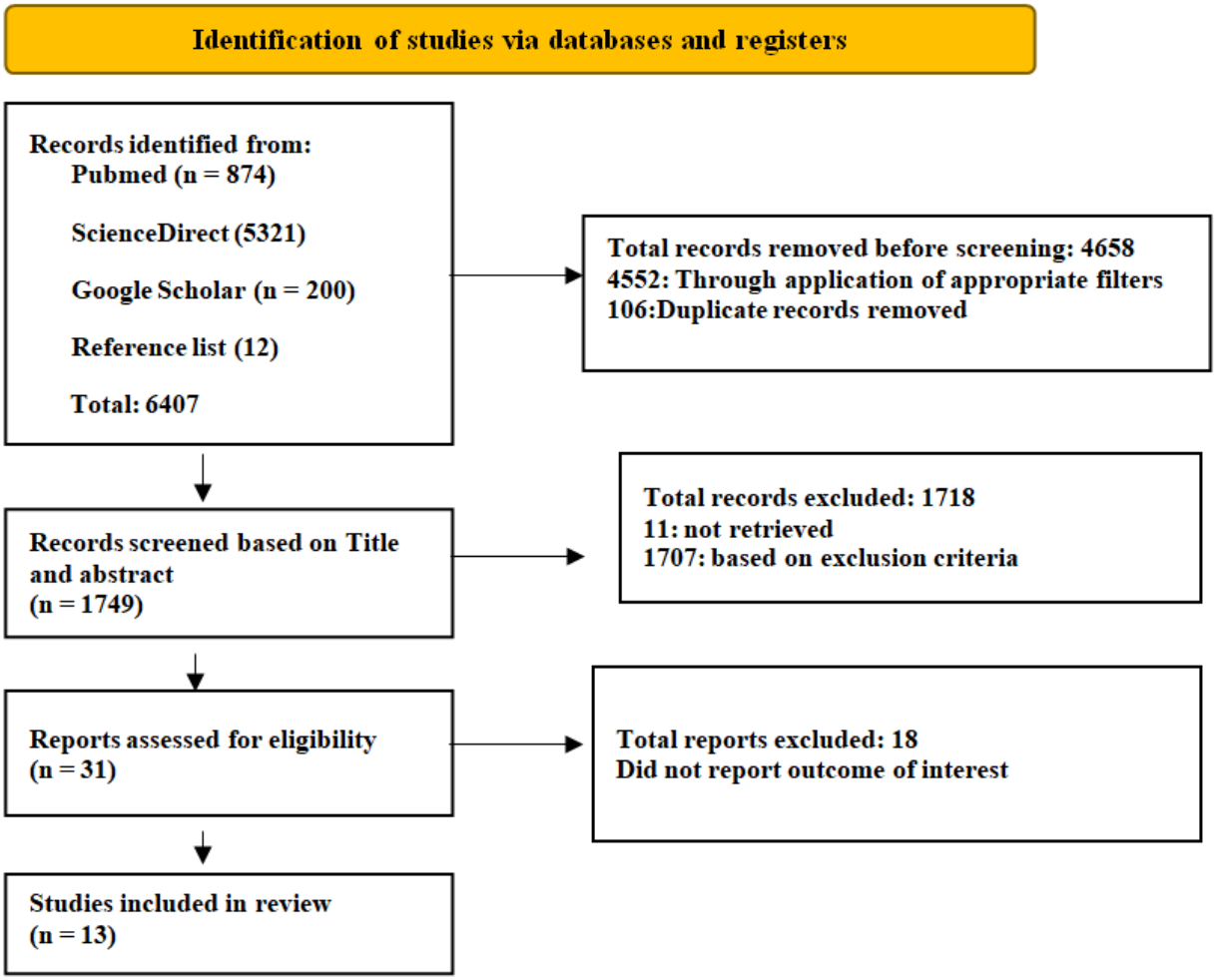

Figure 1: Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flow diagram

Quality Assessment

Quality and risk of bias of included studies were assessed using the Standard Quality Assessment Criteria For Evaluating Primary Research Papers was used to evaluate methodological quality, including sampling, outcome measurement, and reporting bias. This tool was chosen for its comprehensive framework that accommodates various study designs, ensuring a consistent and thorough assessment of the quality and reliability of the studies.

