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Building capacity for sickle cell disease research and healthcare

Edited by
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Building capacity for sickle cell disease research and healthcare

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Editorial: Building capacity for sickle cell disease research and healthcare

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building capacity, sickle cell disease (SCD), research infrastructure, healthcare development, training, SCD knowledge advancement, SickleInAfrica, Africa

Editorial on the Research Topic
Building capacity for sickle cell disease research and healthcare

1 Introduction

Sickle cell disease (SCD) is the most frequent clinically significant genetic disorder that affects the production of hemoglobin, a protein found in red blood cells that carries oxygen throughout the body (Rees et al., 2010). SCD is particularly prevalent in Africa and the Americas. Although, according to the World Health Organization, SCD is a significant public problem, SCD is still classified as a neglected disease (Grosse et al., 2011). Since Africa has a high burden of SCD (Diallo and Guindo, 2014; Makani et al., 2020; Oron et al., 2020) and limited access to care and treatment, research studies and clinical efforts that will help to address the significant health burden of SCD are welcome.

On 02/07/2021, we launched a call for submissions to the Frontiers' Topic series "Building Capacity for Sickle Cell Disease Research and Healthcare" to highlight ongoing projects, healthcare advances, advocacy and capacity building in the SCD field by inviting articles that address translational SCD research, standards of care for SCD patients globally, equitable access to improved and quality healthcare, and global or regional SCD research initiatives.

Nineteen manuscripts were submitted. After peer review, eleven and four manuscripts were accepted for publication in the Frontiers in Genetics and Frontiers in Pediatrics,

respectively. These 15 articles discuss efforts to improve knowledge, the diagnosis, treatment, and management of the disease in African and American populations. Of these, ten are original articles describing SCD interventions. Three are research methodology papers, one is a brief research report and one is a case report.

Most of these articles discuss efforts to build research capacity for SCD in Africa. Nnodu et al. describe the efforts of the Sickle Pan African Research Consortium (SPARCo) with support from the Sickle Africa Data Coordinating Center (SADaCC) to develop skills and abilities for SCD research and healthcare services in Africa. The paper highlighted the training programs and workshops conducted by the consortium to enhance research capacity and improve healthcare services for SCD. About 1,726 participants attained skills development activities across the Ghana, Nigeria and Tanzania SPARCO sites. Skills have been enhanced in data management, SCD and research to underpin the core deliverables of SPARCo. Nkya et al. discuss the challenges of establishing a birth cohort for SCD research in Tanzania. The authors enrolled and followed -up visits of 341 babies with and without SCD. Out of these, 311, 186, 133, 81, 44, and 16 babies have returned for their 1st, 2nd, 3rd, 4th, 5th, and 6th visits, respectively. They collected demographic and clinical information for these babies because this platform may help understand the underlying mechanisms that influence early SCD manifestation and help devise intervention management which will reduce morbidity and mortality rates in children. Okeke et al. describe a new method for newborn screening for SCD in Nigeria using dried blood spots on the HemoTypeSC™ device. Of the 511 newborns from whom heel stick samples were collected (241 males and 270 females), HemoTypeSC using DBS identified 79.0% HbAA, 19.6% HbAS, 1.2% HbSS, and 0.2%) HbAC phenotypes. The isoelectric focusing (IEF) test identified 72.4% HbAA, 26.0% HbAS, 1.0% HbSS, and 0. 6% HbAC phenotypes. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of HemoTypeSC using DBS, compared to standard HemoTypeSC POCT, was 100%. Paintsil et al. report how SickleInAfrica's initiative benchmarked to make recommendations for multi-level standards of care for SCD. The review yielded a guideline with recommendations for the management of SCD on 64 topics and subtopics for six different referral levels of healthcare, with the highest and lowest being the tertiary facilities and the home settings, respectively.

Other articles focus on specific aspects of SCD treatment and management. For example, Chianumba et al. evaluated the use of hydroxyurea (HU) in Nigeria and patients' perceptions and experiences with the treatment. Of the 378 participants in this study, 89.7% were on HU, while 9 (10.3%) had stopped using HU. 92.5% of participants had fewer pain crises, 84.8% had fewer needs for blood transfusion, 86.3% had improved packed cell volume (PCV) and 84.6% had fewer hospital admissions due to HU use. Therefore patient-based advocacy is suggested to improve HU uptake and prioritization of HU availability and affordability. Treadwell et al. describe barriers to hydroxyurea use from the perspectives of healthcare providers, SCD patients and their families in the United States. Their results support strengthening provider understanding and confidence in implementing existing SCD guidelines and the importance of shared decision-making in addressing barriers to hydroxyurea use and combination therapies for SCD. Starosta et al. report on a case of infantile-onset Pompe disease complicated by SCD, highlighting the management challenges and considerations in such cases.

Other papers focus on the prevalence of SCD in different populations. Tutuba et al. report on the prevalence of hemoglobin-S and SCD baseline knowledge among 600 pregnant women attending antenatal clinics in Tanzania. They found a high prevalence of sickle cell trait and a low level of knowledge among the study participants but only 2 (0.3%) knew their SCD status. In comparison, 7.7% reported a family history of SCD. Martella et al. report on the distribution of HbS alleles and haplotypes in a multi-ethnic population in Guinea Bissau among 848 children (498 males and 350 females) and the implications for public health screening. The study found a high prevalence of the sickle cell trait and diverse sickle cell haplotypes in the study population, which has implications for public health screening in the region.

Ahmed et al. conducted a study on the patterns, outcomes, and predictors of pediatric medical admissions at Gadarif Hospital in Eastern Sudan. The study discovered that respiratory infections, malaria, and gastrointestinal infections were the three most common reasons for admission when reviewing 740 medical files, most (61.2%) of which were from males. The study also reported a high mortality rate of 5.7%, especially for babies, and malnourishment was the strongest predictor of death.

The SCD registry infrastructure and resources may help to improve SCD care and research in Africa. Some papers highlighted the efforts to create standards of care and databases for managing SCD. Nnodu et al. describe efforts to establish a database for SCD patient mapping and survival tracking in Nigeria using data from SPARCO among 7,767 people living with SCD at 25 health institutions across the six zones in Nigeria. Paintsil et al. report on establishing an SCD registry in Kumasi Ghana by the Sickle Pan-African Research Consortium in Kumasi, Ghana enrolling 3,148 SCD patients between December 2017 to March 2020. The article provides an overview of the challenges and successes of establishing the registry, including data Research Topic, quality control, and sustainability Research Topic.

Okocha et al. conducted a study on adiponectin and disease severity in sickle cell anemia patients attending a tertiary health institution in Nnewi, Southeast Nigeria. The study found that adiponectin levels were not significantly associated with disease severity and complications such as organ damage and acute chest syndrome. In their second paper, Okocha et al. conducted a cross-sectional survey on barriers to the therapeutic use of hydroxyurea for SCD in Nigeria. The study found that the most common obstacles were a lack of knowledge among healthcare providers, inadequate access to the medication, and concerns about its safety and efficacy. The study recommends interventions to improve awareness, access, and utilization of hydroxyurea for SCD in Nigeria.

Finally, Jonathan et al. conducted a study among 490 nurses and clinicians at Regional Referral Hospitals to investigate the knowledge and resource availability for SCD care in Dar es Salaam, Tanzania. The study found that most healthcare workers had inadequate knowledge about SCD and its management, with only 25.1% having a good knowledge of SCD. The study also found significant resource limitations, particularly regarding the availability of essential medications and laboratory tests. The study recommends the need

for targeted educational programs and investments in healthcare infrastructure to improve SCD care in Tanzania.

The future of research direction from all these studies should inform interventions, including therapeutics that rely upon genomics and SCD markers (Wonkam, 2023).

2 Conclusion

The articles reviewed in this editorial highlight several challenges and opportunities in advancing SCD care and research in Africa. Key challenges include limited resources, inadequate knowledge and awareness, and insufficient research and clinical care infrastructure. However, there is hope, as demonstrated by the growing number of initiatives aimed at improving SCD care and research in Africa. To alleviate the challenges, there is a need for increased investment in SCD research and care, as well as greater collaboration and knowledge sharing among researchers, healthcare providers, policymakers and community stakeholders.

3 Recommendation

We recommend a coordinated and sustained effort to improve and increase capacity for SCD care and research in Africa, including increased funding for research and clinical care, expansion of newborn screening programs, and implementation of evidence-based guidelines for SCD management. Additionally, there is a need for increased community engagement and education to improve awareness and understanding of SCD and to address stigma and discrimination. Collaboration between researchers, healthcare providers, community stakeholders and policymakers is crucial to ensure that efforts are coordinated, aligned with the needs of affected communities and sustainable. By working together, key SCD stakeholders can make progress in advancing SCD care and research in Africa and ultimately improve the lives of those affected by this debilitating disease.

Author contributions

VN, ON, RS, VP, GM, NM, AW, and AM-C conceived and proposed the topic and wrote the editorial. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Barriers to Therapeutic Use of Hydroxyurea for Sickle Cell Disease in Nigeria: A Cross-Sectional Survey

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Background: Sickle cell disease, the inherited blood disorder characterized by anemia, severe pain and other vaso-occlusive complications, acute chest syndrome, disproportionate hospitalization, and early mortality, has significant financial, social, and psychosocial impacts and drains individuals, families, and health systems globally. Hydroxyurea could improve the health of the 300,000 individuals born each year with sickle cell disease in sub-Saharan Africa; however, challenges to adoption and adherence persist. This study assessed the barriers to therapeutic use of hydroxyurea for sickle cell disease within the Nigerian healthcare system, specifically from the level of the patient, provider, and health system.

Methods: We used purposive sampling to recruit participants from 13 regions in Nigeria. A cross-sectional survey was administered to physicians (n = 70), nurses or counselors (n = 17), and patients or their caregivers (n = 33) at 13 health centers. Findings were mapped onto the appropriate Consolidated Framework for Implementation Research (CFIR) domains.

Results: This study was able to identify factors that mapped onto the inner setting, outer setting, and characteristics of individuals domains of CFIR. The majority of physicians (74.3%) prescribe hydroxyurea, and half stated hydroxyurea is the standard of care. Among clinicians, barriers included limited knowledge of the drug, as well as low self-efficacy to prescribe among physicians and to counsel among nurses; perceived side effects; perceived patient preference for traditional medicine; cost for patient and expense of accompanying laboratory monitoring; and limited availability of the drug and equipment for laboratory monitoring. Among patients and caregivers, barriers included lack of knowledge; perceived side effects; cost; religious beliefs of disease causation; and lack of pediatric formulation.

Conclusions: Findings suggest that patient, provider, and health systems-level interventions are needed to improve hydroxyurea uptake among providers and adherence among patients with sickle cell disease in Nigeria. Interventions such as patient education, provider training, and policy change could address the disproportionate burden of sickle cell disease in sub-Saharan Africa and thus improve health equity.

Keywords: hydroxyurea, sickle cell diasease, Nigeria, adoption, health care workers

BACKGROUND

Sickle cell disease (SCD), the inherited blood disorder characterized by anemia, severe pain and other vaso-occlusive complications, acute chest syndrome, disproportionate hospitalization, and early mortality, has significant financial, social, and psychosocial impacts and drains individuals, families, and health systems. Currently, it is projected that more than 300,000 individuals are born annually with SCD in sub-Saharan Africa (SSA) (Ohene-Frempong et al., 2008; Brown et al., 2010; Piel et al., 2013). SCD is a progressively debilitating and a chronic multi-organ disease with a 30–50% incidence of disability and unemployment, as well as the leading cause of stroke in children and adolescents (Corbacioglu, 2016). Hydroxyurea is efficacious in improving hematological parameters of sickle cell patients by promoting the production of younger erythrocytes with higher hemoglobin F (HbF) content and less tendency to polymerize, thereby reducing sickling with resultant increase in hematocrit (Hassan et al., 1995; Youssry et al., 2017; Ofakunrin et al., 2020). These ameliorating effects have translated into improved patient outcomes, including reduced rate of vaso-occlusive crisis, blood transfusions, hospitalizations, and incidence of acute chest syndrome, as well as improved organ function and overall survival (S. Charache et al., 1995; Youssry et al., 2017; Ofakunrin et al., 2020). Although hydroxyurea was approved for SCD management in adult patients by the US FDA in 1998 (Ault, 1998), for pediatric patients in 2017, and specifically for children within low and middle income countries (LMICs) in 2018, (Tshilolo et al., 2019) challenges to its routine use in LMICs persist (Gyamfi et al., 2021a; Gyamfi et al., 2021b).

Nigeria has the highest burden of SCD worldwide and yet, the use of hydroxyurea among SCD patients in Nigeria is very low. Galadanci and colleagues (2014) (Galadanci et al., 2014) found that only eight of 18 SCD specialist health institutions studied in Nigeria prescribed hydroxyurea to their patients, and within those institutions, only 5–33% of their patients were on hydroxyurea (Adegoke et al., 2015; Esezobor et al., 2016; Adewoyin et al., 2017; Adeyemo et al., 2019). Although, the safety and adverse side effects of hydroxyurea—the only cost-effective pharmacotherapeutic compound that can be effectively delivered in SSA—have been documented, (Adewoyin et al., 2017; Adeyemo et al., 2019; Aliyu et al., 2007; Charache et al., 1995; S.; Charache et al., 1995) and the overall clinical effectiveness of hydroxyurea to ameliorate SCD severity is well established in Nigeria and other African countries, (Tshilolo et al., 2019) its adoption is still low. Therefore, we examined the barriers preventing adequate uptake of hydroxyurea, including prescription and adherence, for therapeutic use among SCD patients in the Nigerian healthcare system.

METHODS

Conceptual Framework

Damschroder's Consolidated Framework for Implementation Research (CFIR) (Damschroder et al., 2009), was used as a theoretical framework to guide the conceptualization of the results and understand the barriers preventing adequate uptake of hydroxyurea, including prescription and adherence, for therapeutic use among SCD patients in the Nigerian healthcare system. Specifically because this was a cross-sectional study, we were only able to focus on the following three CFIR domains: inner setting (e.g., health systems characteristics and resources – availability of HU), outer setting (e.g., patients adherence to HU) and characteristics of individuals involved (e.g., providers' prescription practice).

Design

A cross-sectional study was conducted in 13 health facilities across Nigeria using an anonymous questionnaire among clinical providers, patients, and caregivers. We aimed to examine the barriers to therapeutic use of hydroxyurea among SCD patients in the Nigerian healthcare system.

Ethical Approval and Consent to Participate

Ethical approval was secured from the National health research ethics committee of Nigeria (NHREC). NHREC Protocol Number NHREC/01/01/2007- 21/11/2017. NHREC Approval Number NHREC/01/01/2007-03/11/2019C. All adult participants provided verbal consent and parents consented on behalf of their children.

Setting, Sampling, and Recruitment

Using purposive sampling, participants were recruited in-person from healthcare centers across 13 different regions of Nigeria, including Oyo, Osun state, Lagos, Kano, Kaduna, Gombe, FCT, Enugu, Edo, Ebonyi, Delta State, Benue, Anambra. As the survey was anonymous and did not collect identifiable data, verbal consent was sought from in-person respondents or inferred when the participant moved on from the first page of the online survey.

TABLE 1 | Characteristics of study population and various clinical study facilities across Nigeria, 2019 (*N* = 120).

Variables	Frequency	%
Age in years (*n* = 105)		
≤20	14	13.3
21–30	11	10.5
31–40	33	31.4
41–50	27	25.7
>50	20	19.1
Gender (*n* = 120)		
Male	59	49.2
Female	61	50.8
Occupation (*n* = 120)		
Doctor	70	58.3
Nurse	17	14.2
Civil Servant	6	5.0
Teacher	2	1.7
Business	5	4.2
Technician	1	0.8
Youth Corper	1	0.8
Student	17	14.2
Unemployed	1	0.8
Marital status (*n* = 120)		
Married	87	72.5
Single	33	27.5
Level of education (*n* = 118)		
None	1	0.9
Primary	4	3.4
Secondary	15	12.7
Undergraduate	22	18.6
Postgraduate	76	64.4
History of hydroxyurea use by patients (*n* = 33)		
Yes	16	48.5
Yes, but stopped using HU	4	12.1
No	3	9.1
Missing	10	30.3
Level of health care facility (*n* = 119)		
Secondary	17	14.3
Tertiary	102	85.7
Type of health care facility (*n* = 119)		
Public	116	97.5
Private	3	2.5

Data Collection and Analysis

The questionnaire was developed after a focused discussion within a collaborative group of local clinicians and US-based implementation scientists, comprised of individuals with expertise in local context or implementation research. Potential participants were sent the survey *via* Survey Monkey where internet service was available, or by hard copy if internet service was not available (and responses were later transferred online). The questionnaire was administered to 120 respondents in secondary and tertiary healthcare centers where SCD patients receive care, including physicians, nurses or counselors that treat SCD patients, as well as SCD patients or their caregivers. Respondents, depending on level of education and availability of internet services, self-administered the questionnaire on paper or online, or were assisted by a trained data collector. Data collection took place during July 2019.

The structured questionnaire consisted of two parts: socio-demographic characteristics and challenges to therapeutic use of hydroxyurea. Among physicians, drug potency and availability, accompanying laboratory services, patient adherence, and personal objections to use were ascertained. Among nurses, counselors, patients, and caregivers, questions were modified for their respective roles. With nurses or counselors, for example, questions asked about issues affecting ability to counsel the patient appropriately, while questions for patients and caregivers included how religion, availability of alternative therapies, and personal awareness affected hydroxyurea use.

Data analysis was conducted using SPSS version 20.0 (SPSS Inc., Chicago, IL, United States). Descriptive statistics were performed and relevant frequencies and proportions calculated.

RESULTS

Characteristics of Study Sample

A total of 120 respondents completed the questionnaire, including physicians (n = 70), nurses or counselors (n = 17), and patients or their caregivers (n = 33). The sample was 50.8% female, with an average age of 38.5 ± 13.3 years. A majority of the participants were recruited from tertiary (85.7%) and public (97.5%) health facilities (**Table 1**).

Characteristics of Individuals

Uptake: Provider Prescription Practice

Among physicians, three out of 4 (74.3%) reported they prescribed hydroxyurea to their patients (**Table 2**). While 61.4% of physicians knew that SCD clinical management guidelines recommend therapeutic use of hydroxyurea, about half stated that hydroxyurea is the standard of care. Though a few (4.3%) physicians reported they were unaware of the medication, 17.6% of the nurses or counselors stated that they were unaware of hydroxyurea.

Inner Setting

Barriers to Hydroxyurea Prescription

Various barriers to prescribing hydroxyurea for SCD management were reported by clinicians, including lack of knowledge and self-efficacy, perceived affordability for the patient, perceived side effects, and perceived patient preference for traditional medicine. Some (27.1%) of the physicians reported no formal training on prescribing hydroxyurea, along with the majority (70.6%) of nurses or counselors who reported no formal training on counseling patients on hydroxyurea use. A few (7.1%) physicians were not confident about prescribing hydroxyurea to their patients. Some (25.7%) physicians stated that hydroxyurea is expensive and could not be afforded by their patients. The majority (67.1%) of physicians believed that hydroxyurea has side effects; 18.6% believed hydroxyurea is cytotoxic and carcinogenic (**Table 2**). Two doctors agreed that their patients preferred traditional medicines to western drugs, and one doctor was of the opinion that the use of hydroxyurea would make no difference to the health of patients.

TABLE 2 | Clinician knowledge and practice regarding hydroxyurea at clinical facilities across Nigeria, 2019 (*N* = 87).

Questions	Responses
	Yes *n* (%)
Physicians (*n* = 70)	
Hydroxyurea (HU) prescription and knowledge	
Prescribe HU to patients	52 (74.3)
I don't know about HU	3 (4.3)
Have no formal training on HU prescription	19 (27.1)
Have formal training on how to counsel patients about HU use	20 (28.6)
Not confident in providing HU to my patients	5 (7.1)
There is no data that shows it will work in our clime	4 (5.7)
It is the standard of care for SCD	39 (55.7)
The guidelines for care of SCD recommend its use	43 (27.1)
Patients are using HU	28 (40.0)
HU is expensive, my patients cannot afford it.	18 (25.7)
HU is a cytotoxic drug and can cause cancer	13 (18.6)
HU has other side effects	47 (67.1)
Not convinced of the safety of HU for treatment of SCD	3 (4.3)
Patients' compliance	
HU prescribed, but patient compliance is poor	15 (21.4)
Patients complain about the side effects of HU	16 (22.9)
HU is available, but not in the formulation children can use	2 (2.9)
Drug potency	
Prescribed HU and found it ineffective	1 (1.4)
Prescribed HU and found it quite effective	36 (51.4)
Availability of drug/lab services to monitor	
HU is available at my site but the supply is limited	26 (37.1)
HU is not available at my site	6 (8.6)
My patients cannot access it from another location	3 (4.3)
My patients can access it from another location	29 (41.4)
The hospital I work in does not have the laboratory facilities to monitor the use of this drug	6 (8.6)
Nurses or counselors (*n* = 17)	
Personal knowledge	
I do not know about HU	3 (17.6)
I have no formal training on how to counsel patients about HU	12 (70.6)
Cost	
Patients complain about funds to purchase HU	4 (23.5)
Our patients are too poor and cannot afford this drug	4 (23.5)
Our patients usually commence using HU, but stop because they cannot afford the cost of investigations needed to monitor this drug	2 (11.8)
Availability	
HU is good, but our patients can't find it to buy	8 (47.1)
Compliance	
Our patients do not like taking HU because of side effects	1 (5.9)
Patients usually commence taking this drug, but stop because of side effects	4 (23.5)
Our patients usually do well on the drug and compliance is excellent	8 (47.1)
Prescription/Counseling issues	
Our doctors do not prescribe HU	1 (5.9)
Our counseling about this drug is ineffective with our patients	0 (0.0)
I do not have formal training about counselling patients about HU	3 (17.6)
Personal reasons	
The relatives of the patients discourage the use of HU	0 (0)
Patient are not motivated to use HU	2 (11.8)

TABLE 3 | Factors influencing hydroxyurea use among sickle cell disease patients as reported by the patients or their caregivers at various clinical facilities across Nigeria, 2019: *N* = 33 (pediatric (*n* = 7), adults (*n* = 26)).

Questions	Responses
	Yes *n* (%)
Cost	
HU is very expensive, and I cannot afford it	4 (12.1)
I can afford to buy the drug	10 (30.3)
The investigations needed to monitor this drug are too expensive. I cannot afford them	4 (12.1)
Availability	
The drug is available at my health center	11 (33.3)
It is not available in the formulation in which I/my child needs it	5 (15.1)
Faith	
By faith I know I am healed, so no need to continue this drug	6 (18.1)
Alternative therapy	
I do not want to take this drug, because I am waiting to get the opportunity to do a bone marrow transplant	0 (0)
Compliance	
I/my ward vomits whenever this drug is taken, so I discontinued it	1 (3.0)
My/my wards skin color was changing so I discontinued it	0 (0)
Drug potency	
I/my ward had a crisis, while on this drug, so I feel it is not effective. I discontinued it	1 (3.0)
This drug is very good and has relieved a lot of my symptoms that's why I continue to take it	10 (30.3)
Personal awareness	
My doctor/medical counselor said that the drug has ability to cause cancer so I cannot take it	0 (0)
The medical staff don't really know the long term effects of this drug, it has not been used in SCD for long enough. I prefer to wait till they are sure	0 (0)

Barriers to Availability of Hydroxyurea and Laboratory Monitoring

Physicians reported various health system barriers regarding availability of hydroxyurea and laboratory monitoring. About one in three physicians stated that hydroxyurea was available in their center with limited supply, while one in 10 stated that it was not available. Four in 10 physicians also stated their patients could access the drug from another location. Six doctors admitted that the hospitals where they work do not have the laboratory facilities to monitor the use of the drug. Also, 12% of the patients stated that the accompanying investigations needed to monitor the drug are too expensive and unaffordable. Only one in three patients stated that hydroxyurea was available at their health center. Five caregivers stated that the drug was not available in the formulation suitable for their child.

Outer Setting

Uptake: Patient Adherence

For physicians who prescribed the medication, 61.5% stated that most of their patients were on hydroxyurea, while the remaining 38.4% of physicians stated only a few of their patients were on hydroxyurea. One in five physicians reported that patients complain about the side effects of hydroxyurea. Of the nurses, one in four agreed that patients discontinue use due to side effects and one in ten noted that patients are not motivated to use hydroxyurea. Of the patients and caretakers, only 30% could afford to buy the drug (**Table 3**). Six patients saw no need to continue the use of hydroxyurea for religious reasons, since by faith they felt they had been healed.

Barriers to Patient Adherence

Various barriers to patient adherence to therapeutic use of hydroxyurea were reported by clinicians and patients. Among the physicians, one in five noted poor patient adherence after prescription; the same number indicated that their patients reported side effects. Two physicians agreed that hydroxyurea is available, but not in the formulation children can use. For nurses, 47.1% reported that their patients did well on hydroxyurea and that adherence was good. Half of the prescribing physicians found hydroxyurea effective while only one disagreed. Among patients, 30% reported that hydroxyurea is good and had relieved a lot of their symptoms, while one patient found the drug ineffective and discontinued its use.

DISCUSSION

Hydroxyurea, the first line drug of treatment for sickle cell disease, is under-utilized in Nigerian patients, as is likely the case in various other LMICs. This study was able to identify factors that mapped onto the inner setting, outer setting, and characteristics of

individuals domains of CFIR and found that, although the majority of physicians (74.1%) prescribed hydroxyurea to patients, much fewer (40%) report their patients actually use hydroxyurea. This is an improvement on what was observed almost a decade ago in Nigeria (Galadanci et al., 2014); however, there is still a gap between knowledge of this evidence-based practice and its routine implementation.

This work identifies various reasons for this "know-do" gap, which should be examined in future research. Physicians and nurses alike reported they lacked training on hydroxyurea prescription and patient counseling, respectively. The fear of side effects, cost, and unavailability of hydroxyurea and accompanying laboratory monitoring were major barriers to hydroxyurea uptake and patient adherence. Indeed, others have examined how toxicity and safety issues, (Adegoke et al., 2015; Adewoyin et al., 2017; Tshilolo et al., 2019) side effects, patient adherence, and lack of a national guideline for the use of hydroxyurea have discouraged prescription by physicians in Nigeria (Adewoyin et al., 2017; Adeyemo et al., 2019; Aliyu et al., 2007; Charache et al., 1995; S.; Charache et al., 1995). Moreover, side effects such as skin rashes, dark patches on skin, vomiting, and dizziness have been observed in some hydroxyurea users in Nigeria (Adewoyin et al., 2017) and this may further inhibit its use. Previous research has examined concerns about differential host response to hydroxyurea among children with SCD in relation to malnutrition, infections, infestations, and issues of feasibility of lifelong use, considering Nigeria's socioeconomic circumstances and weak healthcare system (Tshilolo et al., 2019).

About half of the patients in this study were taking hydroxyurea, but some stopped due to side effects. Side effects such as hair loss, nausea, neutropenia, and oligospermia are reversible; and often may not reappear when hydroxyurea is stopped and restarted at a lower dose. Therefore, a consent procedure involving patients and their caregivers, emphasizing benefits and clarifying the possibility of reversible side effects, may help to improve hydroxyurea uptake (Smith et al., 2019). Additionally, patients are supposed to be monitored for HbF induction and full blood count parameters and, if undesirable effects such as very low blood cell counts (neutropenia) are observed, medication is discontinued temporarily. A blood count is done 1–2 weeks after to check for recovery, and treatment continued at the same or reduced dose after recovery. Proper education of patients and caregivers about the reversibility of side effects during the recovery window might encourage more patients to continue hydroxyurea uptake until the desired effects are observed. Another concern especially in children is a higher susceptibility to infection due to neutropenia. However, clinical trials by Opoko et al., 2017 showed no difference in susceptibility to malaria in children placed on hydroxyurea compared to those not placed on hydroxyurea. Nonetheless, Tshilolo and colleagues (Tshilolo et al., 2019), have shown a lower rate of malaria cases in children placed on hydroxyurea as compared to those not placed on hydroxyurea.

The unavailability of equipment and reagents to monitor the patients may also pose a barrier to therapeutic use of hydroxyurea for SCD in Nigeria. Equipment to quantify hemoglobin variants and monitor the HbF levels is expensive, so few centers in Nigeria have them (Galadanci et al., 2014). The cost of clinical monitoring is also expensive and unaffordable for many patients. The issue of cost and availability of the drug as raised by the participants of the study is an important one that should also be addressed. A pack of 100 tablets of hydroxyurea is N12, 800 (~$40), which is quite expensive for most Nigerians. The cost of hydroxyurea should be subsidized, the drug made readily available in all sickle cell clinics and registered pharmaceutical outlets, and the paediatric formulation should be made readily available.

Although there are various strengths to this study, there are some limitations to address. The small sample size and the cross-sectional nature of the study may limit generalizability of the findings. Similar studies in Nigeria with a larger sample size and better national coverage may help to uncover additional factors that limit hydroxyurea utility in Nigeria. Also, future research studies should consider an intervention which will allow for examination of additional domains of CFIR including intervention characteristics (e.g., evidence strength and quality, adaptability), and the process of implementation (e.g., planning and executing an intervention protocol). Despite the study limitations, this study sheds light on the challenges to hydroxyurea adoption in Nigeria, a resource limited setting.

CONCLUSION

In Nigeria, hydroxyurea uptake is limited by provider prescription practices and patient adherence. This work identified the barriers and recommends interventions targeting an increase in provider, patient, and caregiver knowledge regarding the benefits of hydroxyurea. Particularly, formal training of haematologists and nurses/counselors on hydroxyurea prescription, as well as monitoring and counseling challenges should be addressed across health centers to ensure that SCD patients can get the drug when it is prescribed in low-resource settings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

Ethical approval was secured from the National Health Research Ethics Committee of Nigeria (NHREC). NHREC Protocol Number NHREC/01/01/2007-21/11/2017. NHREC Approval NumberNHREC/01/01/2007-03/11/2019C.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation and data collection was conducted by all

authors. Data analysis was performed by RC. The first draft of the manuscript was written by EO and all authors commented on versions of the manuscript. Each author has read and approved the final manuscript.

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Patterns, Outcomes and Predictors of Pediatric Medical Admissions at Gadarif Hospital in Eastern Sudan

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Background: The reduction of childhood mortality is a reliable indicator of a national health system's progress and improvement. Sudan's population is still suffering from communicable diseases, with a considerably higher mortality rate among children. Efforts are therefore needed to reduce mortality and achieve the Millennium Development Goals and Sustainable Development Goals. This study was conducted to determine the morbidity, mortality and outcomes of children admitted to Gadarif Hospital in eastern Sudan.

Method: A retrospective study was conducted by reviewing the medical files of pediatric patients who were admitted to Gadarif Hospital between March 1, 2019 and March 31, 2020.

Result: A total of 740 medical files were reviewed. Most, 453 (61.2%) of the admissions were males. The median (interquartile range) age was 3.0 (8.0) years and 433 (58.8%) of the admissions were under 5 years of age. The median (interquartile range) of the length of hospital stay was 9.0 (12.0) days. Visceral leishmaniasis, malnutrition, severe malaria, sickle cell disease, acute watery diarrhea, severe anemia (regardless of its cause), septicemia and acute respiratory infection were the most common causes of admission. The mortality rate was 5.7%, and it was significantly higher in females than males [24/287 (8.4%) vs. 18/453 (4.0%), $P = 0.01$] and in children under 5 years [36/433 (8.3%) vs. 6/307 (2.0%), $P < 0.001$]. Malnutrition, visceral leishmaniasis, septicemia and meningitis/encephalitis were the main diseases causing death in the study population. The case fatality rate was not significantly different in malnutrition than in visceral leishmaniasis [9/93 (9.7%) vs. 7/178 (3.9%), $P = 0.05$].

Conclusion: The main causes of morbidity and mortality for children admitted to Gadarif Pediatric Hospital were communicable diseases. The mortality rate was 5.7%. Females and children under 5 years were the most vulnerable groups for fatality.

Keywords: morbidity, mortality, under 5 years, predictors, children

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INTRODUCTION

Childhood mortality is an essential indicator to monitor child health. Mortality indicators are still considered a starting point for health status evaluation even after marked declines in mortality rates (1). Child morbidity and hospital admission are considered financial burdens to governments, health systems, and parents (2). In Africa, infections and communicable diseases are the leading causes of childhood morbidity and mortality (3). Despite the shift in the causes of mortality toward non-communicable diseases, communicable diseases remain the major causes of mortality and morbidity in middle- and low-income countries (4). Unlike the developed countries, where mortality from non-communicable diseases is escalating (5), in Sub-Saharan Africa, childhood mortality is mainly due to preventable communicable diseases (6, 7). Moreover, pediatric sepsis is a leading cause of hospital admission, with an increased risk of fatality in the African countries, including Sudan (8–10). Therefore, more research is needed to address mortality in children aged 5–9 years and in young adolescents. The World Health Organization (WHO) has reported that preventable diseases, such as respiratory tract infections, diarrheal diseases, and meningitis are responsible for about one million deaths in older children and young adolescents (11). Hence, further efforts are required to evaluate morbidities and mortalities in these age groups in order to improve outcomes. Previous studies have reported a significant variation in the leading causes of mortality between regions, gender, and age groups (4, 12). Most countries have very little information on mortality and general health conditions and, hence, it is of paramount importance to study the mortality conditions in these poor countries. There is a high rate (58.4 deaths per 1,000 live births) of childhood mortality in Sudan (13), which is one of the "least developed" countries in Africa. This study aimed to determine the patterns of morbidity and mortality and their predictors among children admitted to Gadarif Hospital in eastern Sudan.

MATERIALS AND METHODS

Medical files (paper-based) of the children admitted to Gadarif Pediatric Hospital between March 1, 2019 and March 31, 2020 were retrospectively reviewed. The hospital is a tertiary care facility that serves as a referral center in Gadarif State and is staffed with eight consultants, 10 specialists, and 25 medical doctors (registrars and residents).

Inclusion and Exclusion Criteria

All children (aged between 1 month and 18 years) admitted to the hospital during the study period and with complete medical records were included. We excluded patients with missing information on diagnosis, age, or gender. If the patient was admitted more than once during the period of the study, the last admission was considered.

Abbreviations: WHO, The World Health Organization; SPSS, Statistical Package for the Social Sciences; SD, Standard Deviation; HIV, human immunodeficiency virus.

We followed the systematic random sampling technique to select the medical files to review. According to the hospital records, there were 2,273 medical files during the study period. The sampling interval ($\approx$ 3) was assumed in dividing the all-medical files (2,273) by the calculated sample size (2,273/740 $\approx$ 3). Thus, the medical files were reviewed every three intervals to arrive at the required sample size (740). The subsequent medical file was taken if the selected file had incomplete data.

A seven-part questionnaire was used to collect the data, as follows: (1) socio-demographic information about the child and their family, their vaccine status, and their ward admission, (2) clinical diagnosis, (3) symptoms and signs, (4) relative investigations, (5) treatment, (6) outcome, and (7) cause of death.

Sample Size

A sample size of 740 medical files of children was calculated based on the reported rate of death (5.6%) in a previous study in Nigeria of children admitted to hospital (3). We assumed that 55 vs. 35% and 85 vs. 65% were the rates of the females and under-fives in children who died and children who survived, respectively. The gender and the rate of under-five children were chosen because the possible difference in these variables might serve as guidance for future interventions. This sample size had an 80% power, with a precision of 5%, assuming that 10% of the files would have incomplete data.

Statistics

The data were analyzed with the SPSS (Statistical Package for the Social Sciences) software, version 22.0. Frequency tables and percentages were generated for all the major variables of interest. The categorical variables were presented as percentages in tables, while comparisons between the variables were done using the Chi Square test. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 740 children were admitted during the study period. Of these, 287 (38.8%) were female and 453 (61.2%) were male, with a male: female ratio of 1.57:1.

The median (interquartile range) age was 3.0 (8.0) years, and 433 (58.8) were aged $<$ 5 years. The median (interquartile range) of the length of hospital stay was 9.0 (12.0) days.

Visceral leishmaniasis, acute severe malnutrition, severe malaria, sickle cell disease, acute watery diarrhea, severe anemia (regardless to its cause), septicaemia and acute respiratory infection were the most common causes of admission (**Figure 1**).

Forty-two patients died, resulting in a mortality rate of 5.7%. Forty-three children (5.8%) were discharged against medical advice, 638 (86.2%) were deemed well and discharged and 17 (2.3%) were referred elsewhere. The death rate was significantly higher in females than males [24/287 (8.4%) vs. 18/453 (4.0%), $P = 0.01$] and in children under five compared to children over five [36/433 (8.3%) vs. 6/307 (2.0%), $P < 0.001$]. Acute severe malnutrition or its complications, visceral leishmaniasis, septicemia and meningitis/encephalitis were the major diseases causing death in the study population.

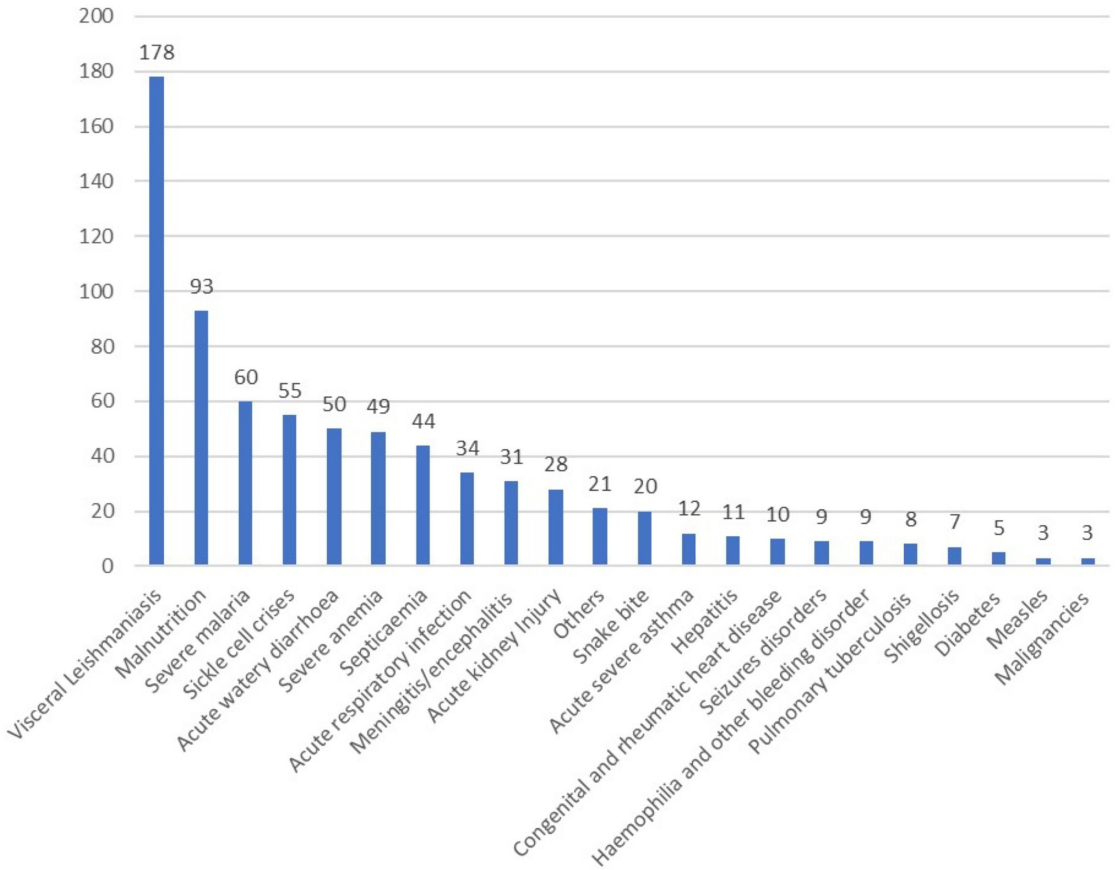

FIGURE 1 | Diagnosis on pediatrics admission in Gadarif Hospital in eastern Sudan in 2020 (number = 740).

The case fatality rate was not significantly different for malnutrition than for visceral leishmaniasis [9/93 (9.7%) vs. 7/178 (3.9%), $P = 0.05$].

DISCUSSION

The main findings of the current study are that around three-fifths (61.2%) of the admissions were males, visceral leishmaniasis was the leading cause of admissions, and 5.7% of these children died. A similar finding of a higher proportion of male admissions than female admissions has been reported in neighboring Ethiopia (14). This may be explained by the underlying social factors affecting the care-seeking behaviors of family members (15). Moreover, some factors related to pediatrics admission, such as breastfeeding, have been reported to be higher in female infants (20% more likely) than in males (16).

In the current study, visceral leishmaniasis, malnutrition, severe malaria and sickle cell disease were the most common causes of admission. Previous studies have shown that severe anemia, sickle cell disease, malaria and visceral leishmaniasis were the main causes of pediatric morbidity and mortality in eastern Sudan (17, 18) and in other African countries, e.g., Nigeria, Tanzania, and Uganda (3, 19, 20).

The current study documented a mortality rate of 5.7%, similar to what has been observed previously in Sudan (5.8%) (13), as well as in Nigeria (5.7%) (3) and in Liberia (5.4%) (21). The mortality rate of children in the current study was lower than that reported in Ghana (7.12%) (22) but higher than in other African countries, e.g., Ethiopia (0.042%) (14), Malawi (3.3%.) (23), and Nigeria (4.9%) (24). The lower mortality rate in these countries may reflect a marked improvement in pediatric health facilities (14, 23). The mortality rate (8.3%) in children under five in this study was higher than the mortality (7.0%) of children under 5 years of age in Sudan (25). In contrast to this finding, a higher mortality rate (12.5%) was documented in Ethiopia in children under 5 years of age (26). It is worth mentioning that the results of our study should be cautiously compared with the results of the later ones because of the difference in socioeconomic status and other factors.

In the current study, despite the higher rate of admission for males, the death rate was significantly higher in females than in males and in children under five compared to over five, (8.4%) vs. (4.0%) and (8.3%) vs. (2.0%), respectively. This is in line with the results obtained in Tanzania (19) and in Ethiopia (15). Conversely, other studies have reported significantly higher mortality among males than females (3, 27). Although this

discrepancy in gender mortality is fully explained, some have proposed a difference in immune response that is influenced by sex hormones (28). In addition, it has been previously reported that the tradition in Africa is to take care of male children first before female children (29).

In this study, malnutrition was the leading cause of mortality, with a case fatality rate of 9.7%, which was lower than the case fatality rate (12.5%) of malnutrition in Omdurman (part of the capital of Sudan) (30). However, a lower rate (3.7%) of case fatality of malnutrition has been reported in central Sudan (31) and in eastern Sudan (32). Visceral leishmaniasis was the second leading cause of morbidity and mortality in this study. Gadarif is an endemic area for this particular disease, which represents a high pediatric health burden (17, 18). Visceral leishmaniasis is also endemic in some areas of Sudan in general (33) and is frequently associated with severe anemia requiring blood transfusion (17). Severe anemia, another major cause of mortality in this study, can result from secondary causes, such as sickle cell disease, malaria, visceral leishmaniasis, severe acute malnutrition, snake bites, and sepsis (17). Severe-to- moderate anemia was also reported to be the main cause of admission to hospital among Ghanaian children (34).

Our study documented a considerably higher morbidity and mortality rate related to malaria infection. Malaria is an endemic disease that is associated with a significant mortality rate (5.3%) (35). Children are the most vulnerable age group for this disease, with a high mortality rate in Burundi (36) and Kenya (37, 38).

Diarrhea was a further cause of morbidity and mortality in this study. It is considered a major childhood medical problem in other areas in Sudan (39, 40) and in some African countries (41). Despite tremendous efforts, through a global initiative, to modify diarrheal-related fatalities in the last two decades, it is still one of the top two deadly diseases (72%) in children under the age of two in Sub-Saharan Africa in particular (42, 43). The common causes for diarrheal infection in this vulnerable group are enteric pathogenic rotavirus (44) and bacterial infections (40, 45).

