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Evidence-based interventions for reducing sickle cell disease-associated morbidity and mortality in sub-Saharan Africa: A scoping review

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Abstract

Objective: Sickle cell disease is a lifelong illness affecting millions of people globally, but predominantly burdensome in sub-Saharan Africa, where most affected children do not live to adulthood, despite available evidence-based interventions that reduce the disease burden in high-income countries.

Method: We reviewed studies evaluating evidence-based interventions that decrease sickle cell disease-related morbidity and mortality among children living in sub-Saharan Africa. We used the Joanna Briggs scoping review methodological framework and grouped identified evidence-based interventions into preventative pharmacotherapeutic agents, newborn screening and comprehensive healthcare, disease-modifying agents, nutritional supplementation, systemic treatment, supportive agents and patient/carer/population education.

Results: We included 36 studies: 18 randomized controlled trials, 11 observational studies, 5 before-and-after studies and 2 economic evaluation studies, with most of the studies performed in West African countries. Included studies suggest evidence-based interventions effectively to reduce the common morbidities associated with sickle cell disease such as stroke, vaso-occlusive crisis, acute chest syndrome, severe anaemia and malaria infection. Evidence-based interventions also improve survival among study participants. Specifically, our review shows hydroxyurea increases haemoglobin and foetal haemoglobin levels, a finding with practical implications given the challenges with blood transfusion in this setting. The feasibility of implementing individual interventions is hampered by challenges such as affordability, accessibility and the availability of financial and human resources.

Conclusion: Our review suggests that regular use of low-dose hydroxyurea therapy, sulphadoxine–pyrimethamine chemoprophylaxis, L-arginine and Omega-3 fatty acid supplementation and establishment of specialist stand-alone sickle cell clinics could reduce the sickle cell disease-associated morbidity and mortality in sub-Saharan Africa countries.

Keywords

sickle cell disease, evidence-based medicine, scoping review, sub-Saharan Africa

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Introduction

Sickle cell disease (SCD) is one of the common inherited haematological disorders, accounting for approximately 300,000 births every year globally, with sub-Saharan Africa (SSA) accounting for 75% of the global births.[1–3] SCD is an autosomal recessive Mendelian disease due to a single-base mutation in the beta-globin gene on chromosome 11.[2] SCD accounts for 6.4% of under-5 mortality in SSA.[4] In the absence of early and appropriate care, at least 50% of

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children born with SCD die before 5 years of age,[5] and the survivors are at an increased risk of infections, severe anaemia, and other morbidities including stroke, hypertension, dactylitis, acute chest syndrome and renal disease.[4,6] About 1%–2% of births in SSA have SCD – the highest worldwide, with the highest prevalence in Nigeria (3%).[7–9]

Patients with haemoglobin (Hb) S alleles from heterozygote parents, Hb AS (sickle cell trait), suffer from sickle cell anaemia (SCA) – the most severe form of SCD.[10] There are over 700 structural haemoglobin variants, but Hb SS disease (called SCA) and Hb SC disease are the two most common syndromes of SCD in SSA.[2,5] The distribution of SCD in the tropical regions is explicable by the 'malaria hypothesis', which asserts that the high incidence of SCD is probably due to the selective advantage conferred by the Hb AS trait to protect against *Plasmodium falciparum* malaria infection in endemic regions.[11] Although the trait is protective, homozygous SCD patients are predisposed to hyperinfection from malaria and reduced survival.[11,12]

The abnormal Hb variants, Hb S and Hb C, deform and become insoluble in low oxygen tension, and they become trapped in the microcirculation. Tissues downstream of this blockade do not receive sufficient blood supply and oxygen, hence suffer ischemic damage, with life-threatening consequences.[10] Although SCD is primarily a disease of red blood cells, multi-organ involvement occurs over time. Anaemia, low foetal haemoglobin (HbF) levels, hypoxia, high leucocyte count and infections with bacteria, viruses and malaria precipitate sickle cell crisis which could be vaso-occlusive crisis (VOC), sequestration crisis, anaemic crisis, hyper haemolytic crisis and aplastic crisis.[1] These severe acute conditions account for the increased morbidity and mortality in SCD patients.[1,13]

Improved health and survival of SCD patients in high-income countries (HIC) is attributed to a well-organized support system with early and adequate care of patients.[14,15] Simple, cost-effective interventions such as newborn screening (NBS) for early identification of SCD patients and the subsequent provision of comprehensive care (hydroxyurea therapy, antibiotic prophylaxis, blood transfusions, etc.) have significantly reduced SCD mortality in HIC; with up to 94% surviving to 18 years in the United States and 99% to 20 years in the United Kingdom.[16,17] Evidence-based interventions (EBIs) have improved the quality of life and survival of SCD patients in HIC, with life expectancy of SCD patients increasing to approximately 55 years.[18]

The World Health Organization (WHO) estimates that about 70% of SCD deaths in SSA are preventable using EBIs.[1] Despite the availability of EBIs that reduce SCD morbidity and mortality, the disease still poses a significant problem in SSA, especially children under-5 years, with catastrophic consequences on household assets.[19,20] EBIs are peer-reviewed practices, methods or programmes with documented empirical evidence of effectiveness.[21] Hence, we sought to review the EBIs that reduce SCD-associated morbidity and mortality among children living in SSA. The objective of this scoping review, therefore, is to identify interventions that effectively reduce SCD morbidity and mortality among SSA children. Our review findings could guide clinical management of SCD patients while providing policymakers evidence for implementing SCD interventions in SSA countries

Methods

We conducted this review of EBIs that reduce SCD-associated morbidity and mortality in children in SSA based on the Joanna Briggs Institute Reviewers' Manual for a Scoping Review's framework and reported following the PRISMA Extension for Scoping Review.[22,23]

Inclusion and exclusion criteria

We included randomized controlled trials (RCTs), before-and-after studies, observational studies and economic evaluation studies that evaluated evidence for the effectiveness of interventions for reducing SCD-associated morbidities and mortality among children living in SSA countries. Participants were children (⩽18 years) who have been diagnosed with all forms of SCD (HbSS, HbSC and HbS beta-thalassemia). There was no limit to the year of publication but limited our search to studies published in English.