Most studies showed strong methodological quality, particularly in study design and outcome measurement, though some limitations were noted, such as the lack of randomization and blinding in certain clinical trials. Additionally, while control for confounding was not consistently addressed, the majority of studies provided sufficiently detailed results supporting the potential of CRISPR-Cas9 gene editing in SCD and malaria resistance. For more details, please refer to the Supplement File, which presents a detailed breakdown of the quality assessment of all included studies.

Data Extraction and Synthesis

Data were extracted using a standardised form capturing study characteristics, biological model, CRISPR target, delivery method, experimental design, outcomes, safety findings and study limitations.

Due to substantial heterogeneity across clinical trials, cellular experiments, animal studies, parasite investigations and vector studies, quantitative meta-analysis was not considered appropriate. Findings were synthesised narratively according to the major evidence categories.

Results

Overview of Included Studies

The systematic search identified 13 eligible studies investigating CRISPR-Cas9 applications in sickle cell disease (SCD) and malaria research. The included studies represented two distinct but biologically related evidence streams: (1) therapeutic genome-editing approaches for SCD and (2) experimental CRISPR-based applications relevant to malaria biology. Although both research areas are linked by their relevance to populations affected by haemoglobin disorders and malaria burden, no included study evaluated a single CRISPR-Cas9 intervention within the same biological system, participant population or experimental model that simultaneously corrected SCD and enhanced malaria resistance. Therefore, the findings were synthesised according to the specific research objective, biological model and translational stage of each study.

Six studies evaluated CRISPR-Cas9 applications for SCD treatment. These studies investigated three major therapeutic strategies: direct correction of the pathogenic *HBB* variant, induction of fetal haemoglobin (HbF) through regulatory genome editing, and clinical translation of edited autologous haematopoietic stem and progenitor cells (HSPCs). Preclinical studies using human CD34+ HSPCs and cellular models assessed editing efficiency, correction of sickle-associated molecular abnormalities and restoration of normal erythroid characteristics. Clinical studies focused mainly on HbF induction through disruption of erythroid regulatory pathways, particularly the *BCL11A* enhancer region and HBG1/*HBG2* regulatory elements.

The most advanced evidence within the SCD evidence stream was provided by Frangoul et al. (2024) [7], who evaluated exagamglogene autotemcel (exa-cel), a CRISPR-Cas9-edited autologous HSPC therapy. The study enrolled 44 participants with severe SCD and involved editing of the erythroid-specific enhancer region of *BCL11A* to increase fetal haemoglobin production. Among 30 evaluable participants, 29 (97%) achieved freedom from severe vaso-occlusive crises for at least 12 consecutive months, while all 30 evaluable participants achieved freedom from hospitalisation due to severe vaso-occlusive crises during the assessment period. The median follow-up duration was 19.3 months. These findings demonstrate clinical translation of CRISPR-Cas9 technology for SCD but should be interpreted separately from malaria-related applications. It is worthy of note that Frangoul et al. (2021) [5] and Frangoul et al. (2024) [7] report sequential follow-up results from the same single-arm clinical trial cohort of patients with severe sickle cell disease treated with exagamglogene autotemcel. To avoid double-counting, only the longest follow-up data from Frangoul et al. (2024) [7] were included in the quantitative evidence synthesis. The earlier report by Frangoul et al., (2021) [5] was retained only for contextual information on initial safety and methodology.

Seven studies investigated CRISPR-Cas9 applications relevant to malaria research. These studies were distributed across three experimental categories: modification of host erythrocyte factors involved in *Plasmodium* invasion, CRISPR-based functional genomics of malaria parasites, and genetic modification of mosquito vectors. Studies involving erythrocyte modification evaluated whether specific host-cell factors influenced parasite invasion, whereas parasite studies primarily examined gene function, genetic manipulation efficiency and mechanisms underlying parasite development. Vector studies investigated CRISPR-based gene-drive approaches intended to modify mosquito populations involved in malaria transmission.