In Sudan, the mortality rate may be explained by the poor distribution of health facilities in rural areas, family poverty, and the lack of hygienic and safe environments for children (46). Other reasons include low socioeconomic status and low educational levels of mothers (47, 48). Violence and war are additional risk factors that increase mortality in this vulnerable group of children (48). Similar risk factors affecting mortality have been demonstrated in several African countries, such as the preceding birth interval, family size, birth type, breastfeeding status, source of drinking water, maternal and child health services, mother's educational level, herbal medication use, sex of the child, and socioeconomic status (42, 49, 50). On the other hand, improvements in socio-demographic status, maternal health, governance, and financial status are likely to be associated with a reduction in the mortality rate (50). Furthermore, there is a growing body of evidence demonstrating that a sufficient density of distributed healthcare workers and health services can have a rapid and positive impact on neonatal and young child mortality and ultimately improve the child survival rate dramatically (51).

It is worth mentioning that human immunodeficiency virus (HIV) was reported as the top cause of death in other African countries (5), but a low incidence rate (0.4%) of HIV was reported in the hospital under study (52).

The limitations of this study are its cross-sectional design and that the data were collected only from major regional hospitals. The use of the incidence rate, a more precise measure, would be ideal to estimate the true at-risk population in etiological research. The study had some challenges, including incomplete reporting, as the hospital was unable to report cases in some years due to the lack of a computer-based system. Due to the retrospective nature of the study, some important factors, such as intubation or the use of respiratory support, were missing. In addition, some patients might have been seen in other health facilities or discharged against medical advice, and death may have occurred within the first month after discharge.

CONCLUSION

Sudan, similar to other developing countries where communicable diseases are the most prevalent causes for morbidity and mortality among children, has a high pediatric mortality rate. Hence, many more efforts are required to achieve the Millennium Development Goals and Sustainable Development Goals in this region.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study received ethical approval from the Research Board at the Faculty of Medicine, University of Gadarif, Sudan (the reference number is 2018/11).

AUTHOR CONTRIBUTIONS

MA and IM made a significant contribution to the data collection and data analysis. OA-W and IA conceived the study and made substantial contributions to the study design and data interpretation. HM contributed to the data collection and drafting of the manuscript. AA-N conceived the study and played a major rule in the study design, data collection, and drafting of the manuscript. All authors read and approved the final version of the manuscript.

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Healthcare Workers' Knowledge and Resource Availability for Care of Sickle Cell Disease in Dar es Salaam, Tanzania

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Background: Sickle cell disease (SCD) is a global public health priority due to its high morbidity and mortality. In Tanzania, SCD accounts for 7% of under-five mortality. Cost-effective interventions such as early diagnosis and linkage to care have been shown to prevent 70% of deaths but require knowledge among healthcare workers and availability of resources at health facilities. In Tanzania, data on these critical determinants are currently lacking.

Objective: To assess healthcare workers' knowledge and resource availability for care of SCD at health facilities in Dar es Salaam, Tanzania.

Methodology: A facility-based cross-sectional study was conducted between December 2020 and February 2021 among 490 nurses and clinicians at Regional Referral Hospitals (Temeke, Amana, and Mwananyamala) and Muhimbili National Hospital in Dar es Salaam, Tanzania. Data were collected using a pre-tested structured questionnaire consisting of 13 knowledge questions (scored good knowledge if correct response in >7) and an inventory check list to record available resources. Pearson's χ^2 was used to determine the association between level of knowledge and demographic factors. Multivariate logistic regression was used to ascertain the strength of associations. A two-tailed p-value <0.05 was considered to be statistically significant.

Results: Of the 490 participants (median age 28 years [IQR = 26–35]), only 25.1% had good knowledge on SCD. The odds of good knowledge was 82% lower in nurses than clinicians (AOR = 0.177; 95% CI: 0.090, 0.349; $p < 0.001$); 95% lower in diploma than Master's degree holders (AOR = 0.049; 95% CI: 0.008, 0.300; $p = 0.001$) and 4.6 times higher in those with 5–9 years than ≥10 years of experience (AOR = 4.564; 95% CI: 1.341, 15.525; $p = 0.015$). The regional-level hospitals lacked diagnostic tests and hydroxyurea therapy.

Conclusion: There was general lack of knowledge on SCD among healthcare workers and limited availability of critical resources for the diagnosis and care of SCD, especially at

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regional-level hospitals. Efforts are needed for their improvement to enhance care to patients, thus reducing the morbidity and mortality due to SCD in Tanzania.

Keywords: sickle cell disease, knowledge, healthcare workers, resources, health facilities, SPARCO, Tanzania

INTRODUCTION

Sickle cell disease (SCD) is an inherited disorder of the hemoglobin (Hb) molecule of the red blood cells (RBCs) that is associated with serious complications and reduced life expectancy (Tluway and Makani 2017). Globally, there are >300,000 births/year of children with SCD (Piel et al., 2013). Over 75% of people with SCD live in Sub-Saharan Africa (SSA), and this proportion is projected to increase to 85% by the year 2050 (Makani et al., 2011). WHO declared SCD a public health priority in 2006 (WHO, 2006) and is part of the Tanzania National Non-communicable Disease Strategy (Ministry of Health and Social Welfare, 2015). In Tanzania, about 11,000 babies are born with SCD/year, ranking 5th in the world behind Nigeria, Democratic Republic of Congo (DRC), Angola, and India (Nkya et al., 2019). Unlike high-income countries, SCD has a higher mortality in SSA. In Tanzania, mortality rate due to SCD is 1.9 per 100 person-years of observation, contributing 7% of under-five mortality (Makani et al., 2018; Makani et al., 2011).

Studies in high-income countries have indicated that simple, cost-effective interventions such as early identification of SCD patients by newborn screening and the subsequent provision of comprehensive care can prevent 70% of deaths due to SCD (WHO, 2006). Comprehensive care includes prompt treatment of acute events, prophylaxis against infections with oral penicillin, and vaccination against *Streptococcus pneumoniae*, plus prompt diagnosis and treatment of complications and educative programs provided to all individuals with SCD (Makani et al., 2018).

Following definitive diagnosis, proper management of SCD requires healthcare workers to have appropriate knowledge of the disease, especially risk factors for complications, symptoms and signs, investigations, and appropriate interventions (Dennis-Antwi et al., 2008; Gomes et al., 2015; Janerrete et al., 2016). However, limited knowledge among implementers is one of the major reasons for poor performance of healthcare interventions (Ambrose et al., 2020), likely contributing to high childhood mortality of 50–90% among patients with SCD in SSA (Makani et al., 2018).

Few studies have investigated on the level of knowledge on SCD among healthcare workers. In the USA, 67% of physicians knew that SCD can be detected early through newborn screening (McWalter et al., 2011). Another study in the USA showed 39% of obstetric-gynecologists were confident in managing pregnant women with SCD after receiving adequate training (Azonobi et al., 2014). In Brazil, approximately 75% of healthcare workers were found to have suboptimal knowledge on management of SCD (Gomes et al., 2011). In Nigeria, the knowledge of healthcare workers at primary health facilities was very poor, whereas only 37.9% had good knowledge on SCD diagnosis and crisis prevention (Adegoke et al., 2018). In the DRC, 80% of physicians knew how to diagnose SCD while 44% followed recommendation on management of vaso-occlusive crisis (VOC) while prescribing analgesia and hydration (Mbiya et al., 2020). In Tanzania, the level of knowledge on diagnosis and treatment of SCD among healthcare workers is not known.

For proper care of SCD, resources should be available at health facilities for the diagnosis and care of SCD patients (Dennis-Antwi et al., 2008). In high-income countries, the resources for diagnosis, treatment, and care of SCD are available (Drive and Quinn, 2017). In low- and middle-income countries, few studies have explored availability of resources for care of SCD showing widespread limitation where all too often resources are limited to private facilities and beyond the reach of the majority who would benefit (Williams, 2015; Mcgann et al., 2018). In the DRC, 65% of the physicians experienced difficulty in performing Hb electrophoresis due to lack of equipment (Mbiya et al., 2020). In Tanzania, the data on the availability of resources for the diagnosis and treatment of SCD appropriate to the level of healthcare facilities are not known.

This study sought to determine the level of knowledge on SCD among healthcare workers and availability of resources at Regional Referral Hospitals and Muhimbili National Hospital in Dar es Salaam for the diagnosis and care of SCD.

MATERIALS AND METHODS

Study Design and Setting

This was a facility-based cross-sectional study conducted from December 2020 to January 2021 at Regional Referral Hospitals (Mwananyamala, Amana, and Temeke) and Muhimbili National Hospital (Upanga and Mloganzila) in Dar es Salaam, Tanzania. These hospitals are public and provide outpatient and inpatient SCD services to majority of SCD patients in the city.

All the hospitals included in this study run dedicated pediatric and adult SCD outpatient clinics, which are operated by medical doctors and nurses. Specialist pediatricians, internal medicine physicians, and hematologists are also part of care when available. In case of admissions, patients are taken care of in general pediatric, internal medicine, general surgery, and or other wards as appropriate.

Non-governmental organizations play a pivotal role in increasing public awareness and advocacy for SCD in Tanzania, and are an important bridge between health systems, researchers, and patient communities. Particularly, the study team at Sickle Cell Programme, Muhimbili University of Health and Allied Science (MUHAS) has worked closely with Tanzania Sickle Cell Disease Alliance (TANSCDA), Sickle Cell Disease Patients Community of Tanzania (SCDPCT), Sickle Cell Youth Foundation (SYF), and Tanzania Sickle Cell Warriors (TASIWA). These have facilitated fundraising for

resources at health facilities, the conduct of public awareness campaigns as well as provision of health education to patients and caregivers of individuals with SCD.

Study Participants

Healthcare workers comprising clinicians and nurses providing services and directly interacting with clients who are seeking medical services for SCD at selected facilities were eligible to participate in this study.

Sample Size

The minimum required sample size of 416 healthcare workers was calculated using the Cochran formula (Cochran, 1977), assuming 37.9% of healthcare workers have good knowledge on SCD (Adegoke et al., 2018) and accounting for 15% non-response rate. Participants were then selected via multistage sampling. In the first stage, the participating hospitals, the Regional Referral Hospitals (Mwananyamala, Amana, and Temeke) and Muhimbili National Hospital (Upanga, Mloganzila), were identified. In the second stage, we identified the participating departments (obstetrics and gynecology, pediatric, internal medicine, surgery, and outpatient department) within the hospitals. In the third stage, the number of participants (clinicians and nurses) from each department in each hospital was determined proportionally by considering their total number at particular hospitals. Finally, the individual participants at each department were recruited consecutively whereby each available healthcare worker who met the inclusion criteria was enrolled until the sample size for each cadre was met. Also, 74 more healthcare workers were added beyond the minimum sample size for a final total of 490 participants.

Study Variables

The dependent/outcome variables were the overall level of knowledge on SCD among healthcare workers and availability of resources for diagnosis and treatment of SCD at healthcare facilities. Independent variables were age (years), sex (male/female), duration since graduation (years), level of facility (regional referral hospital/national hospital), professional cadre (nurse officer/registered nurse/nurse midwife for nurses, assistant medical officer/medical doctor/specialist for clinicians), duration of practice (years), and short course training received on SCD (yes/no).

Data Collection

Data on the sociodemographic characteristics (age, sex, level of education, duration since graduation, years of practice, level of facility, professional cadre, and short course training on SCD) and level of knowledge on SCD (overall, diagnosis and treatment) were obtained using a pre-tested and validated self-administered questionnaire adapted from Brazil (Diniz et al., 2019a) and modified to fit local context. Questions on SCD covered knowledge on diagnosis disease genotype, ideal timing of screening for SCD, confirmatory tests for SCD, clinical features of SCD, conditions that favor sickling of RBCs in patients with SCD warning signs in SCD, and knowledge on treatment of SCD (management of acute complications of SCD, drugs used to treat pain crises in patients with SCD, drugs used to prevent and/or treat complications of SCD, indications for use of antibiotics in SCD, indications for blood transfusion to patients with SCD, means of preventing infections in patients with SCD as well as pregnancy, and use of contraception in patients with SCD). The questions were in a multiple-choice setup and participants had to choose one best response for each question. Data on resources available at the facilities were obtained by inventory checklist adapted from the Tanzania National Guideline for SCD Management (United Republic of Tanzania, 2020) and Basic Health Standard for Facilities in Tanzania (United Republic of Tanzania, 2017) that indicate the facility level-specific minimum required resources through observation method. In each facility, one checklist was filled by interrogating heads of relevant units and cross-checking the mentioned drug (antibiotics and antimalarials, anti-pain medication, folic acid, and hydroxyurea) whether available and not yet expired, equipment (diagnostic equipment, other laboratory investigations, imaging equipment, and point-of-care clinical tests) whether available and functional, blood transfusion and exchange transfusion services, emergency surgical services, and intensive care unit whether available or not. Expired drugs and non-functioning instruments were regarded as not available.

Statistical Analysis

Data were checked for their completeness and consistence before analysis. Open-ended questions in the demographics section were first edited, categorized, and coded (level of education was categorized into certificate, diploma, degree, and Master's level) before entry. Participants' characteristics were first analyzed using descriptive statistics. Continuous variables (age, duration since graduation, and years of practice) were tested for normality of distribution using Shapiro and Wilk test. All variables were found to be not normally distributed, so they were summarized in median and interquartile ranges, then grouped into different categories as follows: age (0–30, 31–40,41–50, and 51–60 years), duration since graduation (≤5, >5 years), and years of practice (0–4, 5–9, >10 years). These, together with other categorical variables (sex, level of education, level of facility, professional cadres, and short course training received on SCD), were summarized in frequencies and percentages and presented in tables.

Knowledge on SCD was assessed by asking 13 multiple-choice questions comprising 6 questions on diagnosis and 7 questions on treatment. For each question, 1 point was assigned to each correctly answered item and 0 points otherwise. For calculation of the overall knowledge on SCD, the sum of all correct answers for diagnosis and treatment was taken, considering the following knowledge score ranges: >7 (more than 54% accuracy), good; ≤7 (54% or less accuracy), poor (Diniz et al., 2019a).

Inferential statistics on factors associated with level of knowledge was done by comparing the different categories between the dependent variable (overall knowledge on SCD) with various independent variables (age, sex, level of education,

TABLE 1 | Socio-demographic characteristics and overall level of knowledge on SCD among healthcare workers in Dar es Salaam (N = 490)

Characteristic	*n* (%)	Overall knowledge on SCD		
		Poor (≤7) N = 367 *n* (%)	Good (>7) N = 123 *n* (%)	*p*-value (χ^2 test)
Age (years), median = 28 [IQR = 26–35]				0.083
21–30	315 (64.3)	234 (74.3)	81 (25.7)	
31–40	116 (23.7)	82 (70.7)	34 (29.3)	
41–50	38 (7.8)	31 (81.6)	7 (18.4)	
51–60	21 (4.3)	20 (95.2)	1 (4.8)	
Sex				0.104
Male	224 (45.7)	160 (71.4)	64 (28.6)	
Female	266 (54.3)	207 (77.8)	59 (22.2)	
Duration since graduation (years)				0.002
≤5	344 (70.2)	244 (70.9)	100 (29.1)	
>5	146 (29.8)	123 (84.2)	23 (15.8)	
Level of education				0.000
Certificate	29 (5.9)	29 (100)	0	
Diploma	87 (17.8)	85 (97.7)	2 (2.3)	
Degree	335 (68.4)	241 (71.9)	94 (28.1)	
Masters	39 (8)	12 (30.8)	27 (69.2)	
Name of facility				
Mwananyamala RRH	50 (10.2)	39 (78)	11 (22.0)	0.813
Temeke RRH	56 (11.4)	43 (76.8)	13 (23.2)	
Amana RRH	67 (13.7)	52 (77.6)	15 (22.4)	
Muhimbili National Hospital	317 (64.7)	233 (73.5)	84 (26.5)	
Level of facility				0.335
Regional Referral Hospital	173 (35.3)	134 (77.5)	39 (22.5)	
Muhimbili National Hospital	317 (64.7)	233 (73.5)	84 (26.5)	
Professional cadre				0.000
Nurses	229 (46.7)	215 (93.9)	14 (6.1)	
Clinicians	261 (53.3)	152 (58.2)	109 (41.8)	
Years of practice (years)				0.010
<5	315 (64.3)	235 (74.6)	80 (25.6)	
5–9	75 (15.3)	48 (64)	27 (36)	
≥10	100 (20.4)	84 (74.9)	16 (25.1)	
SCD training received				0.988
No	450 (91.8)	30 (75.0)	10 (25)	
Yes	40 (8.2)	337 (74.9)	113 (25.1)	

duration since graduation, level of facility, professional cadres, years of practice, and short course training received on SCD) using χ^2 test (for independent variables with all expected values ≥5). Two-tailed *p*-values below 0.05 were considered statistically significant. Subsequently, univariate and multivariate binomial logistic regression were done to test the strength of association between the main dependent variable (overall level of knowledge) with the independent variables. Only independent variables with *p*-values ≤0.2 in univariate analysis (age, sex, professional cadres, duration since graduation, level of education, and years of practicing) were entered into multivariate logistic regression to adjust for effect of multiple predictors. The odds ratio was used to explain the relationship between dependent variable and associated factors, and confidence level at 95% as well as *p*-values were used in determining statistical significance.

In analyzing availability of resources for diagnosis and care of SCD, descriptive statistics were used to summarize the resources available at all health facilities in frequencies and percentages and presented in table and bar chart. Data were analyzed using IBM SPSS Statistics for Windows version 23.0 (IBM Corp., Armonk, NY, USA).

Ethical Considerations

Approval for the study was obtained from the Muhimbili University of Health and Allied Sciences (MUHAS) Research Ethics Committee with ethical clearance number MUHAS-REC-12-2020-452. Permission to conduct the study was sought from executive directors of relevant municipal hospitals and Muhimbili National Hospital. Written informed consent was obtained from all participants before the questionnaires were answered.

RESULTS

Demographic Characteristics of Participants

A total of 490 healthcare workers comprising 46.7% (229/490) nurses and 53.3% (261/490) clinicians completed the questionnaires. As shown in **Table 1**, the age of participants ranged from 23 to 60 years with the median age of 28 years [IQR = 26–35]. The majority of the participants were female 54.3% (266/490); 70.2% (334/490) had graduated ≤5 years;

TABLE 2 | Regression analysis of factors influencing knowledge among healthcare workers

Factors	*n* (%)	Univariate analysis		Multivariate analysis	
		COR (95% CI)	*p*-value	AOR (95% CI)	*p*-value
Age (years)					
21–30	315 (64.3)	6.923 (0.915–52.408)	0.061	0.343 (0.029–4.112)	0.398
31–40	116 (23.7)	8.293 (1.070–64.273)	0.043	0.374 (0.032–4.339)	0.431
41–50	38 (7.8)	4.516 (0.516–39.529)	0.173	0.484 (0.041–5.701)	0.564
51–60	21 (4.3)	Reference			
Sex					
Male	224 (45.7)	1.403 (0.932–2.114)	0.105	0.969 (0.603–1.556)	0.896
Female	266 (54.3)	Reference			
Duration since graduation (years)					
≤5	344 (70.2)	2.192 (1.326–3.622)	0.002	1.231 (0.514–2.948)	0.641
>5	146 (29.8)	Reference			
Level of education					
Certificate	29 (5.9)	0.00 (0.00–)	0.998	0.000 (0.000–)	0.998
Diploma	87 (17.8)	0.01 (0.002–0.050)	0.002	0.049 (0.008–0.300)	0.001
Degree	335 (68.4)	0.173 (0.084–0.356)	0.005	0.284 (0.096–0.837)	0.022
Masters	39 (8)	Reference			
Level of Facility					
Regional RRH	173 (35.3)	0.807 (0.522–1.247)	0.335		
National hospital	317 (64.7)	Reference			
Professional cadre					
Nurses	229 (46.7)	0.091 (0.050–0.164)	0.000	0.177 (0.090–0.349)	0.000
Clinicians	261 (53.3)	Reference			
Years of practice (years)					
<5	315 (64.3)	1.787 (0.989–3.230)	0.05	1.533 (0.391–6.009)	0.540
5–9	75 (15.3)	2.953 (1.448–6.024)	0.003	4.564 (1.341–15.525)	0.015
≥10	100 (20.4)	Reference			
SCD training received					
Yes	450 (91.8)	1.006 (0.477–2.123)	0.988		
No	40 (8.2)	Reference			

COR, crude odds ratio; AOR, adjusted odds ratio; 95% CI, confidence interval at 95%.

64.3% (315/490) had less than 5 years of practicing experience and 76.3% (374/490) had one or two university degrees. Out of 490 participants, 173 (35.3%) worked at Regional Referral Hospitals and 317 (64.7%) at National Hospital. Only 8.2% had received short course training on SCD.

Overall Level of Knowledge on SCD Among the Study Participants

Only 25.1% (123/490) of healthcare workers had good knowledge on SCD. In ascertaining association between the overall level of knowledge on SCD with participants' characteristics, it was observed that the duration since graduation, level of education, professional cadre, and years of practice were significantly associated with the level of knowledge on SCD (**Table 1**).

Regression Analysis of Factors Influencing Knowledge on SCD Among Healthcare Workers

Table 2 summarizes results of univariate and multivariate logistic regression. The final model revealed that there was strong association between overall level of knowledge on SCD with level of education, professional cadres, and years of practice. The odds of nurses having good knowledge on SCD were 82% lower than that in clinicians (AOR = 0.177; 95% CI: 0.090, 0.349; $p < 0.001$). Furthermore, healthcare workers with diploma had 95% lower odds of having good knowledge on SCD compared with those with Master's degree (AOR = 0.049; 95% CI: 0.008, 0.300; $p = 0.001$). Likewise, those with university degree had 72% lower odds of having good knowledge of SCD compared with those with Master's degree (AOR = 0.284; 95% CI: 0.0960, 0.837; $p = 0.022$). The healthcare workers with 5–9 years of practice were 4.6 times more likely to have good knowledge on sickle cell disease than those with practicing experience of 10 years and above (AOR = 4.564; 95% CI: 1.341, 15.525; $p = 0.015$).

Resources Available for Diagnosis and Treatment of SCD

Table 3 shows the resources available at Regional Referral Hospitals (RRH) and Muhimbili National Hospital (MNH) for diagnosis and treatment of SCD. Out of the equipment for SCD diagnosis, only the sickling test was uniformly available at both RRH and MNH while Hb electrophoresis was only available at the MNH. Diagnostic tests such as SickleSCAN, isolectric focusing (IEF), and high-performance liquid chromatography (HPLC) were not available at both the RRH and MNH. All other relevant laboratory equipment were present at the MNH but some, such as equipment for blood and urine culture, and were

TABLE 3 | Resources available at healthcare facilities in Dar es Salaam

S/N	Category of resource	Item	Availability	
			RRHs	MNH
1	Equipment for SCD diagnosis	Sickling test	3/3 (100)	1/1 (100)
		Isoelectric focusing (IEF)	0/3 (0)	0/1 (0)
		Hb electrophoresis	0/3 (0)	1/1 (100)
		HPLC	0/3 (0)	0/1 (0)
		Point-of-care tests (e.g., SickleSCAN)	0/3 (0)	0/1 (0)
2	Other laboratory investigations	Hematology analyzer	3/3 (100)	1/1 (100)
		Peripheral blood smear	1/3 (33.3)	1/1 (100)
		Biochemistry analyzer	3/3 (100)	1/1 (100)
		Blood culture	1/3 (33.3)	1/1 (100)
		Urine culture	1/3 (33.3)	1/1 (100)
		Malaria rapid diagnostic test (MRDT)	3/3 (100)	1/1 (100)
		Blood grouping and cross-matching	3/3 (100)	1/1 (100)
		Erythrocyte sedimentation rate (ESR)	2/3 (66.7)	1/1 (100)
		HIV rapid test	3/3 (100)	1/1 (100)
		PCR machine	0/3 (0)	1/1 (100)
3	Point-of-care clinical tests	BP machine	3/3 (100)	1 (100)
		Stethoscope	3/3 (100)	1 (100)
		Weighing scale	2/3 (66.7)	1 (100)
		Thermometer	3/3 (100)	1 (100)
		Tape measure	1/3 (33.3)	1 (100)
		Pulse oximeter	3/3 (100)	1 (100)
		Oxygen machine	3/3 (100)	1 (100)
		Hemocue machine	3/3 (100)	1 (100)
		Dipstick urinalysis	3/3 (100)	1/1 (100)
4	Imaging	ECHO	2/3 (66.7)	1/1 (100)
		ECG	2/3 (66.7)	1/1 (100)
		Ultrasound	3/3 (100)	1/1 (100)
		TCD	1/3 (33.3)	1/1 (100)
		X-Ray	3/3 (100)	1/1 (100)
		CT machine	0/3 (0)	1/1 (100)
		MRI	0/3 (0)	1/1 (100)
5	Anti-pain medication	Paracetamol	3/3 (100)	1/1 (100)
		Ibuprofen	3/3 (100)	1/1 (100)
		Diclofenac	3/3 (100)	1/1 (100)
		Pethidine	2/3 (66.7)	1/1 (100)
		Morphine	2/3 (66.7)	1/1 (100)
6	Antibiotics and antimalarials	Penicillin V	3/3 (100)	1/1 (100)
		Amoxiclav	3/3 (100)	1/1 (100)
		Ceftriaxone	3/3 (100)	1/1 (100)
		Metronidazole	3/3 (100)	1/1 (100)
		Gentamicin	2/3 (66.7)	1/1 (100)
		Artemether lumefantrine (ALU)	3/3 (100)	1/1 (100)
7	Hydroxyurea		0/3 (0)	1/1 (100)
8	Folic acid		3/3 (100)	1/1 (100)
9	IV fluids	Normal saline/Ringer's lactate	3/3 (100)	1/1 (100)
10	Blood transfusion and exchange transfusion	Blood transfusion	3/3 (100)	1/1 (100)
		Exchange transfusion	0/3 (0)	0/1 (0)
11	Emergency surgical and ICU services	Emergency surgical capability	2/3 (67)	1/1 (100)
		Intensive care unit (ICU)	1/3 (33)	1/1 (100)

only present in 33.3% of the RRH. The point-of-care clinical resources used at the clinics such as BP machine, pulse oximeter, stethoscope, and thermometer were widely available at both the RRH and MNH. All the imaging equipment including X-ray, ECG, echocardiography (ECHO), trans-cranial Doppler ultrasound (TCD), CT scan, and MRI were available at the national level. On the other hand, at regional level, on X-ray machines were uniformly present while ECG, ECHO, and TCD were only present in some RRH while CT scan and MRI machines were not available.

Drugs such as folic acid, antibiotics, and antimalarials as well as painkillers (paracetamol, ibuprofen, diclofenac, and morphine)

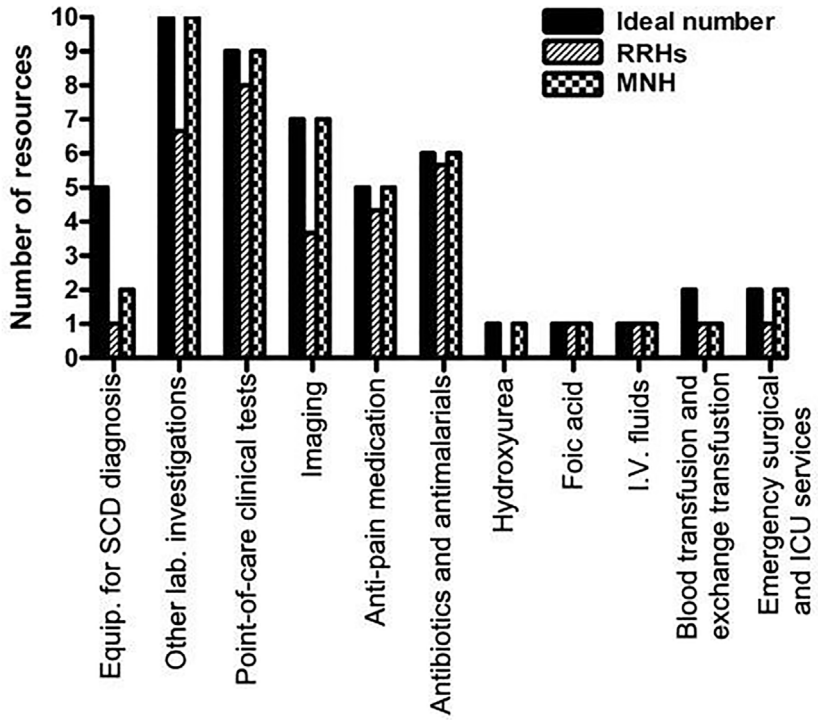

FIGURE 1 | Ideal versus available resources for SCD care at healthcare facilities in Dar es Salaam.

were to a large extent available at both RRH and MNH while hydroxyurea was only available at the national level. Blood transfusion services with whole blood and packed RBCs were available at all RRH and MNH, while exchange transfusion services were not available at all facilities. Capacities for emergency surgical procedures such as splenectomy and intensive care unit were available in 66.7 and 33.3% of the regional referral hospitals, respectively, while both services were available at the MNH. **Figure 1** compares the ideal number of clinical resources required at the facility level with the actual number of resources available at the RRH (average) and MNH.

DISCUSSION

Proper management of SCD requires healthcare workers to have appropriate knowledge of the disease and healthcare facilities to be well equipped for diagnosis and care of individuals with SCD. In the present study, we uncovered substantial lack of knowledge on SCD among healthcare workers in health facilities in Dar es Salaam where only one-quarter of healthcare workers had good knowledge. This proportion is low compared with that reported in the USA where over two-thirds of healthcare workers had good knowledge on SCD (Diniz et al., 2019b). Furthermore, the knowledge was also lower compared with that of healthcare workers in West Africa, particularly in the DRC and Nigeria, where 80 and 37.9% of healthcare workers, respectively, were found to have good knowledge on the nature of the disease, recognizable features, early SCD diagnosis, ideal timing for screening, and efforts to prevent SCD crisis (Adegoke et al., 2018; Mbiya et al., 2020). The low level of education on SCD among healthcare workers may be attributed to limited coverage of SCD in training and continuing education programs. This low level of knowledge on SCD is concerning as it implies lower likelihood of healthcare workers to direct clients toward early diagnosis during infancy and link them to comprehensive care, which are paramount to reversal of morbidity and mortality due to SCD as evidenced in high-income countries (Makani et al., 2018).

Our study showed strong association between level of education, professional cadres, and years of practice with the level of knowledge on SCD among healthcare workers. Specifically, good knowledge on SCD was more common among clinicians, holders of university degrees, and those with experience in clinical practice of between 5 and 9 years. This may be explained by the differential coverage of SCD in training curricula for health sciences, which is more extensive for medical practitioners than nurses, especially at degree level and above (Adegoke et al., 2018; Jain and Lothe, 2015). While it is plausible that the increase in years of practice from below 5 years to between 5 and 9 years was associated with an increase in knowledge on SCD (Jain and Lothe 2015), the fall in level of knowledge with increasing practice experience of 10 years and above is intriguing and is different from observations made in the DRC where physicians with more than 10 years of experience had better knowledge on management of SCD compared with those with less than 10 years of experience (Mbiya et al., 2020. A

potential explanation could be the lack of adequate content of SCD in the training curricula used a decade ago and beyond (Azonobi et al., 2014). In our study, only 8.2% of the participants had undertaken short courses on SCD, hence lacking statistical power to ascertain its contribution to the level of knowledge. However, previous studies in the USA, Brazil, Nigeria, and Ghana have reported significant influence of short course on knowledge on SCD (McWalter et al., 2011; Azonobi et al., 2014; Adegoke et al., 2018; Jain and Lothe, 2015).

To have good clinical outcomes in SCD, resources must be available at facilities for managing both inpatients and outpatients (Ambrose et al., 2020). While our study showed that resources were generally available at national-level hospitals, we uncovered suboptimal levels of resources for care of SCD at regional-level hospitals where items such as SCD confirmatory tests including Hb electrophoresis, isoelectric focusing, and HPLC; imaging equipment including trans-cranial Doppler ultrasound, CT scan, and MRI; blood and urine culture; intensive care services as well as hydroxyurea were uniformly or commonly missing. This may partly contribute to delayed diagnosis and subsequently poor outcome of the disease in Tanzania. The lack of confirmatory tests at healthcare facilities in Tanzania is similar to that reported in other parts of Africa such as in the DRC where two-thirds of the physicians (65%) reported difficulty in performing hemoglobin electrophoresis due to lack of equipment (Mbiya et al., 2020). In Tanzania, only sickling test was commonly available at all facilities (RRH and MNH), which is similar to other hospitals in Africa where screening for SCD is done using the sickling test and solubility test that are unreliable and cannot distinguish homozygous (Hb SS) from heterozygous (Hb AS) state (United Republic of Tanzania, 2017). Availability of SCD confirmatory tests will be a step forward toward universal newborn screening for SCD in Tanzania. Besides SCD confirmatory test, the observed lack of CT scan and MRI at regional-level hospitals is similar to that reported in other studies that showed supporting imaging equipment for diagnosis of SCD complications such as stroke are usually lacking at lower-level facilities in resource-limited countries (Ansong et al., 2013). Similarly, unlike national hospitals, other supporting tests such as urine and blood culture were not readily available at RRHs. However, point-of-care tests such as BP machines, stethoscopes, thermometers, pulse oximeters, hemocue machine, urinary dipstick, and weighing scales were commonly available at both RRH and MNH, implying capability for thorough physical examination, which is paramount during routine clinic visits (Diniz et al., 2019b).

SCD is contributing to the anemia in under-fives and pregnant women in areas of high prevalence. Severe anemia in SCD is life threatening and requires prompt treatment with blood transfusion using whole blood or packed RBCs (Tanyi, 2003). Our study showed common availability of blood transfusion services with whole blood as well as packed RBCs at all RRH and MNH. However, there were no capabilities for exchange transfusion services at all facilities at the time of the study, although such capabilities have since been established at the MNH. It is desirable to develop capabilities for exchange transfusion, which is required for treatment of life-threatening emergencies such as acute chest syndrome, at specialized referral care centers (Chamba et al., 2018).

Comprehensive care of SCD includes treatment of vaso-occlusive crisis, and prevention and prompt treatment of bacterial infections, malaria, and severe anemia. This study showed that drugs such as folic acid, antibiotics, and antimalarials and painkillers (paracetamol, ibuprofen, diclofenac, and morphine) were to a large extent available at both RRH and MNH while hydroxyurea was only available at the national level. While the trend in availability of most essential drugs is encouraging (Ambrose et al.,. 2020; Mbiya et al., 2020), it is concerning that hydroxyurea was not available at RRH. Currently in Tanzania, the RRH are allowed to procure hydroxyurea, and the medical, pediatric, and hematology specialists are allowed to prescribe hydroxyurea to patients with SCD. A major factor therefore hindering availability of hydroxyurea at RRH may be low awareness among the specialists, which leads to lower trends in prescribing the drug and consequently low rate or lack of procurement of the drug by hospital pharmacies. Efforts are required to ensure increased availability of hydroxyurea not only at MNH but also RRH.

Our study was not without limitations. Assessment of the level of knowledge on diagnosis and treatment of SCD was based on a set of 6 and 7 questions, respectively, which may not be comprehensive enough to exhaust all facets of knowledge. However, the questions used interrogated basic concepts and the number of questions used has been validated to be sufficient in evaluating the level of knowledge on SCD among healthcare workers in a previous study (Williams 2015).

In conclusion, there is a serious lack of knowledge on SCD among healthcare workers at healthcare facilities in Dar es Salaam. This calls for interventions through enhancement of the coverage of SCD as a model genetic disease in college and university training programs as well as in mandatory continuing professional development and continuing medical education programs to all staff. While intervention programs are advocated across the entire spectrum, major emphasis should be among the non-clinician cadres and non-degree holders. Further, the RRH should be equipped with vital resources to support SCD diagnosis and care, and specialized services such as exchange blood transfusion should be built at designated centers of excellence, such as the MNH, where in-need patients can be referred to, all aiming to improve the survival and quality of life of individuals with SCD in Tanzania. Similar studies should be conducted in other parts of the country, particularly in lower-level health facilities (district hospitals, health centers, and dispensaries), and include other professional cadres such as pharmacists, dentists, laboratory scientists, and community healthcare workers to provide a broader picture of needs for health education and resources for SCD diagnosis and care in the whole country. Comparison of the level on knowledge on SCD among the various medical specialists on large study will also be of interest.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the primary researcher is still analyzing data for

subsequent publications. Requests to access the datasets should be directed to AJ, ajonathan@blood.ac.tz.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Muhimbili University of Health and Allied Sciences (MUHAS) Research Ethics Committee. Ethical clearance number MUHAS-REC-12-2020-452. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AJ conceived the study, collected data, analyzed the data, and wrote the first draft of the article. HT, WL, and JN assisted in data collection. JM, PR, IM, and EB assisted in data analysis. All authors critically reviewed and approved the final version of the article.

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Adiponectin and Disease Severity in Sickle Cell Anemia Patients Attending a Tertiary Health Institution in Nnewi, Southeast Nigeria

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Background: Hemoglobin polymerization in sickle cell anemia (SCA) leads to abnormally rigid and adhesive erythrocytes that obstruct blood vessels, leading to poor tissue perfusion, hence provoking inflammation and damage of surrounding tissues. Adiponectin, a protein hormone, presumptively has anti-inflammatory characteristics, hence may be an important therapeutic target in SCA.

Aim: The aim of the study was to evaluate the status of adiponectin and its correlation with disease severity in SCA.

Patients and Methods: A total of 84 subjects were recruited for the study comprising 34 homozygous sickle cell (HbSS) subjects (25 in the steady state and nine in the resolving crisis state) and 50 controls (25 heterozygous sickle cell [HbAS] and 25 hemoglobin phenotype AA subjects). The hemoglobin phenotype, adiponectin levels, and full blood counts were evaluated. Anthropometric measurements were also conducted.

Results: A significant difference was observed in the mean body mass index between the different hemoglobin phenotype groups and also between the SCA in crisis resolution patients and the control group ($p < 0.05$). There was no significant difference in the median serum levels of adiponectin in the different hemoglobin phenotype groups and between SCA patients in the steady state compared with those in the crisis resolution state. Also, there was no correlation between disease severity and adiponectin in SCA patients in the steady state ($p = 0.87$).

Conclusion: Our study seems to suggest that in our data set of sickle cell anemia patients in the steady state, adiponectin does not constitute part of the endocrinopathy that affects these patients.

Keywords: adiponectin, sickle cell anemia, body mass index, sickle cell disease severity, endocrinopathy

INTRODUCTION

Sickle cell disease (SCD) is a group of genetic conditions that result from the inheritance of abnormal genes, thereby resulting in the production of abnormal hemoglobin in red blood cells (Akinyanju, 2015). The most common and most severe form of SCD, sickle cell anemia (SCA), refers to homozygosity for the sickle hemoglobin (Hb), known as HbSS (Piel et al., 2017). Hemoglobin polymerization leads to abnormally rigid and adhesive red blood cells (RBCs) that obstruct blood vessels, leading to tissue damage from poor perfusion in HbSS, hence provoking inflammation, as they stimulate and damage surrounding tissues and cells (Serjeant, 1997) (Platt, 2000). Keikhaei et al. showed that pro-inflammatory cytokines, especially lL-8 and IL-17 were increased in SCD patients in the steady state when compared to those in controls (apparently normal individuals) and increased in the crisis state when compared to the steady state (Keikhaei et al., 2013). This suggests that there is a background inflammation in the steady state which escalates during crisis.

The body mass index (BMI) is broadly used to categorize a person as underweight, normal weight, overweight, or obese based on tissue mass (muscle, fat, and bone) and height (Malcolm, 2015). Historically, it is well documented that children with SCD were underweight, particularly those with HbSS due to a characteristic basal hypercatabolic metabolism (Thomas et al., 2000; Barden et al., 2000).

Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid oxidation (Díez and Iglesias, 2003). Adiponectin is secreted from adipose tissue (and also from the placenta during pregnancy) into the blood. It is a specific protein with presumptive antiatherogenic, insulin-sensitizing, and anti-inflammatory characteristics (Chen et al., 2006; (Hotta et al., 2000; (Bełtowski et al., 2008). Adiponectin is considered important in the etiopathogenesis of many vascular and inflammatory disorders due to its anti-inflammatory actions (Zhu et al., 2008; (Cui et al., 2011). It also inhibits the synthesis of pro-inflammatory cytokines such as IL-6, IL-18, and TNF-α synthesis by blocking NF-κB activation (Yamaguchi et al., 2005; Chandrasekar et al., 2008; Ouchi and Walsh, 2017).

Exploring the role of adiponectin in sickle cell anemia hence becomes important, given that sickle cell anemia has a background chronic inflammatory state and adiponectin may be an important therapeutic target in its management.

SUBJECTS AND METHODS

Patient Selection

A total of 84 subjects were recruited for the study from the hematology clinic of a tertiary health center and during community interactive sessions with patients. These included 25 homozygous sickle cell (HbSS) subjects in the steady state [the selection of the steady state group was dependent on subjects' not experiencing crisis for at least 4 weeks, not receiving blood transfusion for at least 3 months, and not having fever for at least 2 weeks prior to the study (Okocha et al., 2014)]. A total of nine homozygous sickle cell (HbSS) patients, whose crisis was resolving, were defined as HbSS patients who did not meet the criteria for the steady state disease but were not in the acute phase of SCA crisis; while 25 heterozygous sickle cell (HbAS) and 25 hemoglobin phenotype AA subjects were used as controls. The ethical approval for this research was obtained from the Nnamdi Azikiwe University Teaching Hospital Ethics Committee, and written informed consent was sought and received from the subjects or their caregivers.

Disease Severity Score in Hemoglobin SS Patients

Disease severity was calculated using an objective severity scoring system, where points were assigned using the following characteristics: number of hospital admissions for crisis per year, rate of transfusions, white blood cell count, number of complications, and the degree of anemia. Scores of ≤3 were considered mild disease; scores of >3–≤ 7, moderate disease; while scores of >7 were considered severe disease (Okocha et al., 2017).

Specimen Collection, Preparation, and Storage

About 5 ml of venous blood was collected aseptically by venipuncture from each subject *via* the antecubital vein using a plastic syringe with minimum stasis, and 2 ml was then dispensed into ethylene diamine tetra acetic acid bottles for the determination of the hemoglobin phenotype and the full blood count. The remaining 3 ml was emptied into a plain bottle and centrifuged at 4000 rpm for 10 min. The serum (supernatant) was stored at −22°C and then used for the determination of adiponectin levels. The hemoglobin phenotype was determined using the Zip Zone electrophoresis chamber and EV 243 power supply (Helena Biosciences, United Kingdom). The adiponectin level was determined using commercially available adiponectin test-kits, and its assay was based on enzyme-linked immunosorbent assay. The full blood count was performed using a Sysmex automated hematology analyzer (KX2IN model, Sysmex Corporation, Kobe, Japan)

Statistical Analysis

Data obtained were analyzed using the Statistical Package for Social Sciences software package version 20 (SPSS Inc., IL, Chicago, United States). Descriptive statistics were used to summarize the variables and characterize the demographics. The statistical analysis was performed using the Kruskal–Wallis test to compare the differences in medians between two and three groups. The Spearman's correlation coefficient was used for correlation of nonparametric variables. The values were deemed significant when $p < 0.05$.

RESULTS

There was a total of 84 subjects recruited for this study which included 25 homozygous sickle cell (HbSS) subjects in the

TABLE 1 | Anthropometric values in different hemoglobin phenotype groups.

Group		N	Age (year)	BMI (kg/m^2)
HbSS genotype	Steady (A)	30	25.50	18.58
	Crisis (B)	10	27.00	18.95
AS (C)		25	23.00	23.00
AA (D)		25	24.00	21.52
Kruskal–Wallis H			2.261	29.363
p-value			0.520	<0.001
A vs. B (*p*-value)			1.000	1.000
A vs. C (*p*-value)			1.000	0.006
A vs. D (*p*-value)			1.000	0.004
B vs. C (*p*-value)			1.000	0.139
B vs. D (*p*-value)			1.000	0.113
C vs. D (*p*-value)			1.000	1.000

TABLE 2 | Levels of Adiponectin in different hemoglobin phenotype groups.