We excluded interventions directed towards only adults with SCD and non-SCD patients. We also excluded a study if only the abstract was available; the publication was a case study or series or the publication was an opinion piece, editorial, commentary or a review.

Search strategy

To identify relevant studies, we searched eight databases: PubMed/MEDLINE, CINAHL (via EBSCO), Cochrane Library, EMBASE (via Ovid), Web of Science, WHO Hemoglobinopathy Trial Registry and Pan African Trials registry, Clinicaltrials.gov from inception of each database to date on 17 June 2022 with the help of a medical/health librarian. We updated our search on 31 May, 2023. Two reviewers (EEA and UJE) combined search terms using 'AND' and 'OR' Boolean operators with the help of a health librarian to retrieve the studies separately from each database. In each of these databases, we used the following MeSH terms: 'sickle cell disease', 'sickle cell anaemia', 'interventions', 'blood transfusion', 'exchange blood transfusion', 'antibiotic prophylaxis', 'oral penicillin prophylaxis', 'newborn screening', 'analgesics', 'analgesic agent', 'antimalarial agent', 'chloroquine', 'antimalarial chemoprophylaxis', 'proguanil', 'pneumococcus vaccine', 'pneumococcal conjugate vaccination', 'vitamin supplementation', 'diet supplementation', ' folic acid', ' folate supplementation', ' iron chelating agent', ' patient education',

'morbidity', 'mortality', 'mortality rate', 'death', 'survival', 'survival rate', 'survival analysis', 'economic evaluation', 'Africa south of the Sahara', 'sub-Saharan Africa', 'Angola', 'Benin', 'Botswana', 'Burkina Faso', 'Burundi', 'Cameroon', 'Cape Verde', 'Central African Republic', 'Chad', 'Comoros', 'Congo Democratic Republic', 'Congo Republic', 'Côte d'Ivoire', 'Djibouti', 'Eritrea', 'Eswatini', 'Ethiopia', 'Gabon', 'Gambia', 'Ghana', 'Guinea', 'Equatorial Guinea', 'Guinea-Bissau', 'Kenya', 'Lesotho', 'Liberia', 'Madagascar', 'Malawi', 'Mali', 'Mauritania', 'Mauritius', 'Mayotte', 'Mozambique', 'Namibia', 'Niger', 'Nigeria', 'Rwanda', 'São Tomé and Príncipe', 'Senegal', 'Seychelles', 'Sierra Leone', 'Somalia', 'South Africa', 'South Sudan', 'Sudan', 'Tanzania', 'Togo', 'Uganda', 'Zambia' and 'Zimbabwe'.

We supplemented these with search of grey literature websites and also searched Google Scholar which retrieved a massive number of hits. Since these hits were ordered based on their relevance, we searched the first 500 hits (i.e. 50 pages). To identify additional studies, we also performed backward citation tracking (i.e. searched the reference lists of the included studies) and forward citation tracking (i.e., searched for studies that cited the included studies).

Two reviewers (EEA and UJE) independently performed the study selection process in three steps. In the first step, we used Mendeley Desktop to remove duplicates from all retrieved studies. In the second step, we checked the titles and abstracts of the remaining articles for eligibility for inclusion. Finally, we screened the full texts of the studies selected in the previous step. Disagreements between them in the second and third steps were resolved through discussion.

Data charting

Three reviewers (EEA, UJE and GOE) extracted data from the selected studies into a predesigned charting table. The data include study author(s), year of publication, study country, study objectives, study population and sample size, study design, intervention type, comparator/control groups and details of these (e.g. duration of the intervention) and study outcomes. We pretested the chart on three of the included studies to ensure feasibility, completeness and consistency of data extraction, and iteratively refined the chart as needed. Disagreements were resolved through discussion.

We (EEA, UJE and GOE) employed the appropriate JBI Critical Appraisal tool to formally assess the methodological quality of the included studies based on their different designs.[22,24,25] We assessed studies for both internal and external validity and categorized included studies based on their aggregate score from this assessment into high-quality study (scored $\geqslant$8.0), moderate quality (scored 5.0–7.99) and low-quality (scored $<$5.0). At least two authors independently reviewed each study, and score disagreements were resolved by the third author.

Data synthesis

Data extracted from the included studies were synthesized using the narrative approach, wherein data were summarized and described using texts, tables and figures. More specifically, we began by describing the metadata of the included studies (e.g. year of publication and country of publication). Then, we presented the EBIs under the following themes as per the WHO SCD guidelines: disease-modifying agents, preventative pharmacotherapeutic agents, supportive care agents, NBS, comprehensive healthcare management, nutritional supplementation, systemic treatments and patients' and population-level health education.[26]

Results

Description of included studies

We identified 1151 articles from the databases and 177 articles from other sources. After removing 41 duplicate articles, the titles and abstracts of the remaining 1287 articles were screened. Out of these, we assessed the full texts of 165 articles for inclusion based on the inclusion criteria. We excluded 129 articles for the following reasons: no empirical evaluation of the effectiveness of the intervention (n=42), non-SSA countries (n=40), non-English language studies (n=12), non-evidenced-based studies (n=10), study protocols (n=5), abstracts (n=5) and adults population only (n=15). Finally, 36 articles were included in this study[7,27–60] – Figure 1.