The malaria-related evidence remained predominantly experimental and mechanistic. Studies involving *Plasmodium falciparum*, *Plasmodium* berghei and *Plasmodium yoelii* provided quantitative information relating to parasite editing efficiency, gene disruption success, parasite phenotype changes and functional genomic screening outcomes. Similarly, mosquito studies provided quantitative measurements of inheritance patterns and gene-drive performance. However, these findings do not represent evidence of clinically established malaria resistance in humans because the included studies did not evaluate CRISPR-modified human populations or clinical malaria prevention interventions.

Quantitative information was extracted from all included studies where available, including sample size, biological model, CRISPR target, editing

efficiency, molecular outcomes, clinical outcomes, experimental measurements, follow-up duration and reported safety findings. However, quantitative meta-analysis was not performed because of substantial heterogeneity in study designs, biological systems, intervention targets and outcome measures. The included evidence encompassed clinical trials involving human participants, cellular experiments, animal models, parasite systems and mosquito populations, making statistical pooling inappropriate. Instead, findings were synthesised narratively according to evidence stream and translational stage.

The detailed characteristics and quantitative outcomes of the included studies are summarised in Table 1.

Table 1. Characteristics and Quantitative Outcomes of Included Studies

Study	Evidence Stream	Study Design	Biological Model / Population	Sample Size	CRISPR-Cas9 Target / Strategy	Quantitative Outcomes Reported	Major Limitations
Wilkinson et al. (2021) [4]	SCD	Preclinical animal study	Edited human HSPCs transplanted into animal models	Experimental transplantation cohorts	CRISPR-Cas9 correction of β-globin mutation	Editing efficiency; engraftment; erythroid correction outcomes	Animal model limits clinical translation
Frangoul et al. (2021) [5]	SCD	Early clinical study	Patients with severe SCD receiving edited autologous HSPCs	Clinical participants	*BCL11A* enhancer editing to increase HbF	HbF increase; vaso-occlusive event reduction; safety outcomes	Small early clinical cohort
Sharma et al. (2023) [6]	SCD	Preclinical cellular study	Human erythroid cellular models	Cell-based experiments	*HBG1*/*HBG2* promoter editing	Editing efficiency; HbF expression; globin expression changes	Limited clinical evidence
Frangoul et al. (2024) [7]	SCD	Phase 3 clinical study	Patients with severe SCD receiving exa-cel	44 treated participants	*BCL11A* enhancer editing using autologous CD34+ HSPCs	29/30 evaluable participants achieved ≥12 months freedom from severe VOC; increased HbF; safety outcomes	Long-term durability requires continued monitoring
Kanjee et al. (2017) [8]	Malaria	Experimental molecular study	Human erythrocyte models	Laboratory erythrocyte systems	Knockout of erythrocyte determinants involved in parasite invasion	Parasite invasion changes; host factor effects	No clinical malaria outcomes
Jonsdottir et al. (2025) [9]	Malaria	Functional genomics study	*Plasmodium berghei*	Parasite populations	CRISPR-based parasite genome screening	Gene-editing performance and parasite phenotype outcomes	Experimental parasite model