Group		N	Adiponectin (μg/L)
HbSS genotype	Steady (A)	25	34.00
	Crisis resolution (B)	9	37.00
AS (C)		25	33.50
AA (D)		25	34.00
Kruskal–Wallis H			0.579
p-value			0.878
A vs. B (*p*-value)			1.000
A vs. C (*p*-value)			1.000
A vs. D (*p*-value)			1.000
B vs. C (*p*-value)			1.000
B vs. D (*p*-value)			1.000
C vs. D (*p*-value)			1.000

steady state, nine homozygous sickle cell (HbSS) patients whose crisis were resolving, 25 heterozygous sickle cell (HbAS) subjects, and 25 hemoglobin phenotype AA subjects. The HbSS subjects in the steady state were 14 nonpregnant females and 11 males; HbSS in crisis resolution included eight females and one male; HbAS included 16 males and 9 females, while HbAA included 14 males and 11 females. Their age range was between 10 and 48 years with the median age of the homozygous sickle cell subjects in the steady state being 25.50 years; the median age for the homozygous sickle cell subjects in crisis resolution was 27.00 years and that for the heterozygous sickle cell subjects was 23.00 years and the HbAA controls was 24.00 years (**Table 1**). **Table 1** also shows the mean BMI (kg/m) in the various hemoglobin phenotype groups. A significant difference was observed in the mean BMI between the different hemoglobin phenotype groups. However, there was no significant difference in the mean BMI between the homozygous sickle cell anemia patients in the steady and crisis resolution states and between the sickle cell anemia in crisis resolution and the control group ($p > 0.05$).

Table 2 shows the median levels of adiponectin in the different hemoglobin phenotype groups. There was no significant difference in the median serum levels of adiponectin in the different hemoglobin phenotype groups and between sickle cell anemia patients in the steady state and crisis resolution state.

TABLE 3 | Correlation studies of BMI, age, and adiponectin levels with disease severity in subjects with sickle cell anemia in the steady state.

Parameter	N	R	*p*
Disease severity vs. BMI	30	–0.012	0.948
Disease severity vs. age	30	–0.035	0.853
Disease severity vs. adiponectin	25	0.032	0.870

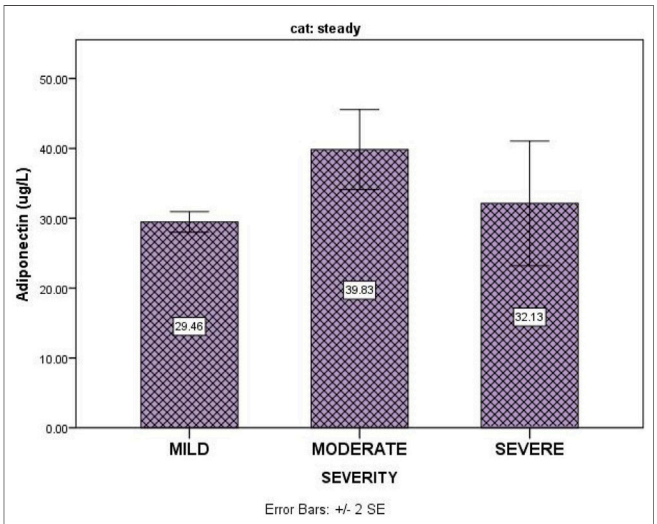

FIGURE 1 | SCD severity in the steady state versus adiponectin levels.

Table 3 shows that disease severity in SCA patients in the steady state had no correlation with serum adiponectin ($p = 0.87$). **Figure 1** shows the relationship between serum levels of adiponectin and sickle cell disease severity for subjects in the steady state.

DISCUSSION

We have shown from this study that the mean serum adiponectin levels were not significantly different amongst the subjects from the different hemoglobin phenotypes, which is in contrast to the findings by Makis et al., who reported elevated adiponectin levels in steady state sickle cell anemia patients when compared with control subjects. This seems to suggest that in our data set of sickle cell anemia patients in the steady state, adiponectin does not constitute part of the endocrinopathy that affects these patients. Genetic variation could be the likely explanation of this difference between our data set and that of Makis et al. (2012).

The finding from this study reveals that the BMI is significantly decreased in sickle cell anemia in the steady state when compared with that of the control group (HbAA) is corroborated by

Odetunde et al. (2016). Poor growth and nutrition are common in children with sickle cell anemia (SCA), which was demonstrated by Oredugba et al. in which the nutritional status in children with SCA negatively affected the anthropometric status, disease severity, and body composition of the patients (Oredugba, 2002). Some have hypothesized that underweight in SCA is caused by a hypermetabolic state, which increases energy demand that may lead to an undernourished state if not offset by increased nutrient consumption (Hibbert et al., 2006). Increased expenditure of energy at rest is a major metabolic change associated with HbSS. Barden et al. reported that energy expenditure at rest is approximately 15–20% higher in adolescents with HbSS than HbAA (Barden et al., 2000). This study showed no significant disparity in the BMI of subjects in the steady state when compared to those in crisis resolution, which is in agreement with the study by Iwalokun et al. (2011). This may be because the crisis duration may not be long enough to significantly alter the patients weight.

Although Makis et al. found a positive correlation between adiponectin and inflammatory markers, we found no correlation between adiponectin and disease severity. This may be because our disease severity scoring system is a composite of many parameters and therefore is more robust in predicting actual disease severity.

Our finding agrees with the report by Hall et al. (2018) which showed no association between BMI of sickle cell anemia subjects and disease severity. Also, no correlation was found between age and disease severity, which contrasts with the study by Adegoke and Kuti (2013), who found a positive correlation between age and disease severity.

CONCLUSION

Our data suggest that adiponectin does not seem to constitute part of sickle cell endocrinopathy in steady state sickle cell anemia patients at Nnewi, Southeast Nigeria. Also from the study, we found that the subjects with sickle cell anemia in crisis resolution and steady states had lower BMI values than HbAA and HbAS subjects. We therefore recommend that the nutritional needs of patients living with sickle cell anemia should be given more attention to improve the general well-being of the patients.

Limitation of the Study

Although this study has presented some insight into the dynamics of adiponectin in SCA clearly, it is limited because a larger longitudinal study starting from when the patients are in steady state through crisis state would have given further insight into the dynamics of adiponectin and BMI in these patients, thereby making for a better patient treatment, monitoring, and outcome.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The ethical approval for this research was obtained from Nnamdi Azikiwe University Teaching Hospital ethics committee, and written informed consent was sought and received from the subjects or their caregivers.

AUTHOR CONTRIBUTIONS

CEO designed the work, wrote the manuscript, and reviewed the manuscript. PO designed the work and wrote the manuscript. CI collected data, performed the experiments, and wrote the manuscript. UO wrote the manuscript. CO performed the statistical analysis. CE wrote the manuscript.

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Establishing a Sickle Cell Disease Registry in Africa: Experience From the Sickle Pan-African Research Consortium, Kumasi-Ghana

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Sickle cell disease (SCD) is the most common clinically significant hemoglobinopathy, characterized by painful episodes, anemia, high risk of infection, and other acute and chronic complications. In Africa, where the disease is most prevalent, large longitudinal data on patients and their outcomes are lacking. This article describes the experiences of the Kumasi Center for SCD at the Komfo Anokye Teaching Hospital (KCSCD-KATH), a Sickle Pan-African Research Consortium (SPARCO) site and a SickleInAfrica Consortium member, in establishing a SCD registry for the evaluation of the outcomes of patients. It also provides a report of a preliminary analysis of the data. The process of developing the registry database involved comprehensive review of the center's SCD patient medical records, incorporating data elements developed by the SickleInAfrica Consortium and obtaining ethical clearance from the local Institutional Review Board. From December 2017 to March 2020, 3,148 SCD patients were enrolled into the SCD registry. Enrollment was during the SCD outpatient clinic visits or through home visits. A significant proportion of the patients was from the newborn screening cohort (50.3%) and was males (52.9%). SCD-SS, SCD-SC, and Sβ $^{+}$thalassemia were seen in 67.2, 32.5, and 0.3% patients, respectively. The majority of the patients were in a steady state at enrollment; however, some were enrolled after discharge for an acute illness admission. The top two clinical diagnoses for SCD-SS patients were sickle cell painful events and acute anemia secondary to hyperhemolysis with incidence rates of 141.86 per 10,000 person months of observation (PMO) and 32.74 per 10,000 PMO, respectively. In SCD-SC patients, the top two diagnoses were sickle cell painful events and avascular necrosis with incidence rates of 203.09 per 10,000 PMO and 21.19 per 10,000 PMO, respectively. The SPARCO Kumasi site has developed skills and infrastructure to design, manage, and analyze data in the SCD registry. The newborn screening program and alternative

recruitment methods such as radio announcement and home visits for defaulting patients were the key steps taken in enrolling patients into the registry. The registry will provide longitudinal data that will help improve knowledge of SCD in Ghana and Africa through research.

Keywords: sickle cell disease, registry, SPARCo, SickleInAfrica, Kumasi-Ghana

INTRODUCTION

Sickle cell disease (SCD) is one of the most common inherited blood diseases, which affect red blood cells (RBCs) in humans. The disease is characterized by painful episodes, anemia, high risk of infection, and other acute and chronic complications (Williams et al., 2009; Grosse et al., 2011; Scott et al., 2011). Worldwide estimates indicate that 20–25 million people are affected by SCD with approximately 60% of those affected, living in sub-Saharan Africa (Aliyu et al., 2008). SCD is most prevalent in sub-Saharan Africa (Munung et al., 2019) with an estimated number of 240,000 patients born with SCD-SS each year (Weatherall, 2011). Ghana accounts for about 15,000 (6.25%) of that number (Ohene-Frempong et al., 2008). The global number of newborns with SCD is estimated to increase to about 400,000 by the year 2050 with 85% expected to be born in sub-Saharan Africa (Piel et al., 2013a). Implementation of early diagnosis of SCD in newborns and a comprehensive management plan including penicillin prophylaxis, vaccination, disease-modifying drugs, screening for and prevention of complications, supported with health maintenance have been shown to significantly reduce mortality and prolong the life of patients (Piel et al., 2013a; Kwarteng-Siaw et al., 2017). In Africa, there are limitations in standards of care for management of SCD, skills development for health care professionals in SCD, and comprehensive databases of patients for monitoring clinical care (Diallo and Tchernia, 2002; Wonkam and Makani, 2019; Oron et al., 2020; RFA-HL-17–006, 2021a).

The Kumasi Center for SCD at the Komfo Anokye Teaching Hospital (KCSCD-KATH) was inaugurated in 1992 as a comprehensive SCD management center in preparation for the start in 1993 of the NHLBI-funded pilot research project entitled, "Newborn Screening for Sickle Cell Disease in Ghana", the first public health-based newborn screening project for SCD in Africa.

In September 2015, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) of the United States of America issued a "request for application" for establishment of a "Sickle Cell Disease in Sub-Saharan Africa: Collaborative Consortium" (RFA-HL-17–006, 2021b) and a related request for a "Sickle Cell Disease in Sub-Saharan Africa: Data Coordinating Center" (RFA-HL-17–006, 2021a). A multinational collaboration among Muhimbili University of Health and Allied Sciences (MUHAS), Dar Es Salaam, Tanzania, as the hub, and two additional sites, the University of Abuja, Abuja, Nigeria, and the Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana, applied for and were awarded the consortium grant. The University of Cape Town, Cape Town, South Africa, was the successful applicant for the data coordinating center. The consortium was named "Sickle Pan-African Research Consortium" (SPARCO) and the data coordinating center was named Sickle Africa Data Coordinating Center (SADaCC) and later together labeled SickleInAfrica (Makani et al., 2020) (https://www.sickleinafrica.org).

The main objectives of this consortium are:

- Formation of a centralized, electronic, patient-consented, sickle hemoglobinopathy database that will facilitate registration and follow-up of SCD patients and serve as the backbone for future SCD in sub-Saharan Africa research network operations.
- Creation of shared database elements as well as harmonized SCD phenotype definitions and ontologies.
- Integration of collaborative consortium activities with those of the Data Coordinating Center, National Heart, Lung, and Blood Institute (NHLBI), Steering Committee, Observational Monitoring Board, and any existing training programs.
- Development of SCD standards of care appropriate to regional resource availability and clinical needs.
- Organization of research and clinical skills development activities.
- Planning for future SCD cohort studies, implementation of preventive/therapeutic practices, and the inclusion of new African sites to constitute the SCD in the SSA research network.
- Accomplishment of collaborative consortium activities over 4 years, with a 2-year development phase, a 1-year pilot/planning phase, and a 1-year implementation phase.

Registries collect longitudinal data on patients and help in a better understanding of their experiences and clinical outcomes and assist in improving their health and well-being (Heeney et al., 2011). Registries are inherently observational which help them to describe the status quo and guide discussion on research and any possible interventions. Registries have been found to provide information that helps in identifying gaps and informing policy and strategies.

One of the most ambitious registries is the SECURE-SCD registry. In the midst of the COVID-19 pandemic, the SECURE-SCD registry has been developed to gather information on SCD patients, who develop COVID-19 worldwide. This registry gathers reported data from health providers (Panepinto et al., 2020).

In the USA, several registries exist including Cooperative Study of Sickle Cell Disease (CSSCD) (Farber et al., 1985), Comprehensive Sickle Cell Centers Clinical Trial Consortium (de-Graft Aikins et al., 2010), Children's Hospital of Pittsburgh

Sickle Cell Research registry (Hillery, 2021), the European Hemoglobinopathy registry (European Haemoglobinopathy Registry » Sickle Cell Society, 2021), the Sickle Cell Disease Implementation Consortium (SCDIC) program (DiMartino et al., 2018; Glassberg et al., 2020), and Sickle Cell Clinical Research and Intervention Program (Hankins et al., 2018).

The Sickle Cell Disease Implementation Consortium (SCDIC) program was also set up in 2016 in the United States of America (USA) to support implementation research in SCD. The 6-year registry project targets 2,400 patients specifically of ages 15–45 across eight centers and captures standardized clinical measures and also patient experiences (DiMartino et al., 2018; Glassberg et al., 2020).

The SCCRIP started in 2014 as a 30-year program aimed at enrolling 10,000 participants across all age groups in five sites and has a pharmacokinetics sub-study to investigate the responses to hydroxyurea (Hankins et al., 2018).

Though SCD is more prevalent in sub-Saharan Africa, there is little data published from registries that gather longitudinal data on patients. Registries require a lot of resources to set up, recruit patients, and maintain over time as longitudinal data are required.

In Africa, prior to the SPARCO initiative, several efforts have been made in establishing various kinds of SCD registries including the Sickle Cell Disorder Registry Nigeria (SCDRN) (Sickle Cell Foundation Nigeria, 2021), Muhimbili University of Health and Allied Sciences, Tanzania (Makani et al., 2018), Sickle Cell Disease Genomics Network of Africa (SickleGenAfrica), Makerere University, Kenya, University of Cape Town, South Africa, University Teaching Hospitals, Children's Hospital, Zambia, University of Rwanda, School of Medicine and Pharmacy, University of Zimbabwe College of Health Sciences, DELGEME, Mali, and University of Abuja, Nigeria.

The Sickle Cell Disorder Registry Nigeria is a collaboration between the Sickle Cell Foundation Nigeria and PointCareHealth Initiative aimed at collecting patient clinical information and patient-reported information across Nigeria, to support management of the patients as well as stimulate research into interventions (Sickle Cell Foundation Nigeria, 2021).

The KCSCD-KATH since its inception developed a clinical database using FileMaker Pro to manage outpatient and inpatient encounters of its cohort of newborn-screened patients. The database has helped in tracking newborns from screening through to their enrollment and management in the clinic.

Registries are varied based on their purpose, target population, duration of enrollment, and the numbers of recruiting sites. This has raised calls for the standardization of the collection of data in these registries to provide more valuable information from large patient populations across countries (McCormick et al., 2021).

SADaCC and SPARCO Hub are building a robust electronic platform to support the activities of SPARCO. SADaCC and SPARCO Hub are responsible for the creation and maintenance of this centralized, electronic sickle hemoglobinopathy database and the development of data management, bioinformatics, and biostatistical skills across the consortium sites (Makani et al., 2020). This database is being designed to collate deidentified data from the consortium sites while sites manage their comprehensive registries. As a precursor to the centralized database, an appropriate SCD registry has been implemented to monitor and document the patient recruitment and follow-ups in Ghana. The registry is generating data for the evaluation of the outcomes of patients and the quality of care provided and hence assists in developing better standards of care for patients. The availability of the registry can enhance research, education, policy, and public health programs that will improve patient outcomes (de Groot et al., 2017).

This report describes the efforts of SPARCO-Kumasi in establishing a SCD patient registry and provides a report of a preliminary analysis of the data generated so far.

METHODS

Study Site

The study was conducted at the Kumasi Center for Sickle Cell Disease, Komfo Anokye Teaching Hospital (KCSCD-KATH), affiliated with KNUST. KATH is located in Kumasi metropolis, the regional capital of the Ashanti Region and the most populous metropolitan area with 3.348 million inhabitants (Macrotrends. Accra, 2021). The hospital is a tertiary hospital with a bed capacity of 1,200 which serves as a major referral center for 12 out of 16 regions of Ghana (About Us | Komfo Anokye Teaching Hospital, 2021).

Since the first babies were tested in February 1995 at KATH, the hospital has screened more babies for SCD than any other site in Africa. Approximately 8,000 presumptive SCD patients have been identified by the newborn screening program (Ohene-Frempong, 2017) and approximately 80% of these patients were enrolled in the SCD clinic. The KCSCD-KATH offers predominantly pediatric services. Newborn babies with SCD are enrolled at the KCSCD by 2–3 months of age and started on twice daily penicillin prophylaxis, infant series of pneumococcal conjugate vaccine, once daily folic acid, and parental or caretaker education about SCD management in young children. Patients up to 3 years of age are scheduled to be reviewed every 2 months and those above 3 years, every 3 months *as* specified in the standard operating procedure of the center. Routine health maintenance evaluations include blood tests, complete blood counts with reticulocyte count, metabolic panel to assess kidney and liver functions, and eye screening for adolescents. Transcranial Doppler ultrasonography is available for patients but on a user-fee basis. Hydroxyurea therapy, previously offered to patients who could afford, is currently being offered for free to all patients under a public–private Partnership between Government of Ghana and Novartis AG (Novartis, 2019; Ministry of Health G, 2020). Since January 2019, KATH has established an electronic health record system for both outpatient and inpatient encounters.

Database Design

The SPARCO-Kumasi site aimed to enroll 3,000 SCD patients over a 4-year period (2017–2020) and entered their basic demographic and clinical details into an electronic database system. The Research Electronic Data Capture (REDCap)

platform was chosen for reasons including its flexibility, ease of design, interoperability, security features, and the ability to switch between web-based and mobile data collection platform in cases where internet was unavailable (Harris et al., 2009; Harris et al., 2019).

Basic data elements from the FileMaker Pro database of the KCSCD-KATH served as a primary source to build the subsequent registry. Subsequently, the Kumasi site initiated steps to design a locally relevant database pending the joint effort at developing a centralized hemoglobinopathy database for SPARCO hosted by SADaCC.

The first step in the process was a review of the SCD-specific patients' chart that was in use for documenting patient clinical encounters at the KCSCD-KATH. The review also took into consideration the clinic visit documentation of the Sickle Cell Program of *the* Muhimbili National Hospital in Dar Es Salaam, Tanzania. A revised chart was then developed incorporating all the necessary changes. The document was then submitted to the Biostatistics Unit of KATH to be incorporated into the hospital's electronic health management system.

The final version of the chart was used in designing the REDCap database. The data elements received from SickleInAfrica were also incorporated to modify the database as required to allow for future data harmonization with the SPARCO/SADaCC registry database. Patient identifiers were appropriately indicated in the REDCap database. Default values were also inserted as appropriate values to ease data encoding. Dummy records were entered to assess the reliability, validity, and precision of the database in the collection of patient information.

Patient Enrollment and Data Collection

All SCD patients reporting for clinical care at the KCSCD-KATH were eligible for enrollment.

Study procedures were explained to patients and/or their caregivers, and those who agreed to participate were asked to sign a written informed consent form to show their approval before they were enrolled into the registry. Informed consent was obtained from caregivers of patients (if the patient was below 18 years) or from patients themselves (if patients were 18 years and over). Assent was obtained from patients aged 7–17 years in addition to caregivers' written informed consent.

Information on hemoglobin phenotype, date of birth/age at enrollment, sex, religion, residence, penicillin V, folic acid, and hydroxyurea usage were collected through interview with the patient/caregiver and review of medical records of the patients. The diagnosis pathway was recorded as either via newborn screening or non-newborn screening. Patients whose hemoglobin phenotypes were diagnosed by the newborn screening were tested using the iso-electric focusing method. Those who were diagnosed beyond the newborn age were tested using the Hb electrophoresis method. S/beta-plus thalassemia would show Hb S > Hb A. Information on the hemoglobin phenotypes was obtained from the patient records. The patients were not tested routinely for alpha-thalassemia and so this was not captured. No genetic testing was performed on patients who were enrolled. Follow-up clinical encounters at each clinic visit were also captured. Patients' diagnosis was classified according to the SCD ontology definitions (Sickle Cell Disease Ontology, 2020), and the following common to the cohort was defined subsequently as in **Table 1**.

Alternative Enrollment Methods

Alternative methods were initiated in January 2019 to enroll patients who had defaulted in clinic visits. A patient was defined to have defaulted if the last clinic attendance was more than a year. The first method was an invitation by radio announcements for a mass enrollment drive over two days in January 2019. Those who responded and presented to the SCD outpatient clinic were registered. The second method involved home visits using the KCSCD existing clinical database. Information on patients who had defaulted in clinic attendance was extracted. Patients were initially contacted on phone, given an appointment, and invited to attend the clinic by trained research assistants. A second contact was made if they failed to honor the clinic appointment, and then a scheduled home visit was made. Same enrollment procedures as described earlier were followed during the home visit. The visit also offered the opportunity to encourage and reschedule the patients to return to the clinic. The home visits started in March 2019.

Data Management

Data quality checks were carried out weekly, and queries were resolved. Data on the server were backed up unto an external hard disk system aside the daily automatic backups of the server. Quarterly automatic backups from the online server were saved online and on a separate external hard disk. Deidentified data were also securely sent to the SPARCO Hub and SADaCC as a form of backup using REDCap.Data were exported from the REDCap system in Stata format and imported into Stata 14.0 (StataCorp 4905 Lakeway Drive Station Texas 77845, United States) for analysis. Basic descriptive analysis was carried out on the data and was presented as appropriate frequency tables and figures.

We estimated the incidence rate (IR) as a rate at which new clinical events (diagnosis) occurred after enrollment of the patients. The total period of observation (person-time at risk) was calculated in months for each SCD genotype (i.e., SCD-SS, SCD-SC, and SCD S beta-plus thalassemia). The IR was evaluated per 10, 000 person-months with 95% confidence interval (C.I.) due to the short observance period. The IRs with their 95% C.I. were generated using an online C.I. calculator for the single incidence rate from the Chinese University of Hong Kong (C.I. for Single Rate, 2022).

Ethical, Legal, and Social Issues

Ethical approval was obtained from the Committee on Human Research Publications and Ethics, a joint committee of the School of Medical Sciences of KNUST and KATH. In consonance with agreed consortium principles, some key ethical, legal, and social issue elements that had been identified and discussed were incorporated into the informed consent and assent forms (Munung et al., 2019). Among these were the importance of

TABLE 1 | Definition of SCD terms.

Name	Definition
SCD-SS	A variant of SCD due to homozygosity of the *E6V* mutation, the amino acid substitution of valine for glutamic acid in the sixth position of the beta-globin chain, resulting in the production of hemoglobin S from both alleles
SCD-S beta-zero thalassemia	A form of sickle cell thalassemia characterized by the absence of hemoglobin A. Patients usually have severe anemia identical to that seen in sickle cell disease
SCD-S beta-plus thalassemia	A mild form of sickle cell thalassemia characterized by the presence of hemoglobin S and a reduced amount of hemoglobin A in the red blood cells. It is characterized by the presence of small red blood cells and mild anemia
SCD-SC	A type of sickle cell disease characterized by the presence of both hemoglobin S and hemoglobin C. It is similar to, but less severe than SCD-SS
Steady state	That period when the patient with sickle cell disease is not experiencing infections, pain, or other acute disease complications
Sickle cell painful event	Pain lasting at least 2 hours that requires an unscheduled emergency room visit or hospitalization or that disrupts daily activities
Acute chest syndrome (ACS)	A lung disease that involves a vaso-occlusive crisis of the pulmonary vasculature seen in patients with sickle cell disease
Nonspecific acute lower respiratory tract episodes	Includes acute respiratory episodes with lower respiratory tract signs that do not meet the criteria for other diagnoses. May include episodes which would have been diagnosed as ACS where radiographic facilities are available
Acute anemia	A "generic" term for a sudden drop (often defined as 20% or more) in the Hb level beyond the baseline and divided into three common pathophysiologic types: "acute splenic sequestration", "transient erythroid aplasia" (most commonly due to parvovirus ^{19}B infection), and "acute hemolysis" of various causes
Hyperhemolysis	Significant change in the blood picture characterized by a precipitous fall in the hemoglobin level associated with jaundice, marked reticulocytosis and polychromasia on the blood smear, and increased unconjugated hyperbilirubinemia and increased urobilinogen content in urine above the steady state level for each individual patient
Malaria	An individual with malaria-related symptoms (fever axillary temperature ≥ 37.5°C, chills, severe malaise, headache, or vomiting) at the time of examination or 1–2 days prior to the examination in the presence of a *Plasmodium*-positive blood smear or a positive malaria rapid diagnostic test
Cerebrovascular accident (CVA)	Characterized by sudden loss of the neurological function due to brain ischemia or intracranial hemorrhages. Presents with sudden onset of weakness, aphasia, and sometimes seizures or coma and results in adverse motor and cognitive sequelae
Avascular necrosis (AVN)	Also known as aseptic necrosis, osteonecrosis, or ischemic necrosis is bone death due to compromised blood supply. The hip joint is the most common site of AVN
Dactylitis	A severe acute inflammatory response affecting the hands and feet of individuals with sickle cell disease. It is caused by vaso-occlusive episodes leading to ischemia and finally infarction of the distal portions of the extremities. Clinical signs of pain, swelling, and tenderness of digits usually begin in early childhood and may be the initial manifestations of sickle cell anemia
Sepsis	The body's severe inflammatory response to infection and mostly presents with fever. Infections that lead to sepsis most often start in the lung, urinary tract, skin, or gastrointestinal tract
Priapism	A sustained unwanted painful erection lasting 4 or more hours and not associated with sexual activity
Osteomyelitis	An inflammatory process accompanied by bone destruction and caused by an infecting microorganism

informed consent and the type of informed consent obtained, the benefits of the study for the study population, and research priorities setting. These were found to be important to guide the use of the registry for research both locally and for the consortium.

RESULTS

From December 2017 to the end of March 2021, 3,148 SCD patients were enrolled into the SPARCO SCD Registry database. This constitutes 104.9% of the targeted 3,000.

Of the total number of patients enrolled, 1,582 (50.3%) were diagnosed from the newborn screening program. Most patients, i.e., 2,016 (64%) of them were enrolled when they reported to the outpatient clinic or upon discharge after an acute illness admission, while the rest 1,132 (36%) patients were enrolled through radio advertisement and home visits (alternative methods of enrollment).

More male patients were enrolled into the database (n = 1,665, 52.9%). Patients with the SCD-SS phenotype formed 67.2% of those recruited. Patients aged 5–9 years were the most common (29.1%) age group recruited, whilst those less than 5 years of age formed 27.6% of those recruited. Patients who were 15 years and older formed 17.3% of those recruited (**Table 2**).

TABLE 2 | Demographic characteristics of patients.

Characteristic	Frequency	Percentage
Sex		
Female	1,483	47.1
Male	1,665	52.9
Age category		
0—4 + years	869	27.6
5–9+ years	915	29.1
10–14 + years	821	26.1
15–17 + years	258	8.2
≥18 years	285	9.1
SCD phenotype		
SCD-SS	2,116	67.2
SCD-SC	1,023	32.5
Sβ+Thal	9	0.3

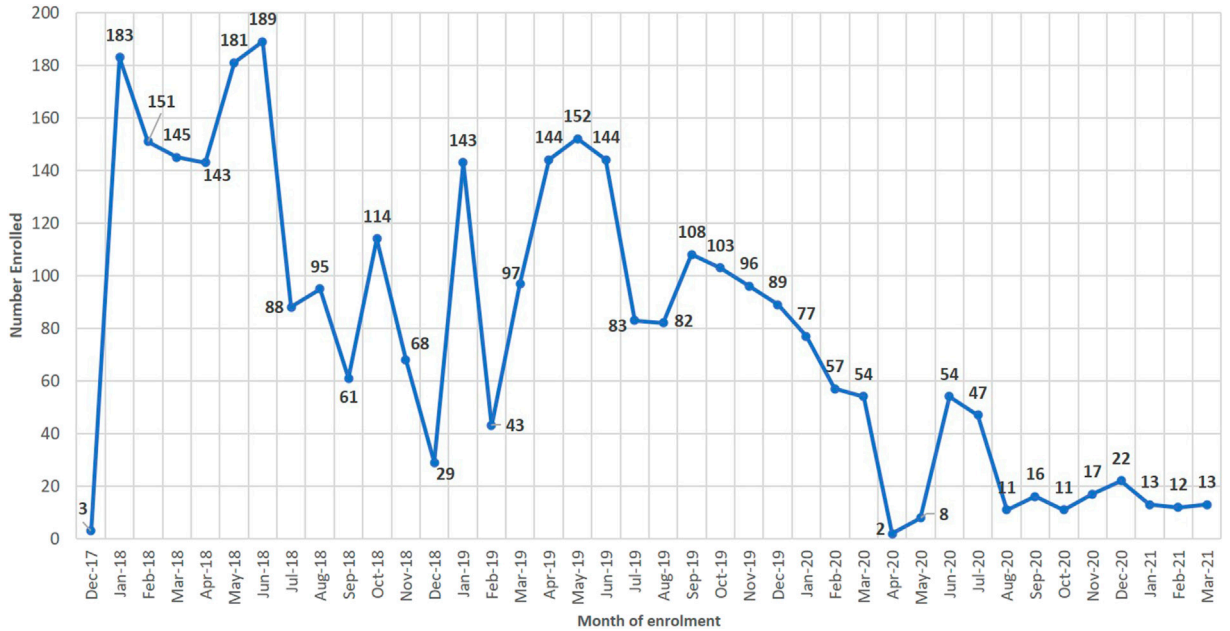

FIGURE 1 | Enrolment trends into the registry.

TABLE 3 | SCD-related diagnosis.

Diagnosis	Incidence rate per 10,000 person months (95% CI)		
	SCD-SS (total person months = 18, 328.14)	SCD-SC (total person months = 5, 662.55)	SCD S beta-plus thalassemia (total person months = 125.52)
Sickle cell painful event	141.86 (125.73, 160.06)	203.09 (169.48, 243.36)	159.34 (40.29, 630.08)
Severe anemia secondary to hyperhemolysis	32.74 (25.43, 42.15)	14.23 (7.07, 28.24)	0
Acute malaria	17.46 (12.35, 24.68)	12.36 (5.90, 25.92)	0
Cerebrovascular accident (CVA)	12.55 (8.34, 18.88)	3.53 (0.88, 14.12)	0
Acute chest syndrome (ACS)	7.64 (4.53, 12.90)	5.30 (1.71, 16.42)	0
Avascular necrosis (AVN)	7.09 (4.12, 12.21)	21.19 (12.04, 37.29)	0
Dactylitis	5.46 (2.94, 10.14)	3.53 (0.88, 14.12)	79.67 (11.31, 561.17)
Sepsis	3.82 (1.82, 8.01)	7.06 (2.65, 18.82)	0
Priapism	2.73 (1.14, 6.56)	1.77 (0.25, 12.54)	0
Osteomyelitis	2.18 (0.82, 5.81)	1.77 (0.25, 12.54)	0

SCD-SS, sickle cell disease SS; SCD–SC, sickle cell disease SC.

The highest number enrolled in a month was in June 2018 (189) and the lowest in December 2017 (3), when the registration was started. Peaks were also realized when alternative methods of enrollment were implemented in January and March 2019. (**Figure 1**).

The enrolled patients had 24,116.22 months of 18,328.14 PMO while the 1,023 SCD-SC patients contributed 5,662.55 PMO. The average period of observation was 8.7 months for SCD-SS patients and 5.5 months for SCD-SC patients groups.

In this period, among the SCD-SS patients, the top two diagnoses were sickle cell painful events with an incidence rate (IR) of 141.86 per 10,000 PMO and severe anemia secondary to hyperhemolysis (IR = 32.74 per 10,000 PMO). In SCD-SC patients, the top two diagnoses were sickle cell painful events (IR = 203.09 per 10,000 PMO) and avascular necrosis (IR = 21.19 per 10,000 PMO). The incidence rate per 10,000 PMO of cerebrovascular accident (CVA) was 12.55 in SCD-SS patients and 3.53 in SCD-SC patients and that of acute chest syndrome was 7.64 in SCD-SS and 5.30 in SCD-SC patients (**Table 3**).

DISCUSSION

The SPARCO-Kumasi, Ghana, has developed a comprehensive registry (**Supplementary Table S1**) capable of collecting and managing information on the clinic encounters of patients. The registry is being harmonized in collaboration with the SADaCC to ensure it is universally acceptable and accurately

captures available data based on the SCD ontology. The standard operating procedures have been developed in collaboration with SPARCO and SADaCC to ensure uniformity in data collection and data quality and also compliance with the FAIR (Findable, Accessible, Interoperable, and Reusable for humans and computers) principles. SPARCO and SADaCC have also provided and supported training in the management of the database and analysis of data. The processes undertaken fairly meet the recommendations for disease registries (de Groot et al., 2017; Kodra et al., 2018).

The results reveal a significant proportion of patients enrolled in the SPARCO registry was identified through the newborn screening program in Ghana. Several initiatives for newborn screening for SCD have been instituted in Africa, but no country has successfully implemented a universal national newborn screening for the SCD program for early diagnosis of SCD (Hsu et al., 2018; Nkya et al., 2019). The most extensive and longest running program has been implemented in Ghana at our center spanning 25 years, and over 9,000 SCD patients have been identified through this method and enrolled for care at our center (Ohene-Frempong et al., 2008; Hsu et al., 2018; Nkya et al., 2019). In the most developed countries, however, most, if not all patients, are identified through newborn testing (Telfer et al., 2007), whereas in countries such as Africa most SCD patients are identified following an acute illness.

In our study, we saw male dominance as also alluded to in registries in Brazil and England (Telfer et al., 2007; Fernandes et al., 2015), but different from registries in Nigeria (Isa et al., 2020) and Accra-Ghana (Asare et al., 2018) in which there was female dominance. This could have been due to the sociocultural practices and health-seeking behaviors in the setting and not necessarily due to genetics and actual population prevalence.

The study reported a large proportion of patients below and within the adolescent age group. The significant proportion of children under 5 years highlights the positive impact of the newborn screening program in which patients identified are enrolled early into the SCD clinic for comprehensive care. The dominance of adolescents reinforces the need to urgently formulate a transition plan including appropriate education of adolescents (Kanter and Kruse-Jarres, 2013; Kwarteng-Siaw et al., 2017; Kwarteng-Siaw et al., 2019) and parents and strengthening adolescent and adult clinics to provide the continuum of care required. The lower number of patients aged over 18 years is attributable to the fact that the enrollment was initially focused on the pediatric sickle cell clinic. The scope of enrollment has now been expanded to cover the adult sickle cell clinic.

The dominance of the SCD-SS phenotype in the population matches several reports (Bardakdjian-Michau et al., 2009; de Castro Lobo et al., 2014; Fernandes et al., 2015; Asare et al., 2018; Isa et al., 2020). It is known that the prevalence of Hb S is high in Africa (Thachil et al., 2013) and specifically in countries below the equator in sub-Saharan Africa (Grosse et al., 2011). In our registry, the proportion of SCD-SS is higher by about 10% compared with data from the newborn screening program in Kumasi reported in 2005 (Ohene-Frempong et al., 2008) and subsequently in unpublished data in 2020. This is also comparable to the adolescent and adult population in Accra reported in 2019 (Asare et al., 2018). The increase in the proportion of SCD-SS in the 2020 report as compared to the 2005 report could be as a result of the inclusion of patients not screened during the newborn period in the current report. They are possibly the ones who will seek care because of the more severe course of the disease and therefore having a higher chance of being enrolled as compared to those with SCD-SC. In our population, there is a unique significant proportion of SCD-SC phenotypes similar to that of the Korle-Bu Teaching Hospital in Accra also in Ghana (Asare et al., 2018) but far higher than that found in Nigeria (Isa et al., 2020). The Hb C is known to be unique to West Africa and more commonly in Mali, Burkina Faso, and Ghana (Grosse et al., 2011; Piel et al., 2013b). In contrast to the situation of Ghana, Burkina Faso has a reverse of the dominance seen in the SCD-SS group in a similar ratio (Kafando et al., 2005).The high level of SCD-SC in West Africa possibly ameliorates the overall severity of SCD in the region. The lower proportion of SCD-SC in our registry compared with the newborn screening SCD-SC population (Ohene-Frempong, 2017) could be due to the milder clinical course, coupled with the health-seeking behavior of affected persons.

Enrollment had fluctuations reflecting patient adherence to clinic visits and the weather pattern. The rainy season in Ghana is between April and July. The wettest month is June, with June 2018 recording one of the highest rainfalls that resulted in flooding in Kumasi (Kumasi, 2020). The rainfall, cold, and humid conditions in this season predispose SCD patients to pain episodes and could have accounted for the peaks between April and June. April also coincides with the vacation periods for the most basic and secondary (senior high) schools, while June also coincides with the vacation periods for tertiary institutions. During these times, most of the SCD cohorts who are students are available for clinics. The other peaks were due to the initiation of enrollment methods: January 2018—start of clinic enrollments, January 2019—mass enrollment, and March 2019—home visits. The alternative methods were rolled out to actively seek the patients who were not adhering to their routine clinic visit schedules. There was a gradual decrease from October to December over the years. In December, there are longer public holidays, and most families spend the Christmas festive season away from their usual residences, a phenomenon also reported by Asare et al. (Asare et al., 2018). Inclusion into the study declined in the last year of the study. During the last year, there was the outbreak of COVID-19 which hampered attendance at the clinic. The alternative methods of recruitment using the home visits were also stopped for staff and patient safety. All these could have led to the reduction in the numbers that was recruited toward the end of the study.

The sickle cell painful event was the most reported event (Powars et al., 2005; Telfer et al., 2007; Kanter and Kruse-Jarres, 2013; Shah et al., 2019) at the outpatient clinic. The incidence rates in these studies were diverse which can be attributed to the designs and the populations of focus. Compared with a study in East London published in 2007 (Telfer et al., 2007) which had a similar design, the painful events incidence rate in our cohort was lower for SCD-SS patients but higher for SCD-SC patients. This is contrary to what is known in the literature. This could be because

these SCD-SC patients were a hospital outpatient population who were the more likely to present with complications. It could also be an indicator that patients with SCD-SC were underrepresented in our registry.

CONCLUSION

The SPARCO-Kumasi site has developed capacity (skills and infrastructure) to design, manage, and analyze data in the REDCap SCD registry.

The REDCap registry will provide longitudinal data of the population that would improve the knowledge of SCD in Africa and serve as a resource for further research in SCD. There is also a need to hasten and enhance transition care for the growing adolescent population.

LIMITATIONS

The registry is a hospital-based registry and enrolled only patients who were seeking care at the Kumasi Center for SCD at the Komfo Anokye Teaching Hospital (KCSCD-KATH), a tertiary facility hosting the main sickle cell clinic in the middle and northern belt of Ghana. It therefore excludes patients receiving treatment at other satellite health facilities in the city of Kumasi and other health facilities in Ghana.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Committee on Human Research Publications and Ethics, a joint committee of the School of Medical Sciences of the Kwame Nkrumah University of Science and Technology and the Komfo Anokye Teaching Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.802355/full#supplementary-material

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Outcome of Hydroxyurea Use in SCD and Evaluation of Patients' Perception and Experience in Nigeria

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Introduction: Hydroxyurea (HU) has been shown to be beneficial in the management of sickle cell disease (SCD) as it improves treatment outcomes. However, despite the benefits of HU, its uptake among SCD patients in Nigeria remains low.

Objective: This study aimed to assess the perception and experience of patients with SCD in Nigeria who are using or had used HU, thereby informing and promoting its use.

Methodology: A multi-centre, cross-sectional study was conducted among 378 SCD patients aged 1–53 years who have enrolled on Sickle Pan African Research Consortium (SPARCO) registry as HU users. The SPARCO project was funded by the National Institutes of Health (NIH) to establish a sickle cell disease (SCD) registry, strengthen skills and plan research in three African countries. The Nigerian SPARCO registry had 6453 SCD patients at the time of this report with <15% of this population on HU. Data on sociodemographics, perception and experience about HU use were obtained and analysed using descriptive statistics.

Findings: Out of the 378 participants, 339 (89.7%) were using HU while 39 (10.3%) had stopped using HU at the time of the study. 281 (74.3%) found HU expensive, while 194 (51.3%) reported none to minimal side effects while using HU. Among patients that stopped HU, cost (59%) and availability (51.3%) were the commonest reasons for discontinuing the drug. Furthermore, 347 (92.5%) had fewer pain crises, 173 (84.8%) had a fewer need for blood transfusion, 145 (86.3%) had improved PCV and 318 (84.6%) had fewer hospital admissions. Finally, the study also showed that 322 (85.2%) respondents would recommend the drug to other patients, whereas 14 respondents (3.7%) would not. Mean corpuscular volume (MCV) and fetal hemoglobin (HbF) levels were not collected in this study and may have improved findings.

Conclusion: This study showed that the majority of the SCD patients had good perception and experience with the use of HU while a few had to stop the medication mostly on account of cost and availability. Patients' based advocacy could be leveraged to

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improve HU uptake while more efforts are needed to ensure that it is readily available and affordable.

Keywords: sickle cell disease, patients perception, patients experience, Nigeria, hydroxyurea

INTRODUCTION

Sickle Cell Disease (SCD) is prevalent in many low and middle-income countries (LMICs) especially in sub-Saharan Africa (SSA). Several studies have reported that more than 75% of the estimated 300,000 individuals born with SCD annually are within the SSA (Adewoyin et al., 2017; Adegoke et al., 2014; Galadanci et al., 2014). This region is characterized by poor health-seeking behaviour, inadequate health amenities, very low or nonexistent neonatal screening programs for SCD, and insufficient government policies to improve health care for SCD patients (Adegoke et al., 2014). These have contributed to the poor survival outcomes and quality of life (QOL) for SCD patients within the region. SCD accounts for the greater proportion of morbidity and mortality of infants and children under 5 years (U5). In Nigeria, more than 100,000 SCD births are estimated annually. Of these, approximately 70% are estimated to die before their fifth birthday (Piel et al., 2013; Nnodu et al., 2021). Other than the high mortality rate, the quality of life of individuals living with this disease is far below normal (Piel et al., 2013; Makani et al., 2013).

This condition is a life-long illness marked by events of painful crisis which require health maintenance and sometimes hospitalization. Some medications and lifestyles of the patients have proven to be very effective in the management of SCD by reducing the symptoms and improving the disease outcome and QOL (Brandow and Panepinto, 2010; Nebor et al., 2013; Badawy et al., 2017). For instance, prophylaxis with immunizations, regular use of anti-malarial medications, antibiotics, and HU have shown to be effective even in resource-limited settings (Nebor et al., 2013)[;] Makani et al., 2013; Ware, 2015).