Included studies were 18 RCTs, 5 before-and-after studies, 11 observational studies and 2 economic evaluation studies (Table 1). Included studies were conducted in Nigeria (n=19), Uganda (n=7), Angola (n=4), Tanzania (n=4), Benin (n=3), Congo DR (n=3), Malawi (n=3), two each in Ghana and Sudan; and one in Kenya. The duration of included studies ranged from 1.4 months to 120 months, with a study mean duration of 31.03 months. Primary studies included between 12 and 228,169 participants, with average female involvements was 49.3%. Included studies identified EBI, which we grouped into eight themes—Figure 2.

Among the 15 to 18 RCTs, 9 were assessed as high-quality,[35,39–41,44,46,50,52] 7 moderate-quality,[7,43,45,47,49,53] and 2 low-quality.[48] Of note, more than 90% of included RCT were rated as low risk of a measurement bias because of the reliability of measurement outcomes and statistical analysis – Supplemental material 1. Of the observational studies, four were rated as high-quality,[34,38,42,51] and seven as moderate-quality[27,32,33] – Supplemental materials 2 and 3. All five before-and-after studies and two economic evaluation studies were moderate-quality studies[28–31,36,37,61] – Supplemental materials 4 and 5.

Comprehensive healthcare management

Comprehensive healthcare provides holistic care for patients including patient education and management of acute

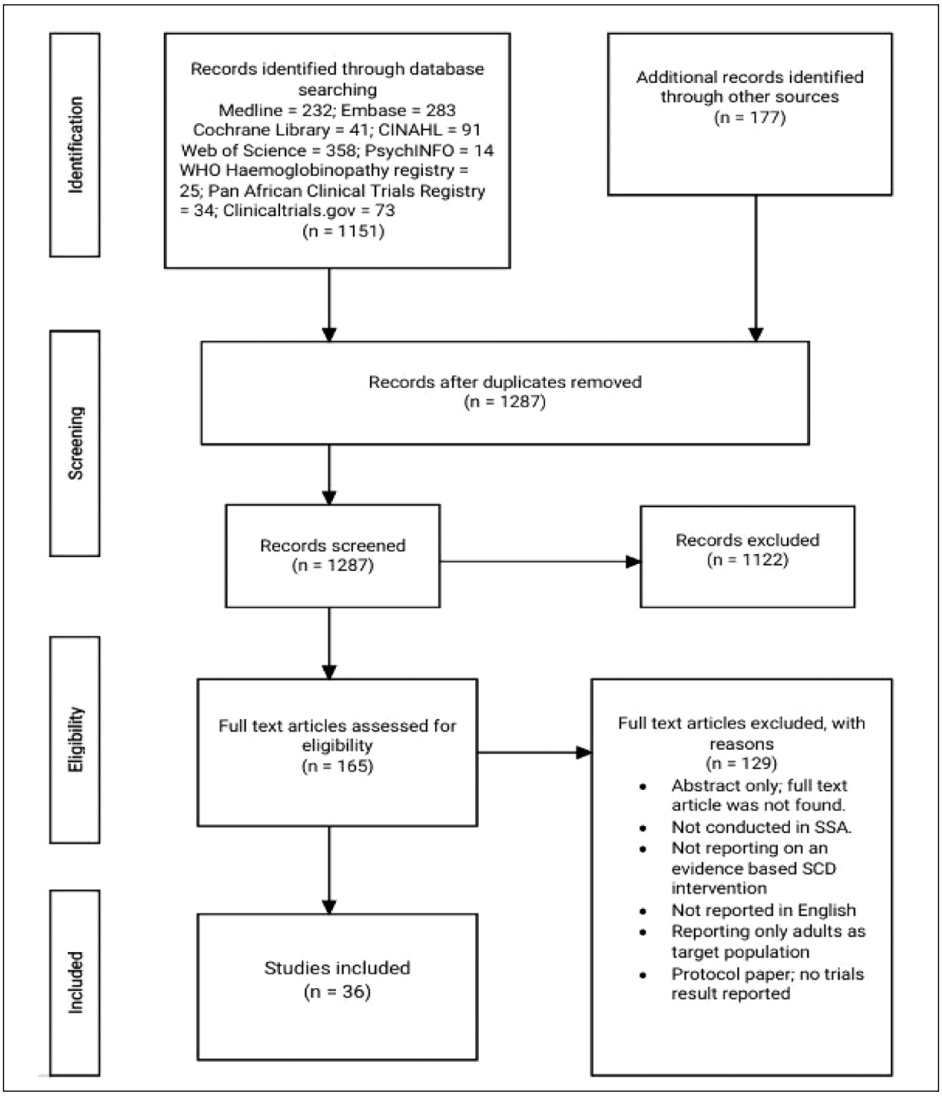

Figure 1. PRISMA flow diagram for the identification process of included studies.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

manifestations of SCD. Both before-and-after study and observational study demonstrated that this intervention provided significant improvements in the clinical outcomes of children.[27,28,30] Akinyanju et al. studied further demonstrating improved survival.[27]

Disease-modifying agents

Hydroxyurea (HU) therapy effectively reduced SCD-related adverse events among children, especially stroke incidence and VOC.[29,31,33–35,54–61] In addition, HU therapy showed favourable haematological indices and led to a decline in mortality among children who received it.[61] Furthermore, HU therapy showed low risk of haematological harm.[61] Galandaci et al. 's study evaluating a moderate fixed-dose HU therapy for prevention of strokes demonstrated HU therapy effectively reduced risk of developing stroke.[31] Studies by Abdullahi et al. further posited that low-dose hydroxyurea therapy also reduces both stroke incidence and recurrence and has no significant difference when compared to moderate dose.[54,55,59]

NBS, comprehensive primary health screening and economic evaluation

Moreover, NBS and comprehensive care was associated with reduced mortality.[62] Furthermore, Kuznick et al. demonstrated that the average cost per disability-adjusted-life-years (DALY) was lower than the gross domestic product (GDP) in 34 SSA countries.[37] McGann et al.'s study likewise demonstrated the cost-effectiveness of the intervention.[36]

Nutritional supplementation

Onalo et al. showed that arginine supplementation reduced inpatient pain, shortened time to crisis resolution,[41] and Cox et al. showed it improved the basal metabolic index,

Table 1. Description of studies included in this scoping review.