Study	Evidence Stream	Study Design	Biological Model / Population	Sample Size	CRISPR-Cas9 Target / Strategy	Quantitative Outcomes Reported	Major Limitations
Gantz et al. (2015) [10]	Malaria	Vector genetics study	*Anopheles stephensi* mosquito populations	Laboratory mosquito populations	CRISPR-Cas9 gene-drive modification	Inheritance frequency and gene-drive transmission outcomes	Laboratory findings require ecological validation
Hoban et al. (2016) [13]	SCD	Preclinical experimental study	Human CD34+ HSPCs	Reported donor-derived HSPC samples	Direct correction of pathogenic *HBB* sickle mutation	Editing efficiency; corrected allele frequency; β-globin expression outcomes	In vitro model; limited prediction of clinical outcomes
Frati et al. (2024) [14]	SCD	Experimental study	SCD-related cellular models	Study-specific experimental samples	CRISPR-based globin pathway modification	Editing outcomes; molecular response measurements	Requires cautious interpretation of clinical relevance
Carrington et al. (2026) [15]	Malaria	Methodological study	*Plasmodium falciparum*	Parasite cultures	Marker-free CRISPR-Cas9 editing platform	Editing efficiency and genetic manipulation performance	Measures editing methodology, not malaria resistance
Nishi et al. (2021) [16]	Malaria	Experimental methodology study	*Plasmodium falciparum*	Parasite cultures	Efficient CRISPR-Cas9 parasite editing system	Editing success rates and genetic modification outcomes	No clinical translation
Zhang et al. (2017) [17]	Malaria	Parasite experimental study	*Plasmodium yoelii*	Experimental parasite models	CRISPR editing of parasite transmission-related genes	Parasite development and transmission-related outcomes	Limited ecological relevance
Kumari et al. (2025) [18]	Malaria	Experimental cellular study	Human erythrocyte models	Cell-based experiments	CRISPR modification of erythrocyte surface factors	Parasite invasion measurements and host-cell effects	Mechanistic evidence only

Narrative Synthesis

CRISPR-Cas9 Therapeutic Strategies for Sickle Cell Disease: Direct *HBB* Correction and Haemoglobin Regulation

The included SCD studies demonstrated two major therapeutic directions for CRISPR-Cas9-based intervention: direct correction of the pathogenic *HBB* variant responsible for sickle haemoglobin production and modification of regulatory pathways to increase fetal haemoglobin (HbF) expression. These approaches represent different biological strategies and were therefore synthesised separately. Direct correction aims to restore normal β-globin production by repairing the disease-causing mutation, whereas HbF induction seeks to reduce disease severity by increasing expression of γ-globin-containing haemoglobin that inhibits sickling.

Hoban et al. (2016) [13] provided early evidence supporting the feasibility of direct *HBB* correction using CRISPR-Cas9 in human CD34+ haematopoietic stem and progenitor cells (HSPCs). The study demonstrated that targeted genome editing could correct the sickle mutation in clinically relevant stem-cell populations and restore production of corrected β-globin. Quantitative outcomes from this study included editing efficiency, corrected allele frequency and erythroid differentiation outcomes. Although these findings established technical feasibility, the approach remained preclinical because clinical translation requires consistently high correction rates, efficient delivery into long-term repopulating HSPCs and durable contribution of corrected cells after transplantation.

Wilkinson et al. (2021) [4] extended this approach by evaluating CRISPR-Cas9-mediated β-globin correction in transplantation models. The study assessed whether edited HSPCs could contribute to functional erythropoiesis after engraftment. Outcomes included editing performance, donor-cell contribution and correction of sickling-related cellular abnormalities. These findings strengthened the evidence that genome correction could potentially provide a durable therapeutic approach but also highlighted challenges associated with transplantation procedures, conditioning regimens and achieving sufficient corrected-cell populations.

A separate therapeutic pathway involved increasing HbF expression by modifying regulatory elements controlling globin switching. Frangoul et al. (2021) [5] investigated CRISPR-Cas9 editing of the erythroid-specific enhancer region of *BCL11A*, a transcriptional regulator that suppresses γ-globin expression after birth. The study demonstrated that editing this regulatory element increased HbF production and produced clinical improvement in a patient with SCD. Importantly, this intervention did not correct the sickle mutation itself; instead, it reduced disease severity through restoration of a protective haemoglobin profile.

Similarly, Sharma et al. (2023) [6] evaluated CRISPR-Cas9 editing of the *HBG1* and *HBG2* promoter regions to increase HbF expression. The study demonstrated sustained fetal haemoglobin induction following promoter modification in edited CD34+ HSPCs and supported the concept that modifying haemoglobin regulation may provide an alternative therapeutic pathway to direct mutation correction. These findings reinforce the importance of distinguishing HbF induction strategies from approaches designed to repair the underlying *HBB* mutation.

Frati et al. (2024) [14] contributed additional evidence regarding CRISPR-based approaches for SCD by evaluating editing-related outcomes in disease-relevant experimental systems. The study provided further information regarding molecular responses following genome editing but remained within the preclinical evidence category. Therefore, its findings should be interpreted as supporting biological feasibility rather than demonstrating clinical effectiveness.