HU has been shown by several studies to be beneficial in the management of SCD; it improves treatment outcomes in addition to reducing the financial burden of the disease on families (Badawy et al., 2017; Crego et al., 2020; Smith et al., 2011; Wang et al., 2013). However, despite the benefits of HU in the management of SCD, its utilization among health care providers, caregivers and patients has remained low. Some documented reasons for this low level of utilization include side effects, cost, availability, poor awareness about the use of HU, adherence, or unavailability of guidelines on the administration and monitoring of HU (Thornburg et al., 2010)[;] Yawn et al., 2014; OD Ofakunrin et al., 2021; Adegoke et al., 2014; Adewoyin et al., 2017; Badawy et al., 2017; Adeyemo et al., 2019; Brandow and Panepinto, 2010). In Nigeria, the Sickle Pan African Research Consortium (SPARCO), which was established to maintain a registry of 13,000 SCD patients for 4 years across the three participating countries, Ghana, Nigeria and Tanzania, was able to enrol 6,453 patients into the Nigeria registry using the Research Electronic Data Capture software (REDCap). Of this number, less than 15% had used HU (Isa et al., 2020; Makani, 2021)

In view of this, we hypothesized that evaluating the perception and experience of patients with SCD who are using or had used HU could help in gaining insight into the possible barriers and promoters/facilitators of HU uptake, hence this study.

METHODOLOGY

Study Design

This study employs both a cross-sectional and retrospective study approach for the participation of SCD patients who reported the use of HU in the treatment of SCD in the SPARCO Nigeria SCD registry. At the time of this study, a total of 6,453 patients, from 20 health facilities, were enrolled in the SPARCO REDCap Registry; 917 (14.2%) of these patients reported the use of HU. Considering the study population estimates, we selected five tertiary health facilities which accounted for most of the patients using HU in the database. University of Abuja Teaching Hospital, Gwagwalada, Federal Capital Territory (FCT), Jos University Teaching Hospital, Jos Plateau State, Aminu Kano Teaching Hospital, Kano State, National Hospital Abuja, Abuja FCT, and Irrua Specialist Teaching Hospital, Edo State accounted for 70.6% (647) of the number of patients who reported the use of HU in the registry (**Figure 1**).

Inclusion Criteria

Participants of this study had to be SCD patients registered in the SPARCO REDCap database, with a history of the use of HU, whose telephone number was valid and could be reached during the period of data collection, and who attended clinics such that their medical record folders could be accessed.

Exclusion Criteria

SCD patients who had no history of the use of HU, who could not be reached.

Sampling and Sample Size

Using the known population size of 917 patients on HU in the registry, confidence interval of 95%, the margin of error of 5%, population proportion of 50%, we were able to reach a minimum sample size of 271 for this study. We also adopted the 50% proportion size across the participating sites to generate the minimum sample size per site (**Table 1**). We then used a simple random sampling technique to recruit the patients. We went further to design a structured interviewer-administered multiple-choice questions using the REDCap data collection tool for the study (https://redcap.uniabuja.edu.ng/surveys/?s=YH9HH9FLTT). We contacted these patients via telephone calls or had a face to face interaction with those who were scheduled for clinic visits during the time of data collection. Since they had previously consented to participate in the SPARCO project, verbal consent was obtained from

TABLE 1 | Patient distribution across participating centres

Hospital Name	Patients in Database =N	Patients on HU n(% of N)	Minimum sample size based on 50% proportion	Patients recruited U=378 n(% of U)
Jos University Teaching Hospital	505	310 (61.4)	155	163 (43.1)
National Hospital Abuja	247	80 (32.4)	40	71 (18.8)
University of Abuja Teaching Hospital, Gwagwalada	911	97 (10.6)	48.5	62 (16.4)
Irrua Specialist Hospital	99	90 (90.9)	45	46 (12.2)
Aminu Kano Teaching Hospital	222	70 (31.5)	35	36 (9.5)

Values represented in numbers and percentages, n=number, U=number of patients included in the study.

TABLE 2 | Characteristics for participants

Variable	Frequency	Percentage
Age (years)	—	—
0–15	273	72.2
16–30	97	25.7
31–45	7	1.9
>45	1	0.3
Median age (years) = 11	—	—
Sex	**Frequency**	**Percentage**
Male	212	56.1
Female	166	43.9
History of HU use	—	—
Currently on HU	339	89.7
Stopped HU	39	10.3
Duration of HU use (years)	**Frequency**	**Percentage**
≤1	60	15.9
>1–5	238	63.0
>5	33	8.7
Not Sure	47	12.4
Start dosage of HU (mg)	**Frequency**	**Percentage**
250	98	28.9
500	115	33.9
1000	10	2.9
1500	1	0.3
Others	106	31.3
Mean (SD)=640.5 (269.5), Min= 100 mg, Median= 600 mg, Max= 1500 mg	—	—
Current dosage of HU (mg)	**Frequency**	**Percentage**
250	39	11.8
500	87	26.4
1000	75	22.7
1500	2	0.6
Others	127	38.5
Mean (SD)= 638.4 (270.0), Min= 150 mg, Median= 600 mg, Max= 1500 mg	—	—
Minimum dose of HU = 7 mg/kg	—	—
Median dose of HU = 21 mg/kg	—	—
Maximum dose of HU = 35 mg/kg	—	—
Frequency of HU use	**Frequency**	**Percentage**
Daily	322	85.2
Weekly	2	0.5
Others	6	1.6
Missing	48	12.7

TABLE 3 | Perception on the use of hydroxyurea

Perception	Currently using HU	Stopped using HU	*P*-value
HU is affordable	—	—	—
True	57 (16.8)	12 (30.8)	0.034
False	258 (76.1)	23 (59.0)	—
Don't know	14 (4.1)	3 (7.7)	—
Missing	10 (2.9)	1 (2.6)	—
HU is available	—	—	—
True	247 (72.9)	16 (41.0)	0.0329
False	66 (19.5)	20 (51.3)	—
Don't know	16 (4.7)	2 (5.1)	—
Missing	10 (2.9)	1 (2.6)	—
HU has no side effect	—	—	—
True	167 (49.3)	27 (69.2)	<0.01
False	83 (24.5)	9 (23.1)	—
Don't know	79 (23.3)	2 (5.1)	—
Missing	10 (2.9)	1 (2.6)	—
Is HU prescribed	—	—	—
True	320 (94.4)	30 (76.9)	<0.01
False	2 (0.6)	6 (15.4)	—
Don't know	7 (2.1)	2 (5.1)	—
Missing	10 (2.9)	1 (2.6)	—
Would you recommend HU	—	—	—
True	306 (90.3)	16 (41.0)	—
False	10 (2.9)	4 (10.3)	—
Don't know	20 (5.9)	19 (48.7)	—
Missing	3 (0.9)	—	—

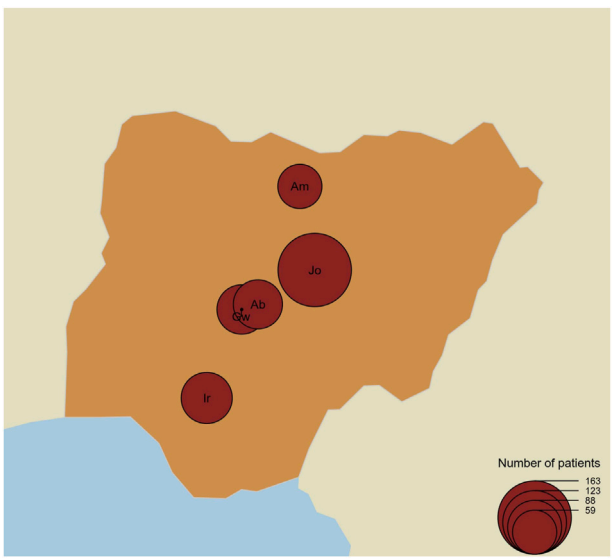

FIGURE 1 | Map of Nigeria showing the number of patients per centre and locations of the study centre. The map shows the location of the study centres and the size (black circles) of patients recruited for the study per centre. Gw = University of Abuja Teaching Hospital, Gwagwalada, Jo = Jos University Teaching Hospital, Jos, Am=Aminu Kano Teaching Hospital, Kano, Ab = National Hospital Abuja, Abuja, and Ir=Irrua Specialist Teaching Hospital, Edo.

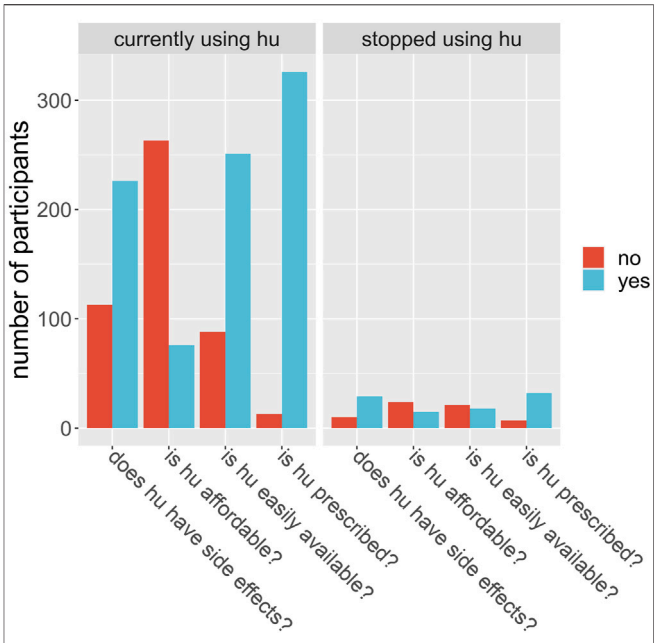

FIGURE 2 | Participants were asked a set of 4 questions, shown on the x-axis, around their perceptions of hydroxyurea (hu). The number of participants (y-axis) answering yes (blue) or no (red) are shown by the bars, for those who are currently using hu (left plot) and for those who did use hu but had stopped at the time of the questionnaire (right plot).

respondents. Furthermore, we extracted demographic data and other relevant information for the participants from the registry, this was analyzed alongside the data from the phone interview to inform the outcome of this study (**Table 1**).

Data Analysis

We analysed responses from participants asked if they were still using or had stopped HU treatment, how long they used HU, what dose they started with or were using at the time of the report, and how often they took the medication. We also analysed responses concerning pain experience using HU, questions like frequency of pain crises before and during HU treatment, SCD complications and frequency of hospital admission were asked to the participants. Lastly, we looked at responses pertaining to blood transfusion history, PCV values before and during the treatment with HU, and perception on cost, availability and side effects using HU. The data collected were processed and analysed using the R statistical software, and the tidyverse R package. Missing values were imputed using a random forest imputation algorithm implemented in the random forest R package. All binary outcomes were modelled with logistic regression using the multinomial distribution. We considered *p*-values statistically significant if they were below 0.05. All plots were developed with ggplot2 and the map of Nigeria was created using the R package Cartography.

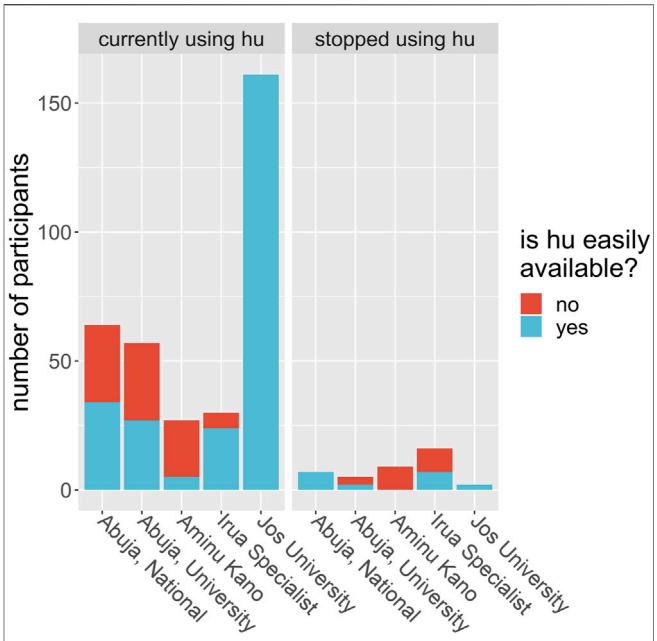

FIGURE 3 | Study participants were asked if hydroxyurea (hu) was easily available to them at the time of the study. Each bar shows the number of participants at each study center (x-axis) who responded yes, it is easily available (blue) or no, it is not easily available (red) given that they were either currently using hu (left plot) or did use hu but had stopped at the time of the questionnaire (right plot). The blue and red bars are stacked on top of each other, so the height of each bar represents the total number of patients at that hospital.

RESULTS

A total of 378 patients were interviewed between April 18, 2021, and 9 July 2021, for this study. Seventy-four (16.5%) of these patients received care from the University of Abuja Teaching Hospital, Gwagwalada FCT, 163 (36.4%) from Jos University Teaching Hospital, Jos Plateau State, 59 (13.2%) from Aminu Kano Teaching Hospital, Kano State, 73 (16.3%) from National Hospital Abuja, FCT and 79 (17.6%) Irrua Specialist Teaching Hospital, Edo state (**Table 1**). The patients comprised 212 (56.1%) males and 166 (43.9%) females between the ages of 1–53 years and a median age of 11 years (**Table 2**). At the time of the study, 339 (89.7%) patients were on HU while 39 (10.3%) had stopped using the drug. We found also that 322 (95.0%) patients adhered to the daily use of HU, while others who did not adhere to the prescription, either took the drug weekly, three times a week or whenever the drug was available.

Perception of the Use of Hydroxyurea

We evaluated patients' perception of the use of HU based on if they found the drug affordable, accessible, without side effects and if care providers prescribed the drug routinely. We observed that doctor's advice significantly influenced whether or not the patient will use the prescription. Of all the 378 participants interviewed, 281 (74.3%) said they believed HU was expensive. For the subgroup of participants who were using HU at the time of the interview, 258 out of 339 said they believed the drug was expensive; for the rest of the participants, those who were using HU at some time in the past but have since stopped, 23 out of 39 (59%) said they believed it was expensive. Is this difference in opinion between users and nonusers significant? A chi-square test is illuminating here. Take the null hypothesis to be that a person who believes HU is affordable is no more or less likely to continue to use HU over a person who does not believe it is affordable. Using the data, and a Pearson's chi-square test with Yates' continuity correction, we find the probability of obtaining these proportions given the null hypothesis is 0.034. Therefore, we found strong evidence that cost is a factor in determining who will and will not use HU. Similarly, we found that accessibility of HU significantly influenced if the patient continues to use the drug (**Table 3**; **Figure 2**). Is a participant's local hospital an important factor in their decision to continue to use HU? From **Figure 3** we see that this may be true. For example, at Jos University teaching hospital 161 out of 163 patients (99%) were using the drug whereas at Irrua Specialist 30 out of 46 (65%) were using it. Assuming a null hypothesis that a patient at Jos is equally likely to continue to use HU as one who is at another hospital in the study, a simple chi-square test gives us a *p*-value of less than 0.001 of obtaining the same data given this null hypothesis is true. We therefore find strong evidence that the patient's local hospital can be an influencing factor in their decision to continue HU treatment. Why might the hospital itself be an influencing factor in this decision? We propose that HU is not equally available in the different hospitals across Nigeria and that this difference may account for some of this influence. For example, hospitals may not always have enough stores of the drug to meet their demand, or they may not receive

TABLE 4 | Experience with the use of hydroxyurea

Experience	Before using HU n (%)	Currently using HU n (%)
Number of VOC per year	—	—
0–1	47 (12.5)	240 (63.5)
2–3	140 (37)	92 (24.4)
4–5	106 (28.1)	29 (7.7)
6–7	29 (7.7)	4 (1.1)
>7	53 (14)	9 (2.5)
Number of hospital admission per year	—	—
0–1	161 (42.6)	308 (81.5)
2–3	129 (34.1)	50 (13.2)
4–5	57 (15.1)	15 (4.0)
6–7	13 (3.5)	1 (0.3)
>7	16 (4.4)	1 (0.3)
Number of transfusion	—	—
0	123 (32.5)	260 (68.8)
1–3	187 (49.5)	77 (20.4)
>3	45 (11.9)	15 (4.0)
PCV%	—	—
<20	36 (21.4)	8 (4.8)
20–25	106 (63.1)	64 (38.1)
>25	26 (15.5)	96 (57.1)
Minimum PCV (Min)	14%	18%
Maximum PCV (Max)	39%	39%

shipments as regularly as in other areas. To test this proposal, we looked at how a participant's perception of the availability of the drug depends on their local hospital. At Jos, we find that 163 of 163 participants (100%) said they believed that HU was easily available, whereas, for participants at all other hospitals combined, only 105 out of 215 participants (49%) said they believed it was easily available. A chi-square test is not advisable in this instance, but it is clear that there is a correlation between the availability of the drug and its continued use, in this example. Furthermore, we were able to deduce that the reason most significantly associated with continued HU use as given by the participants was that the doctor prescribed it and that it is easily available. Finally, side effects did not significantly influence this outcome as most participants reported little or no side effects (**Table 3**).

Experience With the Use of Hydroxyurea

We considered whether HU was able to reduce the number of severe complications to sickle cell disease the participant experienced and whether it had serious side effects. In the first case, each participant was asked whether they suffered from a range of known complications of sickle cell disease at two different time points; before they began HU treatment, and during their treatment. For each complication, and for each time point, the participants answered either yes, they did experience that complication at that time, or no, they did not. We then defined a score for each patient at each time point by counting the number of complications each patient claimed to experience. We ran a *t*-test for these scores and found the *p*-value of obtaining them given that there was no systematic difference in the population between the two-time points, before or during treatment, was less than 0.001. We found evidence to suggest that HU reduced complications of sickle cell disease in this population. Similarly, 347 (92.5%) participants had less frequency of vaso-occlusive crises per year, 173 (84.8%) had fewer transfusion needs, and 318 (84.6%) had fewer hospital admissions per year (**Table 4**). On the other hand, in the second case, 92 of 378 participants (24.3%) claimed to experience side effects of HU while 194 (51.3%) participants reported none to minimal side effects using HU. We also found that the packed cell volume (PCV) of patients greatly improved while using HU (**Table 4**; **Figure 4**). We found some evidence to support that exceptionally high HU doses were prescribed to patients with exceptionally high frequencies of painful episodes (**Figure 5**). Furthermore, patients with such high frequencies of painful episodes before the commencement of HU used doses as much as 35 mg/kg/d. They also reported a reduction in those painful crises since the commencement of HU (**Table 4**). Finally, we saw good visual evidence in this study that HU reduces the complications of sickle cell disease dramatically, except for bone pain **(Figure 6A** and **Figure 6B**).

Statistical Models of Patient Responses

The participants were asked whether they thought HU is affordable, easily available, has been prescribed by their doctor, and has no severe side effects. We performed a Pearson's Chi-squared test with Yates' continuity correction for the responses to each question, wherein each case the null hypothesis was members of the two groups (those currently using HU, and those not currently using HU) are equally likely to say "yes" to the question. For the question on affordability, we found no strong evidence to reject the null hypothesis that a patient who finds HU expensive is just as likely to

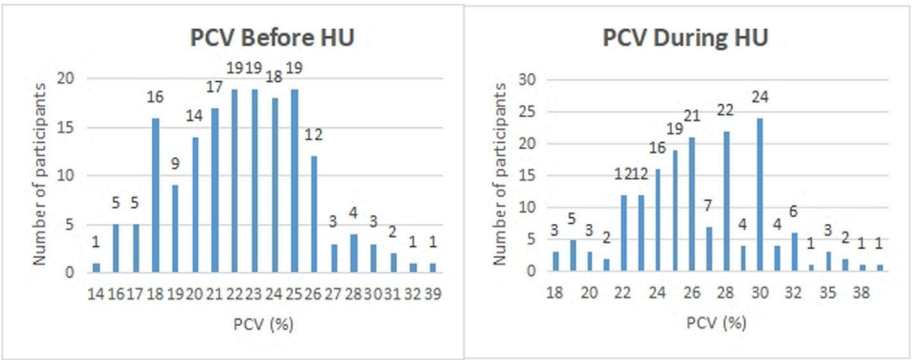

FIGURE 4 | Participants were asked what their PCV was before and during the period of hydroxyurea treatment. The PCV (%) reported by participants are shown on the x-axis while the number of participants on the y-axis.

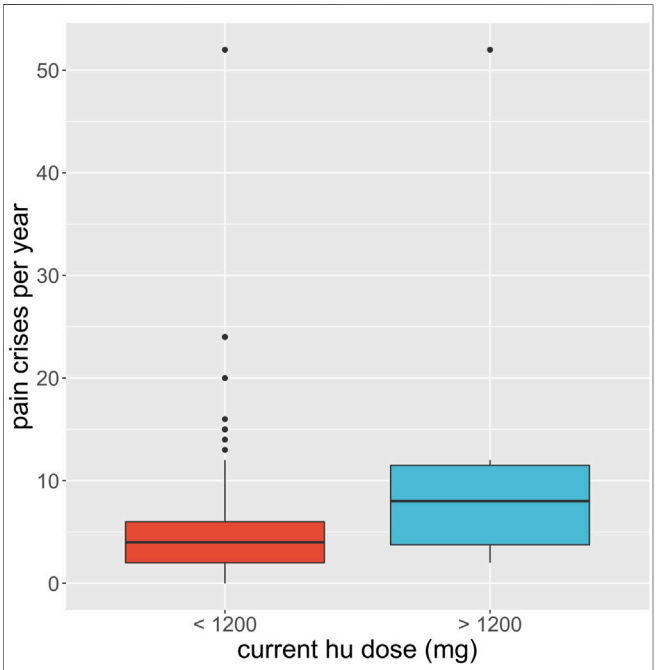

FIGURE 5 | Boxplot of the average recalled number of painful crises a participant experiences per year (y-axis) is compared for participants on regular hydroxyurea (hu) doses, less than 1200 mg per week (red), to those on exceptionally high doses, more than or equal to 1200 mg per week (blue). Black dots show the outlying participant responses.

use the drug as one who does not (chi-squared = 2.7991, df = 1, *p*-value = 0.09). For the question on availability, we found strong evidence to reject the null hypothesis that a patient who finds HU more easily available will be just as likely to use the drug (chi-squared = 15.415, df = 1, *p*-value = 9e-05). For the question on side effects, we found no evidence to reject the null hypothesis that a patient who has no severe side effects will be as likely to use the drug (chi-square = 0.41891, df = 1, *p*-value = 0.5). For the question on prescription, the proportion of participants who had not been prescribed the drug by their doctor (whether they currently use it or not) was too small for a chi-square test to be valid.

Also, we fit logistic regression models to the same data. In each model we constructed, the predictor was the response to one of the questions described above (affordable, available, prescribed by their doctor, and no severe side effects) and in each case, the outcome chosen was the same: is the patient currently using the drug (where "success" is defined as a "yes" response). We fit models for crude odds ratios (without covariates) and separately for adjusted odds ratios where the covariates were gender, age, and hospital location. Below we quote the odds ratios as log odds for both the crude and adjusted models.

For the question on affordability, we found no significant association in the crude model or the model where we adjusted for our chosen covariates (age, gender, and hospital location). For the question on availability, we found the crude log odds of a patient currently using HU, given that they find HU easily available, was 1.4 ± 0.3 (*p*-value: 9.43e-05) over a patient who does not find it easily available. After adjusting for gender, age, and hospital location, this became a log-odds of 0.5 ± 0.4 (*p*-value: 0.001). For the question on prescription, we found the crude log odds of a patient currently using HU, given that it has been prescribed by their doctor, was 1.7 ± 0.5 (*p*-value: 0.0005) over a patient who has not had the drug prescribed. After adjusting for the selected covariates, the log odds became 2.9 ± 0.8 (*p*-value. For the question on side effects, we found no association, for the crude model, between patients currently using HU, and patients who experience HU side effects. However, after adjusting for the covariates, the log odds of a patient currently using HU, given that they do not experience side effects of the drug, became −1.9 ± 0.5 (*p*-value: 7e-6) over a patient who does experience side effects.

DISCUSSION

Studies have shown the efficacy of HU in the management of sickle cell disease. HU improves numerous adverse events resulting from the complications of SCD including severe painful episodes, anaemia, hospitalization and transfusion frequencies (Charache et al., 1996; Ware, 2010; Thornburg et al., 2010; Cunningham-Myrie et al., 2015). The findings of this study equally showed these benefits as participants reported a reduced need for blood transfusion, hospital admissions and annual painful episodes. We found that the mean start dose of

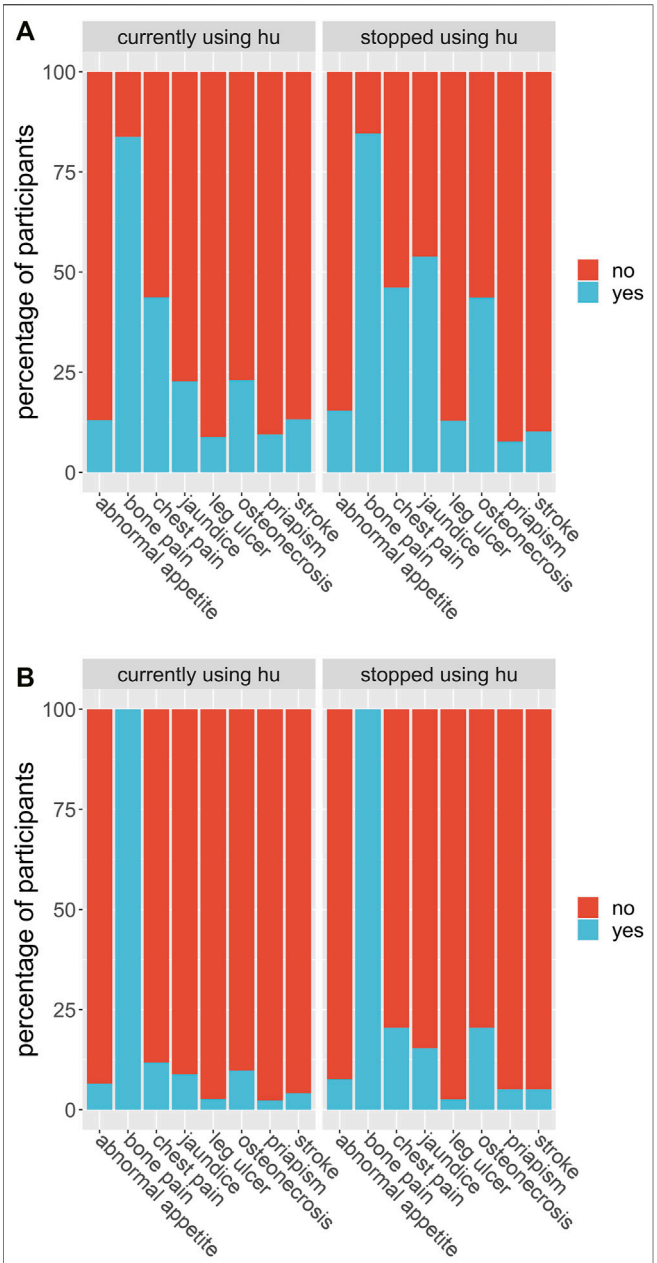

FIGURE 6 | (A) Participants were asked if they suffered from each of a list of known sickle cell disease complications *before* they began their hydroxyurea treatment. The proportion of participants out of the entire study group who answered yes, they did suffer from that complication before treatment (blue) or no, they did not (red) are shown in the bar labelled by that complication (axis), for each complication in the list. **(B)** Participants were asked if they suffered from each of a list of known sickle cell disease complications after they began their hydroxyurea treatment. The proportion of participants out of the entire study group who answered yes, they did suffer from that complication during treatment (blue) or no, they did not (red) are shown in the bar labelled by that complication (axis), for each complication in the list.

HU for our participants was 18 mg/kg/d which complies with earlier studies that recommend initiating HU at doses not more than 20 mg/kg/d. Similarly, our study found that high doses of HU were prescribed to patients with exceptionally high frequencies of painful crisis. These patients with high frequencies of painful episodes used HU up to 35 mg/kg/d since the commenced treatment of SCD using HU therapy. The PCV count of most patients increased after the commencement of HU compared with the values before the patient started using the drug. This finding agrees with earlier studies that support an increase in PCV count as a result of HU therapy (McGann and Ware, 2011; Smith et al., 2011; Heeney and Ware, 2010; Charache et al., 1995). A medication that significantly reduces the severity and frequency of painful crises, hospital admissions and need for blood transfusion among SCD patients is worth recommending.

This study has also demonstrated that most participants, whether they used the drug or had discontinued, felt the drug was expensive. Other than HU being expensive for most patients in this study, many of those who discontinued HU reported inaccessibility as a factor. These factors have been reported by Adeyemo et al., as a major barrier to the use of HU in Nigeria. The study went ahead to show that nearly all participants had been recommended on HU therapy by their doctors. The majority of participants represented also claimed that they do not suffer from severe side effects using HU therapy. However, HU availability potentially explained at least some of the variation in the cohort concerning HU use. Those who used HU in this study could access it easily, while those that had stopped did not have easy access. We also found that 306 (90.3%) patients who were using HU and 16 (41.0%) patients who had discontinued the use of the drug would recommend it to other patients.

There are several unique aspects of this study that are worth noting. Firstly, the diversity of the patient population, which would be crucial for generalizing the perception and experience with the use of HU treatment in different Nigerian settings. Also, the location of the five tertiary institutions across three geopolitical zones in Nigeria. These sites reported the highest number of patients using HU among the 20 participating hospitals in the SPARCO registry. Lastly, the patients' responses in the study were corroborated with their medical reports as recorded in the registry.

CONCLUSION

In this study, we were able to demonstrate that patients significantly had a good experience with the use of HU, minimal side effects while using HU, fewer pain crises per year as a result of the therapy, less need for blood transfusion, improved PCV and fewer annual hospital admissions. We were able to also deduce that a participant who finds HU easily accessible is more likely to use HU treatment than a participant who does not. We found that majority of participants felt that HU was expensive whether they used it or not, and that doctors routinely prescribe HU to their patients, whether it is easily available or not. Most patients make out-of-pocket payments for medications, while a few of them are covered by the national insurance scheme. This can be financially burdensome considering that this is a medication expected to be taken every day for the rest of their lives. Government intervention is needed to subsidize the drug or provide them

free of charge as can be obtained in some climes. This can be achieved if resources are made available through a collaboration of the government and the indigenous companies manufacturing HU. We can conclude that our study has shown that patients had a positive outcome using HU by demonstrating that HU is effective in reducing the frequency of vaso-occlusive crises, need for blood transfusions, and hospitalizations among SCD patients who have reported the use of HU in the SPARCO Nigerian registry. It has also been shown that patients themselves would recommend the drug whether they were using it or not. We can therefore say that HU is safe among the study participants. The findings of this study may increase the use of hydroxyurea in Nigeria if the major barriers of cost and access to hydroxyurea are addressed on a national level.

LIMITATION

This study was designed to take responses from patients via phone as such, information such as patients current weight and Packed Cell Volume (PCV) count was available for only patients who had visited the clinic recently and/or had checked the value a day or two before the interview. Similarly, MCV and HbF values were not collected since it goes beyond the scope and design of this study.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, following the approval of the funders.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Nigerian National Health Research Ethics Committee (NHREC) to the Sickle Pan African Research Consortium (SPARCo) project. The SPARCo Research Working Group gave approval for the study. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual (s), and minor (s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

The study was designed by RC, ON, HI, and AO reviewed the study design. JM designed the statistical analysis and analysed the data. AO, OO, AG, UN-A, and ON provided leadership contacting the patients and obtained data. RC, AO, and JM interpreted the data. RC, AO, and JM wrote the report. The report was reviewed by HI and ON.

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BRIEF RESEARCH REPORT
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Distribution of HbS Allele and Haplotypes in a Multi-Ethnic Population of Guinea Bissau, West Africa: Implications for Public Health Screening

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Background: Sickle Cell Disease (SCD) is an inherited condition that is widespread globally and especially in malaria-endemic West African countries. Limited epidemiological data on SCD are available for Guinea Bissau, where newborn screening is not yet implemented, routine diagnosis is not available, and care is case directed.

Methods: Dried blood spots were collected from children accessing two hospitals managed by Italian Non-Governmental Organizations in the capital city of Bissau and sent to Padova for Hemoglobin (Hb) quantification through HPLC and molecular analysis. Beta globin gene analysis was performed in all; and Hb haplotype of the HbSS and HbSA patients was performed in South Africa. One hundred samples belonging to the most frequent ethnic groups were randomly selected for detection of G6PD mutations.

Results: Samples from 848 consecutive children (498 males and 350 females, mean age 6.8 years) accessing the two hospitals were analyzed: 6.95% AS (4.42% allelic frequency), 0.94% SS, and 0.23% AC. 376G G6PD allelic frequency was 24%; 14.8% in AS individuals. The Senegal haplotype was the most prevalent (31%), and the proposition of chromosomes with the atypical haplotype was surprisingly high (56%).

Conclusion: Our study demonstrates a significant frequency of the HbS allele in the population of Guinea Bissau supporting the implementation of screening strategies. The differences among ethnic groups can help guide targeted interventions for SCD awareness campaigns and determine priority areas for public health interventions. The pilot analysis on haplotypes reveals a large proportion of the atypical haplotype, which may be indicative of a genetically heterogeneous population.

Keywords: HbS, sickle cell, screening, Guinea Bissau, multi-ethnic, haplotypes

INTRODUCTION

Sickle Cell Disease (SCD) is an inherited condition frequently found in people of African descent. SCD is the most common monogenic disease worldwide (1) and is recognized by the World Health Organization (WHO) and the United Nations (UN) as a global public health problem. A call to action was launched by the two organizations in 2006 and 2008 due to the burden of SCD on childhood mortality in sub-Saharan Africa, as it contributes to 9-16% of deaths in children under 5 years of age on that continent (2–4). Neonatal screening, penicillin prophylaxis, immunization, and stroke prevention have dramatically increased survival for patients with SCD in developed countries but they are seldom available in Africa (5, 6), where the majority of patients live. Recent population movements have increased the number of people carrying the HbS allele coming to Europe, thereby challenging health systems to adapt to this particular group of patients with SCD (7–10).

Guinea Bissau (**Supplementary Figure 1**), a former Portuguese colony located in the West African Atlantic Coast, embedded between Senegal and Guinea Conakry, lies in the malaria belt. Malaria is endemic in the country with a peak transmission during the rainy season (July–October). Guinea Bissau has a population of 1,726,170 inhabitants and children aged 0–14 years constitute 39.53% (male 340,575/female 341,747). The capital of Bissau has 492,000 inhabitants (2015). The population is multi-ethnic, because more than 20 ethnic groups are present in the country, the most frequent being Balanta and Fula (11). The official national language is Portuguese-creole, although many people speak only the local languages.

In spite of the high prevalence of SCD in the surrounding West African countries, like Senegal, Mali, Guinea Conakry, and Liberia (12–14), there are limited data on the frequency of HbS (15) in Guinea Bissau. The actual health burden of SCD in the country is not known and there are no national SCD screening programs yet.

Accurate epidemiologic information is necessary for the development of sustainable health interventions and targeted health education and prevention programs in the field of SCD. The two main objectives of our pilot study were, therefore, to determine the feasibility of a SCD screening program in two hospitals in the capital city of Bissau (in terms of capacity of correct sample collection, data recording and affected patient tracking and counseling), and to determine the prevalence of SCD among the various ethnic groups of Bissau. These data, collected through a public-private partnership with non-Governmental organizations (NGOs), could help develop further research in the field of SCD in Guinea-Bissau.

MATERIALS AND METHODS

Setting and Patient Population

This cross-sectional study took place in two hospitals in the capital city, Bissau: the Raoul Follereau Hospital (HRF, public hospital) and the Bor Children's Hospital (BCH, private hospital), both managed within the National Health System of Guinea Bissau by Italian NGOs that had already conducted projects regarding children's health in the country (16–20).

Doctors and laboratory technicians received training on SCD and sample collection in December 2012. Sample collection began during the same month, using leftover blood from samples of children who consecutively accessed both hospitals in the following 8 months. During a routine clinical visit for any health reason in which a blood sample collection was planned for other purposes, parents were offered the possibility to perform the HbS analysis utilizing the leftover blood of their child. In case of acceptance, dried blood spots were prepared from the already drawn blood samples. Basic demographics (age, gender, ethnic group, residence) were collected for each patient in a dedicated paper form and transferred to excel for data analysis.

The study was approved by the local hospital ethics board and oral informed consent was collected from the parents.

Dried Blood Spot Collection

After oral informed consent from parents, peripheral blood samples were collected on filter paper (Whatman^{TM} 3MM Chr Chromatography Paper). The blood spots were air dried at room temperature, individually wrapped in aluminum film, placed in a single envelope, kept in the dark, and in a location without humidity to ensure the integrity of the sample during the processes of collection, storage, and transport. Every "*collection card*" had 4–5 blood spots with demographic and ethno-linguistic records. The samples were shipped via courier to the Laboratory of Pediatric Onco-Haematology of University of Padova, Italy for processing. At arrival in Padua, all samples underwent Bglobin gene molecular analysis and High-performance Liquid Chromatography (HPLC) analysis. After genetic analysis, the DNA from HbAS and HbSS subjects was shipped to South Africa to determine the Hb haplotype.

High Performance Liquid Chromatography HPLC Analysis

Analyses were performed on all samples with the Alliance e2695 liquid chromatography (Waters) connected with a UV-Vis detector (Waters 2489), and settled at 415 nm. The system was equipped with a 35 length × 4.6 I.D. mm, chromatography column packed with a strong cation-exchanger, 6.5 μm microparticulate (IEC SP-420N, Shodex).

The gradient was made up of mobile phase A [MES, 2-(N-morpholino) ethanesulfonic acid 20 mM, pH = 5.6] and mobile phase B (MES+ Na2SO4 0.5 M, pH = 5.6) with a flow rate of 1 ml/min. After injection of the sample, the proportion of B was increased linearly to B:A (90:10) at 5 min and to 100:0 at 9 min; finally, the mobile phase was returned to A:B 95:5 at 11 min, for equilibration.

HbS Molecular Analysis

Genomic DNA of high molecular weight, extracted according to the QIAGEN protocol by dried blood spot, was subjected to amplification (Applied Biosiystems Thermal Cycler 2720) of the exons of the β-globin and direct sequencing. DNA samples that were heterozygous HbS/HbA were also analyzed at exon 2 and 3.

The entire coding sequence of the βglobin gene, 11p15.5 (NM_000518; OMIM#603903), was PCR-amplified with 30 cycles reactions at 94°C for 1 min, at 56°C for 1 min and at 72°C for 1 min. The reaction was done in a final volume of 50 μl comprising 50 ng DNA, Buffer II 10X, $MgCl_2$ Solution 25 mM, dNTP's 10 mM, Primers 100 μM, AmpliTaq Gold DNA Polymerase 5 u/μl. The purified PCR products were subjected to direct sequencing (3500Dx Genetic Analyzer, Applied Biosystems).

Hemoglobin Haplotype

The concentration and purity of each DNA sample was determined by Nanodrop spectrophotometry and dilutions of 100 ng/μL concentration were used for all reactions. A previously optimized 5 restriction-site PCR protocol was used for the SCD haplotype analysis. The reaction comprised 5 μL GoTaq 5X colorless buffer (Promega, USA), 1 μL dNTPs (Fermentas, USA), 0.5 μL of each primer (iDT, RSA), 0.1 μL GoTaq (Promega, USA), 1 μL DNA and made up to 25 μL with distilled water. Briefly, the reaction was cycled on the BIO-RAD Thermal cycler (BIO-RAD T100, USA) at 95°C for 5 min, 35 cycles of 94°C for 30 s, 53 or 55°C for 40 s, 72°C for 2 min and lastly kept at 72°C for 7 min. To confirm correct amplification, a 2% agarose gel (Seakem Lonza, RSA) was prepared in 1 X TBE buffer to visualize the amplicons using SYBR Safe DNA gel stain (Invitrogen, Life Technologies SA). The electrophoresis was carried out for approximately 60 min at 160 V and gel images were acquired using a protected imaging capture system (UVIPro Gold transilluminator, UK). To genotype the samples, restriction digests were done using 0.5 or 1 μL of the specific restriction enzyme (Promega, USA), 2 μL of the associated buffer (Promega, USA), 10 μL PCR product and made up to 15 μL using sterile deionized water. The digests were incubated overnight at 37°C on a thermal cycler (BIO-RAD T100, USA) and electrophoresed on a 2% agarose gel for 60 min at 160 V. Visualization was done using the UVIPro Gold transilluminator (UVItec, UK).

TABLE 1 | Basic demographics of the pediatric population in the two hospitals.

Variables	Total		BOR		HRF	
	N°	%	N°	%	N°	%
	848	100	503	59,3	345	40,7
Gender						
Male	498	58.7	294	58.4	209	60.6
Female	350	41.3	204	40.5	141	40.9
Age (years)						
Median	6.8		6		8	
Ethnic groups						
Balanta	136	16	82	16.3	54	15.6
Fula	121	14.27	73	14.5	50	14.5
Papel	123	14.50	82	16.3	41	11.9
Mandingo	111	13.08	41	8.1	70	20.3
Manjaco	75	8.84	49	9.7	26	7.5
Mancanha	66	7.78	39	7.7	40	11.6
Biafada	50	6.01	4	0.7	46	13.3

BCH, Clinica Pediátrica Bor; HRF, Hospital Raoul Follereau.

G6PD Genotyping

G6PD genetic variants that confer resistance to severe malaria including 202, 376, 542, 680, and 968 A-deficiency polymorphisms referred as G6PD202, G6PD376, G6PD542, were evaluated after performing HPLC and HbS molecular Analysis in 100 randomly selected DNA samples belonging to the five more frequent ethnic groups (Balanta, Fula, Papel, Manjaco, Mandingo), and in HbS gene carriers who had DNA remaining for the analysis.

The coding sequence of exons analyzed of the G6PD gene, Xq28 (NM_X03674; OMIM#305900), for G202A, A376G, A542T, T968C polymorphisms, was PCR-amplified with 30-cycle reactions at 94°C for 1 min, at 58°C for 1 min and at 72°C for 1 min. The reaction was done in a final volume of 50 μl comprising 50 ng DNA, Buffer II 10X, $MgCl_2$ Solution 25 mM, dNTP's 10 mM, Primers 100 μM, AmpliTaq Gold DNA Polymerase 5 u/μl.

The amplification products for G6PD202, G6PD376, G6PD542, G6PD968 polymorphisms were subjected to direct sequencing (3500Dx Genetic Analyzer, Applied Biosystems), instead the product PCR for G6PD680 was digested with BstNI restriction enzyme (New England, BioLabs): 4 μl PCR product with 2 μl of enzyme at 60°C for 15 min.

RESULTS

Eight doctors and three technicians from the two hospitals were trained on SCD and sampling techniques through several on site meetings. Accessing the two hospitals consecutively, 848 children (503 from BCH 345 from HRF) were tested comprising of 498 males and 350 females, with a mean age of 6.8 years (range: 1–16). The children belonged to the most frequent ethnic groups of Guinea Bissau (**Table 1**). The families all resided in the capital city and came from different parts of town.

The blood samples collected on absorbent paper were of excellent quality.

HPLC and Molecular Analysis

HBB molecular analysis identified 8 individuals with Hb SS SCD (0.94%) (mean age 7.27 years), 59 individuals with HbSA (6.95 %) (mean age 6.05 years), 2 individuals with HbAC (0.23%) (mean age 2 years), 1 individual bearer of a sequence variant samesense (0.19 %) (8 years). None had HbSC or HbSβthalassemia, frequent in other West African countries.

HbS allelic frequency was 4.42%. Details are given in **Table 2**.

A significant difference in the frequency of HbS was found between ethnic groups: Fulas 25.42%, Mandingas 18.64%, Pepel 11.86%, Mandjau 6.77%, Biafada 13.55%, 10.16% Balanta, and 11.86% the others (**Table 3**).

Hemoglobin Haplotypes

Thirty-two patients with the HbS gene had enough genetic material to be analyzed for the SCD haplotype background:

TABLE 2 | Genotype and hemoglobin F %.

Genotypes	Samples (*n*)	Patient's age (Median)	Hemoglobin F (%)	Hemoglobin range (g/dl)
AS	59	6.05	8.26	7.6–16.2
SS	8	7.27	9.15	8–10.3
AC	2	2	8.95	5.1–12.8

TABLE 3 | Distribution of abnormal hemoglobin in the different ethnic groups.