Interventions	Study and year	Country	Study objective(s)	Study design	Sample size (sex/gender)	Study duration (months)	Intervention type	Target population	Outcome: morbidity	Outcome: mortality	Result
Comprehensive healthcare	Akinyanju et al.[27]	Nigeria	To examine the outcome of holistic care for patients with SCA.	Prospective observational study	1223 (NR)	92	Comprehensive care management.	Children and adults	Hospital admission, blood transfusion.	Yes	Yes ($p < 0.0001$). Improved survival and clinical outcome for participants.
	Mbiya et al.[28]	Congo DR	To demonstrate the feasibility and accessibility of adapted care for children with SCD from low-income families based on reference centre creation	Uncontrolled before-and-after study	143 (Male 80; Female 63)	12	Comprehensive care management.	Children	Frequency of hospitalization episodes of vaccination blood transfusion, infections, ACS	No	Yes ($p < 0.001$) Improved clinical outcome for participants
	Rahimy et al.[30]	Benin	To evaluate the effects of a comprehensive care programme of clinical care on the course of SCA in young children	Uncontrolled before-and-after study	236 (Male 124; Female 112)	78	Comprehensive care programme	Children	Painful crisis, duration and frequency of hospitalization, frequency of transfusion	No	Yes ($p < 0.001$). Improved clinical outcome for participants
Disease-modifying agents	Abdullahi et al.[54]	Nigeria	Use of standard protocol for secondary prevention of stroke in children	Prospective cohort study	29 (Male 18; Female 11)	15	HU therapy	Children	Morbidity- Stroke recurrence rate	No	Yes. Stroke recurrence rate: 17.4 events per 100 patient-years (95% CI 7.1–36.3) compared to 22.0 events per 100 patient-years (95% CI 10.2–41.8)
	Abdullahi et al.[55]	Nigeria	To test the hypothesis that for secondary stroke prevention among children with SCA and stroke, fixed moderated dose HU therapy results in 80% relative risk reduction when compared to fixed low-dose HU therapy	RCT	101 (Male 56; Female 45)	36	HU therapy	Children	Recurrence of stroke or transient ischemic attack (TIA)	Yes	No. Stroke recurrence; IRR of 1.53; 95% CI: 0.20–3.34. $p = 0.999$. Mortality; IRR 1.53; 95% CI: 0.18–18.30. $p = 0.98$. No difference observed between moderate and fixed low-dose
	Abdullahi et al.[59]	Nigeria	To test the hypothesis moderate dose HU therapy for primary stroke prevention results in 66% relative risk reduction when compared to fixed low-dose HU therapy	RCT	220 (Male 106; Female 114)	28.8	HU therapy	Children	Initial stroke or TIA, All cause hospitalization	No	No, Stroke occurrence; IRR of 0.62; 95% CI: 0.10–3.20. $p = 0.77$. Yes, All cause hospitalization; IRR 1.70; 95% CI: 1.15–2.57. $p = 0.0071$. No difference observed between moderate and fixed low-dose for stroke occurrence, but a significant difference was observed in all cause hospitalization
	Ambrose et al.[60]	Tanzania	To estimate stroke risk in children with SCA in Tanzania and to determine efficacy of HU therapy to decrease and prevent stroke.	Open-label clinical trials.	196 (Male 103; Female 93)	24	HU therapy	Children	Change in TCD velocity	No	Yes. TCD decreased from 182 cm/s (SD 12) to 149 cm/s (SD 27) with an average decline of 35 cm/s, $p < 0.0001$
	Lagunju et al.[56]	Nigeria	To compare stroke recurrence following treatment with and without HU therapy	Retrospective cohort study	32 (NR)	(NR)	HU therapy	Children	Stroke recurrence	No	Yes. OR 3.808; 95% CI 1.556, 9.317. $p = 0.001$. Reduced stroke recurrence among patients that received HU therapy
	Lagunju et al.[57]	Nigeria	To determine the long-term outcomes of the stroke prevention programme of children with SCD in Ibadan (SPIBBA), Nigeria	Prospective cohort study	396 (Male 226; Female 170)	120	HU therapy	Children	Stroke risk reduction (Reduction in TAMMN)	Yes	Yes. Reduction in TAMMN from 199.5 ± SD16.34 cm/s to 155.5 ± SD 20.9 cm/s; $p < 0.001$. Mortality; no difference between groups, $p = 0.863$
	Mvalo et al.[58]	Malawi	To establish a prospective longitudinal SCD paediatric cohort receiving standard care and to determine clinical characteristics and outcomes	Prospective cohort study	187 (Male 98; Female 86)	43	HU therapy	Children	Hospitalization, fever, transfusion, annual school absenteeism	No	Yes. $p < 0.05$ for all outcomes. Improved clinical outcomes

(Continued)

Table 1. (Continued)