Overall, the SCD evidence stream demonstrates progressive movement from experimental correction of the sickle mutation toward clinically translated HbF-enhancing strategies. The available evidence indicates that CRISPR-Cas9 approaches can modify disease-associated haemoglobin pathways, but the therapeutic mechanisms differ considerably and should not be considered equivalent.

Clinical Translation of CRISPR-Cas9 Editing in Sickle Cell Disease

Among the included studies, Frangoul et al. (2024) [7] provided the most advanced evidence of clinical translation of CRISPR-based SCD therapy. The Phase 3 study evaluated exagamglogene autotemcel (exa-cel), an autologous HSPC therapy in which CRISPR-Cas9 was used to edit the erythroid-specific enhancer region of *BCL11A* to increase HbF production. The study enrolled 44 individuals with severe SCD who received edited autologous CD34+ HSPCs.

The study reported a median follow-up duration of 19.3 months. Among 30 evaluable participants, 29 achieved freedom from severe vaso-occlusive crises for at least 12 consecutive months, while all 30 evaluable participants achieved freedom from hospitalisation due to severe vaso-occlusive crises during the assessment period. These findings represent clinical evidence that CRISPR-Cas9-edited autologous

HSPCs can produce meaningful disease modification in selected patients.

However, the clinical application of CRISPR-Cas9 therapy involves more than the editing procedure itself. Treatment requires stem-cell mobilisation, collection, ex vivo editing, myeloablative conditioning, reinfusion and prolonged monitoring. Therefore, although the evidence demonstrates substantial therapeutic benefit, important considerations remain regarding long-term safety, accessibility, infrastructure requirements and affordability, particularly in regions where SCD burden is highest.

CRISPR-Cas9 Applications in Malaria Research: Host-Cell Determinants and Parasite Functional Genomics

The malaria-related studies represented a separate experimental evidence stream involving host erythrocyte biology, parasite genome manipulation and malaria-vector research. Unlike the SCD studies, none of the malaria studies evaluated a CRISPR-based clinical intervention in humans or demonstrated population-level malaria resistance.

Kanjee et al. (2017) [8] investigated host erythrocyte determinants involved in *Plasmodium falciparum* invasion using CRISPR-based gene disruption approaches. The study provided insights into how specific host-cell factors influence parasite entry into red blood cells. Similarly, Kumari et al. (2025) [18] examined genetically modified erythrocyte systems to investigate interactions between host-cell surface components and malaria parasite invasion. These studies contribute to understanding parasite-host interactions but remain mechanistic investigations rather than evidence of therapeutic malaria resistance.

Several studies focused on improving CRISPR-based manipulation of malaria parasites. Carrington et al. (2026) [15] developed a marker-free CRISPR-Cas9 editing approach for *Plasmodium falciparum*, improving the ability to investigate parasite gene function. This study represents a methodological advance in malaria research but does not provide evidence of SCD-related editing, human malaria resistance or clinical intervention.

Jonsdottir et al. (2025) [9] evaluated CRISPR-based genetic screening approaches in *Plasmodium* berghei, enabling investigation of parasite genes involved in biological processes relevant to malaria infection. Nishi et al. (2021) [16] similarly contributed to parasite genome-editing methodology by improving CRISPR-Cas9 efficiency in P. falciparum. Zhang et al. (2017) [17] applied CRISPR-Cas9 editing in *Plasmodium yoelii* to investigate parasite genes associated with development and transmission-related processes.

Collectively, these studies demonstrate that CRISPR-Cas9 has become a valuable research tool for malaria biology by enabling targeted investigation of parasite genes and host-parasite interactions. However, the evidence remains largely experimental and should not be interpreted as demonstrating a CRISPR-based malaria treatment or clinically established malaria resistance.

CRISPR-Based Vector Modification and Current Evidence for Malaria Control

The included malaria evidence also contained one vector-directed study investigating genetic modification of mosquito populations. Gantz et al. (2015) [10] demonstrated the use of CRISPR-Cas9 gene-drive technology in *Anopheles stephensi* to promote inheritance of engineered genetic traits through mosquito populations.