	HbAS		HbSS		HbAC	
Variables	**N°**	**%**	**N°**	**%**	**N°**	**%**
Total	59	6.95	8	0.94	2	
Median Age (*years*)	6.05		7.27		2	
Ethnic group-*n* (%)						
Balanta	6	10.16	1	12.5		
Fula	15	25.42	1	12.5	2	100
Papel	7	11.86	1	12.5		
Mandingo	11	18.64	3	37.5		
Manjaco	4	6.77	1	12.5		
Mancanha	1	1.69				
Biafada	8	13.55				
Others	7	11.86	1	12.5		

5 HbSS and 27 HbAS. Sixty-four chromosomes were therefore analyzed.

The Senegal haplotype was the most prevalent of all 5 SCD haplotypes with 31% ($n = 20$) followed by Cameroon haplotype with 11% ($n = 7$), with 1 chromosome from the Benin haplotype (2%). There was neither the Indian-Arab nor Central African haplotypes in this study (**Supplementary Table 1**; **Supplementary Figure 2**). The proposition of chromosomes with the atypical haplotype was surprisingly high (56%; $n = 30$) with 83.3% ($n = 30$) positive for the HinfI(5'β) restriction site.

G6PD Molecular Analysis

One hundred forty-one samples were analyzed for G6PD: 100 randomly selected samples of the five more frequent ethnic groups (20 each from Balanta, Fula Pepel, Mandjaco, Mandingo) with HbAA genotype, 37 samples from individuals with HbAS, and 4 samples from HbSS individuals (details in **Supplementary Table 2**) according to the availability of DNA.

Mutational analysis with PCR and direct sequencing of the G6PD gene showed the presence of 376G and 968G alleles, not 202A, 542T, and 680T.

376G allele is 35% of 100 samples belonging to five ethnic groups more frequent in the population, and 21.6% of HbAS carriers with allelic frequency, respectively, of 24 and 14.8%.

G6PD molecular analysis in HbSS samples gave no significant results.

Interestingly, differences are noted between different ethnic groups: 11/35 (31.4%) 376G individuals are Fulas (1 homozygous female, and 5 heterozygotes, 5 hemizigous males); 8/37 (21.6%) HbAS samples have 376G and 3/8 (37.5%) are Fulas.

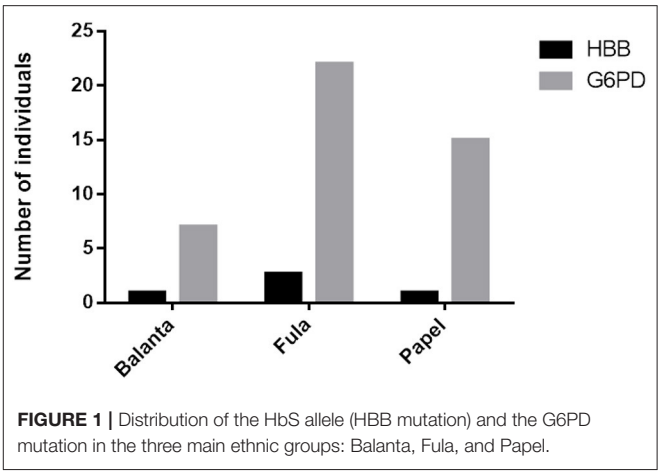

FIGURE 1 | Distribution of the HbS allele (HBB mutation) and the G6PD mutation in the three main ethnic groups: Balanta, Fula, and Papel.

Allele 968G is 8% of 100 samples evenly distributed between five ethnic groups (1 homozygous female, and 3 heterozygotes, 4 hemizigous males), 2.7% of SCD HbAS and 25% of HbSS patients, 37.5% of AS and 25% of SS are Fulas. The percentage of 376G/968G is the same between different ethnic groups.

Figure 1 displays the distribution of G6PD mutation and HbS allele in the three main ethnic groups.

DISCUSSION

In this first study after the publication of the 2008 UN recommendation to strengthen SCD programs throughout the world (21), we found higher prevalence of HbS allele in a pediatric population in Bissau, Guinea-Bissau, compared to previous studies (15), confirming the need to develop nationwide SCD screening and comprehensive care programs in the country. Moreover, our results demonstrate the feasibility of good sample collection by staff that has been adequately trained within the framework of North-South and South-South international collaborative projects.

The overall HbS allelic frequency was 4.42%, lower than neighboring countries. The prevalence of HbSA carriers also seems lower, which was 6.95% (12–14). Interestingly, the prevalence of the carrier state was different in the various ethnic groups, being higher in the Fula and the Mandingo. Minor differences were also observed among ethnic groups in the neighboring Republic of Guinea (22), although not as high. Specific characteristics of Guinea Bissau might justify this data. It is a very secluded country, with less connections to the other West African countries and to Europe, with a widely spread rural population and significant numbers of interfamily marriages between some of the ethnic groups. The country is therefore not new to unique epidemiological characteristics. It was, for example, the only country in which HIV 2 was more widespread than HIV 1 in the past decades (23); and multidrug resistant uberculosis (TB) has lower incidence than in other West-African countries (24). Furthermore, the very high maternal and infant mortality rates of Guinea Bissau (child mortality rates are the highest worldwide at 152.5 per 1,000 livebirths) (25), as well as the increased risk of stillbirth in SA carriers (26), could justify

a higher number of children with SS dying earlier and not being diagnosed. Also, there is a lower rate of HbSA children being born from S carrier mothers. Moreover, the relatively high mean age of our pediatric cohort (mean age 6.8 years) and of the children with SCD (mean age 7.27 years) could have excluded children with SCD who might have died before 5 years of age (4). Taken together, these data reinforce the need for screening early in life, such as in newborn screening programs, in Guinea Bissau.

It is also often difficult to know exactly how the coupling of individuals in a population happens, in particular, it is difficult to know if a population presents the rule of panmixy. If there is genetic isolation between subpopulations, it is possible that there is also a certain differentiation of allele frequencies, so the population shows a deviation from the Hardy-Weinberg equilibrium, even if the balance is respected within each population (27).

While the different ethnic distribution of the HbS allele warrants a deeper understanding of the genetic background of the population and further research (28–30), it can also aid to prioritize actions for SCD, such as starting awareness campaigns and screening in areas of the country or sectors of the city where the highest rate of carriers is living. Unfortunately, Guinea Bissau has very limited resources allocated to health care and other urgent health priorities like infectious diseases -HIV, TB, and cholera which catalyzed health care energy and resources in the past years. No resources were available for non-communicable diseases. Implementing screening in a stepwise manner with a priority list could be beneficial in this limited resource setting.

The co-existence of the HbS allele and the G6PD mutation in the setting of Guinea Bissau is important for phenotypic variability of hematological diseases. In fact, G6PD has been shown to influence severity of hemolysis and cerebrovascular manifestations (31–33). Moreover, the G6PD 376G allele is present in 35% of the HbAA samples and in 21.6% of the HbAS carriers, with an allelic frequency of 24 and 14.8%, respectively. The prevalence of G6PD genotypes in HbSS and HbSA did not differ ($p > 0.05$) from those found in the controls. The prevalence of G6PD deficiency did not change when patients were stratified by age, suggesting that there is no advantage of the association of G6PD deficiency with HbSS.

The Senegal haplotype is the most prevalent in our cohort, followed by the Cameroon haplotype. This could justify the relatively high percentage of HbF found in our cohort as it is well known that the Senegalese haplotype presents higher HbF (34). However, there is also a large proportion of atypical haplotypes in this cohort, which may be indicative of a genetically heterogeneous population that may have high levels of admixture or be a site of early migration. In fact, atypical haplotypes not belonging to the 5 most common ones (Senegalese, Benin, Bantu, Cameroon, Arab), have been described in other populations (Brazil, Nigeria, India) and could be responsible for the extreme phenotypic diversity of SCD (34–36). Future genetic studies are needed in this field.

Our study has several limitations. First of all, the sample collection involved only children living in the capital city of Bissau and occurred in a timeframe of only 8 months due to limited funding and staff capacity. Therefore, a wider sample, including also children from rural areas might be useful to estimate the real nationwide prevalence. Secondly, the organization of the blood sample analysis was complex and cannot be reproduced on large scale. Today, several rapid tests have become available and allow point-of care testing through a less complex diagnostic pathway than the one evaluated in this study. Nevertheless, the prevalence of HbS carriers and HbSS was high and warrants the development of a newborn screening program in Guinea Bissau. The possibility to screen with the different types of rapid tests that are now on the market (37) will hopefully enhance the screening capacity, both in the urban and rural areas of Guinea Bissau, as a pilot project has demonstrated (38).

CONCLUSION

This was the first study where data on sickle cell trait and G6PD deficiency frequencies were obtained for Guinea-Bissau pediatric populations. These data contribute to the evidence of the need to develop a SCD screening program in the country. Moreover, our results support the need to further explore the genetic background of various SCD populations across Africa in order to contextualize the heterogeneous clinical phenotypes seen across the continent. Such diverse populations are ideal for more precise haplotyping techniques to investigate the genomic background of SCD in West Africa, where there is an apparent lack of literature on SCD and the understanding of genotype-phenotype correlations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Hospital RAoul Follereau in Guinea Bissau; Ethics Committee of the Province of Padova, Padova, Italy. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

RC, FR, and MM designed the study. DC, AA, and SD collected the samples. MC, MM, FM, AW, GP, and GV performed the analysis. RC wrote the manuscript. All authors reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.826262/full#supplementary-material

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Prevalence of Hemoglobin-S and Baseline Level of Knowledge on Sickle Cell Disease Among Pregnant Women Attending Antenatal Clinics in Dar-Es-Salaam, Tanzania

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Background: Sickle cell disease (SCD) is the single most important genetic cause of childhood mortality globally. Newborn screening (NBS) is the recommended intervention aimed at early identification of babies with SCD and their linkage to care. To ensure success of NBS, pregnant women need to have the required knowledge on SCD and therefore motivation to screen their babies.

Objective: The aim of this study was to determine the prevalence of hemoglobin-S and assess the baseline level of knowledge on SCD among pregnant women attending antenatal clinics in urban settings in Dar-es-Salaam, Tanzania.

Methods: This cross-sectional study was conducted between August 2020 and February 2021, involving 600 pregnant women at 20–28 weeks of gestation attending antenatal clinics at Buguruni Health Center, Mbagala Hospital, and Sinza Hospital in Dar-es-Salaam, Tanzania. We administered a structured questionnaire to all participants to assess socio-demographic characteristics and baseline level of knowledge on SCD, where those scoring 7 or higher out of 10 questions were considered to have good knowledge. We screened for SCD a total of 300 participants from two centers (Buguruni Health Center and Mbagala Hospital) by using Sickle SCAN point-of-care test (BioMedomics Inc., United States). We used SPSS version 23 to analyze the data. On determining the association between level of knowledge and socio-demographic factors, we used Pearson's Chi-square and multivariate logistic regression in ascertaining the strength of associations.

Results: Of the 600 participants, the majority were of the age between 26 and 35 years (51%), with the parity of 1-3 children (55.8%) and secondary level of education (43%), while 56% were self-employed. Only 14.7% had good knowledge on SCD. The majority of the participants had ever heard of SCD (81.3%), most of them heard from the streets (42.4%),

and only 2.4% heard from hospitals. Of all 600 study participants, only 2 (0.3%) knew their SCD status while 7.7% declared having a family history of SCD. A proficient level of knowledge on SCD is associated with a high level of education, occupation, and knowing personal status of SCD. Among 300 participants who were screened for SCD, 252 were Hb-AA (84%), 47 were Hb-AS (15.7%), and 1 (0.3%) was Hb-SS.

Conclusion: Despite the high prevalence of hemoglobin-S among pregnant women attending antenatal clinics in urban settings in Tanzania, there is a poor level of knowledge on SCD and personal knowledge of SCD status. Maternal screening and health education on SCD should be included as part of the comprehensive package for health promotion at antenatal clinics.

Keywords: sickle cell disease, knowledge, pregnant women, maternal screening for SCD, hemoglobin-S, health education, antenatal clinic, awareness of SCD

INTRODUCTION

Sickle cell disease (SCD) is the single most important genetic cause of childhood mortality globally. Worldwide, it is estimated that about 400,000 babies are born with SCD each year, with the greatest burden being from sub-Saharan Africa where more than 75% of all sickle cell disease occurs, with this proportion projected to increase by 2050 (Piel et al., 2013). The sickle cell trait (SCT) and disease are more prevalent in sub-Saharan Africa; in Benin, the prevalence is estimated to be 25%, in Nigeria it ranges from 24 to 25%, and in Uganda the trait manifests in up to 30% of the population (Rahimy et al., 2003; Ndeezi et al., 2016). Tanzania has one of the highest annual births of SCD individuals in the world, estimated to reach 11,000 births a year, while the prevalence of sickle heterozygous state in Tanzania is between 13 and 20% (Ambrose et al., 2018; Nkya et al., 2019). In the absence of care, the majority of children with SCD succumb early on in life due to severe anemia, vaso-occlusive crisis, and invasive bacterial infection such as pneumonia, septicemia, and meningitis (Nwabuko et al., 2016; Manuscript, 2017).

The World Health Organization (WHO) recommended a set of public health interventions to reduce the burden of SCD which includes increased awareness, early diagnosis, and improving the quality of health care to affected individuals. Measures to prevent disease severity should be taken through the counseling of individuals with high risk of having a child with SCD (Clavagnier, 2012; Manuscript, 2017).

Health promotion refers to any activity that aims to achieve better health in a community. It includes health education, disease prevention, and health screening (Al-Ateeq and Al-Rusaiess, 2015). Health education is an important component of health promotion where medical and other health professionals provide information, advice, counseling, reassurance, and support in order to help people adopt behaviors that will enable them to control and change their lifestyles in order to improve their health (Al-Ateeq and Al-Rusaiess, 2015).

Antenatal care (ANC) is a major platform for health promotion among pregnant women. In Tanzania, the care, that is, provided during antenatal visits, include identification and management of obstetric complications such as preeclampsia, tetanus toxoid immunization, intermittent preventive treatment for malaria during pregnancy (IPTp), as well as identification and management of infections such as HIV, syphilis, and other sexually transmitted infections (Clavagnier, 2012). Studies have shown that early identification of patients and linkage to care can significantly reduce the morbidity and mortality associated with SCD. Particularly, newborn screening for SCD has had a major impact in overturning the morbidity and mortality associated with SCD in Europe and the United States (Nwabuko et al., 2016; Marcheco-Teruel, 2019).

With regards to health education, information given during ANC visits in Tanzania mostly aims to promote attendance to health facilities at birth and health behaviors such as breastfeeding, early postnatal care, and planning for optimal pregnancy spacing (Kearns et al., 2014; Al-Ateeq and Al-Rusaiess, 2015). Currently in our settings, no SCD health education or screening is provided at ANCs, also no similar study has been conducted to assess the prevalence of hemoglobin S and baseline level of knowledge among pregnant women attending antenatal clinics in Dar-es-Salaam.

ANCs are an important platform for health promotion in Tanzania. With approximately 11,000 babies born with SCD each year, it is important to evaluate the feasibility of integrating SCD screening services in ANCs in Tanzania. Education and screening for SCD to pregnant women during ANC visits will help women know if they are among the 13–20% of the population with sickle cell trait (SCT) (Ambrose et al., 2018; Nkya et al., 2019), also be aware of the importance of screening their newborn babies as they may either have SCD or SCT despite them not having the disease. Furthermore, it will empower mothers of children who will be born with SCD to know the importance of early attendance to SCD clinics. Ultimately, this will increase in the number of newborns with SCD who are identified and linked to care early on in life, leading to the reduction in the morbidity and mortality due to SCD in Tanzania.

Our study team at the Sickle Cell Programme, Department of Haematology and Blood Transfusion, Muhimbili University of Health and Allied Sciences (MUHAS) in Dar-es-Salaam has been at the forefront of conducting research on SCD in Tanzania. Over

the years, research from our team has delineated various aspects including clinical epidemiology, health systems, research ethics, and genomic profiles of SCD in Tanzania (Makani et al., 2011; Costa et al., 2021; Jacob et al., 2020; Bukini et al., 2020; Masamu et al., 2020; Nkya et al., 2020; Urio et al., 2020). Since 2017, the Sickle Cell Programme is part of the SickleInAfrica consortium, funded by the United States National Institutes of Health (NIH) through the National Heart, Lung and Blood Institute (NHLBI), with the aims to foster connectedness among stakeholders, develop an electronic database of patients, advance standards of care, provide training, and conduct research on pertinent areas on SCD in the sub-Saharan African context (Makani et al., 2020).

MATERIALS AND METHODS

Study design and setting: This cross-sectional study involved 600 pregnant women at Buguruni Health Center, Mbagala Hospital, and Sinza Hospital. All are public health facilities in Dar-es-Salaam, Tanzania. The antenatal clinics from these health facilities are conducted from Monday to Friday every week with exception of public holidays and provide different services including vaccination, Prevention of Mother to Child Transmission (PMTCT), family planning, and health education (mostly on danger signs in pregnancy, hypertension in pregnancy, anemia in pregnancy, and Rhesus incompatibility, for about 1 h per session) but no education is given on SCD. Mondays and Wednesdays are the clinic days for those attending for the first time, while Tuesdays, Thursdays, and Fridays are for those making a follow-up visit. About 50 to 100 pregnant women attend an ANC every day at each health facility.

There are neither SCD clinics nor newborn screening services in any of the study sites though the facilities provide post-natal immunization services. All the study sites are within 1–10 km away from their respective regional referral hospitals which are Amana, Temeke, and Mwananyamala where SCD clinics are conducted weekly.

Study participants: This study involved pregnant women who were attending antenatal clinics at the respective sites. This study population was selected because there was no study done to assess the prevalence of hemoglobin S and the baseline level of knowledge among this group.

Sample Size and Sampling Technique

The formula for sample size calculation was

$$m1 = \frac{\left[Z_{\alpha}\sqrt{(r+1)P(1-P)+Z_{\beta}} + \sqrt{rp_0(1-P_0)+p_1(1-p_1)}\right]^2}{r(p_0-p_1)^2}$$

where: $p = P_0 + rp_1/r+1$

P^0 is the proportion in the population that received health education only, and P^1 is the proportion in the population that received health education and maternal screening, r is the case and control ratio.

Assumptions: alpha = 0.05 (two sided), Power = 95%, $P^0 = 0.5$, $P^1 = 0.35$, **m0/m1** = r = 1

Attrition rate = 20%

M1 = 220.

The minimum sample size for this study was 440 participants, of which a minimum of 220 were to be screened and receive health education while a minimum of 220 were to receive only health education. Participants were selected by using a convenient sampling technique where pregnant women of gestation age between 20 and 28 weeks, with no complications that risk termination of pregnancy (such as heart failure, pregnancy-induced hypertension, threatened abortion, hyperemesis gravidarum, and gestational diabetes) were enrolled. Also, participants included pregnant women who had no history of blood transfusion within the past 4 months prior to enrollment as the donor blood may interfere with the results of the SCD screening test (this was applicable to those of the screening population). A total of 160 more pregnant women were added beyond the minimum sample size for a final total of 600 participants.

Collection of Socio-Demographic Data and Knowledge on Sickle Cell Disease

We conducted this study from August 2020 to February 2021, whereby 600 pregnant women who attended antenatal clinics at the respective sites and met the criteria were enrolled in the study. Following written informed consent, we administered a structured questionnaire to all 600 participants collecting the socio-demographic information and assessed the knowledge on SCD through a series of 10 questions. The questions assessed, the attitude on relating SCD to blood cancer and life expectance of SCD patients, knowledge on the mode of acquiring and diagnosis of SCD as well as the most common signs and symptoms of SCD. After administration of the questionnaire, we provided the health education on SCD to all 600 participants.

Maternal Screening for Sickle Cell Disease

Following collection of socio-demographic information, we counseled and then screened for SCD a total of 300 participants from two sites (Buguruni Health Center and Mbagala Hospital) by using Sickle SCAN® point-of-care test, which is a rapid, qualitative, lateral flow immunoassay kit for the identification of sickle cell disorder of hemoglobin A, S, and C (BioMedomics Inc., United States). We conducted the screening at antenatal laboratories where other screening activities took place (HIV, HB level). A small amount of whole blood (5 µl) was taken by finger prick using the provided capillary sampler. The sampler was placed into the buffered loaded pretreatment module to release hemoglobin by lysing erythrocytes. Three drops of the treated sample were dropped from the pretreatment module and added to the sample inlet of the Sickle SCAN® cartridge. Results were read within 5 min. The presence of hemoglobin variants A and S was indicated by blue lines in their designated regions. The remaining 300 patients from Sinza Hospital were not screened for SCD (**Figure 1**). This will allow future assessment of the uptake of newborn screening for SCD among babies born to mothers who were screened (300 participants) compared to those who were not screened (300 participants).

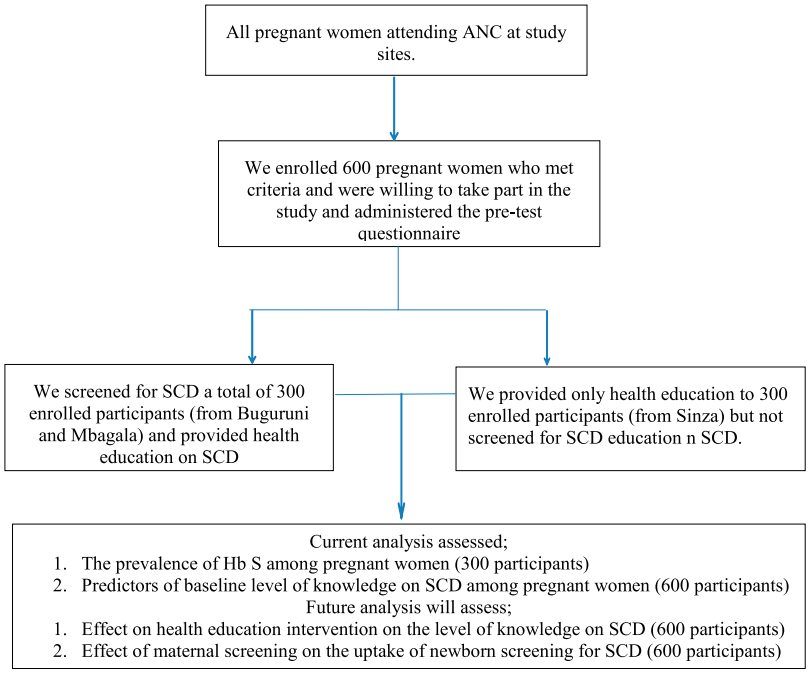

FIGURE 1 | Summary of data collection procedure.

Statistical Analysis

We used Statistical Package for the Social Sciences (SPSS) version 23 for data analysis. We obtained the prevalence of S-hemoglobin as the number of screened participants with Hb AS plus those with Hb SS divided by the number of all who were screened (Hb AA + Hb AS + Hb SS) times 100 ((Hb AS + Hb SS)/(HbAA + Hb AS + Hb SS) * 100).

We expressed the descriptive statistics such as participant characteristics in frequencies and presented in tables. We graded the level of knowledge depending on the number of correct responses scored from the questionnaires which was constructed from different literature which assessed the level of knowledge on SCD in different groups including pregnant women, also modified to fit the local context (Babalola et al., 2019; Obed et al., 2017a; Al-Qattan et al., 2019). A correct answer was scored as "1" while a wrong response was scored as "0". Total knowledge score ranging from 0 to 10 was calculated as the sum of all correct answers considering the following score range; < 7 poor knowledge, 7–10 good knowledge.

We did inferential statistics on factors associated with level of knowledge by comparing the different categories between the dependent variable (overall knowledge on SCD) with various independent variables (age, parity, marital status, level of education, occupation, if ever heard of the term SCD, the source of information on SCD, personal status, and family history on SCD) using Chi square test (for independent variables with all expected values ≥ 5). We considered a two-tailed p-value below 0.05 to be statistically significant. Subsequently, we did univariate and multivariate binomial logistic regression to test the strength of association between the main dependent variable (overall level of knowledge) with the independent variables. We entered into multivariate logistic regression only independent variables with p-values ≤ 0.2 in univariate analysis (level of education, occupation, and family history of SCD) to adjust for the effect of multiple predictors. We used the odds ratio to explain the relationship between dependent variables and associated factors and used a confidence level at 95% in determining statistical significance.

Besides delineation of the baseline level of knowledge and predictors of knowledge on SCD (all 600 participants), current analysis also reported on the prevalence of hemoglobin S among pregnant women who were screened (300 participants). In the future, we will assess the effect of health education intervention on the level of knowledge on SCD as well as the uptake of newborn screening for SCD among babies born to mothers who were screened (300 participants) compared to those who were not screened (300 participants).

Ethical Consideration

We obtained ethical clearance for this study from Muhimbili University of Health and Allied Sciences research ethics committee with certificate number **MUHAS-REC-08-2020-333**. We obtained the permission to conduct the study from Regional Medical Officer- Dar-es-Salam, the District medical officers from Ilala, Ubungo, and Temeke districts, as well as the respective hospitals, Buguruni Health Center, Sinza Hospital, and Mbagala Hospital. We obtained the written informed consent from every participant. Following collection of socio-demographic information and baseline knowledge on SCD, all participants received health education on SCD, the importance of screening their babies for SCD, and were also informed on the available SCD services in Dar-es-Salaam. Participants who were

TABLE 1 | Socio-demographic characteristics of pregnant women attending antenatal clinics in Dar-es-Salaam (N = 600).

Pregnant women characteristics	n	Percent (%)
Age (years)		
<18	2	0.3
18–25	217	36.2
26–35	306	51.0
>35	75	12.5
Parity		
0	243	40.5
1–3	335	55.8
>3	22	3.7
Marital status		
Married	495	82.5
Not married	105	17.5
Level of education		
Illiterate	19	3.2
Primary level	249	41.5
Secondary level	258	43.0
College/university	74	12.3
Occupation		
Employed	65	10.8
Self-employed	340	56.7
Homemaker	195	32.5
Heard of the term SCD		
Yes	488	81.3
No	112	18.7
Source of information on SCD (N = 488)		
School	121	24.8
Media	72	14.8
Home	76	15.6
Street/peers	207	42.4
Hospital	12	2.4
Knowing personal status		
Yes	2	0.3
No	598	99.7
Family history of SCD		
Yes	46	7.7
No	554	92.3

screened for SCD were informed of their SCD status. One participant who was found to be HbSS was encouraged to start clinic at her respective regional referral hospital.

RESULTS

Demographic Characteristics of Participants

We enrolled a total number of 600 pregnant women from the antenatal clinics in the study. The majority of participants were in the age range of 26–35 (51.0%), with parity of 1–3 children (55.8%). Furthermore, most of the participants were married 495 (82.5%), self-employed 340 (56%), and had a secondary level of education 250 (43%) (**Table 1**). A total of 488 participants (81.3%) reported to have heard of the term SCD. The major sources of information on SCD were the streets 207 (42%) and schools 121 (24.8%) and only 12 participants (2.4%) heard of SCD at the hospital. Moreover, 46 participants (7.7%) reported having a family history of SCD and only 2 (0.3%) knew of their SCD status (**Table 1**).

Prevalence of S-Hemoglobin Among Pregnant Women

Table 2 shows results of maternal SCD screening among 300 pregnant women from Sinza Health Center and Mbagala Hospital. Most of the participants were Hb-AA 252 (84%). There were 47 participants (15.7%) who had sickle cell trait and one participant (0.3%) had Hb-SS. None of the participants had Hb-SC.

Overall Level of Knowledge on Sickle Cell Disease Among the Study Participants

Only 88 participants (14.7%) had good overall knowledge on SCD. From the individual questions which assessed the attitude, mode of acquiring, and diagnosis of SCD, only 22% believed that SCD is different from blood cancer while only 28% believed that individuals with SCD can live to normal life expectancy. Almost half of the participants (48%) knew that SCD is an inherited disease, only 27.7% knew that phenotypically normal parents may have a child with SCD in case both parents have sickle cell trait. On assessing the level of knowledge on the common signs and symptoms of SCD, anemia was the most known sign (49.8%), while pain was known to only 25.7% of the participants, with the least one being dactylitis (13%). Other symptoms assessed were jaundice known to only 26.7% and abdominal distension due to enlarged spleen known to only 17.5% of the participants (**Table 3**).

Factors Influencing Knowledge on Sickle Cell Disease Among Pregnant Women Attending Antenatal Clinics in Dar-Es-Salaam

In ascertaining the association between the overall level of knowledge on SCD with participants' characteristics, we observed that the overall level of knowledge was associated with participant's level of education (p-value < 0.001), occupation (p-value 0.014), and knowing their personal status of SCD (p-value 0.021). Among those who had ever heard of SCD, the level of knowledge was associated with the source of

TABLE 2 | The prevalence of hemoglobin-S among pregnant women attending antenatal clinics in Dar-es-Salaam (N = 300).

Sickle cell status	Frequency (n)	Percent (%)
HbAA	252	84.0
HbAS	47	15.7
HbSS	1	0.3
TOTAL	300	100

TABLE 3 | Response to questions on knowledge on SCD.

Question	True answer	Correct responses n (%)	Wrong responses n (%)
SCD is the same as blood cancer.	No	132 (22)	468 (78)
Do the lives of SCD patients have an age limit?	No	172 (28.7)	428 (71.3)
Mode of acquiring SCD.	Inheritance	290 (48.3)	310 (51.)
What is the mode of diagnosing SCD?	Blood test	179 (29.8)	421 (70.2)
Can the phenotypically normal parents get a child with SCD?	Yes	166 (27.7)	434 (72.3)
Are the following signs and symptoms of SCD?			
Anemia	Yes	299 (49.8)	301 (50.2)
Pain	Yes	154 (25.7)	446 (74.3)
Jaundice	Yes	160 (26.7)	440 (73.3)
Abdominal distention due to splenomegaly	Yes	105 (17.5)	495 (82.5)
Dactylitis	Yes	82 (13.7)	518 (86.3)

TABLE 4 | Socio-demographic characteristics and overall level of knowledge on SCD among pregnant women attending antenatal clinics in Dar-es-salaam (N = 600).

Characteristic	n (%)	Overall knowledge on SCD N = 600		*p*-value (chi-square test)
		Poor (<7) N = 512 (85.3%) n (%)	Good (≥7) N = 88 (14.7%) n (%)	
Age (years)	—	—	—	0.687[a]
<18	2 (0.3)	2 (100.0)	0 (0)	—
18–25	217 (36.2)	188 (86.6)	29 (13.4)	—
26–35	306 (51.0)	257 (84.0)	49 (16.0)	—
>35	75 (12.5)	65 (86.7)	10 (13.3)	—
Parity	—	—	—	0.378[a]
0	243 (40.5)	202 (83.1)	41 (16.9)	—
>3	22 (3.7)	20 (90.9)	2 (9.7)	—
1–3	335 (55.8)	290 (86.6)	45 (13.4)	—
Marital status	—	—	—	0.430
Married	495 (82.5)	425 (85.9)	70 (14.1)	—
Not married	105 (17.5)	87 (82.9)	18 (17.1)	—
Level of education	—	—	—	<0.001
Illiterate/primary	268 (44.7)	249 (92.9)	19 (7.1)	—
Secondary	258 (43.0)	207 (80.2)	51 (19.8)	—
College/university	74 (12.3)	56 (75.7)	18 (24.3)	—
Occupation	—	—	—	0.014
Employed	65 (10.8)	52 (80.0)	13 (20.0)	—
Self-employed	340 (56.7)	282 (82.9)	58 (17.1)	—
Homemaker	195 (32.5)	178 (91.3)	17 (8.7)	—
Source of information (N = 488)	—	—	—	<0.001[a]
School	121 (24.8)	89 (73.6)	32 (26.4)	—
Media	72 (14.8)	61 (84.7)	11 (15.3)	—
Home	76 (15.6)	58 (76.3)	18 (23.7)	—
Street	207 (42.4)	182 (87.9)	25 (12.1)	—
Hospital	12 (2.4)	10 (83.3)	2 (16.7)	—
Knowing personal status	—	—	—	0.021[b]
Yes	2 (0.3)	0 (0.0)	2 (100)	—
No	598 (99.7)	512 (85.6)	86 (14.4)	—
Family history of SCD	—	—	—	0.159
Yes	46 (7.7)	36 (78.3)	10 (21.7)	—
No	554 (92.3)	476 (85.9)	78 (14.1)	—

[a]= *Likelihood ratio.*
[b]= *Fisher' exact test.*

information on SCD (p-value < 0.001), which was higher among those who heard of SCD from school and home compared to those who heard from the streets. Other participant characteristics such as age, parity, marital status, and having a family history of SCD were not found to be associated with having good knowledge on SCD (**Table 4**).

TABLE 5 | Regression analysis of factors influencing knowledge of SCD among pregnant women attending ANC in Dar-es-Salaam.

Factors	n (%)	Univariate analysis COR ((95% CI))	Multivariate analysis AOR ((95% CI))
Age			
<18	2 (0.3)	*	—
18–25	217 (36.2)	1.00 (0.46–2.17)	—
26–35	306 (51.0)	1.24 (0.60–2.58)	—
>35	75 (12.5)	References	—
Parity			
0	243 (40.5)	2.03 (0.46–9.02)	—
1–3	335 (55.8)	1.55 (0.35–6.87)	—
>3	22 (3.7)	References	—
Marital status			
Married	495 (82.5)	0.80 (0.45–1.40)	—
Not married	105 (17.5)	References	—
Level of Education			
Illiterate/Primary	268 (44.7)	References	—
Secondary	258 (43.0)	3.23 (1.85–5.64)	2.94 (1.67–5.18)
College/university	74 (12.3)	4.21 (2.08–8.54)	3.88 (1.89–7.94)
Occupation			
Employed	65 (10.8)	2.62 (1.19–5.74)	1.83 (0.82–4.10)
Self-employed	340 (56.7)	2.15 (1.21–3.82)	1.84 (1.02–3.29)
Homemaker	195 (32.5)	References	—
Family history			
Yes	46 (7.7)	1.70 (0.81–3.55)	2.08 (0.93–4.42)
No	554 (92.3)	References	—
Source of information			
School	121 (24.8)	2.62 (1.46–4.68)	—
Media	72 (14.8)	1.31 (0.61–0.82)	—
Home	76 (15.6)	2.26 (1.15–4.43)	—
Hospital	12 (2.4)	1.46 (0.30–7.03)	—
Street/peers	207 (42.4)	References	—

**Predicts outcome perfectly.*
COR, crude odd ratio; AOR, adjusted odd ratio, 95%CI, confidence interval at 95%.

Table 5 summarizes results of univariate and multivariate logistic regression analysis. The final model revealed a strong association between overall level of knowledge on SCD with level of education of participants and on participant's occupation. The odds of having good knowledge on SCD among pregnant women with college/university level of education was 3.9 times higher than those who were illiterate/primary level (AOR = 3.94; 95% CI = 1.89–7.94). Also, those having a secondary level of education had 2.9 times higher odds of having good knowledge than the illiterate/primary level of education (AOR = 2.94; 95% CI = 1.67–5.18). Occupation was also seen to be associated with the level of knowledge on SCD among pregnant women whereby those who were self-employed had 1.8 times higher odds of having good knowledge than those who were homemakers (AOR = 1.84; 95%CI = 1.02–3.29).

Besides these predictors, we also found the source of information on SCD to be associated with the level of knowledge on SCD during univariate analysis where those who heard of SCD at school had 2.6 times higher odds of having good knowledge compared to those who heard from the streets/peers (COR = 2.62; 95% CI = 1.46–4.68), and also those whose source of information was home (have a family member or have ever lived with an SCD patient) had 2.2 times higher odds of having good knowledge compared to those who heard of SCD from the streets/peers (COR = 2.26; 95% CI = 1.15–4.43). However, this factor was not included in multiple regression due to its collinearity with level of education which was strongly associated with level of knowledge on SCD and also since only a subset of 488 participants who had ever heard of SCD provided responses on the source of information.

DISCUSSION

Overall Findings

Adequate maternal level of knowledge on SCD could act as a catalyst for planned parenthood and uptake of newborn screening for SCD, especially in settings where the prevalence of SCD is high. Here, we show strikingly low levels of knowledge on SCD in a population of pregnant women where the prevalence of hemoglobin S was high. The level of knowledge on SCD was associated with level of education, occupation, and knowing personal status of SCD. These findings have implications in planning interventions such as newborn screening for SCD, and uncovers antenatal clinics as a potential platform for providing health education and maternal screening for SCD

with the ultimate goal of improving the uptake of newborn screening for SCD.

Knowledge of Personal Sickle Cell Disease Status

We found high prevalence (16%) of hemoglobin S among pregnant women attending antenatal clinics in Dar-es-Salaam, concordant with the high prevalence in the general population in Tanzania which ranges from 13–20% (Makani et al., 2011; Ambrose et al., 2018). Despite the high prevalence of hemoglobin S and although 46 participants (7.7%) admitted having a family history of SCD, only 2 of 600 (0.3%) participants reported to know their SCD status. Among the 300 participants who were screened for SCD, none knew of her SCD status prior to screening in the current study, including one participant who was found to be Hb-SS. This level of knowledge of personal SCD status is very low compared to that reported by Obed et al. in Ghana where 10% of pregnant women self-reported sickle cell trait, and that reported by Treadwell et al. where 16% reported knowledge of their sickle cell trait status (Treadwell et al., 2006; Obed et al., 2017b). Also, in a study of 147 African-American patients aged 18–50 years seen in an emergency department, 31% knew of their own trait status (Burnham-Marusich et al., 2016). Furthermore, in a cohort of recent tertiary graduates during their National Youth Service Corps (NYSC) in Benin City, Edo state, Nigeria, about 94.6% of the respondents reported to know their SCD carrier status and 80.8% were willing to avoid carrier marriage, the commonest indication for carrier status check being school entry followed by a doctor's request and premarital screening (Adewoyin et al., 2015). The observed difference in the level of knowledge on personal SCD status, particularly between Tanzania and sites in Ghana and Nigeria, is possibly attributed to SCD being much more common in West Africa than East Africa (Piel et al., 2013; Bukini et al., 2020).

General Level of Knowledge on Sickle Cell Disease

Tanzania has one of the highest annual births of SCD individuals in the world, estimated to reach 11,000 births a year (Makani et al., 2011), but there is a poor level of knowledge among pregnant women attending antenatal clinics in Dar-es-Salaam. In this study we found that only 14.7% of participants had good knowledge on SCD. This was almost similar to studies done in West Africa, such as that done in Nigeria assessing the level of knowledge among tertiary level graduates which showed that only 17.8% of respondents had good knowledge of SCD (Adewoyin et al., 2015). Also, the other one done in Ghana among university students showed only 7.1% had excellent knowledge on SCD (disease). The finding that only 27.7% of the pregnant women in the study population knew that parents who are phenotypically normal may have children with SCD is concerning as it heralds a major lack of public awareness on the mode of inheritance of SCD and hence lack of consideration of sickle cell trait status among partners prior to the decision to get married or have a baby. This was also seen in a study done aiming to uncover the levels of knowledge, attitude, and practice (KAP) associated with SCD and premarital genetic counseling in 351 Saudi adults which showed that 28.8% had good knowledge on SCD while only 14.8% of participants were aware of SCD inheritance pattern (Al-Qattan et al., 2019).

Particularly in the study setting, since newborn screening is not yet universal in Tanzania, awareness on SCD among pregnant women could have significant impact by motivating mothers to seek newborn screening or early infant diagnosis of SCD for their babies after birth.

Factors Associated With the Level of Knowledge on Sickle Cell Disease

The level of knowledge among pregnant women in this study was significantly predicted by the level of education which increased with the increase in level of education; as those with college/university level education as well as secondary level of education had higher odds of having good knowledge compared to those of primary/illiterate level. The good level of knowledge on SCD was also associated with hearing of SCD at school and having lived with a patient with SCD and therefore obtained the information from home.

These findings are similar to observations in a study in Nigeria which showed that the level of knowledge on SCD increased with higher levels of education and also mothers who were already caregivers of SCD patients had a higher knowledge score and a better understanding on SCD inheritance than those who had no children with SCD (Babalola et al., 2019). This was again the same as other studies conducted in Nigeria which showed that higher level of education and knowing a relative with SCD or sickle cell trait was significantly associated with high knowledge of SCD (disease; Ezenwosu et al., 2021). Another study done by Obed et al. showed that respondents with at least secondary education scored an average one point higher on the knowledge test than those with lower education, and knowing someone with SCD was associated with a higher level of knowledge than in individuals who did not know any affected individual (Obed et al., 2017b).

Contrary to our study, the study done by Al-Qattan et al. showed that age group is associated with the level of knowledge (Al-Qattan et al., 2019). Also, another study done by Burnham-Marusich et al. showed age and employment were associated with accuracy on self-reported status of SCD, while marital status was not significantly associated (Burnham-Marusich et al., 2016). In our study, age, parity, marital status, and having a family history of SCD were not found to be associated with having good knowledge on SCD.

Our study showed that knowing personal SCD status was associated with having good knowledge on SCD. This had a perfect prediction where all 2 participants who knew their status had a proficient level of knowledge on SCD. This was similar to a study that showed better knowledge on SCD among individuals with knowledge of their sickle cell trait status compared to those who did not know (Obed et al., 2017b). Occupation was another

factor that was associated with good knowledge on SCD in this study where those who were self-employed had higher odds of having good knowledge than homemakers did.

Sources of Information on Sickle Cell Disease

In this study, over 80% of participants reported to have ever heard of the term SCD, with the majority of them having heard from the street/peers), followed by school, through living with a patient with SCD at home, mass media such as television and radio, and at hospitals. This finding is not far different from another study where the majority of participants seemed to get information on SCD from schools (84.6%), media (12.6%), and health center/ family and friends (2.9%) (disease), similar to that shown by Adewoyin et al. (2015). Also, another one showed only 10.1% of participants received information on premarital genetic counselling from health care workers (Al-Qattan et al., 2019). Of note, although over 80% of the participants in the present study reported to have heard of SCD, only 14.7% had good knowledge on SCD. This implies inadequate or inappropriate education provided through the reported outlets. Particularly, it is concerning that only 2.4% of participants reported to have heard of SCD at hospitals where the right information is expected to be provided as shown by Ezenwosu et al. (2021).

The fact that SCD health education is not part of the information offered to pregnant women during their regular antenatal visits may be the reason for this and represents a large missed opportunity. In Tanzania, by 2008, 94% of pregnant women made at least one visit to the antenatal clinic and 62% of pregnant women made at least four visits (Clavagnier, 2012). Besides antenatal clinics, mass media may also be an effective platform for educating the population on SCD.

CONCLUSION

The prevalence of hemoglobin S was high among pregnant women in Dar-es-Salaam, Tanzania, although most of them have never been screened and were not aware of their SCD status. Despite the high prevalence of hemoglobin S, an overwhelming majority of pregnant women did not have good knowledge on SCD, implying a missed opportunity for planned parenthood and a high likelihood of not soliciting newborn screening for their babies. Most pregnant women seemed to have received information on SCD from the streets which appeared to have been incorrect or inadequate, and a large opportunity is missed to provide proper health education on SCD in hospital settings, particularly antenatal clinics, as well as through mass media. Inclusion of maternal screening and health education for SCD is advocated as part of the comprehensive package for health promotion at antenatal clinics.

DATA AVAILABILITY STATEMENT

Raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved. Ethical clearance for this study was obtained from Muhimbili University of Health and Allied Sciences (MUHAS) Research Ethics Committee with certificate number MUHAS-REC-08–2020-333. Written informed consent to participate in this study was provided by all study participants.

AUTHOR CONTRIBUTIONS

HT conceived the study, collected data, analyzed the data, and wrote the first draft of the manuscript. AJ, WL, FL, EM and JN assisted in data collection. JM, BK, PR, IM and EB assisted in data analysis. All authors critically reviewed and approved the final version of the manuscript.

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METHODS
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Skills Capacity Building For Health Care Services and Research Through the Sickle Pan African Research Consortium

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Skills development, the building of human capacity, is key to any sustainable capacity building effort, however, such undertakings require adaptable and tailored strategies. The Sickle Pan-African Research Consortium (SPARCo) is building capacity in sickle cell disease (SCD) management and research in sub-Saharan Africa, including a multi-national SCD patient registry, this is underpinned by skills development activities in data, research, and SCD management.

Method: The SPARCo Skills Working Group was set up with the mandate of coordinating skills development activities across the three SPARCo sites in Ghana, Nigeria and Tanzania. To tailor activities to the requirements of the consortium, a needs assessment was conducted at the start of the project which identified skills required for SCD management and research and catalogued existing external and internal training programmes. The needs assessment highlighted differences in skill levels between the sites and different organisational structures which required tailored skills development activities at individual, site and consortium levels.