Interventions	Study and year	Country	Study objective(s)	Study design	Sample size (sex/gender)	Study duration (months)	Intervention type	Target population	Outcome: morbidity	Outcome: mortality	Result
	Ofakunrin et al.[29]	Nigeria	To evaluate the effectiveness and safety of HU in children living with SCD.	Uncontrolled before-and-after study	54 (Male 30; Female 24)	12	HU therapy	Children	Clinical (painful crisis, ACS, blood transfusion, and duration of hospitalization), and haematological parameters.	No	Yes ($p < 0.001$). Improved clinical and haematological outcome post treatment
	Galandaci et al.[31]	Nigeria	To evaluate if HU is associated with an increased risk of death	Controlled before-and-after study	235 (Male 122; Female 113)	48.7	HU therapy	Children	Stroke incidence rate	Yes	Yes (morbidity: $p = 0.603$; Mortality: $p = 0.081$). No difference observed between intervention and control group in a RDD study design. Thus, reduced stroke incidence with HU
	Lagunju et al.[33]	Nigeria	To evaluate the effect of HU in reducing the risk of primary stroke in children with SCD	Prospective observational study	104 (Male 55; Female 49)	96	HU therapy	Children	Reduction in TCD velocities, laboratory features, stroke incidence, haematological parameters	No	Yes ($p < 0.001$) Stroke Incidence: 0.27/100 person years. Reduced stroke incidence
	Oniyangi et al.[34]	Nigeria	To review the indications of the use of HU, laboratory monitoring and outcome in children with SCD	Retrospective observational study	74 (Male 42; Female 32)	48.7	HU therapy	Children	Indications for use of HU (VOC, ACS, TCD velocities, stroke)	No	Yes ($p < 0.05$) Improved clinical outcome following treatment with HU
	Opoka et al.[35]	Uganda	To evaluate the safety and efficacy of HU therapy in malaria-endemic region	RCT	208 (Male 112; Female 96)	12	HU therapy	Children	Clinical events (VOC, dactylitis, ACS, splenic sequestration, blood transfusion), and haematological parameters	No	Yes ($p < 0.001$). Improved clinical and haematological outcome
	Tshilolo et al.[61]	Angola Congo DR Kenya Uganda	To evaluate the benefits of HU therapy in young children with SCA living in SSA	Uncontrolled before-and-after study	606 (NR)	48	HU therapy	Children	Clinical events (VOC, ACS, infection, blood transfusion), and haematological parameters.	Yes	Yes (IRR-0.47; 95% CI 0.38–0.57, Mortality: IRR-0.30; 95% CI 0.10–0.88). Improved clinical outcome, and a favourable haematological index.
NBS, comprehensive primary health screening, and economic evaluation	McGann et al.[36]	Angola	To assess the cost-effectiveness of a pilot NBS and treatment programme for SCD	Cost-effectiveness analysis	36,453 (NR)	84	NBS and treatment programme	Children	Average cost per HLY gained that is below the GDP in Angola	NR	Yes (estimated cost per HLY gained is $1380–$3565)
	Kuznik et al.[37]	47 SSA countries	To assess the cost-effectiveness of a NBS and intervention package for SCA	Cost-effectiveness analysis	228,169 (NR)	N/A	NSPI	Children and adults	Average cost per DALY averted below GDP of the countries		Yes (Average cost per DALY averted in 34 countries is USD 190
	McGann et al.[32]	Angola	To evaluate the feasibility of a NBS and treatment programme in a limited-resource setting	Prospective observation al study	244 (NR)	24	NBS and treatment programmes	Children	NR	Yes	Yes (p value or 95% CI not reported). Improved survival of infants who received the intervention
	Rahimy et al.[38]	Benin	To develop a strategy for neonatal screening of SCD and effective enrolment of affected neonates in a comprehensive follow-up programme	Prospective observation al study	135 (NR)	36	Neonatal screening and treatment programme	Children	NR	Yes	Yes (p value or 95% CI not reported) Improved survival of infants who received the intervention
Nutritional supplementation	Cox et al.[39]	Tanzania	To test the hypotheses that protein energy supplementation in the form of ready to use supplementary food improve height-for-age and body mass index for age Z-scores in children with SCD	RCT	145 (NR)	18	Supplementary arginine, citrulline, and daily chloroquine	Children	Mean height for age Z-score and mean body mass index (BMI) for age Z-score	No	Yes, for BMI to age Z-score ($p = 0.001$). Height for age Z-score ($p = 0.081$).
	Daak et al.[40]	Sudan	To investigate the therapeutic potential of Omega-3 fatty acids for patients with homozygous SCD	RCT	140 (Male 61; Female 79)	12	Omega-3 fatty acids supplement	Children and adults	Rates of clinical VOC and haemolytic crisis, blood transfusion rate, and school attendance	No	Yes ($p < 0.05$). Improved clinical outcome following intervention

(Continued)

Table 1. (Continued)