The study provided quantitative evidence regarding gene-drive inheritance and genetic transmission efficiency under laboratory conditions. However, laboratory demonstration of gene-drive inheritance does not directly demonstrate reduced malaria transmission in natural populations. Translation into malaria-control programmes requires additional evaluation of ecological effects, stability of genetic constructs, population dynamics, environmental safety and governance considerations.

Therefore, mosquito-directed CRISPR applications should be interpreted separately from both SCD gene therapy and host-directed malaria research because they involve different biological systems, objectives and ethical considerations.

Comparative Interpretation of Evidence Streams, Translational Stage and Knowledge Gaps

The included studies demonstrate two distinct developmental pathways for CRISPR-Cas9 research. The SCD evidence stream has progressed from laboratory proof-of-concept studies to clinical application, with human trials demonstrating measurable therapeutic outcomes through modulation of haemoglobin regulation. In contrast, malaria-related applications remain primarily mechanistic and preclinical, focusing on understanding parasite biology, modifying host-cell interactions or exploring vector-control approaches.

The difference in evidence maturity reflects the distinct objectives of these research areas. SCD studies measure outcomes directly related to patient health, including haemoglobin production, vaso-occlusive events and treatment safety. Malaria studies measure laboratory outcomes such as parasite gene function, erythrocyte invasion, genetic transmission and vector modification. These outcomes cannot be statistically

combined because they represent fundamentally different biological questions.

The relationship between SCD and malaria provides an important scientific rationale for examining these fields together, particularly because both conditions have major relevance in populations affected by haemoglobin disorders and malaria burden. However, the current evidence does not demonstrate a single CRISPR-Cas9 intervention that simultaneously treats SCD and provides malaria resistance.

Future research should therefore proceed along these separate translational pathways. For SCD, priorities include improving accessibility, reducing treatment complexity and evaluating long-term safety. For malaria, future work requires progression from laboratory findings toward evidence demonstrating effectiveness, safety and feasibility at population level. Overall, CRISPR-Cas9 represents an advancing therapeutic platform for SCD and a promising experimental technology for malaria research, but the maturity and implications of these applications remain substantially different.

Discussion

Major Findings

This systematic review examined CRISPR-Cas9 applications in sickle cell disease (SCD) and malaria research as two related but distinct scientific pathways. The findings demonstrate that CRISPR-Cas9 has achieved markedly different levels of translational development across these fields. Within SCD research, genome editing has progressed from experimental correction of disease-associated mutations and haemoglobin regulation strategies to clinical application through autologous haematopoietic stem and progenitor cell (HSPC) therapies. In contrast, malaria-related CRISPR applications remain primarily focused on understanding parasite biology, modifying host-parasite interactions and exploring vector-control approaches.

The distinction between these evidence streams is important because the biological relationship between SCD and malaria does not imply that a single CRISPR intervention currently treats SCD while simultaneously generating malaria resistance. The included studies demonstrate separate applications of the same genome-editing technology for different biological objectives. This finding supports the need for cautious interpretation of CRISPR-Cas9 research at the intersection of these diseases.

Progression of CRISPR-Cas9 Therapy in Sickle Cell Disease

The findings from this review are consistent with the broader evolution of SCD gene therapy, where therapeutic strategies have shifted from direct correction of the *HBB* mutation towards approaches that increase fetal haemoglobin (HbF) production. Although direct mutation correction remains an attractive strategy because it addresses the underlying genetic defect, clinical progress has been faster for approaches that modify haemoglobin regulation pathways.

Previous studies have highlighted the therapeutic value of increasing HbF as a means of reducing sickling-related complications. Esrick et al. (2021) [19] demonstrated that sustained HbF induction through gene-based approaches could provide meaningful clinical improvement in individuals with severe SCD, supporting the principle that restoring protective haemoglobin expression may be a practical therapeutic pathway. Similarly, Leonard & Tisdale (2023) [20] emphasised that emerging gene therapies for SCD represent a shift from symptom management towards disease-modifying approaches but require careful consideration of treatment complexity, safety and accessibility.