Strategy: Based on the needs and the resources available, different types of training activities were implemented: these included online, blended and face to face activities. In order to create a sustainable skills development programme, existing short, medium, long-term, on-job training activities were used wherever possible. World Sickle Cell Day (19th June) was leveraged for training and health education activities.

Results: SPARCo has recorded 1,726 participants in skills development activities across the three sites. Skills have been enhanced in data management, SCD and research to underpin the core deliverables of SPARCo.

Conclusion and Lessons Learned: The baseline needs assessments and continual review and adjustment were critical for development of an effective skill development strategy for the consortium. This adaptability was particularly valuable during the COVID-19 pandemic. The sustainability plan leveraged existing programmes and activities and has created a pool of people with required skills for health care and research in SCD. To be effective, skills development programmes need to take into account existing capacity, training opportunities and local conditions. The model was applied to SCD and is adaptable to other skills development in healthcare and research in low and middle-income countries.

Keywords: capacity building, health care, research, data management, sickle cell disease, Africa

BACKGROUND

The Sickle Pan African Research Consortium (SPARCO) and the Sickle Africa Data Coordinating Centre (SADaCC) set out to develop a multi-national standardised electronic patient consented database of sickle cell disease (SCD) patients in sub-Saharan Africa (SSA) (Makani et al., 2017; Wonkam and Makani, 2019). The success of this initiative would depend on the concurrent development of skills in SCD healthcare and research within an acceptable ethical, legal and socially acceptable framework to support research and improve healthcare for SCD (Makani et al., 2017; Munung et al., 2019). SPARCO and SADaCC, funded by the United States (United States) National Heart, Lung and Blood Institute (NHLBI) (Grant Numbers U24HL13045881 the Sickle Pan African Research Consortium (04/01/2017–03/31/2021) and U24HL135600 and Sickle Data Coordinating Center, (04/01/2017–03/31/2021)] started in May 2017 with sites in Tanzania (Muhimbili University of Health and Allied Sciences - MUHAS), Nigeria (University of Abuja), and Ghana (Kwame Nkrumah University of Science and Technology) with the aim of registering 13,000 SCD patients by 2021. Coordination was provided by SPARCO Hub, located at MUHAS, and the Sickle Africa Data Coordinating Center (SADaCC) based in the University of Cape Town (South Africa) which is the administrative centre coordinating data standardisation and supporting communications. Coordination between the three sites was achieved through five working groups representing the consortium's areas of focus: Database and Registry, Health and Standards of Care, Research and Skills supported by a Management Committee (MC) Principal Investigators (PIs) and working group leads. The MC in turn reports to a Steering Committee which includes the Program Officer from the NHLBI, the PI of SPARCO, PI of SADaCC and the Principal Investigators from Ghana, Nigeria and Tanzania (Makani et al., 2017; Makani et al., 2020). The Steering Committee met monthly with responsibility for coordination and management of the project.

Database and Registry

SPARCO will generate a vast amount of data (demographic, clinical, social, laboratory and genomic data) hence the need for capacity in data collection, database management, data analysis and a standardized terminology for SCD in an ontology (Adekile et al., 2019). In addition to SPARCO, other initiatives such as the Sickle Cell Genomics Network of Africa (SickleGenAfrica) and the Consortium for Newborn Screening (NBS) in Africa for Sickle Cell Disease (CONSA) program of the American Hematology Association (Ghana, Liberia, Kenya, Nigeria Tanzania, Uganda, Zambia) will substantially add to the amount of data available on SCD patients in the near future (Ofori-Acquah, 2020).

Health and Standards of Care

Patients with SCD require multidisciplinary care, which is not readily available in most settings in SSA. Even when available, care is often limited to the tertiary level of healthcare which may not be accessible as the first point of call by a significant number of SCD patients (Noubouossie et al., 2016). The management of SCD-related complications is highly variable both between and within countries in SSA. SPARCO is creating multi-level Standards of Care for use across SPARCO sites to provide consistent and best practice care for SCD patients in order to strengthen capacity in SCD management.

Research

There are many unknowns about the prevalence, clinical manifestation and disease progression of SCD in SSA (Williams, 2016). To undertake research to better understand these issues, more skills in epidemiology, genetics and molecular diagnosis, clinical and laboratory phenotyping of SCD, clinical trials, research management, scientific communications, data management and bioinformatics, standardization of specimen collection, processing and shipment, good laboratory practice to minimize variation in preanalytic, analytic and post-analytic processes are required on the continent (Makani et al., 2020).

At the conception of the project, it was recognised that SPARCO sites had some skills gaps in data management, healthcare and research. It was, therefore, proposed to address these skills deficits at undergraduate and specialist levels to involve all cadres of health workers including doctors, nurses, laboratory scientists, community health extension workers (CHEWS), counsellors, health planners and policymakers as well as patient and community groups.

TABLE 1 | Selected courses identified in priority areas.

Program	Category of program	Institution	Country/ Region
ASH Consultative Hematology Course	Clinical	American Society of Hematology	United States
ASH Visitors Training Program	Clinical and Research	American Society of Hematology	United Kingdom
Haematology Short Course	Clinical and Research	University of West Australia, School of Pathology and Laboratory Medicine	Australia
Laboratory Aspects of Haemoglobinopathy Diagnosis	Clinical	Imperial College, London	United Kingdom
Haematology in Obstetrics Course	Clinical	British Society for Haematology	United Kingdom
Clinical Research Training in Hematology (CRTH)	Research	European Hematology Association	Europe
Graduate Certificate in Cancer and Haematology Nursing	Clinical	University of Sydney	Australia
Blood Science MSc (Distance Learning)	Research	London Metropolitan University	United Kingdom
Master of Science (Msc) electronic (e)-Learning course in Haemoglobinopathies	Research	University College London	United Kingdom
ESH-ENERCA Training Course on Haemoglobin Disorders: Laboratory Diagnosis and Clinical Management	Clinical and Research	European School of Haematology	Europe (Past)
Renzo Galanello Fellowship Programme 2018	Clinical and Research	Thalassaemia International Federation (TIF)	United Kingdom
Module in haemoglobinopathies	Clinical	London Metropolitan University	United Kingdom
Haemoglobinopathies: short counselling course	Clinical	Royal College of Midwives	United Kingdom
Genetic risk assessment and counselling module (Sickle Cell and Thalassaemia Screening)	Clinical	Royal College of Midwives	United Kingdom
T32 Training Program in Hematology	Research	Division of Hematology, John Hopkins University	United States
Hematology Training Program	Research	Boston University Medical Center	United States
Hematology and Oncology Fellowship Program	Clinical and Research	Boston University Medical Center and the Boston VA Health Care System	United States
Hematology Training Program at Herbert Irving Comprehensive Cancer Center	Clinical and Research	Herbert Irving Comprehensive Cancer Center, Columbia University Medical Centre	United States
Haematology and Transfusion Science MSc	Clinical and Research	Manchester Metropolitan University	United Kingdom
Haematology	Clinical and Research	University of Nottingham	United Kingdom
Haematology MSc (by research)	Research	University of Nottingham	United Kingdom
Biomedical Blood Science MSc, Postgraduate Diploma, Postgraduate Certificate Transfusion, Transplantation and Tissue Banking MSc University of Westminster, London	Clinical and Research	University of Keele University of Edinburgh	United Kingdom United Kingdom
Biomedical Science (Haematology) MSc	Clinical and Research	University of Wolverhampton	United Kingdom
Biomedical Sciences (Haematology) MSc	Clinical and Research	University of Westminster, London	United Kingdom
Blood Sciences MSc (PGCert PGDip)	Clinical and Research	University of Brighton	United Kingdom
Blood Science (Distance Learning) MSc	Clinical	London Metropolitan University	United Kingdom
Blood Science - MSc	Clinical	London Metropolitan University	United Kingdom
Haematology MSc	Clinical and Research	University of Chester	United Kingdom
Advances in Haematology in Africa	Clinical	Muhimbili National Hospital and Muhimbili University of Health and Allied Sciences	Tanzania
MMed Haematology (10,250,281)	Clinical	University of Pretoria	South Africa
Clinical Haematology Unit CMJAH	Clinical	The University of Witwatersrand, Joburg	South Africa
Advanced Postgraduate Diploma Course in Clinical Research and Data Management	Research	James Lind Institute, Switzerland	Switzerland

METHODOLOGY

A. Setting Up of Working Groups

The Skills Working Group (SWG) was formed with the mandate of coordinating skills development activities to support the other specific aims of SPARCO, which are to develop: i) database of SCD patients attending clinics at participating centres, ii) guidelines for locally-appropriate standards of care and iii) plans for research projects. The SWG includes two representatives from each site, the Site Skills Coordinator, a representative from SPARCO Hub and from three from SADaCC. The Chair and a Co-Chair of the SWG are the site PIs for the Nigeria site and the co-PI for the Ghana site, respectively.

Title
Background/Premise/Justification/Need
Aim (clear indication of the aim of the training and the expected outcome at the end of the training)
Scope of course
Target participants and numbers
Curriculum including what tasks the participants will be expected to perform at the training
Training materials
Learning outcomes - knowledge and skills acquired
Faculty involved
Assessment (pre and post course)
Equipment required (laptop computers, video projector etc.)
Budget including cost to participants
Date and venue(s)
Course leader
Feedback form for evaluation of course by participants
A report on the course to be submitted within 1 month of the course to include:

a. 1-page narrative on the course including expectations versus actual delivery, any challenges faced and any notable successes.
b. Pictures illustrating the training undertaken.
c. A summary of results from assessment (pre and post) and feedback from participants and facilitators.

FIGURE 1 | Training SOP.

The SWG meets monthly, using online video conference platform with face-to-face meetings at the twice-yearly consortium meetings.

B. SWG Plan Guide

Identification of deliverables and identification of skills priority areas The main deliverables of the SWG were the review of existing skills development programmes, the development of short and medium-term skills training programmes and participation in independently funded training programmes. A work plan was developed to guide activities. Needs assessment was carried out by consortium members. Each site reviewed its own existing skills development programmes, developed training materials/schedules and curricula and these were collated and followed by an assessment of the strengths and weaknesses as well as those common to all. This enabled the SWG to determine the skills required to achieve the aims of the consortium and identify priority training areas to support the work as listed in **Table 1**.

Training Programs

Identification of Programs

With the knowledge of training gaps and needs so identified, the SWG decided to seek for programmes/courses where individuals could be trained in these areas. A search on the internet using search terms like haemoglobinopathies, Sickle Cell Disease, Haematology, and others, was done to identify training institutions and programmes that are aligned to the identified needs. Existing partners were also identified who could provide expertise in these areas.

Identification of Training Materials

Training material on database management, healthcare, health education and research related to SCD were compiled in both soft and printed versions from all the three sites.

Identification of Participants

The skills development activities targeted a health care worker, i.e., doctors, nurses, pharmacists, medical laboratory scientists and community health extension workers, patients and parents.

Where SPARCO had identified gaps in training in priority areas, new training courses and curricula were developed in data, healthcare and research.

C. Working Group Procedures

Each consortium country had a SWG which meeting regularly and delivered skills development training activities on weekly/monthly basis at site level. Initially these were limited to face to face but with the COVID pandemic and onset of online meeting platforms, workshops, seminars were held which were open to individuals from other consortium sites and countries. Monthly pan consortium meetings took place to report on progress against planned targets. Biannual reports were given.

Workshops were conducted according to the following standard operating procedure which was filled and submitted to SADACC in order to advertise the workshop to a wider audience at the Consortium website (https://sadacc.org/). The Details of the SOP for Training Workshop can be seen in **Figure 1**. The monthly SWG consortium meetings provided opportunities to share activities from each site with a healthy exchange of ideas and learning from each other.

D. Training Program Development

Based on the gaps identified, resources and expertise available within the consortium and collaborating partners, the following training programs were developed:

FIGURE 2 | The Organizational Structure of the Sickle Pan African Research Consortium (SPARCO).

DATA

Data Collection

Skills in data collection and data management are central to the aim of SPARCO to collect data on SCD patients (**Figure 2**) and so training in data management was prioritized taking advantage of differing skill levels at different sites and amplifying these by virtual delivery and face to face workshops. SPARCO and SADaCC developed and provided training in data collection instruments and management focusing on REDCap, big data analytics, epidemiology and study design to help address the increasing demands for big data analytics and public health skills for pan-African audiences (Nembaware et al., 2020). The curricula were tightly aligned with the SPARCO goal to implement a SCD database for a large multinational African cohort. The training was designed for the African context, taking into account the constraints of poor access to resources, insufficient computer resources and unreliable internet connections even though the training would ideally be highly computer-intensive with strong and reliable internet connections.

Study Design

The Consortium sites had been involved in the care of patients with SCD and had their own data collection instruments with different data elements. One of the first things done was to compare these data collection instrument and develop basic data elements for transfer linked to the Sickle Cell Ontology (SCDO) The research assistants were then trained in the use of uniform case report forms (CRFs) for enrolment of patients into the SPARCO registry and for active follow up of patients enrolled in the registry.

Quality Assurance and Accuracy

Standard operating procedures (SOPs) were developed for use by the Consortium sites. These SOPs covered user name and password management for the electronic registry, user rights and data access groups management, data recording, data receipt, entry and validation, database design, lock, export and archiving, data transfer from sites (depending on the data agreement) patient recruitment and informed consent processes.

Data Collection and Management Training

A data collection and management workshop curriculum were developed and implemented in a competency-based manner (manuscript in development). The curriculum was designed to become incrementally more advanced with the aim of enabling trainees to build data collection instruments, store clinical records or case report forms containing SCD patients' medical and environmental information using the research electronic data capture (REDCap) platform and ensure high quality database and export and import datasets.

Quality Assurance Processes and Data Quality Checks

Data quality and assurance are a major component of the data management pipeline and therefore training was provided in data quality assurance processes and data quality checks to assess accuracy, completeness, consistency, integrity, validity, timeliness and ethical integrity. Data management and quality assurance Standard Operating Procedures (SOPs) were created and sites

TABLE 2 | Selected courses identified in priority area.

Category	Programme and Institution	Content	Country	Target Population
Clinical	1. ASH Consultative Hematology Course American Society of Hematology	This is a practical programme involving commonly encountered clinical problems in which participants engage in case-based presentations and have the opportunity to interact with haematology experts	United States	Clinicians-mainly Physicians
	2. Laboratory Aspects Of Haemoglobinopathy Diagnosis Imperial College, London	Participants learn the practical aspects of haemoglobinopathy diagnosis including microscopy, blood count interpretation, cellulose acetate and agarose gel electrophoresis and high-performance liquid chromatography.	United Kingdom	Physicians, Laboratory Scientists
	3. Haematology in Obstetrics Course British Society for Haematology.	An Interactive and informative programme providing up-to-date insights from experts in the field. The course is suitable for any health care professional interested in this field.	United Kingdom	Consultants or registrars in obstetrics, haematology or obstetric anaesthesia, senior nurses, midwives, scientists, and pharmacists
	4. Module in haemoglobinopathies London Metropolitan University	Course provides an understanding and knowledge of the theory and practice of haemoglobinopathy screening, diagnosis and ethical issues arising, aetiology, Epidemiology, Genetics and Pathophysiology of Haemoglobinopathies (focusing on Thalassaemia (Thal) and Sickle Cell (SC)) Counselling, management, and treatment considerations	United Kingdom	Physicians, scientists, Genetic counsellors etc
	5. Haemoglobinopathies: short counselling course Royal College of Midwives	Short counselling courses for health professionals who care for families affected by sickle cell disease or thalassemia. Particularly valuable for staff caring for people affected by sickle cell disease or thalassemia.	United Kingdom	Nurses, midwives, scientists, Genetic counsellors
	6. Genetic risk assessment and counselling module (Sickle Cell and Thalassaemia Screening) Royal College of Midwives	Course is to: help develop an understanding of the antenatal and newborn sickle cell and thalassaemia screening programme, gain a basic knowledge of sickle cell and thalassaemia and how these conditions are inherited, learn how to interpret screening results and Genetic risk assessment and counselling module	United Kingdom	Nurses, midwives, Health Educators etc.
	7. Blood Science (Distance Learning) MSc London Metropolitan University	Programme focuses on the diagnostic techniques, quality assurance/quality control (QA/QC) and regulatory issues within this field. It offers the advantage of the opportunities for knowledge and career development	United Kingdom	Physicians, Laboratory Scientists, Staff of regulatory bodies in lab sciences
	8. Blood Science – MSc London Metropolitan University	Helps students to develop extensive knowledge in the emerging area of blood science	United Kingdom	Scientists
	9. Advances in Haematology in Africa Muhimbili National Hospital and Muhimbili University of Health and Allied Sciences	Training in clinical haematology especially areas of haemoglobinopathies, sickle cell disease	Tanzania	Physicians
	10. MMed Haematology (10250281) University of Pretoria	4-years Training in clinical haematology especially areas of sickle cell disease, haemophilia.	South Africa	Physicians
	11. Clinical Haematology Unit CMJAH The University of Witwatersrand, Joburg	Clinical Haematology provides a consultative service to patients at the CMJAH and Adult Haemophilia Clinics. Registrars rotate through Clinical Haematology. There is also a formal two-year fellowship programme	South Africa	Physicians
Research	1. Clinical Research Training in Hematology (CRTH) European Hematology Association	Provides early career researchers with a 9-month long unique training and mentoring experience focused on clinical research in	Europe	Scientists, Early career Clinical Researchers, Haematologists

(Continued on following page)

TABLE 2 | (*Continued*) Selected courses identified in priority area.

Category	Programme and Institution	Content	Country	Target Population
		Europe, with a global scope. It offers improved skills and knowledge in clinical science.		
	2. Blood Science MSc (Distance Learning) London Metropolitan University	The course offers extensive knowledge in the emerging area of blood science. Helps to develop high-level reasoning skills and contribute to lifelong learning and continuous professional development (CPD)	United Kingdom	Laboratory scientists
	3. Master of Science (Msc) electronic (e)-Learning course in Haemoglobinopathies University College London	Objective is to teach health care professionals all aspects of SCD and Thalassemia with emphasis on holistic patient care	United Kingdom	Physicians, Scientists
	4. T32 Training Program in Hematology Division of Hematology, John Hopkins University	The Training Program in Hematology provides interdisciplinary laboratory training for postdoctoral fellows preparing for full-time careers in hematology research. The curriculum emphasizes individual research training, incorporates specified courses and seminars, and provides trainees with professional development opportunities.	United States	Physicians, Scientists
	5. Hematology Training Program Boston University Medical Center	"Research Training Program in Blood Diseases and Resources," T32HL07501. This is an interdepartmental training programme designed to train predoctoral PhD degree candidates and postdoctoral MDs, PhDs, and MD, PhDs in hematology related research	United States	Physicians, Scientists, Haematologists
	6. Advanced Postgraduate Diploma Course in Clinical Research and Data Management James Lind Institute, Switzerland	This programme is designed to provide overview of clinical trials, clinical research management, clinical trial monitoring and data management	Switzerland	Junior Clinical researchers, Research Assistants, Data managers
Clinical and Research	1. ASH Visitors Training Program American Society of Hematology	Designed to help build hematology capacity in low- and middle-income countries by providing funding for hematologists and hematology-related health care professionals in these regions to receive up to 12 weeks of training on a specific topic or technique. Training is designed to address a specific hematology need and is carried out in the clinic or laboratory of an ASH member, under his/her supervision and mentorship	United States	Haematologists and haematology-related healthcare professionals
	2. Haematology Short Course University of West Australia, School of Pathology and Laboratory Medicine,	Short course for participants with advanced qualifications and it is designed to upskill or reskill in the field	Australia	Haematologists,
	3. ESH-ENERCA Training Course on Haemoglobin Disorders: Laboratory Diagnosis and Clinical Management European School of Haematology	Course is to promote and facilitate access to state-of-the-art and cutting-edge knowledge in haematology and related disciplines. Course exposes participants to the current state-of-the-art science and insight into new developments in the fields of basic, clinical, and therapeutic research in Haematology	Europe	Physicians, Scientists, Pharmacists,
	4. Renzo Galanello Fellowship Programme 2018 Thalassaemia International Federation (TIF)	Training in haemoglobinopathies and to become a trainer of others.	United Kingdom	Paediatricians or Internal Medicine physicians already working with patients with Thalassaemia or Sickle Cell Disease
	5. Hematology and Oncology Fellowship Program Boston University Medical Center and the Boston VA Health Care System	An extensive programme of patient care, education, and research in various clinical and basic science research projects.	United States	Clinicians,
	6. Hematology Training Program at Herbert Irving Comprehensive Cancer Center Herbert Irving Comprehensive Cancer Center, Columbia University Medical Centre	Offers training to become genetic counselor with compassion, a sense of self, and the skills to be a leader in genetic and genomic health care.Curriculum combines basic	United States	Physicians, Nurses, Geneticists, others.

(Continued on following page)

TABLE 2 | (*Continued*) Selected courses identified in priority area.

Category	Programme and Institution	Content	Country	Target Population
		science and clinical medicine with humanism and professionalism Clinical research in many fields		
	7. Haematology and Transfusion Science MSc Manchester Metropolitan University	Course enables development of an advanced theoretical understanding and the practical techniques needed to apply in research or clinical context.	United Kingdom	Clinicians, Scientists
	8. Haematology University of Nottingham	Course trains individuals in peripheral blood stem cells for matched and unrelated donor transplantation	United Kingdom	Clinicians, Scientists
	9. Biomedical Blood Science MSc, Postgraduate Diploma, Postgraduate Certificate University of Keele	Course offers postgraduate training in Biomedical Blood Science in combination with generic higher level scientific training in areas such as writing grant proposals and business plans. The programme builds on existing, undergraduate knowledge in basic science and applying it to clinical, diagnostic and research applications relevant to Clinical Biochemistry, Medical Immunology, Haematology and Transfusion Science	United Kingdom	Clinicians, Scientists
	10. Transfusion, Transplantation and Tissue Banking MSc University of Edinburgh	The course is expected to achieve background academic knowledge and an understanding and the application of this in many fields such as: donation of blood, organs, and tissues; components, reagents, and products - principles and processes; clinical transfusion practice; clinical laboratory practice (as it relates to transfusion, transplantation and tissue banking); transfusion microbiology	United Kingdom	Clinicians, Scientists
	11. Biomedical Sciences (Haematology) MSc University of Wolverhampton	Course focuses on recent advances in genetics and immunology, which equips individuals with skills necessary to complement clinical laboratory responsibilities	United Kingdom	Scientists
	12. Biomedical Sciences (Haematology) MSc University of Westminster, London	This course focuses on the physiology and pathology of blood and its use as a diagnostic and therapeutic tool. Involves a variety of areas of molecular and cellular bioscience with an emphasis on new technologies and developments in Haematology and related disciplines.	United Kingdom	Clinicians, Scientists, Pharmacists
	13. Blood Sciences MSc (PGCert PGDip) University of Brighton	A 2-year part-time course leading to MSc in blood sciences	United Kingdom	Physicians, Scientists
	14. Haematology MSc University of Chester	The course is designed to enable you to develop an up-to-date, advanced understanding of the disorders of blood in Research and Clinical Medicine cores	United Kingdom	Physicians, Scientists

were trained on how to implement these SOPs to improve data quality across the three sites.

Training in Big Data Analytics SCD and Epidemiology Study Design

The main goal of the Big Data analytics course was to create a cohort of individuals, Big Data Analytics Fellows, with the skills to analyse big data sets such as those being generated at SPARCO sites: specifically, data cleaning, analysis, and study design, from a Big Data perspective, using the SPARCO database. The training covered fundamental concepts of probability, statistics and programming in R, which includes sampling and estimation theory, logic of inferential statistics, testing hypothesis, statistical power calculation and sample size estimation. To build generic research skills and provide fellows with the skills to interrogate the literature and identify gaps in the knowledge base, training on systematic reviews was provided, the systematic reviews resulting from this exercise will be the foundation of crossconsortia studies led by these young investigators.

TABLE 3 | Numbers of participants in priority training areas by SPARCO sites.

Skill area	Broad Competence Outcomes	Ghana	Nigeria	Tanzania	Total
Data management	Data Quality Assurance REDCap & integration with other data tools Big data analysis	80	73	124	277
Health - Management of SCD	Multi-level care for SCD Primary level Secondary level Tertiary level ₀Indices and indicators for SCD referrals SCD diagnosis (POCT, HPLC, IEF)	537	569	212	1318
Research skills	Grant proposal Scientific writing	36	58	6	100
SPARCO Fellowships	Research proposal development on SPARCO priority areas under mentorship	9	8	12	29

HEALTH

SCD Management

Advances in Haematology in Africa was a 4-day workshop held in Tanzania in August 2018 designed to build skills and knowledge in haematology, specifically focussing on the African context. The course included a day devoted to SCD and was attended by members of SPARCO Hub and site teams. The trainers were experts in haematology from Africa and outside Africa with funding, including bursaries to assist attendance, provided by the Fondazione Internazionale Menarini, Italy. Additionally, the Standards of Care (SoC) Working Group, another working group of SPARCO developed Standards of Care Guidelines for the clinical management of SCD patients. These guidelines are also being used for training of health care workers in the multidisciplinary management of SCD at all levels of health care including home care management.

Health Education

SPARCO recognizes health education as one of the key components for the execution, implementation, and success of its agenda in the three key areas: establishing a patient registry, generating locally appropriate standards of care and research. To help achieve these, sites have to provide health education in SCD engaging with key stakeholders and communities using all available existing structures and platforms.

RESEARCH

Target

The target of SPARCO's research training were not only physicians in laboratory medicine internal medicine, community medicine but also basic medical scientists, pharmacists, nurses, medical laboratory scientists, laboratory technicians, medical records officers and community health extension officers.

Core Intercalating SCD Training in Existing Programmes

During the term of the project, SPARCO sought to build skills by building on utilising existing training or developing training programmes where gaps in provision were identified. As proposed, SPARCO made use of local strengths and resources available across the different regions by keying into existing programmes such as the Fellowship of the West African College of Physicians (WACP) and College of Pathology for East Central and Southern Africa (COPECSA) and the African Society of Laboratory Medicine (ASLM) in partnership with the American Society of Hematology, (2021), Royal College of Pathologists and Physicians in London and the European Hematology Association (EHA) as well as collaboration with the Medical Education Partnership Initiative (MEPI), and Human, Heredity and Health in Africa (H3Africa). It was envisioned that the incorporation of sub-specialization in SCD in disciplines such as haematology and paediatrics the WACP and COPECSA will lead to the creation of SCD units/centres in hospitals to be overseen by specialists trained by these programs thereby enhancing skilled manpower within these settings. A second platform for long term skill development is postgraduate academic programs in the tertiary institutions within the network. The consortium is working to infuse advanced training in SCD into these existing programs such as Masters level degrees in haematology and clinical research.

Consequently, a Masters (MSc) in Clinical Research 2-year programme, was developed at the University of Abuja, Nigeria site. It is targeted at physicians in laboratory medicine, internal medicine, general practice and other specialties to enable them undertake research geared towards solving health care problems. Core courses include biostatistics, epidemiology, fundamentals of clinical trials, scientific communication, with options modules to allow for specialisation including haemoglobinopathies, diagnostic pathology and transfusion medicine. It is planned to offer the course online to make it available across the continent, including other SPARCO sites.

Training Modalities

The training modalities employed have been Train -the -Trainer through data management training workshops by SADACC at the University of Cape Town, face to face training through lectures, seminars, workshops. These were supplemented by use of e-learning platforms for genetic counseling, ethics in health research and webinars as a result of the corona virus disease pandemic.

Long Term Skills Development Plan

The SPARCO Fellowship programme was initiated in the fourth year. Early-career scientists were invited by the sites to apply for funds to undertake research in SCD tailored towards SPARCO priority areas with mentored guidance from site members. They were guided in this process by the use of the project concept documents earlier developed by the consortium. The Fellowship project is a mentored research training in research, scientific communication and publication.

Aside physicians, the need to train other cadres of healthcare workers such as nurses, laboratory scientists, community health extension workers (CHEWs), etc. is also part of the long-term skill development plan. The training of the latter will ensure effective NBS biosampling, SCD diagnosis and basic care for SCD patients especially at the primary healthcare level. It is generally accepted that at this level of care, patients are initiated to the concept of active participation in their care. Whereas self-management driven by the concept of behavioural adaptation (BA) has been pushed for adolescents and young adults with SCD, as drivers for overall efficacy in management, there is a need to inculcate these BA skills appropriately for optimal care delivery.

Another important factor for training targeted staff at this level of healthcare delivery, is to create effective coordination and liaison between the patient and the SCD specialists, commonly restricted to tertiary level practice, for management beyond these levels of primary care.

Participation in Independently Funded Training Programmes

A key component of the SPARCO approach has been leveraging on existing training programmes in African Universities and professional training programmes within the African continent as a sustainable method of providing training past the end of the SPARCO funding. One of the primary activities of the SWG is to facilitate the participation of SPARCO staff in independently funded training programs. During the last year of the project, some SPARCO members participated in the ARISE project training workshops as faculty.

RESULTS AND DISCUSSION

Overall Achievements

Patient Registry

By the end of March 2021 (end of the research), the consortium had registered in the database at the three sites a total of 13,170 SCD patients (Tanzania 3,594; 90% of target of 4000., Nigeria 6,453, 107.6% of target of 6000 and Ghana 3,146, 104.9% of target of 3000). This clearly shows that the target for the aim of the registration was fully achieved and exceeded within the time frame for the project.

Data Management

In the first 3 years of SPARCO 277 people across all sites in the consortium participated, including data clerks, data coordinators, doctors, laboratory scientists, researchers and postgraduate students received data management and analysis training.

Training in Big Data Analytics SCD and Epidemiology Study Design

With 20 registered candidates and 10 invited trainers, representing a ratio of approximately 2:1 trainee-trainer, training was provided in person, virtually and in a blended format through workshops, site visits, mentorship, monthly meetings and during annual face to face consortium meetings.

Identification of Priority Training Areas (Needs Assessment) and Review of Existing Training Programs

During the period 2017–2018, the SWG reviewed existing training programmes to identify relevant programmes and significant gaps in training opportunities in SPARCO priority areas (**Table 1**). SWG identified and reviewed 41 existing training programmes around the world and 31 were found to be relevant and aligned to the consortium priority areas: data management, management of SCD, health education and research on SCD (**Table 2**). Gaps were noted in existing programmes in areas related to laboratory diagnosis, NBS, genetic counselling and research. Twenty-eight (i.e, 90.3%) of training programmes/courses identified were located outside of Africa. Areas where gaps were identified, were noted in the development of short, medium- and long-term courses related to SPARCO priority areas. During the project, the SWG undertook continual needs assessment taking into consideration the developments in the project environment and implemented skills development activities, created training materials and identified courses based on these new needs. For instance, in 2018, when the SCD clinical phenotypes from 3,622 patients in the SPARCO Nigeria registry were analysed, it was noticed that hydroxyurea utilisation was 9.4% while blood transfusion rate was 67.5%, showing a gap in the use of hydroxyurea. These results prompted the development of webinars that focused on hydroxyurea (Isa et al., 2020). Similarly, another Webinar on gene editing was carried out as interest in gene edited arose as a result of clinical trials on gene editing.

Training Evaluation and Outcomes

Course evaluation was mapped to specific learning outcomes, including processing epidemiological data from multi-site observational studies (from cleaning or performing data quality checks to analysing large diverse data sets), drafting a proposal for ethics clearance for a multi-site retrospective study or systematic reviews on designing a multi-site epidemiological study. To assess how well trainees assimilated and understood the online training content, they were tested on their understanding of Linux commands, databasing, statistics and probability, Python and R programming languages, emphasizing on Python SciPy and R tidyverse libraries: the average mark was above 80%. Trainees presented their systematic review at the fourth SCD Ontology (SCDO) workshop in November 2019 (Nembaware et al., 2020). Assessment of quality of training was conducted in a form of a survey using course evaluation forms to capture feedback from trainees. Feedback showed that most of the fellows recommended ongoing training, and highlighted the difficulties with internet connections during

the online training. One of the best outcomes was seeing trainees (one at each site) becoming trainers in data management and analysis at their respective sites during the 2019 site visits and working together in the first publication by a big data fellow (Chianumba et al., 2022).

Health and SCD Management

Up to 34 Courses were attended or offered by the SPARCO consortium related to the management of SCD involving 1,318 participants in the first 3 years of SPARCO (**Table 3**). The courses included, clinical management of SCD, genetic counselling, NBS for SCD, hydroxyurea prescription and use in SCD, infections in SCD, drug addiction and psychosocial issues in SCD, health education for health care providers (HCP), genomic medicine and SCD analgesics and adherence to medications. Courses for diagnosis of SCD included: use of laboratory diagnostic platform for SCD including High-Performance Liquid Chromatography (HPLC), Isoelectric Focusing (IEF) and Hemoglobin Electrophoresis (HbE), and Transcranial Doppler (TCD) ultrasonography. Attendance at these courses improved the ability of qualified HCP to offer quality care to patients with SCD in the three sites. Additionally, the Standards of Care Working group (SoC), Standards of Care Guidelines for the clinical management of SCD patients across the various levels of Health care institutions augmented the knowledge and skills of the HCPs in the management of patients at the sites.

Health Education

Sites have engaged with key stakeholders and communities to provide health education designed to build knowledge of SCD, the target audiences being patients and their families, healthcare workers, academic and research communities as well as the general population. The 19th June, World Sickle Cell Day, which has been used to commemorate SCD and increase awareness about the disease, is a key part of this approach with events in health facilities and community as well as interviews in the media. SPARCO, recognizing the key role played by community organisations in mobilizing patients to participate in research and engage with healthcare organisations to receive preventative treatment, has identified a skills gap in these organizations and has worked with patients and patient communities to facilitate participation in site activities and provide training and support in project management and developing grant applications. This has been done utilizing both in-person and online approaches.

Health Education on Nutrition in Pregnancy and SCD

With increasing survival rates in SCD patients, supporting pregnant mothers with SCD is becoming more important. A short course on Health Education on Nutrition in Pregnancy and SCD was developed and offered to nurses and midwives working at SCD clinics, antenatal and reproduction and child health clinics in Dar-es-Salaam, Tanzania.

Research

Research skills development was mainly through participation in independently funded training courses and SPARCO fellowships (12 Tanzania, nine Ghana, eight Nigeria) SPARCO Fellowships have been awarded to date. The Novartis Next Generation Scientist provided research training opportunities to five (5) SPARCO members at all three sites.

There have been 50 publications from the various research works that have been carried out across the three sites (List of publications available upon request). There are other manuscripts in preparation for publication.

Lessons Learned

The SPARCO sites and SADACC are embedded in academic institutions with SPARCO personnel holding academic positions and being integrated in academic departments. SPARCO personnel have increased their competencies and skills in health, research and data management and will make a positive impact on the quality of teaching, supervision and mentoring of students at undergraduate and postgraduate levels at the three SPARCO academic institutions.

SPARCO was successful in skills development in SPARCO priority areas of data management, management of SCD and research skills. In data management, a different approach to training was required as it was not always practical or feasible to conduct residential or in-person training across the consortium., Online training methods using prerecorded videos stored in Google for download and self-study, Vula (a learning management system which allowed people to leave questions online when they had internet) were suitable for participants even with limited quality internet which was suitable for participants even with limited quality internet. Within the healthcare sector, three key lessons were learned when delivering skill development activities in SCD management. First, health care workers rotated frequently which meant that there was a need to offer training on a regular basis to new clinical staff. Second, it was not practical to conduct training away from health facilities as the staff were required to provide health services. Third, although health education material can be developed and shared at the consortium level, it needed to be adapted to local situations such as the use of malaria prophylaxis which was not uniformly practiced in some countries. In research, training was best integrated into research projects, allowing skills to be acquired and applied in the context of a project rather than in theory. As well as developing skills in priority areas through participating in SPARCO, the SPARCO team developed skills in non-technical areas such as project management and curricula development, however, specific development of competencies in curriculum development and accreditation and project management would have helped delivery of SPARCO skills development activities.

CONCLUSION AND FUTURE PLANS

Going forward, SPARCO plans to strengthen skills in SCD by engaging with existing training programs in institutions at national, regional and global levels. With the availability of digital education tools and lessons learned in online

activities in the wake of the COVID-19 pandemic, SPARCO skills development activities have the potential to draw upon the large pool of expertise from participating consortium and collaborating institutions and other independently funded training programs. This strategy of working with existing training programs to develop and utilise resources that will greatly contribute to raising the skilled workforce required for the management of SCD in all levels of health in SSA countries and to support, basic, clinical and translational research in SCD and is designed to enhance the sustainability of skills development in SCD beyond the end of the SPARCO.

Skills development will focus on the priority areas of data management, management of SCD and research methodology and be aligned to the specific aims of governance, operations, management, SCD Registry and database, Integration of SCD Standards of care and clinical skills, cohort and implementation research skills and engagement with partners. Skills development activities will be delivered to researchers, health care workers, data and registry personnel, faculty in collaborative institutions and hospitals, patients/community, as well as key stakeholders and decision-makers to enhance sustainability. We will respond to emerging skill requirements by identifying or developing training courses. We will collate training courses available at all SPARCO sites, so as to avoid duplication of effort. More effort will be made to have cross consortia skills development activities in order to maximally utilise expertise at local sites for the benefit of all.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

ON conceived the idea and wrote the first draft. AO-A, VN, JK, MN, IM, GM, JM, and AW contributed sections and critically reviewed the manuscript. All the authors approved the submission.

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Barriers to hydroxyurea use from the perspectives of providers, individuals with sickle cell disease, and families: Report from a U.S. regional collaborative

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Sickle cell disease (SCD) is an inherited blood disorder that affects about 100,000 people in the U.S., primarily Blacks/African-Americans. A multitude of complications negatively impacts quality of life. Hydroxyurea has been FDA approved since 1998 as a disease-modifying therapy for SCD, but is underutilized. Negative and uninformed perceptions of hydroxyurea and barriers to its use hinder adherence and promotion of the medication. As the largest real-world study to date that assessed hydroxyurea use for children and adults with SCD, we gathered and analyzed perspectives of providers, individuals with SCD, and families. Participants provided information about socio-demographics, hospital and emergency admissions for pain, number of severe pain episodes interfering with daily activities, medication adherence, and barriers to hydroxyurea. Providers reported on indications for hydroxyurea, reasons not prescribed, and current laboratory values. We found that hydroxyurea use was reported in over half of eligible patients from this large geographic region in the U.S., representing a range of sickle cell specialty clinical settings and practices. Provider and patient/caregiver reports about hydroxyurea use were consistent with one another; adults 26 years and older were least likely to be on hydroxyurea; and the likelihood of being on hydroxyurea decreased with one or more barriers. Using the intentional and unintentional medication nonadherence framework, we found that, even for patients on hydroxyurea, challenges to

taking the medicine at the right time and forgetting were crucial unintentional barriers to adherence. Intentional barriers such as worry about side effects and "tried and it did not work" were important barriers for young adults and adults. For providers, diagnoses other than HgbSS or HgbS-β0 thalassemia were associated with lower odds of prescribing, consistent with evidence-based guidelines. Our results support strengthening provider understanding and confidence in implementing existing SCD guidelines, and the importance of shared decision making. Our findings can assist providers in understanding choices and decisions of families; guide individualized clinical discussions regarding hydroxyurea therapy; and help with developing tailored interventions to address barriers. Addressing barriers to hydroxyurea use can inform strategies to minimize similar barriers in the use of emerging and combination therapies for SCD.

KEYWORDS

sickle cell disease, barriers to adherence, disease modifying therapies, models -adherence, hydroxyurea

Introduction

Sickle cell disease (SCD) is an inherited blood disorder that affects the hemoglobin of red blood cells (Piel et al., 2017). Sickle cell genotypes include HgbSS, HgbSβ^0 or Sβ^+thalassemia, and HgbSC, with varying levels of disease severity (Ballas et al., 2012). In the U.S., about 100,000 people have SCD, with about 1 in every 365 African-American infants born with the disease (Centers for Disease Control and Prenvention, 2020). The sickling of red blood cells secondary to HgbS polymerization leads to a variety of pathophysiological consequences such as inflammation, oxidative stress, hemolytic anemia, hypoxia, and hypercoagulability (Chakravorty and Williams, 2015; Piel et al., 2017) which can result in vaso-occlusion and ischemia. Clinically, SCD can cause severe pain associated with vaso-occlusive episodes (VOE), splenic sequestration, acute chest syndrome (ACS), bacterial sepsis, ischemic strokes and silent cerebral infarcts (Chakravorty and Williams, 2015; Piel et al., 2017).

Recurrent and repetitive VOEs may lead to frequent healthcare visits or interference with daily functioning, even in the absence of healthcare utilization, that negatively affect the quality of life for children and adults with SCD [National Heart, Lung and Blood Institute, National Institutes of Health (NHLBI, NIH), 2014; Jerrell et al., 2011; Tanabe et al., 2012]. Long-term management of SCD requires chronic medical care with access to education about prevention as well as current and future disease modifying and curative therapies (Wang et al., 2011; Alvarez et al., 2013; Yates et al., 2013; DeBaun et al., 2014; Lebensburger et al., 2015; McGann and Ware, 2015; Fitzhugh et al., 2017; Niihara et al., 2018; Quinn, 2018; Krishnamurti et al., 2019). In addition to hydroxyurea, other recently FDA approved therapies include voxelotor, L-glutamine, and crizanlizumab (Ataga et al., 2017; Howard et al., 2019; Vichinsky et al., 2019). Other disease modifying therapies in clinical trials include fetal hemoglobin inducers (Molokie et al., 2017), anti-inflammatory agents (Field et al., 2017a, 2017b; Hoppe et al., 2017; Daak et al., 2018), anti-platelet agents (Hsu et al., 2018), pyruvate kinase activators, heme binders, and anti-adhesion agents (Ataga et al., 2017).

Although the recently approved and investigational therapies hold the promise of better outcomes for people living with SCD, hydroxyurea has been FDA approved since 1998 as a disease-modifying therapy for SCD (Ault, 1998) but is underutilized. The U.S. National Heart, Lung and Blood Institute (NHLBI) guidelines recommend that all individuals with HgbSS or HgbSβ^0 thalassemia be offered hydroxyurea, beginning at the age of 9 months (National Heart, Lung and Blood Institute, National Institutes of Health, 2014). Further, eligibility criteria for hydroxyurea use in adults and children include: the experience of three or more sickle cell-related moderate to severe pain episodes in a 12-month period; pain that interferes with daily activities and quality of life; history of severe and/or recurrent acute chest syndrome (ACS); or severe anemia regardless of the genotype (National Heart, Lung and Blood Institute, National Institutes of Health, 2014). Multiple studies worldwide have demonstrated the benefits of hydroxyurea for the management of SCD (Wang et al., 2011; Lobo et al., 2013; Luchtman-Jones et al., 2016; Rigano et al., 2018; Tshilolo et al., 2019), including its safety for long-term use (Steinberg et al., 2010). However, perceptions of hydroxyurea and barriers continue to hinder full adherence and promotion of the medication for individuals with SCD. These barriers include: providers' lack of knowledge about hydroxyurea and its indications, manufacturers' lack of liquid formulations being widely available for children, refill procedures for different pharmacies, and medication costs. Patient/family barriers include: aversion to taking medications, lack of education about hydroxyurea, doubt about its effectiveness, forgetfulness, cost, getting refills on time, and concerns about potential and experienced side effects (Haywood et al., 2011; Badawy et al., 2017; Sinha et al., 2018; Hodges et al., 2020). Because of its origin as a chemotherapy agent (Kennedy, 1972), some have concerns that hydroxyurea use can lead to increased risk of cancers and impact fertility and the fetus of a pregnant woman (Björkholm et al., 2011; Algiraigri and Radwi, 2014; Castro et al., 2014).