Interventions	Study and year	Country	Study objective(s)	Study design	Sample size (sex/gender)	Study duration (months)	Intervention type	Target population	Outcome: morbidity	Outcome: mortality	Result
	Onalo et al.[41]	Nigeria	To determine the safety and efficacy of oral arginine therapy in Nigerian children with SCD	RCT	68 (Male 38; Female 30)	24	Oral L-arginine supplement.	Children	Daily pain scores, time to crisis resolution, length of hospital stays	No	Yes ($p < 0.05$) Improved clinical outcome following intervention
Patient care	Hau et al.[42]	Tanzania	To determine the effectiveness of a linkage to care intervention with social workers to improve post-hospital mortality for children with SCD	Prospective observation al study	116 (Male 66; Female 50)	12	Adaptation of the antiretroviral treatment and access services	Children	NR	Yes	Yes ($p = 0.023$) Adjusted Hazard Ratio, 0.26; 95% CI, 0.08–0.83
Pharmaco-therapeutic agents	Adjei et al.[43]	Ghana	To evaluate the efficacy and safety of ACTs in children with SCD	RCT	119 (NR)	1.4	Antimalarial treatment, artesunate-amodiaquine, AA, or artemether lumefantrine, AL	Children	Parasite reduction ratio, Adequate clinical and parasitological response (ACPR)	No	Yes (p value of 95% CI not reported). AA and AL effectively reduced malaria attacks
	Dawam et al.[44]	Nigeria	To evaluate the efficacy and affordability of monthly SP vs daily proguanil in patients with SCD	RCT	154 (Male 75; Female 79)	3	SP vs. Proguanil.	Children and adults	Episodes of malaria attacks, frequency SCD crisis	No	Yes ($p < 0.05$) SP more effective than proguanil
	Eke et al.[45]	Nigeria	To compare the efficacy and tolerability of pyrimethamine with proguanil and placebo in malaria prevention in children with SCD	RCT	101 (Male 51; Female 50)	9	Pyrimethamine, Proguanil vs. placebo	Children	Frequency of hospitalization (Reasons; malaria infection, bone pain, haemolytic crisis)	No	No ($p > 0.05$) The intervention did not significantly improve outcomes compared to placebo
	Nakibuuka et al.[46]	Uganda	To compare the efficacy of monthly SP presumptive treatment to weekly chloroquine for malaria prophylaxis	RCT	242 (Male 121; Female 121)	5	Chloroquine versus SP	Children	Incidence of malaria episodes	No	Yes ($p = 0.042$). SP more effective in reducing malaria attacks
	Nwokolo et al.[7]	Nigeria	To compare the efficacy and tolerability of Mefloquine and Proguanil in malaria prophylaxis in SCA	RCT	113 (Male 56; Female 57)	6	Mefloquine versus Proguanil	Children and adults	Efficacy (evaluated by absence of parasitemia)	No	No ($p > 0.05$). Both antimalarials were equally effective
	Olasebikan et al.[47]	Nigeria	To determine if IPT with a fixed dose of MQAS or SPAQ was more effective than daily proguanil for malaria prevention in subjects with SCA	RCT	270 (Male 129; Female 141)	19	IPT with a fixed dose combination of MQ-AS or SP-AQ versus proguanil	Children and adults	Protective efficacy against clinical malaria	No	Yes (p value of 95% CI not reported) IPT more protective of malaria than proguanil
	Warley et al.[48]	Uganda	To evaluate the effect of chemoprophylaxis with an antimalarial and long-acting penicillin on SCA complications	RCT	126 (Male 62; Female 64)	21	Long-acting penicillin with chloroquine versus placebo	Children	Dactylitis	No	Yes ($p < 0.1$). The intervention more effective than placebo
Supportive care agents	Eke et al.[49]	Nigeria	To compare the efficacy of oral Piroxicam with soluble Aspirin in children with SCD	RCT	58 (Male 31; Female 27)	9	Piroxicam	Children	Osteoarticular pain, limitation of movement, fever	No	Yes ($p < 0.05$) Improved clinical outcome
	Wambebe et al.[50]	Nigeria	To assess the efficacy and tolerability of Niprisan	RCT	69 (Male 38; Female 31)	12	Niprisan	Children and adults	Reduction in the frequency of SCD crisis, severe pain, absenteeism from work, and hospitalization	No	Yes ($p < 0.05$) Improved clinical outcome
Systemic treatment	Akinsete et al.[51]	Nigeria	To review the outcome data of children with SCD managed with an exchange-blood transfusion algorithm	Retrospective observational study	12 (NR)	35	Exchange-blood transfusion	Children	NR	Yes	Yes (p value of 95% CI not reported) Improved survival following intervention
	Dhabangi et al.[52]	Uganda	To determine if longer storage red blood cell units are not inferior to shortage red blood cell units for tissue oxygenation	RCT	290 (Male 138; Female 152)	28	Red blood cell transfusion	Children	Clinical events (Coma, respiratory distress, duration of hospitalization)	Yes	No ($p < 0.05$) No difference in clinical outcome between treatment arms
	Maitland et al.[53]	Uganda	To determine if larger initial transfusion volumes of whole blood compared to standard volumes safely treated severe anaemia	RCT	3196 (NR)	32	Whole blood transfusions	Children		No	No ($p = 0.12$) No difference in clinical outcome between treatment arms

ACS: acute chest syndrome; CI: confidence interval; DALY: disability-adjusted life years; DRC: Democratic Republic of Congo; GDP: gross domestic production; HLY: healthy life year; IPT: intermittent preventive therapy; IRR: incidence rate ratio; MQAS: mefloquine-artesunate; N/A: not applicable; NR: not reported; RCT: randomized clinical trial; RDD: regression discontinuity design; SPAQ: sulphadoxine-pyrimethamine and amodiaquine.