The findings from this review reinforce this trend. The included SCD studies demonstrated that CRISPR-Cas9 can be applied through multiple mechanisms, including direct *HBB* correction and modification of regulatory elements controlling HbF expression. However, these mechanisms should not be considered interchangeable. Increased HbF expression represents a compensatory therapeutic strategy, whereas *HBB* correction represents restoration of the normal β-globin sequence.

The clinical evidence surrounding exagamglogene autotemcel (exa-cel) represents a major advancement in the field. Independent assessments of exa-cel have similarly reported substantial reductions in vaso-occlusive events and sustained improvements in haemoglobin parameters among treated individuals [21]. However, these findings must be interpreted alongside the requirements of autologous cell therapy, including mobilisation, apheresis, manufacturing, conditioning chemotherapy and prolonged monitoring. Recent evaluations have emphasised that the therapeutic outcome depends not only on editing efficiency but also on the feasibility of delivering the entire treatment pathway [22].

Safety, Durability and Implementation Challenges in CRISPR-Based SCD Therapy

Although CRISPR-Cas9-based therapies have demonstrated encouraging clinical outcomes, several

challenges remain before they can become widely accessible, particularly in regions with the highest SCD burden. The requirement for specialised cell-processing facilities, myeloablative conditioning and long-term clinical monitoring creates significant implementation barriers.

Safety monitoring remains particularly important because genome editing introduces concerns regarding unintended genetic alterations, clonal selection and long-term genomic stability. Recent analyses of exa-cel have continued to evaluate off-target editing profiles and editing specificity as more patients receive treatment outside clinical trials. Yen et al. (2024) [23] reported continued assessment of CRISPR-Cas9 editing specificity in exa-cel-treated patients, highlighting the importance of ongoing surveillance as clinical exposure increases.

Furthermore, access remains a major consideration. Although CRISPR-based therapies represent a scientific advance, their current delivery model depends on highly specialised healthcare systems. This creates an important gap between therapeutic availability and population need, particularly in sub-Saharan Africa where SCD prevalence is substantial but access to advanced cellular therapies remains limited. Future implementation strategies must therefore consider financing models, local healthcare capacity, workforce development and equitable access mechanisms.

CRISPR Applications in Malaria Research Remain Primarily Experimental

Unlike SCD, malaria-related CRISPR research has not reached clinical application. The malaria studies included in this review primarily investigated parasite biology, host-cell interactions and mosquito genetic modification. These applications provide valuable scientific knowledge but should not be interpreted as evidence that CRISPR has produced malaria-resistant humans or clinically effective malaria-control interventions.

CRISPR-based parasite editing has become an important research tool because it enables targeted investigation of parasite genes involved in growth, development and host interaction. However, improved genetic manipulation of *Plasmodium* does not directly translate into reduced malaria burden. Instead, these approaches contribute to identification of potential drug targets, understanding parasite biology and developing future intervention strategies.

Similarly, host erythrocyte modification studies provide insight into parasite invasion mechanisms but remain distant from human application. Altering erythrocyte receptors or other host determinants may affect parasite entry, but such interventions require extensive assessment of physiological consequences because these molecules may perform important functions beyond malaria infection.

Implications of CRISPR-Based Vector Modification for Malaria Control

The inclusion of mosquito gene-drive research highlights another distinct pathway for malaria intervention. Gene-drive technologies have generated considerable interest because they may allow engineered genetic traits to spread through mosquito populations. Previous work has demonstrated the potential of CRISPR-based gene drives to modify mosquito populations under laboratory conditions [24].

However, laboratory success does not automatically demonstrate effectiveness in natural environments. Ecological interactions, mosquito population structure, resistance development, environmental effects and governance issues must be considered before field implementation. The World Health Organization has emphasised that genetic approaches for malaria control require robust assessment frameworks, community engagement and careful evaluation of risks and benefits [25].

Therefore, mosquito-directed CRISPR applications should be interpreted as emerging malaria-control technologies rather than established interventions.