Understanding barriers to hydroxyurea use, given its role as a cornerstone for disease modification, will be helpful as newer therapies begin to be utilized. Previous studies have often used small samples or limited age ranges, or were conducted at a single site (Haywood et al., 2011; Badawy et al., 2017; Sinha et al., 2018). A notable exception is a recent study from the NHLBI Sickle Cell Disease Implementation Consortium (SCDIC) that used qualitative data to examine intentional and unintentional hydroxyurea nonadherence as a framework to understand hydroxyurea use (Hodges et al., 2020). Participants (n = 90 adults) came from five sites across the U.S. and completed semi-structured interviews about barriers to hydroxyurea adherence. For over half of the participants (n = 52, 57.8%) who were currently taking hydroxyurea, nonadherence was most commonly unintentional (70%, i.e., forgetting, competing life demands) versus intentional (30%, i.e., concerns about adverse effects, aversion to taking medications in general). For those who had never taken hydroxyurea (n = 12, 13%), participants reported that they were never offered the medication by their providers.

The goal of this study was to describe factors associated with hydroxyurea use from the perspectives of providers, individuals with SCD, and families. Gaps intended to be filled by this analysis include: 1) improving understanding of barriers to hydroxyurea in order to ensure optimal use of newer disease modifying therapies as they come available and may be used alone or in combination with hydroxyurea; 2) utilization of a framework to understand barriers to adherence, to potentially improve educational efforts and tailor interventions to promote adherence; 3) complement data from clinical trials with hydroxyurea with real-world evidence. We describe clinical characteristics, healthcare utilization, barriers to hydroxyurea use and adherence from the perspectives of 412 pediatric and adult patients with SCD. Providers reported on their prescribing patterns and laboratory values in relation to hydroxyurea for eligible patients. Our aims were to first, delineate factors contributing to hydroxyurea utilization for a larger sample size and broader age range in a single study than previously undertaken. Second, our aim was to gain in-depth insights about barriers to hydroxyurea within the framework of intentional and unintentional nonadherence. We established a shared strategy for data capture in routine clinical settings to allow for the assessment of factors associated with hydroxyurea use within a range of clinical practices and settings situated in the diverse geography of seven western states in the U.S.

Materials and methods

Participant recruitment and setting

Parents/caregivers (referred to as caregivers hereafter) of children with SCD younger than 18 years and adults with SCD 18 years and older were recruited from nine clinical sites across seven western U.S. states comprising the Pacific Sickle Cell Regional Collaborative (PSCRC, pacificscd.org). The PSCRC is funded by the U.S. Health Resources and Services Administration (HRSA) and uses a regional model to improve access to care for individuals with SCD. At the time of data collection in 2015–2017, the PSCRC sites included three in California—University of California San Francisco (UCSF) Benioff Children's Hospital Oakland (BCH-Oakland), University of California Davis, and the Center for Inherited Blood Disorders (coordinating center). The six other PSCRC sites were Providence Hospital in Anchorage, Alaska; the University of Arizona Cancer Center in Tucson; St. Luke's Health System in Boise, Idaho; Children's Specialty Center Nevada in Las Vegas; Oregon Health and Sciences University in Portland; and Seattle Children's Hospital/Odessa Brown Children's Clinic in Washington.

Eligible patients were either mailed a brochure describing the "PSCRC Minimum Dataset" or their healthcare providers described the project at a regular clinic visit. Individuals were eligible for the study if they 1) had a confirmed SCD diagnosis, 2) were followed at one of the nine PSCRC sites, and 3) were eligible for hydroxyurea therapy according to the NHLBI guidelines (National Heart, Lung and Blood Institute, National Institutes of Health, 2014).

Ethical considerations

Approvals were obtained from BCH-Oakland institutional review board (IRB) and from Western IRB (now WCG IRB, https://www.wcgirb.com) prior to study startup. The remaining clinical sites relied on Western IRB. Once introduced to the study, participants reviewed the study and procedures with trained study staff in a private area of the clinic. Participants were allowed to ask questions and had the opportunity to discuss the study with family or others before providing their written informed consent.

Study design and data collection

A convenience sample of caregivers of children with SCD and adults with SCD completed a 15–20-min survey with 17 questions at study enrollment for this cross-sectional descriptive study. Data were collected by research staff using an iPad on the hospital network, a clinic desktop, or a paper-based form, and were entered into a secure REDCap database housed at UCSF.

Questions came primarily from the consensus measure of Phenotypes and eXposures (PhenX) Toolkit - Sickle Cell Disease Core (Eckman et al., 2017), supplemented with additional data elements. Participants provided information about socio-demographics, including age, gender, race/ethnicity, annual

household income, household density, head of household education, and health insurance. Participants indicated SCD diagnosis, the number of hospital admissions and emergency department (ED) visits for pain (0, 1, 2, 3, or 4 or more) and number of severe pain episodes that interfered significantly with daily activities (less than 4, or 4 or more) in the previous 12 months. For patients prescribed hydroxyurea, caregivers or adults reported current dose and number of days adherent in the past 2 days (0, 1, or 2) (Stirratt et al., 2015). Both those "on" and "not on" hydroxyurea completed a checklist of 12 potential barriers to hydroxyurea use (i.e., forgetting, worry about side effects, heard "scary" things, frequency of monitoring). Providers reported on current dose of hydroxyurea, indications for its prescription, and current laboratory values (i.e., white blood count, total hemoglobin, and hemoglobin F%). Providers specified indications for hydroxyurea prescription from a checklist (recurrent pain, ACS, neurologic, empiric, or other) or for those not on hydroxyurea, the reasons not prescribed (i.e., not indicated, patient/family preference, had to be discontinued).

Statistical analysis

Descriptive statistics (frequencies, percent, means, standard deviations) were used to characterize demographics, clinical characteristics and patient/caregiver reports of barriers to hydroxyurea, pain interference and healthcare utilization, as well as provider reports of laboratory values, indications for hydroxyurea or reasons not prescribed. Categorical variables were analyzed using chi-square, or Fisher's exact test for sparse tables. Continuous variables were compared using *t*-test or Mann-Whitney *U* test, as appropriate. Barriers to hydroxyurea were further categorized as those outside of the individual's/family's control that might lend to "unintentional nonadherence" (i.e., doctor does not recommend; too many other priorities; don't know enough about hydroxyurea; challenges with taking medicines on time; forgetting) and barriers that might contribute to "intentional nonadherence" [i.e., not interested in hydroxyurea; worry about side effects; dislike of additional blood tests and/or clinic visits; prefer not to think about SCD when feeling well; "I tried it and it did not work;" and "heard scary things about (hydroxyurea)"] (Hodges et al., 2020).

Univariate analysis was used to evaluate potentially significant variables ($p = 0.10$) that were independently associated with the dependent variables, for inclusion in multivariable models. Separate multivariable logistic regression models were run for the variables of provider reported prescription of hydroxyurea (yes/no) and patient/caregiver report of "currently on hydroxyurea" (yes/no). Variable selection for the final models used stepwise variable selection, with age and gender identity kept in the models as potential confounders. Significance levels were set at $p = 0.01$, to account for multiple testing. If more than 25% of data for a particular measure (i.e., lab values) were missing, the participant was dropped from the analysis. All data analyses were conducted in SAS Version 9.4 (SAS Institute Inc., Cary, NC, United States).

TABLE 1 Participant socio-demographics ($N = 412$)[a].

Category	n (%)
Age	
Children (≤12 years)	178 (43.2)
Mean ± SD	6.7 ± 3.4
Adolescents (13–17 years)	66 (16.0)
Mean ± SD	15.0 ± 1.4
Young Adults (18–25 years)	54 (13.1)
Mean ± SD	21.1 ± 2.4
Adults (≥26 years)	114 (27.7)
Mean ± SD	38.7 ± 10.6
Gender Identity	
Female	212 (51.5)
Male	200 (48.5)
Race/Ethnicity	
Black/African American race	385 (93.4)
Other race	27 (6.8)
Hispanic/LatinX ethnicity	35 (8.5)
Annual household income	
<$30,000	181 (43.9)
$30,000–$59,999	63 (15.3)
≥$60,000	61 (14.8)
Unknown	107 (25.9)
Highest education completed by head of household	
<High school graduate	141 (34.2)
≥High school graduate	254 (61.6)
Unknown	17 (4.1)
Health insurance[b]	
Public	281 (68.2)
Private	111 (26.9)
Other government-sponsored	94 (22.8)
Other/Unknown	9 (2.2)
State[c]	
California ($n = 3$ sites)	283 (68.6)
Other PSCRC sites ($n = 6$ sites)	129 (31.3)

[a]Responses were reported by adults with SCD, or caregivers of children with SCD., Some responses (i.e., race/ethnicity and health insurance) are >100% due to multiple responses by adults with SCD, or caregivers of children with SCD.
[b]Public health insurance includes Medicare and Medicaid/Medi-Cal. Other Government-sponsored health insurance includes State Children's Health Insurance Program (SCHIP), Military Health Care (Tricare/VA/CHAMP-VA), and state-sponsored health plan. Other health insurance includes Indian Health Service.
[c]Sites in California included University of California San Francisco Benioff Children's Hospital Oakland; University of California Davis, and Center for Inherited Blood Disorders. Sites in other states included Children's Specialty Center of Nevada; University of Arizona Cancer Center (Tucson); Oregon Health and Sciences University; Seattle Children's Hospital/Odessa Brown Children's Clinic (Washington); St. Luke's Health System (Idaho); and Providence Hospital Anchorage, Alaska.

TABLE 2 Clinical characteristics, barriers to care and health behaviors (N = 412)[a].

Characteristic	n (%)
Sickle cell disease diagnosis	
HgbSS or HgbSβ^0 Thal	331 (80.3)
HgbSC	57 (13.8)
Other	24 (5.8)
Hospital admissions for pain, previous 12 months	
0	171 (41.5)
1 - 3	67 (16.3)
4 or more	171 (41.5)
Emergency Department visits for pain, previous 12 months	
0	152 (36.9)
1 - 3	58 ((13.6)
4 or more	201 (48.8)
Severe pain episodes, interfering with daily activities, previous 12 months	
Less than 4	248 (60.2)
4 or more	158 (38.3)
Hydroxyurea use	
Yes	232 (56.3)
No	162 (39.3)
Hydroxyurea adherence	
Not adherent (0/2 days)	23 (9.9)
Partially adherent (1/2 days)	15 (6.4)
Adherent (2/2 days)	187 (80.6)
Barriers to Hydroxyurea Contributing to Unintentional Nonadherence[b]	
No barriers	257 (62.4)
1 barrier	139 (33.7)
2 or more barriers	16 (3.9)
Barriers to Hydroxyurea contributing to Intentional Nonadherence[c]	
No barriers	302 (73.3)
1 barrier	77 (18.7)
2 or more barriers	33 (8.0)
Total Barriers to Hydroxyurea	
No barriers	157 (38.1)
1 barrier	179 (43.4)
2 or more barriers	76 (18.4)

[a]From patient/caregiver reports.
[b]Barriers to Care contributing to Unintentional Nonadherence included: doctor does not recommend it; competing priorities; don't know enough about hydroxyurea; hard to take the medicine at the right time; forgetting.
[c]Barriers to Care contributing to Intentional Nonadherence included: not interested in another medicine; worry about side effects; don't like frequent blood tests and/or clinic visits; don't like to think about sickle cell disease when feeling well; tried and did not work; heard scary things about hydroxyurea.

Results

A total of 412 participants with SCD were enrolled, with a median age of 15 (range 0.75–69 years). Participants were categorized as children 12 years and younger (the predominant age group at 43.2%); adolescents 13–17 years; young adults 18–25 years; and adults 26 years and older (Table 1). Over half (51.5%) identified as female and the majority (90%) identified as Black/African American race, not Hispanic/LatinX ethnicity (91.5%). Almost 44% of participants reported an annual household income of less than $30,000 with an average household density of 3.8 ± 1.9 people per household. The most common educational attainment of the head of household was high school diploma and higher (61.6%). Similar to other SCD populations, 68.2% of patients were publicly insured. The majority were followed at the three California sites (68.7%), while the remainder were followed at the other PSCRC sites in six states.

Patient/caregiver reports: Clinical characteristics, healthcare utilization, barriers to hydroxyurea and adherence

The majority (80.3%) of patients were diagnosed with sickle cell anemia (SCD genotypes SS or HgbSβ^0 thalassemia) per patient/caregiver report (Table 2). While 41.5% reported no hospital admissions in the previous 12 months, an equal percentage (41.5%) reported 4 or more admissions in the previous 12 months. Almost half of the sample (n = 48.8%) reported 4 or more ED visits in the past 12 months and the majority (60.2%) reported fewer than 4 visits for pain managed at home but that interfered with daily functioning in the previous 12 months. Adults (26 years and older) had the highest proportion of 4 or more ED visits for pain (37.5%, p = 0.001) and pain episodes interfering at home (57% reporting 4 or more such episodes in the past year (p < .0001)) while adolescents (13–17 years) had the highest proportion of 4 or more hospitalizations for pain in the past year (28.8%, p = 0.003).

Out of the 412 eligible participants, 232 participants (56.3%) reported being on hydroxyurea therapy, including 65.2% of children, 62.1% of adolescents, 55.6% of young adults, and 39.5% of adults 26 years and older (p = 0.0003). Out of the 232 participants reporting to be on hydroxyurea, 187 (80.6%) reported being completely adherent with taking hydroxyurea over the previous 2 days, while 38 participants (16.3%) reported partial or non-adherence. Twenty eight percent of young adults and adults reported two or more barriers to hydroxyurea, compared with 11.6% of caregivers of children (p < 0.0001). Forty-one percent of participants who were not on hydroxyurea reported that their doctors did not recommend it, compared with 1.7% of those on hydroxyurea (p < 0.0001, Figure 1). Not knowing enough about the medicine (13.8 vs. 4.3%, p < 0.000 = 1), not being interested in taking another medicine (10.2 vs. 1.7%, p < 0.001) and "tried it and it did not work" (9 vs. .4%, p < 0.0001) were more common barriers for those not on hydroxyurea compared with those who were on it. Forgetting was a more common barrier for those on hydroxyurea (19.8 vs. 7.2%, p < 0.001). A common barrier for both participants on and not on hydroxyurea was worry about side effects (16.8 and 19.8%

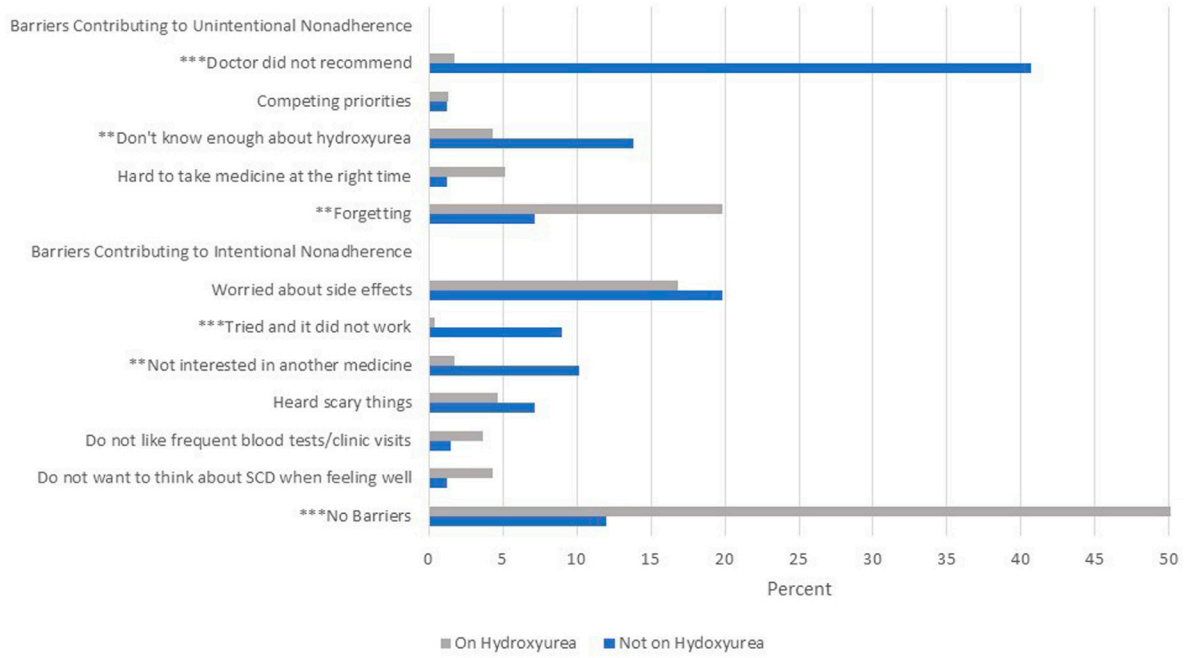

FIGURE 1
Barriers to hydroxyurea use as reported by adults and caregivers of children with sickle cell disease (SCD). Notes: Side effects worried about included cancer, hair loss, nail discoloration, nausea/dizziness. "Scary" things heard about included cancer, infertility, risk of infection and hair loss. $^{**}p < 0.001$ $^{***}p < 0.0001$.

respectively). Over half (52.6%) of participants on hydroxyurea reported no barriers to its use compared with 12% not on hydroxyurea ($p < 0.0001$). The presence of one or more barriers approached significance as negatively associated with complete adherence ($p = 0.012$). There were not significant age differences in reports of barriers contributing to unintentional nonadherence, but young adults and adults were more likely to report barriers that contributed to intentional nonadherence compared with caregivers of children with SCD (38.7% versus 18.4%, $p = 0.0007$).

Provider reports: Reasons for prescribing or not prescribing hydroxyurea, laboratory values

The number of participants that providers reported were on hydroxyurea ($n = 236$ participants) were consistent with patient/caregiver reports. The most frequent indications reported by providers for prescribing hydroxyurea (Table 3) were recurrent episodes of pain (66.5%) and history of acute chest syndrome (19.9%). Hydroxyurea was prescribed less often for other complications (11.9%) and for neurological complications (7.2%), while it was prescribed for empiric use 9.3% of the time. Of 22 participants who were prescribed hydroxyurea for empiric use, only 1 participant (4.5%) reported that they had experienced 4 or more hospitalizations for pain in the past 12 months. Fewer patients who were prescribed hydroxyurea for empiric use reported 4 or more episodes of severe pain interfering with daily activities in the previous 12 months compared to participants who were not prescribed hydroxyurea for empiric use ($p = 0.004$).

For the 176 participants not on hydroxyurea, providers reported the medication was not indicated for 34.7% (Table 3), although 38 of the 61 patients had diagnoses of HgbSS or HgbSβ^0 thalassemia. Reasons for discontinuing hydroxyurea included patient/family preference (34.5%), chronic transfusion therapy (31.1%), side effects (24.1%), or other reasons (24.1%). Providers reported that 22.7% of patients/families offered hydroxyurea were not interested, it had to be discontinued (16.5%) or hydroxyurea had not yet been introduced (10.2%). Providers were concerned about adherence for 7 patients (4.0%).

Providers recorded laboratory data for the study, for 206 participants on hydroxyurea and 106 participants not on hydroxyurea. The total white blood cell count (WBC) and absolute neutrophil count (ANC) were lower ($p = 0.01$ and $p = 0.002$ respectively) and HbF was higher ($p < 0.001$) for participants on hydroxyurea compared to those not on hydroxyurea (Table 4).

TABLE 3 Provider-reported indications & reasons for hydroxyurea prescription[a].

Category	n (%)
Indications for hydroxyurea prescription (*n* = 236)	
Recurrent Pain Episodes	157 (66.5)
Acute chest syndrome	47 (19.9)
Empiric use	22 (9.3)
Neurological complications	17 (7.2)
Other indication (e.g., anemia, dactylitis)	28 (11.9)
Reasons not on hydroxyurea (*n* = 176)	
No indications	61 (34.7)
Hydroxyurea offered but not interested	40 (22.7)
Hydroxyurea discontinued	29 (16.5)
Chronic transfusion	25 (14.2)
Hydroxyurea not yet been introduced	18 (10.2)
Concerns about adherence to medication/monitoring protocol	4 (2.3)
Other reason (e.g., hemoglobin levels stable, hgbsc or hgbsβ+ genotype, didn't feel well on hydroxyurea, kidney issues, liver issues, pregnancy)	20 (11.4)
Reasons hydroxyurea discontinued (*n* = 29)	
Patient/family preference	10 (34.5)
Chronic transfusion	9 (31.1)
Side effects	7 (24.1)
Other reason (e.g., not helping patient, pregnancy)	7 (24.1)

[a]Some responses add up to >100% due to multiple responses.

TABLE 4 Provider-reported laboratory values by hydroxyurea use (*n* = 312)[a].

Category	On hydroxyurea (*n* = 206) Mean ± SD	Not on hydroxyurea (*n* = 106) Mean ± SD	References range
CBC			
White blood cell count (x10^3 cells/ul)	10.3 ± 0.3	11.9 ± 0.5	5.0–10.0*
Hemoglobin (g/dL)	9.0 ± 0.1	9.3 ± 0.2	13.5–17.3 (M)
			12.0–15.5 (F)
Platelet count (x10^3 cells/ul)	349.8 ± 9.2	352.0 ± 14.8	150.0–400.0
Absolute neutrophil count (x10^3/ul)	5.1 ± 0.2	6.5 ± 0.4	2.0–8.0*
Hb f (%)	15.6 ± 0.9	7.9 ± 1.1	<2.5%**
Liver			
Bilirubin, total (mg/dL)	2.5 ± 0.1	2.7 ± 0.2	0.0–1.2
ALT (U/L)	28.0 ± 1.6	31.4 ± 3.0	0.0–41.0 (M)
			0.0–33.0 (F)

*$p < 0.01$, **$p < 0.001$.

Multivariable models for hydroxyurea use/prescription

Based on results from univariate models, diagnosis, HbF, indications for hydroxyurea prescription (empiric use, recurrent pain), total barriers and barriers contributing to unintentional nonadherence were entered into a multivariable model for patient/caregiver reports of being on hydroxyurea, that controlled for age and gender. Adults aged 26 years and older had lower odds of hydroxyurea use compared with the younger age categories ($p = 0.0002$). As reports of total barriers to hydroxyurea increased, the odds of hydroxyurea use decreased ($p < 0.0001$). The variable "not interested in (hydroxyurea)" from the providers' perspective, was associated with lower odds of being on hydroxyurea. There was little variability in hydroxyurea use for the indication of recurrent pain, so that the odds associated with being on hydroxyurea were very high, with very wide confidence intervals. Gender was not associated

TABLE 5 Significant multivariable relations between patient/caregiver reports of being on hydroxyurea and provider prescription of hydroxyurea.

Model	Variable	Odds ratio (95%confidence interval)
Patient/Caregiver report of being on hydroxyurea		
	Age	
	12 years and younger	Reference
	13–17 years	1.9 (0.66–5.2)
	18–25 years	0.48 (0.15–1.53)
	26 years and older	0.13 (0.04–0.38)**
	Total Barriers	
	None	Reference
	1 barrier	0.08 (0.03–0.20)***
	2 or more barriers	0.19 (0.07–0.57)*
	Indication—Recurrent Pain	811.5 (87.7–7504.3)***
	Not Interested in hydroxyurea	0.06 (0.01–0.31)**
Provider prescription of hydroxyurea		
	Age	
	12 years and younger	Reference
	13–17 years	1.1 (0.56–2.1)
	18–25 years	0.65 (0.33–1.30)
	26 years and older	0.45 (0.25–0.78)*
	Total Barriers	
	None	Reference
	1 barrier	0.15 (0.09–0.26)***
	2 or more barriers	0.27 (0.14–0.52)**
	Diagnosis	
	HgbSS and HgbSβ^0 thalassemia	Reference
	HgbSC	0.21 (0.10–0.41)***
	Other diagnoses	0.35 (0.13–0.90)

*$p < 0.01$, **$p < 0.001$, ***$p < 0.0001$.

with hydroxyurea use. Greater odds associated with empiric use [OR = 16.9, 95% CI (1.90–149.6), $p = 0.011$] and lower odds associated with diagnoses other than HgbSS and HgbSβ^0 thalassemia [HgbSC OR = 0.291, 95% CI (0.097–0.874), other diagnoses OR = 0.069, 95% CI (0.006–0.737), $p = 0.0285$] approached significance.

Based on results from univariate models, diagnosis, HbF, total barriers and barriers contributing to unintentional nonadherence were entered into a multivariable model for provider prescription of hydroxyurea, that controlled for age and gender. Adults aged 26 years and older had lower odds of hydroxyurea use compared with the younger age categories ($p = 0.0048$). As reports of total barriers to hydroxyurea increased, the odds of hydroxyurea use decreased ($p < 0.0001$). Lower odds of prescribing hydroxyurea were associated with diagnoses other than HgbSS and HgbSβ^0 thalassemia. Gender was not associated with hydroxyurea use.

An ad hoc analysis was performed to assess the potential contribution of site in the multivariable models. We performed multiple logistic regression analysis, where we used being on hydroxyurea as the binary outcome, with age, and site (binary variable—California sites (3) compared with other states (6 sites) as independent variables. Consistent with our main finding in Table 5, patients aged 26 years and older had significantly lower odds of being on hydroxyurea compared with the patients aged 12 years and younger. The results (available from the first author upon request) also showed that the patients from other states had significantly higher odds of being on hydroxyurea compared with the patients in California.

Discussion

To our knowledge, this is the largest real-world study to date that assesses hydroxyurea use for children and adults with SCD, from the perspectives of providers, adults, and caregivers of children. We found that hydroxyurea use was reported in over half of eligible patients from a large geographic region in the U.S., representing a range of sickle cell specialty clinical settings and practices. Provider and patient/caregiver reports

about hydroxyurea use were consistent with one another, as was the importance of age as a factor associated with hydroxyurea use. Adults were significantly less likely than children, adolescents, and young adults to be on hydroxyurea, consistent with other studies (Sinha et al., 2018). Barriers to hydroxyurea were also factors associated with its use for both providers and patients/caregivers, with the likelihood of being on hydroxyurea decreasing with one or more barriers.

From the perspectives of adults with SCD and caregivers, the indication of recurrent pain was associated with higher odds of hydroxyurea use. Patient/caregiver perspectives that they were "not interested" in taking the medication were significantly associated with lower odds of its use. However, patients/caregivers also cited worry about side effects, not knowing enough about the medicine and providers not recommending hydroxyurea as barriers. Our results suggest that providers may need a greater appreciation of these important perspectives of adults and caregivers of children with SCD, in order to increase its use among eligible patients (Adeyemo et al., 2015; Okocha et al., 2022).

We adopted the intentional and unintentional medication nonadherence framework in the present study to enhance understanding of unique barriers to hydroxyurea for the SCD population (Hodges et al., 2020). We demonstrated that, even for patients on hydroxyurea, challenges to taking the medicine at the right time and forgetting were crucial unintentional barriers to adherence, consistent with other reports (Badawy et al., 2017; Jose et al., 2019; Hodges et al., 2020). Forgetfulness may be associated with neurocognitive deficits, including memory impairment and diminished executive functioning, that may occur in SCD (Feliu et al., 2011; Prussien et al., 2019; Martin et al., 2020). Healthcare providers should consider strategies that lessen the reliance on memory and planning to support adherence, including mobile apps (Creary et al., 2014; Badawy et al., 2016; Inoue et al., 2016; Makubi et al., 2016; Leonard et al., 2017; Curtis et al., 2019) and automated text message reminders (Estepp et al., 2014; Pernell et al., 2017) in addition to encouraging patients to incorporate hydroxyurea into their daily routines. Community health workers have also been utilized to facilitate adherence to treatment regimens, including hydroxyurea (Green et al., 2017).

Intentional barriers such as worry about side effects (Haywood et al., 2011; Oyeku et al., 2013; Hodges et al., 2020) and "tried and it did not work" were particularly important barriers for young adults and adults and possibly reflect a general lack of knowledge about hydroxyurea. Smith and colleagues (Smith et al., 2019) found a 158.8% increase in the number of patients initiating hydroxyurea after concerted education, suggesting the efficacy of educational interventions. Sinha and colleagues (Sinha et al., 2018) found that for 95 adults with SCD, those who could explain the mechanism of action for hydroxyurea and its benefits were more likely to be taking hydroxyurea and reported a more positive experience. Patient/family education to increase knowledge about hydroxyurea may thus mitigate barriers lending to intentional nonadherence (Pecker et al., 2018; Crosby et al., 2019). Our findings can assist providers in understanding choices and decisions of their families affected by SCD; guide individualized clinical discussions regarding hydroxyurea therapy; and help with developing tailored interventions to address barriers (Hodges et al., 2020). Shared decision making is an opportunity for the provider and patient/family to meet and discuss the purpose, benefits, mechanism of action, and side effects of hydroxyurea, as well as address any questions or concerns. Shared decision making may also enhance understanding and confidence in explaining and prescribing hydroxyurea on the part of the provider.

For providers, diagnoses other than sickle cell anemia (HgbSS or HgbS-β^0 thalassemia), particularly HgbSC, were associated with lower odds of prescribing. Provider behavior was thus consistent with the NHLBI evidence-based guidelines in this regard (National Heart, Lung and Blood Institute, National Institutes of Health, 2014). However, adults 26 years and older had the most frequent reports of four or more visits to the ED for pain and interference from pain episodes experienced at home in the past year while being the least likely age group to receive prescriptions from their providers. Adults also were not prescribed hydroxyurea for empiric use, consistent with other studies (Thornburg et al., 2012). The NHLBI guidelines explicitly state that all patients with sickle cell anemia and their families should be educated about hydroxyurea and that infants, children and adolescents 9 months of age and older with sickle cell anemia should be offered hydroxyurea, regardless of clinical severity. The guidelines list a number of specific complications in adults with sickle cell anemia that should prompt treatment with hydroxyurea, perhaps creating confusion on the part of some providers about prescribing hydroxyurea empirically for adults. Implementing standard practices for hydroxyurea therapy across patients' lifespans, including its empiric use, and considering their eligibility even if they do not have a diagnosis of sickle cell anemia, should be deliberated upon with future guidelines. Studies with larger sample sizes are needed to evaluate whether there are differences by age when hydroxyurea is prescribed for empiric use or prophylaxis rather than for disease related complications. Additional guidance about strategies for education about hydroxyurea, that emphasize avoidance of cumulative damage and the suffering associated with severe and frequent pain, may be helpful for providers, patients and families alike.

Cabana et al. (2019) reported that provider hesitancy in prescribing hydroxyurea, may be due to provider concerns about patient adherence to the medication, and this was the case for a handful of patients in our study. Furthermore, SCD providers in a previous study also expressed a lack of self-efficacy, particularly in identifying which patients may benefit from hydroxyurea, prescribing the correct dose, recognizing side

effects, and discussing risks of the medication with patients/families (Cabana et al., 2019). Strengthening provider understanding and confidence in implementing the NHLBI SCD guidelines should not be taken for granted, even for providers with more experience with and support for SCD care, as in the PSCRC. The need to attend to the multiple factors that undermine quality of life and quality of care for adults with SCD remains more critical than ever (Kanter et al., 2020).

Short-term self-reported adherence with hydroxyurea was very high for those for whom it was prescribed in the present study and available laboratory values were consistent with patient/caregiver reports. Multiple measures of adherence that are triangulated are generally recommended, to optimally support shared decision-making (Lam and Fresco, 2015). However, in our study 25% of laboratory values were not recorded, perhaps given that we asked providers to report the values. This additional step may have been too burdensome in busy clinical settings. While we were pleasantly surprised at the alignment of patient/caregiver/provider assessments of adherence and of laboratory values that we had access to, future studies in real world settings must carefully weigh trade-offs in clinical relevance compared with feasibility of data capture.

Of note, over 40% of our patients/families were officially below the poverty line in the U.S., with low incomes and high household densities. Although not otherwise directly assessed in this study, we acknowledge that there are multiple social determinants of health that can impact uptake of and adherence with hydroxyurea and other aspects of treatment regimens (Power-Hays et al., 2020). Assessment of social determinants of health such as food and housing insecurity; employment and education; and experiences of racism and discrimination; should be routine, using valid and reliable measures. When assessments reveal negative impacts of social determinants of health, individuals with SCD and their families must be provided access to comprehensive team support and evidence-based therapies.

Limitations

Several factors limit the generalizability of the present findings. First, despite the relatively large sample size, patients were from sites only in the western U.S. Individuals with SCD followed in other parts of the U.S. and across the globe might experience different barriers which may influence which interventions will be most helpful to increase hydroxyurea prescription and minimize barriers. Second, patients in this cohort were associated with clinics with an interest in improving SCD care as these centers were part of the PSCRC, that might not be the case in all clinics where patients with SCD are followed. Third, differences in access to comprehensive healthcare services may affect frequencies of ED visits and hospitalizations for pain.

In the present study, healthcare utilization was not associated with hydroxyurea use, unlike prior studies (Charache et al., 1995; Thornburg et al., 2012) that demonstrated that hydroxyurea use was associated with decreased frequency of pain and ED and inpatient admissions. This could be due to differences in study design and purpose. In addition, our data are limited by indication bias, as participants were offered hydroxyurea primarily for sickle cell related complications rather than for empiric use. Previous studies were randomized trials looking at the effects of hydroxyurea with a set medication start date. Our goal was to leverage a large regional collaborative to understand barriers to hydroxyurea use in real world clinical settings and establish an infrastructure for future quality improvement work on identifying the barriers to hydroxyurea use, regardless of length of time on hydroxyurea and dosage. Given how wide-ranging our sample sizes were across sites, we were not able to fully explore the influence of site. Such an analysis has a high potential for confounding and loss of statistical power and is beyond the scope of the present study. An ad hoc analysis did confirm that our findings held, that the patients aged 26 years and older have lower odds of being on hydroxyurea compared with younger patients even after adjusting for site differences. Our real-world evidence complements clinical trials with increased variability within our sample and by permitting a fuller understanding of patient/family and provider perspectives about hydroxyurea. Provider reasons for not prescribing hydroxyurea for “empiric use” could not be explored further given the term “empiric use” was not clearly defined. Lastly, these data were collected prior to the availability of other new therapies for SCD so we are unable to assess barriers to use of these newer therapies that might be different than barriers to hydroxyurea therapy.

Conclusion

The purpose of this study was to describe factors associated with hydroxyurea use from the perspectives of providers, individuals with SCD, and families. We described clinical characteristics, healthcare utilization, barriers to hydroxyurea use and adherence from the perspectives of pediatric and adult patients with SCD and prescribing patterns and laboratory values in relation to hydroxyurea for eligible patients as reported by providers. Our findings support the importance of enhancing the knowledge base about hydroxyurea, particularly among adults living with SCD, as well as their providers. With the advent of new disease modifying therapies that will likely need to be utilized together, it will be important to spend adequate time in shared decision making so that individuals with SCD can optimally benefit from these therapies, including hydroxyurea.

Addressing the barriers to hydroxyurea use among individuals with SCD can lead to steps to minimize similar barriers in the use of emerging and combination therapies for SCD. Sorting through issues with treatment guidelines and gaps in knowledge and shared decision making will support more effective implementation of disease modifying therapies in high and low-resource settings across the globe (Power-Hays and Ware, 2020).

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the UCSF Benioff Children's Hospital Oakland Institutional Review Board and Western Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Study conception and design: MT, MB, TEW, TW, AM, NB, and DN; Data collection: MT, MB, TEW, TW, AM, NB, SN, and DN; Analysis and interpretation of results: MT, LD, NB, and JC; Draft manuscript preparation: LD, NB, and MT. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Building research capacity for sickle cell disease in Africa: Lessons and challenges from establishing a birth cohort in Tanzania

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Sickle Cell Disease (SCD) is a known public health burden in sub-Saharan Africa (SSA). The manifestation of SCD starts in early childhood and if not well-managed may lead to early death (before the age of 5 years). Understanding the underlying mechanisms that influence early SCD manifestation is of great importance for early disease and intervention management which will in turn, reduce both morbidity and mortality rates in children. One approach of achieving this is by establishing SCD birth cohorts that can be followed for a period of time (3–5 years) whilst documenting necessary information related to early childhood illnesses. To date, there are few SCD birth cohorts in Africa. To address this gap, we have established a birth cohort of babies with and without SCD (with sickle cell trait and healthy babies). These babies are followed up for 3 years with their study visits synchronized to the immunization schedule. During enrollment and follow-up visits, information on demographic, clinical, and laboratory parameters are collected. To date, we have enrolled a total of 341 babies with and without SCD. Out of these, a total of 311, 186, 133, 81, 44, and 16 babies have returned for their 1st, 2nd, 3rd, 4th, 5th, and 6th visits, respectively. We have collected both demographic and clinical information for these babies at enrollment and during follow-up. We have also utilized this platform to learn on the best approaches of establishing and maintaining a research birth cohort in an African context. We have analyzed the practical issues pertaining to the integration of the birth cohort with the immunization platform which seems to be the most effective and sustainable strategy for maintaining a birth cohort in our context.

KEYWORDS

Sickle Cell Disease, newborn screen (NBS), birth cohort, immunization, genetics

Introduction

Sickle cell disease (SCD) is a global public health issue and calls for global initiatives which can also work in the local contexts. In 2010, the annual global estimate for children born with SCD was 300,000. This number is expected to increase to 404,200 in 2050 (1). The burden is bigger in SSA and India where there is severe morbidity and high mortality among children. Early-life mortality in Africa ranges between 50 and 90% of children born with SCD (2). In most of tropical African countries, including Nigeria, Congo and Cameroon, SCD has not yet received much attention compared to other diseases such as malaria, malnutrition, HIV/AIDS, and other neonatal illnesses (3, 4).

Early screening of SCD either at birth or through the first immunization clinic has proven to be a game-changer associated with early disease management and reduced mortality and morbidity of up to 75% (3). There are no universal screening programs for SCD in Africa, however, few countries including Ghana, Nigeria, Angola, Uganda, and Tanzania have conducted newborn screening (NBS) programs covering some parts of their countries (4–6). Comprehensive care for these newborns and educational programs for their families have been proven to improve the health of the babies. To date, there is a strong push toward the establishment of universal NBS programs for SCD, especially in low resource countries such as those in Africa (7). These NBS programs are not only important for early diagnosis and comprehensive care provision but are also utilized to generate data for the cost-effectiveness of NBS and early interventions for SCD in SSA (7–9). In Tanzania for example, it is estimated that more than 11,000 babies are born with SCD each year and without proper intervention, these children will die before reaching adulthood (10, 11). These estimates are based on the partial NBS programs conducted in the country. To date, Tanzania has conducted NBS in the capital city, Dar es Salaam through the support of donors including the Foreign, Commonwealth & Development Office, UK and the American Society of Hematology (ASH) and the National Institutes of Health (NIH), USA.

Following NBS initiatives, there is a great opportunity to establish birth cohorts that can be followed up with the aim of investigating and understanding childhood illnesses and the best management strategies. This is especially important for babies with SCD who are more vulnerable to the causes of under-five mortality. SCD birth cohorts can also serve as platforms for planning appropriate interventions both at childhood and adult levels. Despite their importance, the establishment of such birth cohorts faces similar challenges to the establishment of NBS in Africa mainly due to limited resources, including human, financial and logistical.

TABLE 1 Immunization schedule for under-five children in Tanzania (Adapted from the Expanded Program of Immunization (EPI), Tanzania) (13).

Age	Vaccine
At birth	BCG, OPV 0
6 weeks	OPV1, DTP-HepB-Hib1, PCV1, Rota 1
10 weeks	OPV2, DTP-HepB-Hib2, PCV2, Rota 2
14 weeks	OPV3, DTP-HepB-Hib3, PCV3
9 months	MR 1
18 months	MR 2

BCG, Bacillus Calmette-Guerin; DPT, Diphtheria, Pertussis, Tetanus vaccine; HepB, Hepatitis B vaccine; Hib, Hemophilus Influenzae type B vaccine; PCV, Pneumococcal Vaccine; Rota, Rotavirus vaccine.
OPV 1, 2, 3, OPV type 1, type 2 and type 3 Oral Poliovirus Vaccine respectively.
OPV0, zero dose Oral Polio Vaccine.
DTP-HepB-Hib1, PCV1, first dose of DTP, HepB, Hib and PCV.
DTP-HepB-Hib2, PCV2, second dose of DTP, HepB, Hib and PCV.
DTP-HepB-Hib3, PCV3, third dose of DTP, HepB, Hib and PCV.
MR1, Measles and Rubella virus vaccine first dose.
MR2, Measles and Rubella virus vaccine second dose.

One approach to address these challenges is to learn and integrate such cohorts with successful childhood programs. National immunization programs are among the most successful healthcare programs in the world. In Tanzania for example, the immunization program is described to be among the best performing programs in Africa (12) with more than 95% of babies being vaccinated as scheduled following the "Reach Every Child" approach. Therefore, establishment of research birth cohorts can utilize such platforms in order to tap into the existing resources which will ensure increased sustainability of the research interventions and outcomes. According to the Tanzania Expanded Program of Immunization (EPI), vaccines for under-five children are provided at birth, 6 weeks, 10 weeks, 14 weeks, 9 months, and 18 months of age (Table 1) (13).

From 2019, The Muhimbili University of Health and Allied Sciences (MUHAS) through the support from Fogarty International Center Emerging Global Leader Award, has established a birth cohort of babies with and without SCD. The main purpose of this cohort is to investigate the genetic determinants of fetal hemoglobin decline and how this phenomenon may influence the clinical manifestation of SCD in the first 3 years of life. The birth cohort is followed for the first 3 years of life utilizing the immunization platform through (i) synchronizing study visits with the national immunization clinics, (ii) utilizing the expertise of nurses at the immunization clinics in providing health education/counseling, and (iii) sharing logistical/infrastructural resources. In this report, we share the lessons, challenges, and experiences of establishing a birth cohort in Tanzania. We believe that most of the lessons can be applied to any African setting as well as other countries with limited resources.

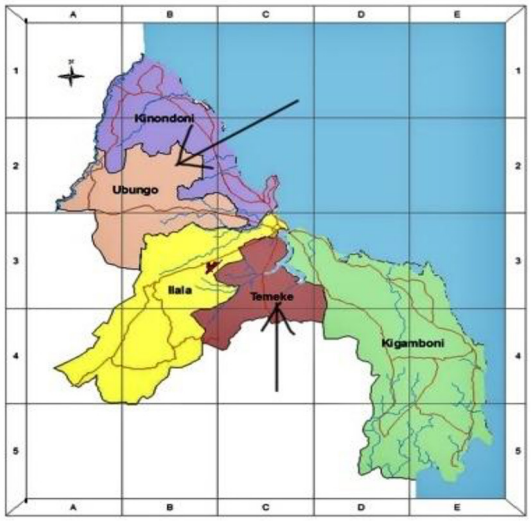

FIGURE 1
Map of Dar-es-Salaam region showing the study sites (Ubungo and Temeke Municipalities).

Materials and methods

Study design and sites

This is a prospective study involving a cohort of newborns born at Mbagala and Sinza hospitals from 2019 to 2021. It is a part of a larger project on the "role of fetal hemoglobin decline and its determinants on Sickle Cell Disease expression in the first three years of life." The study will involve both babies with and without SCD. Both Mbagala and Sinza hospitals are classified as district hospitals in the Temeke and Ubungo municipalities in Dar es Salaam region (Figure 1). These health facilities are designed to offer inpatient and outpatient services to a large number of people from diverse social backgrounds. Provided services include but are not limited to women's health, labor & delivery, counseling and minor/major operating theaters which are required settings for the practicum experience. In addition, both facilities were selected due to their designation for providing immunization services for newborns residing in their catchment areas.

Study population

This study involved babies delivered at Mbagala and Sinza hospitals. Screening was conducted at birth for all newborns whose mothers consented for their babies to participate in the study. However, we excluded all newborns with other illnesses that may lead to admission and/or blood transfusion such as infection (severe malaria, bacterial infection) and as well as development of fever at birth and prematurity with complications. We also excluded babies whose mothers did not consent to participate in the study.

Establishment of birth cohort

Municipal level

In order to ensure ownership, proper supervision, and management, any project or initiative that involves a health facility under a particular municipality in Tanzania, approval from the particular municipal office must be acquired before the initiation of the project. In this case, we received approval from the Temeke and Ubungo municipalities. We also received approvals for project staff to be allowed to take part in the study at the health facilities especially within the labor ward.