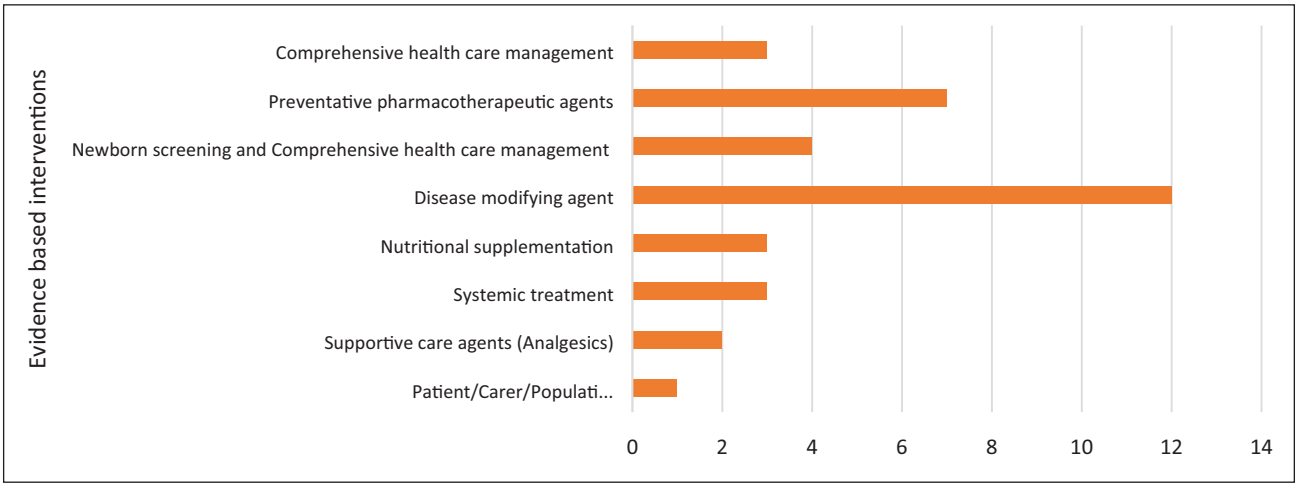

Figure 2. Distribution of the EBIs included in the study.

BMI, for age and the arginine-to-asymmetric dimethylarginine (ADMA) ratio was increased (vasculo-protective against atherosclerosis).[39] Omega-3 supplementation improved the clinical outcome of children with SCD that suffered VOC.[40]

Patients/carer/population education

Hau et al. showed that well-organized social care services that provided intensive education, visited patients' homes and reminded patients of their clinic days contributed to the reduced mortality observed in the study cohort.[42] This intervention is usually offered as part of the comprehensive healthcare.[42]

Pharmacotherapeutic agents

Several studies showed that Proguanil, Sulphadoxine Pyrimethamine (SP), Mefloquine, Chloroquine (CQ) and Artemisinin combination therapies: Artemisinin-Amodiaquine (AA) and Artemether-Lumefantrine (AL) effectively reduced malaria attacks in patients living with SCD, especially among children.[7,43–46,48] Moreover, available evidence showed SP to be more effective than proguanil, CQ and cheaper than proguanil. Also, CQ and long-acting penicillin were demonstrated to reduce the incidence of dactylitis.[48] Warley et al. demonstrated oral penicillin in the management of SCD.[48] However, Adjei et al. used groups with a different baseline characteristic and did not compare the interventions (AA and AL) against a control treatment.[43] Also, Eke et al. did not have a sufficient sample size to show a statistical difference in the comparison groups, which may be why no difference was observed between pyrimethamine/proguanil versus placebo.[45] Furthermore, Nwokolo et al. did not estimate their sample size and could not detect a difference in the efficacy between mefloquine and proguanil.[7] However, 23.9% of patients screened at baseline had parasitaemia (even though these patients were supposed to be on an active proguanil chemoprophylaxis), which may be suggestive of a possible resistance to proguanil.[7]

Systemic treatments

Several studies also demonstrate that exchange blood transfusion significantly reduced the mortality rate among children managed for acute chest syndrome.[51–53] Studies by Dhabanji et al. and Maitland et al. showed the therapeutic use of blood transfusion in the management of SCD.[52,53]

Supportive care agents (analgesics)

RCTs by Eke et al. and Wambebe et al. demonstrated that Piroxicam and Niprisan significantly reduced painful episodes.[45,50] These studies provide support for the use of analgesics in treating episodes of SCD crisis.

Discussion

In summary, this review identified EBIs that improve clinical outcomes among children living with SCD in SSA comparable to those in HIC.[62,63] These include reduction in the incidence of stroke, VOC and malaria infection. Also, they reduce incidence of acute chest syndrome, anaemia and splenic sequestration among participants and overall survival. HU therapy was the single most common intervention identified and the only disease-modifying agent in this study. Most participants tolerated a dose of 20 to 25 mg per kg per day, which elicited favourable haematological responses.[64,65] HU stimulates foetal haemoglobin and haemoglobin level elevations, which offers both prophylactic and therapeutic effects on vaso-occlusive events.[66] In addition, the risk of bone marrow suppression, a common adverse effect of HU was low at the tolerated dosage levels. These findings align with recommendations from the National Heart, Lung, and Blood Institute and the American

Society for Haematology.[62,67] Our study provides evidence that hydroxyurea doses as low as 10 mg/kg/day significantly reduces stroke incidence and can be used to prevent stroke recurrence in children with SCD where blood transfusion concerns exist.[54,55,59]

Unfortunately, HU is expensive and inaccessible in most countries in Africa.[68] Our review suggests pharmacy compounding of the medicine at the primary care pharmacy could alleviate the unavailability and unaffordability of HU – a routine medication for a life-long illness. Drug compounding is common practice in tertiary hospitals in SSA countries with most pharmacists sufficiently proficient in it.[69] Furthermore, the WHO showed that compounded HU was effective and 3.6 times cheaper than commercially available hydroxyurea in hospitals, and 5–10 times cheaper than in the retail market.[28] However, compounded sterile preparations pose the risk of microbial contamination to patients. Also, since there are poor manufacturing practice regulations on compounded drugs, it increases the potential for preparation errors.[57] Other potential efforts to make HU accessible include international donation in SCD vertical programmes and negotiating prices with pharmaceutical companies through tendering or purchasing agreements. Other barriers have been reported by providers, patients with SCD as well as their families to the use of hydroxyurea in the management of SCD. Some of the barriers reported include concern about side effect, poor/inadequate knowledge about hydroxyurea, provider not recommending medication, unavailability of equipment to monitor patient, expensive and unaffordable cost of clinical monitoring, providers concern about patient noncompliance with medication or laboratory medication monitoring.[1,2]