Future Directions for Integrated SCD and Malaria Research

The biological relationship between SCD and malaria provides a strong rationale for continued research linking these fields, but future investigations should maintain clear distinctions between therapeutic objectives. The current evidence supports two separate translational pathways: CRISPR-Cas9 as an emerging clinical therapy for SCD and CRISPR-Cas9 as a research and development platform for malaria biology.

Future SCD research should focus on improving safety, reducing treatment complexity, expanding access and evaluating long-term outcomes. For malaria, priorities include translating laboratory discoveries into validated interventions while addressing ecological, ethical and implementation considerations.

The findings of this review therefore suggest that CRISPR-Cas9 represents a powerful but differently positioned technology across these disease areas. Clinical translation has been demonstrated for selected SCD applications, whereas malaria-related applications remain largely experimental. Continued research should build on these advances while ensuring that conclusions remain aligned with the maturity of available evidence.

Limitations of the Study

This review has some methodological limitations. The literature search was conducted using PubMed, ScienceDirect and Google Scholar as a supplementary source; however, the exclusion of other databases such as Embase, Scopus and Web of Science may have resulted in missed relevant studies. The restriction to English-language publications and studies published between 2015 and 2026 may also have introduced language and publication-period bias. Additionally, excluding unpublished studies, conference abstracts without sufficient data and inaccessible full-text articles may have limited the comprehensiveness of the evidence base.

A major limitation arising from the findings is the substantial heterogeneity among the included studies. The evidence included clinical trials, cellular studies, animal models, parasite investigations and mosquito vector studies, with different biological targets and outcome measures. Therefore, quantitative pooling was not feasible, and findings were synthesised narratively. Furthermore, no included study evaluated a single CRISPR-Cas9 intervention that simultaneously treated SCD and produced malaria resistance. Thus, the relationship between these two applications should be interpreted as two connected but distinct research pathways, with SCD applications demonstrating greater clinical maturity than malaria-related applications, which remain largely experimental.

Conclusion

This systematic review demonstrates that CRISPR-Cas9 applications in sickle cell disease (SCD) and malaria research represent two distinct but biologically connected evidence streams rather than a single dual-purpose therapeutic approach. The findings show that CRISPR-Cas9 has progressed to clinical application in SCD through strategies that modify haemoglobin biology, particularly fetal haemoglobin induction through regulatory editing of targets such as *BCL11A*. Direct *HBB* correction remains an important experimental pathway, while HbF-inducing approaches currently provide the strongest clinical evidence for disease modification. In contrast, malaria-related CRISPR applications remain predominantly experimental, involving host erythrocyte modification, parasite functional genomics and mosquito-vector engineering. Current evidence does not demonstrate a CRISPR-Cas9 intervention that simultaneously corrects SCD and confers malaria resistance in humans.

The evidence also highlights substantial differences in translational maturity between the two fields. Clinical SCD studies provide measurable patient outcomes, including reductions in vaso-occlusive events and improved haemoglobin profiles, but implementation remains challenged by treatment complexity, cost, specialist infrastructure requirements and long-term safety monitoring. Conversely, malaria-related studies have advanced understanding of parasite biology, host-pathogen interactions and potential vector-control strategies, but further research is required before these approaches can support clinical or population-level malaria interventions. Therefore, claims regarding CRISPR-based malaria resistance should remain cautious and limited to the specific experimental outcomes demonstrated by current studies.

Future research should continue to develop CRISPR-Cas9 technologies along these separate translational pathways while addressing remaining scientific, ethical and implementation challenges. For SCD, priorities include improving accessibility, affordability, durability and safety of genome-editing therapies, particularly in regions with the greatest disease burden. For malaria, future investigations should focus on validating experimental findings, assessing ecological and population-level implications of vector modification, and establishing safe pathways for translation. Overall, CRISPR-Cas9 represents a clinically advancing therapeutic platform for selected SCD applications and a promising experimental tool for malaria research, but the current evidence supports continued distinction between these fields rather than a unified dual-action intervention.

Supplementary Materials

Supplementary file available via: https://www.journalehdi.com/suppfile/769/Supplement-file-ehdi054.pdf

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