Malaria infection precipitates haemolytic and painful crisis and is a common cause of SCD-related mortality in SSA.[43,47] Although a daily dose of proguanil administered as prophylaxis to children with SCD is the common practice in some SSA countries,[43] our review suggests that SPs were more effective in reducing malaria incidence in these children. Besides, SP is cheaper than proguanil and could reduce the households financial burden[19,20], and administered monthly ensuring satisfactory adherence. Good adherence will reduce the risk of *Plasmodium falciparum* resistance to antimalarial drugs, a common problem in malaria-endemic regions of SSA. Although there is an increasing trend of SP-resistant *Plasmodium falciparum* infection in the East African region, it remained unchanged in most other SSA countries.[70] In Nigeria, for example, *Plasmodium falciparum* resistance to SP reduced by 14.4% between the years 2000 and 2020.[70] Antimalarials are readily available in most African countries through donations from malarial programmes supported by international agencies and subsidized cost of antimalarials by private organizations such as the Gates foundation.[71]

Our study showed that screening for SCD complemented with comprehensive healthcare, improved participants' clinical outcomes, decreased frequency of painful crisis, a decline in the frequency and duration of hospitalization, reduced rate of blood transfusion and reduced mortality.[27,28,30,32,38] In a study in California, Vinchisky et al. demonstrated that the mortality rate following NBS (early screening) and comprehensive healthcare intervention was 1.8%, compared to a mortality rate of 8.5% amongst children diagnosed based on their symptoms.[72] Besides, WHO advocates early screening for SCD and early introduction of interventions to reduce the burden of the disease.[26] Although NBS and comprehensive healthcare management of SCD are cost-effective, they may pose an undue economic burden to patients and their families in low resource settings where health expenditure is mostly out of pocket payment with no health insurance options.[19,20] SSA countries could establish specialist stand-alone 'sickle cell clinics' where government and partner non-governmental organizations can provide standard care at a low cost. Also, governments in SSA countries can take actions to facilitate the activities of the Consortium on NBS in Africa initiative – an international network established in some SSA countries. The network aims to show the benefits of NBS and early interventions for children with SCD in SSA countries.[73–75]

Our study also showed the impact of nutritional supplementation on the clinical outcomes of children with SCD. Malnutrition and SCD are the prevalent non-communicable diseases in SSA, and the effect of poor nutrition is worse among children living with SCD. Similar to our review findings, studies have demonstrated significant improvement in the anthropometric indices of children with SCD following dietary supplementation,[62] but little is known of the impact of nutritional supplements on clinical outcomes. Our review showed that L-arginine hydrochloride and Omega-3 fatty acids supplementation significantly reduced VOC events and shortened the length of hospital stay among participants.[40,41] L-arginine supplements are also vasculo-protective against atherosclerosis and reduces the use of parental opioids for painful crisis.[39] In like manner, dietary Omega-3 fatty acids effectively reduced the frequency of pain episodes that require hospitalization.[76] Protein-rich foods, such as walnuts, soybeans and mackerel fish, are rich in both Arginine and Omega-3 fatty acids and will not only improve the nutritional status of the children living with SCD but also improve their clinical state.[76]

Lagunju et al. and Ambrose et al., in their studies, demonstrated a reduction in TCD velocities following hydroxyurea therapy.[33,56,57,60] Abnormal or elevated TCD velocity has been linked with increased risk of stroke incidence. Studies in high-income settings have shown reduced stroke incidence in patients with elevated TCD velocities following blood transfusion (STOP trials).[77] However, chronic blood transfusion is a herculean task and not sustainable in low- and middle-income countries because of unavailability of blood products, increased risks of blood related adverse

events relating to poor screening and cross-matching of blood. The SPIN trial shows that even though hydroxyurea therapy is not as effective as blood transfusion, it is better than no therapy in the prevention of primary stroke in children with abnormal TCDs.[31]

To the best of our knowledge, our study represents the first attempt to comprehensively review the EBIs that reduce SCD-related morbidity and mortality among children living in SSA. Furthermore, we assessed the quality of included studies, thus reviewing the best research evidence for advising and recommending the interventions to policymakers and clinicians. One of the limitations of this study is that only English-language articles were reviewed and may have inadvertently missed crucial findings in non-English studies. The poor study design employed in studies evaluating NBS and comprehensive healthcare approach limits the strength of our conclusions on these interventions.

Notwithstanding these limitations, our study finding is a call to action for governments in SSA countries to elaborate guidelines on EBIs to reduce SCD-related morbidity and mortality. Inadequate access to EBIs continues to pose risks to the survival of children living with SCD in SSA, significantly contributing to the under-5 mortality rate. Furthermore, knowledge gaps in the use of EBIs for SCD management, especially in rural communities, should be addressed. Our study also suggests that establishing specialists' services in primary healthcare, which offer early intervention programmes, including vaccination, moderate daily doses of HU therapy, antimalarial and penicillin prophylaxis and patient and carer education for children diagnosed with SCD, could improve accessibility for children with SCD. Also, given that children with SCD consume more healthcare services, establishing health insurance schemes, including community-based health schemes, is required to guaranteed continued access to care while protecting SCD-affected households from impoverishment.[20,78] Finally, cost-effectiveness analyses are needed to guide implementation of these EBIs.

Conclusions

Our study has identified EBIs that reduce SCD-related morbidities and mortality among children in SSA. Our study also showed significant improvement in SCD morbidities and overall survival. SSA countries need to adopt and implement these EBIs in the management of SCD, especially for children who are the most vulnerable population. Additional cost-effectiveness and cost–benefit analyses of these EBIs are needed that could guide the implementation of these EBIs and steer individual SSA countries toward achieving sustainable development goals.

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Data availability statement

All relevant data are within the paper and its supporting Information files.

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Supplemental material

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