Facility level: Project meetings

The medical officer in charge (MOI) at the health facility serves as the project's core host, giving all necessary instructions to ensure the project's successful operation. We first engaged with the MOIs at Mbagala and Sinza to introduce the project and together discussed the best practices that will allow the research to operate successfully, such as how best to engage the management of the facility, the leads of the respective units, required hospital staff, and the study participants. We then conducted a number of meetings with the hospital management and respective units which included Medical Officer In charge (MOI), heads of units, doctors, and nurses practicing at the Labor ward and Reproductive and Child Health (RCH) clinics. During the meeting, we introduced the project, highlighted the study protocol, and indicated the involved hospital sections including the labor, postnatal wards as well as RCH unit. We used these meetings to get inputs from the doctors and nurses on the best patient engagement approaches to be used during the enrollment and screening process as it deemed fit to the respective facility. Some of the issues that were highlighted in these meetings included the best staff-patient engagement approaches and remunerations. The investigators discussed matters relating to patient's beneficence, autonomy and the value of voluntariness in conducting the study. For the ward nurses that were directly involved in counseling and study activities, plans for remuneration were also discussed.

Labor ward training

At the labor ward, nurses' training sessions were conducted on various aspects including (i) counseling before and after enrollment (ii) consenting process, and (iii) filling of the enrollment case report form (CRF). Practical sessions were also conducted on the collection of umbilical cord blood for SCD screening and storage for other laboratory assays.

RCH training

Nurses' training at RCH was mainly focused on SCD counseling and health education as well as SCD screening using point of care test for babies of 6 weeks of age. We also provided training on dissemination of SCD screening results and counseling sessions for the mothers. Practical training sessions on sample collection and storage at the follow-up visits were conducted at each facility.

Enrollment into the birth cohort

Counseling of mothers at the labor ward

All mothers admitted at the labor ward, either in labor or not, received counseling to take part in the study. A trained project nurse provided education on SCD, neonatal SCD screening, and its significance in SCD management. The study nurse also utilized this opportunity to explain the importance of the study. The mothers were also informed that no cost of screening will be directed to them. All communications were conducted in Swahili language.

Consenting of study participants

Following the counseling session, the mothers who agreed for their babies to take part in the study were required to consent before the screening process. A written informed consent in Swahili language was provided and mothers received information about the study including an explanation of how to participate in the study, possible risks, and benefits of participating in the study, and the freedom of choosing to or not to take part in the study. If they agreed to participate in the study, the participants were provided with the consent forms to sign. Exceptionally, for some pregnant women who were in active labor and were unable to sign the forms, oral informed consent was administered, followed by written consent post-delivery.

Newborn screening for SCD

Immediately after delivery, the umbilical cord was clamped and umbilical cord vein was identified. In aseptic conditions, 5 ml of umbilical cord blood was collected and stored in ethylenediaminetetraacetic acid (EDTA) tubes. Out of the 5 ml, 2 ml was used for SCD screening using a point of care test, Hemotype SC, by following the manufacturer's procedure (Silver Lake Research Corporation, United State of America). The rest of the blood sample was processed and archived at the Hematology Clinical and Research Laboratory **(HCLR)** MUHAS for molecular and genetic assays at a later stage. For the babies who test positive for SCD, High performance Liquid Chromatography (HPLC) was used as a confirmatory SCD test.

Enrollment of study participants into the study

Following delivery and stabilization of mother and baby, an enrollment form was filled. Trained research assistants collect clinical and socio-demographic information about the baby including; any presenting symptoms at birth and during newborn's examination, the health facility details (Hospital ID, etc), gestation age, baby's gender, and date of birth. In addition, parents' information such as parents' names, tribes, residence, and contact information was collected. Finally, sample collection details were also recorded. In order to ensure good compliance with the study, we focused our enrollment on babies whose families reside around the health facility (i.e., Mbagala and Sinza hospitals) as their babies were most likely attending immunization clinics at the same facilities. Following the completion of the enrollment process, the mothers were informed about the study follow-up plan for up to 3 years of age with the follow-up visits synchronized with the immunization schedule. The mothers were also informed of two additional visits of the study which were to be conducted at the age of 24 and 36 months.

Maintenance of birth cohort

Utilizing the immunization platform for follow up schedule

To maximize adherence, scheduling of the first six follow-up visits (1.5, 2.5, 3.5, 6, 9, 18 months) was done according to the immunization schedule (Table 1), working closely with the designated nurses at immunization units. The scheduling was synchronized and done in accordance to the Tanzania Expanded Program of Immunization (EPI) (Table 1). Collaboration with the hospital RCH unit encouraged compliance of the mothers to the study due to the respect, trust, and familiarity they had to the immunization program and the RCH services.

Provision of clinical services through the immunization platform

During each follow up visit, we worked with the RCH nurses to ensure the following: (i) supervision of the enrolled babies to complete the vaccination process, (ii) synchronization of the subsequent immunization visit with that of the study follow up, (iii) blood sample collection for laboratory tests, and (iv) provision of clinical services for the babies including SCD and full blood count results feedback, clinical history documentation and counseling. Each baby who tested negative for SCD received their first results on the first visit day at the age of 42 days (6 weeks). For newborns who tested positive for SCD, home visits were done as soon as they were diagnosed to inform the parents of the test results. These visits were conducted by a doctor, and a nurse and followed up later by a research assistant. During these visits, parents were given SCD health education

on; etiology of disease, presenting symptoms, possible danger signs, treatment and home care, and possible complications. In addition, the parents were also educated on the significance of early enrollment into care as part of disease management. Finally, scheduling of the first follow up visit at 6 weeks coupled with the first immunization was conducted.

Follow up visit reminders

Before leaving the RCH clinic the mothers were reminded of the babies' next follow up visit. In addition, regular reminders through phone calls and text messages were often made to all study participants to enhance adherence to follow-up visits. A week before the scheduled clinic visit, the parents were reminded three times through calls and text messages to ensure their babies attend their follow-up visit and immunization clinic.

Follow up visits processes

At the first follow up visit (6 weeks or 1.5 months), all mothers were guided for their newborns to receive their vaccination at the RCH clinics as per EPI. After vaccinations, a trained study nurse in collaboration with the RCH nurse were responsible for providing the mothers with their babies' results for SCD testing and CBC. In addition, the nurse utilized this visit to provide a refresher health education on SCD and the importance of the study. Clinical and demographic information was collected using standardized case report forms (CRF) for follow-up visits. As part of clinical monitoring of the babies, 2 milliliters of blood sample were collected for conducting laboratory tests. The laboratory assay included complete blood count (CBC), hemoglobin subtype quantification by HPLC, F cell count by flow cytometry, and archiving of samples for genomic studies considered to be conducted in the future on advanced therapy for patients with SCD. For the subsequent follow-up visits, the same procedures were conducted except for the SCD results feedback which was conducted once at the first visit. For all visits, severely deranged laboratory results were immediately communicated to the mothers and appropriate measures were taken to ensure that the baby received the required care. These cases were treated as emergencies and therefore results communication was performed prior to the scheduled follow up visits.

Data management

Demographic and clinical information were collected using standardized CRFs and were subsequently entered into a Research Electronic data capture (REDCap): backed up with the MySQL relational database management system. Each participant was assigned a unique study number that was linked to their study information. Data access was restricted to the approved project staff who have received training in ethical data management with considerations to data privacy and security.

Ethical consideration

This study received ethical approval from MUHAS Institutional Review Board (IRB) committee with reference number Ref.No.DA.282/298/01.C/. All study participants received a unique identifier that is used to link to other study information. All project data/files are secured and can only be accessed by designated study personnel.

Results

Establishment of the cohort

At the initiation of the study, we first engaged the top management of the hospitals. In the course of the study, we observed poor buy-in especially in the sections that were relevant to the study. Through consultations with the top management, we received guidance on how best to address this challenge. We then conducted meetings with the leaders of various units both directly or indirectly related to the study, resulting in the resolution of the challenges.

Our initial approach at the labor ward and RCH clinics was to involve only a few staff. However, this became challenging due to routine duty rosters in which different nurses would work at different work shifts. Similarly, through guidance by the management, we conducted refresher training for all staff leading to increased capacity for involvement in the study by all staff. This approach increased the study buy-in at all levels of the facility.

Enrollment to the birth cohort

Our study projection was to enroll a total of 400 babies with and without SCD in equal proportions by 2021. To date, we have enrolled a total of 341 babies. The average weekly delivery capacity for Sinza and Mbagala is estimated to be 60–80, with Mbagala being on the higher side. Between the period of January 2020 and September 2021, there were a total of 6,700 deliveries (Figure 2). Of these, 37.3% of the pregnant women received SCD health education. This number was much higher than our sample size (400) and weekly targets. Nevertheless, we aimed at utilizing this opportunity to reach out to all the pregnant women with SCD health education regardless of the final deliberation of being enrolled into the study. Therefore, the lack of counseling for the 4,220 pregnant women was mainly because of shortage of staff and time as counseling was only done during the day while

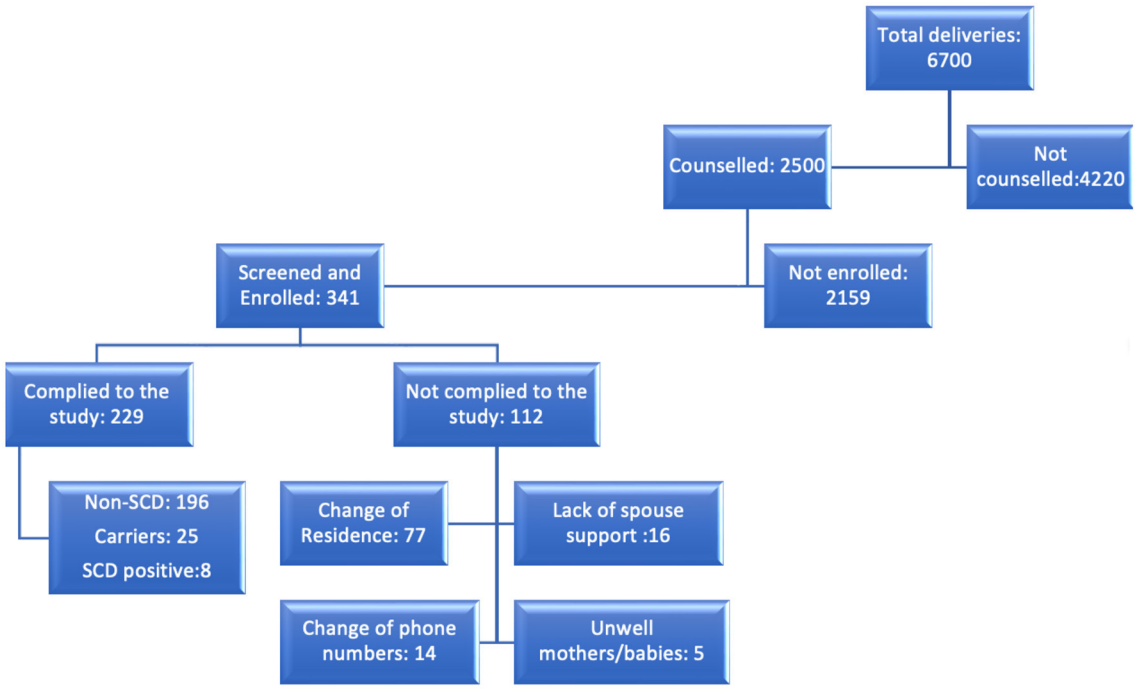

FIGURE 2
A flow chart showing the flow of events/steps and involved individuals on each of these. The deliveries reported here are between the period of January 2020 and September, 2021.

pregnant women were admitted and deliveries happened both during the day and night.

This delivery capacity was more than our weekly target which was set at 50 babies. In addition, despite the large delivery capacity of these facilities, our enrollment target was not met as planned. In this report, we describe some of the reasons/challenges that contributed to this.

First, provision of SCD health education followed by consenting, forms a critical part of this study. Initially, we attempted to conduct these two aspects of the study at the labor ward for already admitted pregnant women. This was challenging due to the fact that some of the pregnant women who were experiencing mild or active labor could not really follow through the process. This led to difficulties in obtaining consent which was important before delivery. We encountered challenges such as some of the pregnant women agreeing to consent while in active labor and later lacking memory to have done so. To address this challenge, all pregnant women who were in active labor were only informed about the study at the labor ward and if agreed, the proper counseling and signing of consent forms were done after delivery. Efforts were also made to ensure the counseling process is done earlier, during admission to the labor ward. This ensured the proper consenting process before the pregnant women progressed into active labor. We therefore agreed to focus on a few pregnant women and ensure a proper counseling process is conducted.

Second, complete filling of data in the enrollment case report forms (CRF) was necessary for this study to be successful. At enrollment, we expected to capture all basic and baseline information. We encountered a challenge of missing/wrongly entered details including contact and residence information. Due to this, we could not reach some of the mothers for follow-up reminders and hence we had to exclude their babies from the study. The main reason for this challenge was the high workload for the labor ward nurses. To address this challenge, a full-time study nurse was recruited to work closely with the labor ward nurses. We also used the staff credentials records (included in the CRF) to identify the nurses who may need further training or reinforcement on counseling and enrollment procedures.

Third, during the training we insisted on ensuring that enrolled babies are from families residing in the health facilities' catchment areas. We later established that a number of pregnant women (26) who consented for their babies to take part in the study were from upcountry and had visited the health facility only for delivery purposes. Some of the babies were enrolled in the program despite their families residing outside Dar es Salaam, some pregnant women were referred from other hospitals only for delivery and post-delivery care, while others resided around the mentioned facilities for socio-cultural

reasons. This posed challenges during follow-up as many of them did not adhere to the follow-up schedule and hence their babies were excluded from the study.

Therefore, due to the sensitivity of this process, we had to review our targets and focus on the quality of the data rather than quantities leading to changes to our enrollment targets and timelines.

Maintenance of the birth cohort

The ultimate goal of maintaining any birth cohort is to be able to follow up the babies successfully in order to monitor or evaluate a particular course. The purpose of this birth cohort was to follow up babies with and without SCD for a period of three years of age. To date, a total of 311, 186, 133, 81, 44 and 16 babies have returned to their 1, 2, 3, 4, 5, and 6 visits, respectively with 50–80% attrition rate (Table 2). We have also succeeded in maintaining 229 babies (Figure 2) who have returned to more than 3 follow up visits. Out of these, 196 are normal, 25 are carriers, and 8 babies with SCD.

The success of the study has been greatly influenced by utilizing the immunization platform. However, some of the babies missed their visits for various reasons.

The main challenge reported was a lack of understanding for some mothers. Despite adequate counseling before and after giving birth, some women were still hesitant to continue with follow-up, especially those with healthy babies which led to dropouts. To address this challenge, we continued with regular counseling and health education sessions which were provided during the follow up clinics at the RCH.

Ideally, the pre and post-delivery counseling sessions would have been more effective if provided to the expectant couples to ensure mutual understanding and consenting. As per the hospital and labor wards settings, the presence of spouses in the labor ward was not allowed, for that matter, counseling was done only to expectant mothers. This lack of spouse engagement and involvement during counseling had posed a challenge in maintaining some of the enrolled babies due to a lack of understanding of their partners.

Our study was designed to maximize the utilization of the RCH clinic. This approach has proven to work, however, since most RCH nurses trained for the follow-up activities are also involved in the vaccination activities at the RCH, they sometimes face challenges with the clients' workload. For this reason, the mothers with babies enrolled into the study had to wait longer to complete both vaccination and the follow up visit processes. To address this, we strengthened the team by hiring an additional study nurse to assist the RCH nurses. We also established a mechanism for the research assistant to assist the nurses in scheduling and documentation of visits.

Due to some of the reasons explained above, we experienced several dropouts; up to October 2021, we had a total of 112 dropouts from the cohort (Figure 2). Below are a number of attributable factors for the dropouts and loss to follow up.

Reasons for dropouts include (i) change of residence (77) reflecting gaps in the counseling process; some mothers and newborns reallocated after delivery and could not be traced at the respective RCH clinics (ii) spouses not supportive; Some spouses advised the mothers to drop out from the study due to lack of understanding, also some mothers feared that their partners would not agree to their involvement in the study (16) and (iii) change of phone numbers (14) (iv) mothers/babies being unwell (5). Some of these factors are continuously being addressed by enhancing health education to mothers and families where possible, establishing new ways of disseminating information such as digitalization of reminders and health education as well as general health education to the community.

Discussion

This is among few reports on birth cohorts (14) established for SCD research in Africa. Here we have described the steps we undertook to establish a birth cohort which forms a strong basis for executing a larger study on genetic determinants of fetal hemoglobin decline and how this influences SCD expression in the first 3 years of life. SCD is a public health condition that has been recognized by WHO (15). Unfortunately, most of the affected individuals are babies under 5 years of age residing in sub-Saharan Africa. SCD contributes significantly to under five mortality rates (3) in many affected African countries (16), SCD is now included in the strategic plans to prevent and control Non-Communicable Diseases (NCDs) in most African countries, Tanzania included (17).

Newborn screening (NBS) coupled with comprehensive care is proven to reduce mortality and morbidity caused by SCD (18–20). Unfortunately, most African countries have not been able to establish national NBS programs due to various reasons including cost and limited human and logistical resources (21). However, there is currently a great push to establish sustainable national NBS programs that will screen for a number of conditions including SCD. This is a great initiative which will allow early interventions and reduction of both morbidity and mortality contributed by SCD.

Successful NBS are those coupled with comprehensive care as well as early childhood research to better understand the mechanisms of disease expression, management, and treatment outcomes. One of the approaches to achieve this is to establish manageable birth cohorts that can be followed up for a period of time, preferable up to five years (22).

In this report, we have documented the process we undertook for establishing a birth cohort in Tanzania (2019-to date). In order to better understand SCD expression in babies, we set to follow a cohort of babies with and without SCD for a period of 3 years. Based on the estimated SCD prevalence

TABLE 2 The number of babies who have attended follow up visits at Mbagala and Sinza.

	Visit 1 (1.5 months)	Visit 2 (2.5 months)	Visit 3 (3.5 months)	Visit 4 (6 months)	Visit 5 (9 months)	Visit 6 (18 months)
Mbagala	253	163	120	72	39	14
Sinza	58	23	13	9	5	2
Total	**311**	**186**	**133**	**81**	**44**	**16**

(0.8%) in Dar es Salaam, Tanzania we expected to recruit babies without SCD much faster than those with SCD. We therefore coupled our study with two existing platforms NBS and the immunization program. We also anticipated low compliance to follow up visits especially for babies without SCD due to the fact these babies are not sick and the parents may not see the necessity of participating in such a study. It was therefore necessary to establish such a cohort on a robust and sustainable early childhood program, in this case the national immunization platform which has proven to be successful. Therefore, we attempted to synchronize as much as possible all the aspects of the study to the immunization program including identifying study sites with immunization services, synchronizing the follow up study visits to follow the immunization schedule and utilizing the RCH resources (personnel and infrastructure).

Through this work, we have learnt to tap into expertise and experience that health facilities have in taking part in research projects. We observed that conducting the initiation and feedback/progress meetings increased the project buy-in at the health facilities and enhanced a smooth addressing of the challenges. It is clear that the health facilities are overburdened by the routine healthcare provision, however, in most cases research is also accommodated especially when there is a direct involvement of the staff.

It was notable that the staff based at the facility understood much better the language and the communication/social-cultural barriers with the study participants (local mothers/families) and hence their involvement in the study helped to address some of these challenges. Although it was important to have a full-time study nurse at the health facility, it was necessary for the nurse to work closely with the in-house nurses. This was experienced both at the labor ward and the RCH clinics. Therefore, since our study success largely depended on site personnel at the labor ward and RCH, we started building the capacity of these nurses especially on SCD health education, counseling for SCD screening and enrollment into the study. Most of the nurses were receptive to the SCD knowledge, and it was more so for the nurses who had encountered SCD patients either at the hospital or at personal level. We chose a training mode which allowed interaction and hands on experience for both counseling and sample collection.

Our initial enrollment strategy was to target the pregnant women who were already admitted to the labor ward. The main reason for this was to increase the chances of dealing only with the pregnant women who will end up delivering at that site. Both Mbagala and Sinza sites are regional hospitals and hence in case of any indicators of complicated deliveries the pregnant women were referred to the next tier of referral hospitals. However, it was later evident that the labor ward was not a conducive environment for conducting health education since some pregnant women may be in active labor. Our second approach which was implemented at the admission stage worked better in terms of having a calmer environment for provision of both SCD health education and counseling of the pregnant women. During the course of providing SCD health education we observed that dealing with pregnant women who had prior SCD knowledge was much easier than those without. For this reason, we endeavored to provide health education to all pregnant women regardless of the ultimate enrollment status of their babies in the study. Compared to our study sample size of 400, health education was provided for a much higher proportion of pregnant women (Figure 2).

One of the challenges faced during the establishment of this birth cohort is couples' collective involvement during the consenting process. In our context, the presence of male spouses in the labor ward is not conveniently allowed, especially in public hospitals. This posed a challenge to partners' involvement in the consenting process which later on led to dropouts following the couple's disagreement and lack of proper counseling for men. This cultural aspect is also reflected in the antenatal clinic attendance in the country, where it is most common for women to attend antenatal clinics (ANC) without their partners (23). Traditional gender roles for males hinder their direct involvement in pregnancy and childbirth (24) and hence limit their general understanding of matters pertaining to babies let alone research issues. We therefore attempted to conduct home visits and phone calling to provide education to the partners of the mothers involved in the study. This has proven to work; however, it is anticipated to bear many fruits if it will be done at the enrollment stage.

For follow up purposes, contact details were collected from expecting mothers for close monitoring, immediate provision of results if needed and for reminding the parents to bring back the baby to attend both immunization and study visits which were synchronized. Considering the context in the labor ward, most mothers were not in possession of their phones,

making the process prone to errors and the possibility of missing contact details from the mothers which led to some defaults. To address this challenge, we consulted with hospital records in order to fill in some of the missing information. This shows the importance of linking study and hospital databases. It also shows the importance of strengthening our hospital databases to capture demographic information that may be relevant for research purposes.

Since the enrollment involved a number of activities, insufficient time for proper counseling was also one of the challenges that hindered the proper recording of contact details and filling of the CRFs. This challenge was mostly addressed by the cooperation between the study and the hospital nurses. Although it was necessary to organize and clarify roles between the study and hospital nurses, the cooperative atmosphere built the capacity for research for both sides.

Geographical reallocation after delivery was another factor that led to a loss to follow up, this challenge for maintaining birth cohorts has been reported elsewhere (25). Although this is a common practice in our cultural context, it should be handled well-during counseling and enrollment such that sufficient information is gathered to avoid study dropouts. Again, the cooperation between the study and the hospital nurses during counseling and enrollment assisted in addressing this challenge for our study.

Our study follow-up visits were impacted positively by the utilization of the immunization platform. Establishing birth cohorts and conducting newborn studies using local and traditional setting and contexts is not a popular method except in Nigeria and Ghana (9). However, since most of our study participants were babies without SCD, linking their study visits to their immunization clinics increased compliance to the study. We also ensured that those babies enrolled into the study received immunization services in a fast-tracked manner before being attended by the project team so as to reduce the turnaround time. In cases where the project doctor observed a situation that required additional clinical attention, the hospital pediatricians were informed so as to provide the necessary care to the baby. This way the integration of the study and hospital services were more benefitting to the study participants and hence increased compliance to the study.

Our integration with the NBS program has also been productive both ways. On one hand our study has enrolled SCD positive babies who have been screened through NBS. On the other hand, babies who have been screened through the study have been also enrolled into the NBS program for further follow up and planning of the comprehensive care.

Our study is exemplary of the importance of integrating early childhood programs for building research that will inform early childhood events, especially in limited resource settings. In this case we have utilized the integration of our study with existing NBS and immunization programme. Many African and other low-income countries are still facing challenges of sustaining NBS services. This is largely because of limited logistical and human resources because they tend to be costed and managed independently. One approach that can address these challenges is utilization of immunization programs as reported previously in Nigeria by Nnodu (6). In addition, further integration of early childhood research programs on such platforms as the immunization program increase not just compliance to the study but also sustainability and utilization of research findings.

Despite the crucial role of birth cohort especially in genomic studies, establishing birth cohort is prone to high rates of attritions (14) which has also been the case in this study. This approach however, is feasible and implementable in resource limited settings.

Conclusion

To the best of our knowledge, this is among the first reports that describe the utilization of immunization platforms for establishment of the birth cohort with a component of longitudinal follow up of more than two years. This is an excellent platform for establishment of birth cohorts especially in places with limited resources. It is important to enhance the research capacity of the RCH units including the immunization platforms especially for early childhood programs. In the coming years, research training for RCH nurses will be useful especially for incorporating pilot childhood research. For SCD, this is especially important for both screening and follow up of babies with SCD. It is therefore important to continue the exploration of better ways of building the research capacity of this important early childhood section. Our study has provided a proof of concept of how immunization platforms can be utilized for research especially those related to birth cohorts.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Muhimbili University of Health and Allied Sciences Institutional Review Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

SiN and DN were involved in conceptualization, proposal development, study participant enrollment, data collection, data analysis, interpretation, and manuscript drafting. BN, FK, GN, DS, and SaN participated in conceptualization, data interpretation, and manuscript preparation and revision. EM, MM, and JM participated in conceptualization and manuscript revision. All authors read and approved the final version of this manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Infantile-onset Pompe disease complicated by sickle cell anemia: Case report and management considerations

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Infantile-onset Pompe disease (IOPD) is a rare, severe disorder of lysosomal storage of glycogen that leads to progressive cardiac and skeletal myopathy. IOPD is a fatal disease in childhood unless treated with enzyme replacement therapy (ERT) from an early age. Sickle cell anemia (SCA) is a relatively common hemoglobinopathy caused by a specific variant in the hemoglobin beta-chain. Here we report a case of a male newborn of African ancestry diagnosed and treated for IOPD and SCA. Molecular testing confirmed two *GAA* variants, NM_000152.5: c.842G>C, p.(Arg281Pro) and NM_000152.5: c.2560C>T, p.(Arg854*) in *trans*, and homozygosity for the *HBB* variant causative of SCA, consistent with his diagnosis. An acute neonatal presentation of hypotonia and cardiomyopathy required ERT with alglucosidase alfa infusions preceded by immune tolerance induction (ITI), as well as chronic red blood cell transfusions and penicillin V potassium prophylaxis for treatment of IOPD and SCA. Clinical course was further complicated by multiple respiratory infections. We review the current guidelines and interventions taken to optimize his care and the pitfalls of those guidelines when treating patients with concomitant conditions. To the best of our knowledge, no other case reports of the concomitance of these two disorders was found. This report emphasizes the importance of newborn screening, early intervention, and treatment considerations for this complex patient presentation of IOPD and SCA.

KEYWORDS

glycogen storage disorder type II, alpha-glucosidase, sickle cell anemia, immune tolerance induction, enzyme replacement therapy, methotrexate, newborn screening

Introduction

Pompe disease (MIM #232300), also known as "glycogen storage disease type II", is an autosomal recessive inborn error of glycogen metabolism that leads to lysosomal storage of undigested glycogen in muscle tissues. It is caused by a deficiency of acid alpha-glucosidase (GAA; EC 3.2.1.20), coded by *GAA* on chromosome 17q25.3. Pompe disease is generally categorized according to the age of onset of clinical manifestations: infantile-onset Pompe disease (IOPD) is characterized by onset of generalized hypotonia, macroglossia, and left ventricular hypertrophy before 12 months of age, and it generally leads to death by respiratory and cardiac failure before the second year of age unless early enzyme replacement therapy (ERT) is instituted (1, 2). Late-onset Pompe disease (LOPD), on the other hand, presents as proximal skeletal muscle weakness that progresses to involve bulbar, respiratory, and distal skeletal musculature as well as visceral smooth muscle, with relative sparing of cardiac muscle (3). Alglucosidase alfa, a recombinant form of acid alpha-glucosidase, is the only ERT modality currently available for the treatment of IOPD and has been shown to increase overall survival and ventilator-free survival, as well as to decrease left ventricular mass and increase left ventricular ejection fraction in patients with classic IOPD (4). The standard, FDA-approved alglucosidase alfa dose is 20 mg/kg every 2 weeks (4), although there is increasing evidence of improved outcomes with administration of higher doses (5–7). Before starting ERT for IOPD patients, the cross-reactive immunological material (CRIM), which is the presence of protein epitopes derived from acid alpha-glucosidase remnants in peripheral blood, needs to be ascertained as CRIM-negative individuals are at higher risk for developing sustained titers of anti-alglucosidase alpha neutralizing antibodies which can lead to treatment resistance and poorer outcomes (8). To prevent the development of anti-ERT antibodies, different immune tolerance induction protocols are used for CRIM-negative (9) and CRIM-positive (10) patients.

Sickle cell anemia (SCA, MIM #603903) is an autosomal recessive disorder of hemoglobin structure caused by the common *HBB* pathogenic variant (NM_000518.5):c.20A>T, p.(Glu7Val) which causes polymerization of deoxyhemoglobin, resulting in chronic intravascular hemolysis and intercurrent vaso-occlusive episodes. The chronic anemia of SCA requires cardiovascular adaptation with increased cardiac output to maintain tissue oxygen delivery, and individuals with SCA demonstrate increased stroke volume, left ventricle dilatation, and left ventricular hypertrophy starting in childhood and proportional to the severity of anemia (11, 12). Individuals with SCA also demonstrate decreased muscle microvascular oxygen delivery, decreased growth velocity, and lower muscle mass compared with healthy children (12, 13).

In this article, we report a patient diagnosed with IOPD and SCA. Although treated with ERT since the first month of life, his clinical course was complicated by left ventricular hypertrophy followed by early-onset dilation in infancy. This is a unique case where both conditions co-occurred in a patient with a severe clinical presentation and course.

Case report

A male newborn of African American ethnicity was born at 39 weeks gestational age from non-consanguineous parents, both previously diagnosed as heterozygous carriers for the *HBB* c.20A>T, p.(Glu7Val) variant. The pregnancy was otherwise uncomplicated. Shortly after birth, he developed respiratory distress requiring transient non-invasive respiratory support and admission to the neonatal intensive care unit. A chest radiograph exhibited marked cardiomegaly (Figure 1A) and physical exam was significant for hypotonia and mild macroglossia. An echocardiogram showed severe left ventricular hypertrophy (Figure 1B). Further studies revealed elevated pro B-type natriuretic peptide (pro-BNP) at 25,701 pg/mL (normal <10,000 pg/mL), creatine-kinase (CK) at 1,374 U/L (normal <300 U/L), and aldolase at 37.8 U/L (normal 0.1−8 U/L). Work-up for other metabolic and genetic diseases, including acylcarnitine profile, total and free carnitine, ammonia, lactate, serum amino acids, and urine organic acids, was non-contributory. Karyotype and chromosomal microarray did not detect abnormalities. A cardiomyopathy next-generation sequencing (NGS) panel analyzing the coding regions of 163 genes associated with cardiac disease was performed at the Washington University Genomic and Pathology Services. Two *GAA* variants, NM_000152.5: c.842G>C, p.(Arg281Pro) and NM_000152.5: c.2560C>T, p.(Arg854*) were found in compound heterozygosity. While the genetic panel was pending, newborn screening (NBS) showed a decreased GAA enzyme activity at 4% (normal >22%). The hemoglobinopathy portion of the NBS showed absence of Hb A and presence of Hb F and S, consistent with SCA. Confirmatory GAA enzyme activity was low at 0.8 pmol/punch/h (normal >3.88) and urine glucotetrasaccharide (Hex4) was elevated at 29.2 mmol/mol creatinine (normal <20) on day of life (DOL) 14. CRIM status determined by Western blotting was positive. The patient was started on alglucosidase alfa infusions (20 mg/kg every 2 weeks) with an immune tolerance induction protocol comprised of methotrexate at 0.4 mg/kg for three consecutive days, starting on the day prior to the infusion, on DOL 30. This protocol was used for the first three enzyme replacement therapy (ERT) infusions (total of 9 doses of methotrexate), as previously described (10).

The SCA diagnosis was confirmed by *HBB* sequencing showing homozygosity for c.20A>T and negative *HBB* duplication/deletion analysis, ruling out hereditary persistence of fetal hemoglobin. He was started on penicillin V potassium

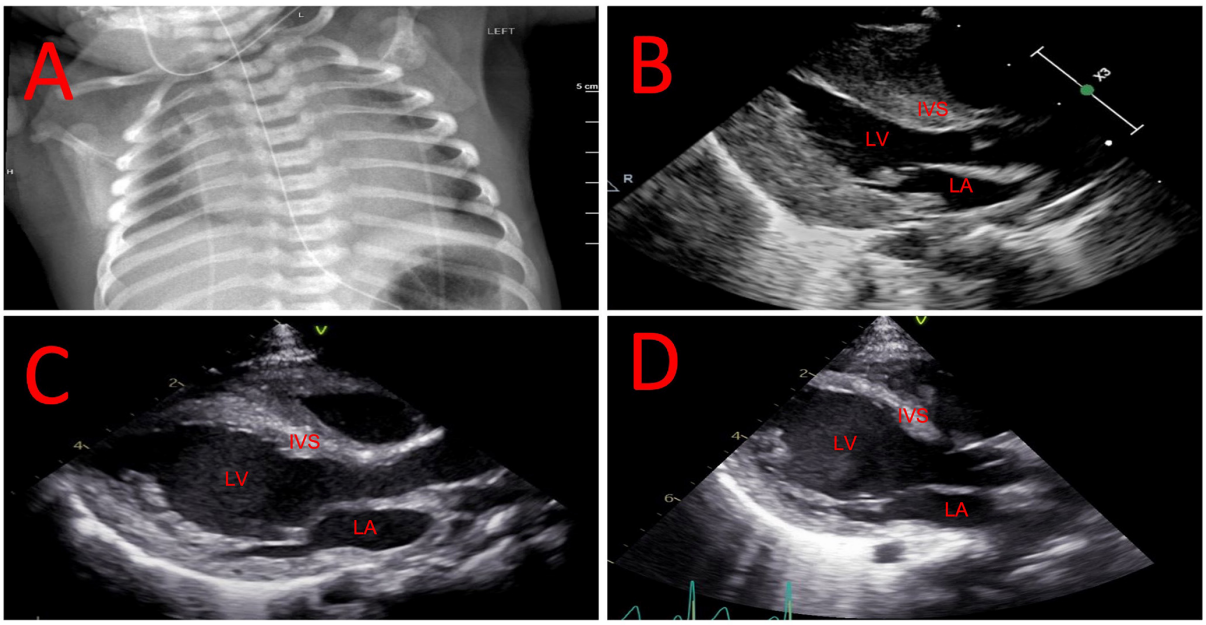

FIGURE 1
Evolution of cardiac hypertrophy and dilation. **(A)** Chest radiograph showing marked cardiomegaly in the neonatal period. **(B)** Echocardiogram showing hypertrophic left ventricle in the neonatal period. **(C)** Echocardiogram showing mixed left ventricular hypertrophy and dilation at 2 months of age. **(D)** Echocardiogram showing resolution of left ventricular hypertrophy with worsening of dilation at 7 months of age. IVS, interventricular septum; LA, left atrium; LV, left ventricle.

prophylaxis at 1 month old. Due to concern that chronic anemia would adversely impact his cardiac function, and that any SCA vaso-occlusive complications such as acute chest syndrome or splenic sequestration in infancy would be poorly tolerated, chronic red blood cell transfusion therapy was chosen as his primary disease-modifying therapy. His first transfusion was administered at 2 months of age when Hb decreased to 8.4 g/dl. His transfusion therapy goal is to maintain Hb >9.5 g/dl to minimize the physiological stress of anemia. At 2 months of life, the patient was noticed to have new-onset left ventricular dilation in addition to cardiac hypertrophy (Figure 1C). Due to concerns for a decrease in left ventricular systolic function the patient was started on enalapril to prevent cardiac remodeling.

He has had 3 readmissions for respiratory decompensation due to viral infections: dual SARS-CoV-2 and respiratory syncytial virus infection at 3 months old (requiring high-flow nasal cannula), human metapneumovirus infection at 5 months old (requiring high-flow nasal cannula in the ICU setting) and rhino/enterovirus at 6 months old (requiring BiPAP in the ICU setting). At 7 months old, his outpatient ERT dosing was noted to having been based solely on birth weight, which resulted in a progressively decreasing ERT dose per kg body weight; on his most recently outpatient infusions this was ∼13 mg/kg, and was corrected to 20 mg/kg. He was admitted subsequently at 7 months old due to respiratory failure with concern for an aspiration event requiring admission to the intensive care unit for non-invasive respiratory support. A repeat echocardiogram showed resolution of left ventricular hypertrophy with continuing dilation (Figure 1D). Evolution of systolic function and cardiac indices are presented in Figure 2. He has received a lifetime total of 10 pRBC transfusions at the time of this report, with a hemoglobin nadir of 7.7 g/dL. He remains gastrostomy-dependent. He continues to exhibit very low axial and appendicular muscle tone. He has required ∼150–160 kcal/kg/day of enteral nutrition since birth for growth; nonetheless, he was at <1% (Z-score = −2.53, WHO Boys 0–2 years) for weight and <1% (Z-score = −3.57, WHO Boys 0–2 years) for weight-for-length at his most recent admission.

Discussion

IOPD, with early onset and a lethal prognosis, can be modified through intervention and therefore meets generally accepted consensus criteria for inclusion in NBS programs (14). In the United States of America, the inclusion of Pompe disease in NBS was recommended in 2015, and currently more than 20 states have started the necessary implementation steps (15). The incidence of Pompe disease is historically reported as ∼1:40,000 live births Western countries (16); however, this epidemiology has been calculated mainly based on European populations, with blind studies showing a higher incidence in other populations

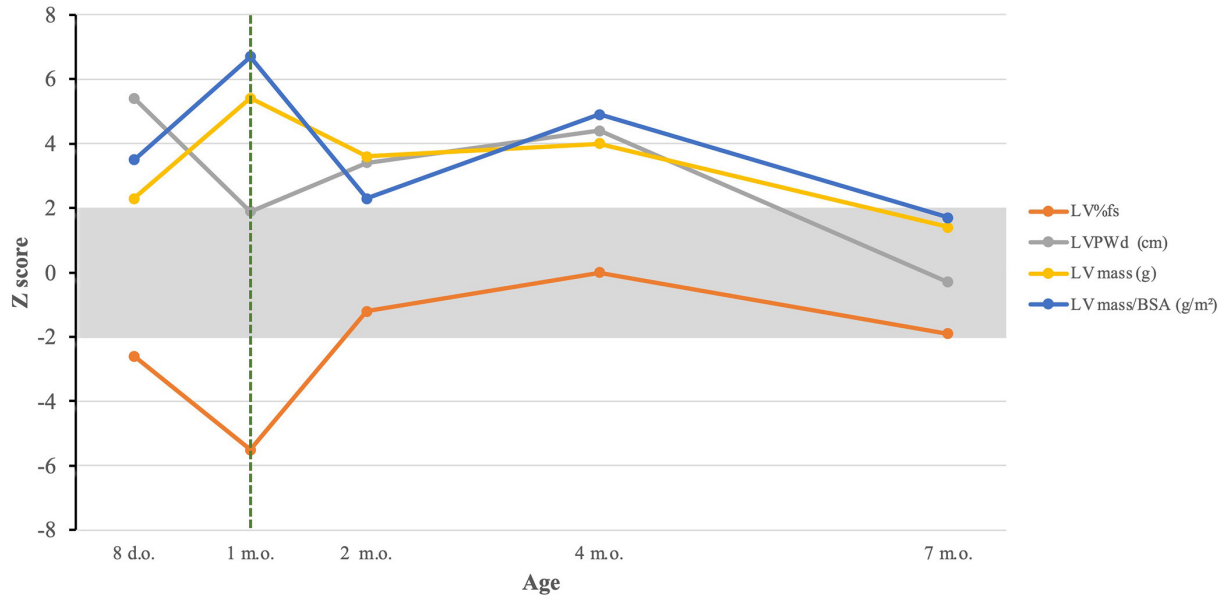

FIGURE 2
Evolution of cardiac indices in response to treatment. The dashed green line represents initiation of ERT. LV%fs, left ventricular percentual fractional shortening; LVPWd, left ventricular posterior wall dimension; LV mass, left ventricular mass; LV mass/BSA, left ventricular mass/body surface area.

including people of African ancestry (17). Moreover, after implementation of universal screening through NBS there have been many reports of an incidence up to 4x higher than expected [as summarized by Davids et al. (18)], pointing to a substantial amount of historically missed diagnoses. SCA, also an autosomal recessive disorder included in NBS, contrasts with Pompe disease by having a high populational prevalence, with ~100,000 diagnosed Americans, of whom ~90% are of African ancestry (19). Prenatal genetic diagnosis for SCA and IOPD, as for most genetic disorders, is still incipient but may allow for even swifter initiation of treatment in future patients. In this article, we have presented a case of concomitant Pompe disease—presenting as IOPD—and SCA. The lack of previous reports of this co-incidence may reflect an epidemiological gap and probable underdiagnosis of Pompe disease in people of African ancestry, reinforcing previous studies (17) and underscoring the importance of universal NBS for equanimity in healthcare.

Two heterozygous *GAA* variants were detected. The p.(Arg854*) variant is predicted to result in a premature stop codon, nonsense-mediated decay, and has been demonstrated to result in an absent gene product (20); this variant has been observed in homozygous or compound heterozygous states in CRIM-negative individuals diagnosed with Pompe disease (21, 22). Published functional studies of the p.(Arg845*) variant have shown negligible activity compared to wild-type protein (23). This variant is commonly observed in individuals of African descent with IOPD (24, 25). This variant meets criteria PVS1, PM2, PM3, and PP4 of the American College of Medical Genetics/Association for Molecular Pathology (ACMG/AMP) guidelines for the interpretation of sequence variants (26) and is thus classified as pathogenic. We also identified a novel variant, c.842G>C, p.(Arg281Pro), in this patient, not previously observed in individuals with Pompe disease. A different amino acid change at the same codon, c.841C>T, p.(Arg281Trp), has been reported as a known likely pathogenic variant (27). Our patient's variant is absent in gnomAD, and multiple *in silico* prediction algorithms are in agreement that this variant may have a deleterious/probably damaging effect on protein function. Given the available evidence and in accordance with the ACMG/AMP guidelines, as well as the ClinGen *GAA* sequence analysis recommendations from ClinGen, the *GAA* p.(Arg281Pro) variant meets criteria PM2, PM3, PM5, PP3, and PP4 and was classified as likely pathogenic. Segregation studies on parental sample further confirmed that the p.(Arg845*) and p.(Arg281Pro) are in *trans* configuration, consistent with biallelic disruption of the gene product.

Treatment of IOPD with alglucosidase alfa ERT has been shown to improve survival, functionality, cardiomyopathy, and weight gain of individuals with IOPD (28), with the better outcomes observed in patients started on ERT in the first month of life (29), as was the case in our patient. In contrast with most other lysosomal diseases, the start of treatment in IOPD is contingent upon determination of CRIM status for appropriate immune tolerance induction as without immunomodulation, virtually all CRIM-negative patients develop a high sustained immune response to ERT that leads to dismal outcomes (9,

30). Although approximately half of CRIM-positive patients do not have significant antibody titers, 32–40% of CRIM-positive patients who receive ERT without immune tolerance induction can develop intermediate- or high sustained antibody titers, leading to worse outcomes when compared to CRIM-positive patients that received immunomodulating agents (8, 31). Currently, the validated immune tolerance induction regimen for CRIM-positive patients contains methotrexate (10), a potent myelotoxic folate antagonist that can lead to myelosuppression. Although this regimen utilizes low-dose, short-term methotrexate, which is generally welltolerated in IOPD patients, this may not be the most suitable regimen for a patient with concomitant bone marrow disease. Evidence for the use of methotrexate in patients with SCA is scarce and includes reports of transient cytopenia despite the concomitant administration of folinic acid (32). In this case report, anemia—which may have been exacerbated by the use of methotrexate—may have led to worsening cardiac dilatation despite ERT, highlighting the complexity of medical care in individuals with a dual diagnosis. As the incidence of Pompe disease increases as a result of universal NBS, more patients with concurrent IOPD and SCA (or other hemoglobinopathies) are expected to be diagnosed, and it becomes necessary to study novel immune tolerance induction protocols without the use of methotrexate, or with maximized support (with agents such as leucovorin or with preventive blood transfusions) for safe ERT initiation in this population. As newer recombinant enzymes and gene therapies are being tested, it will be important that ITI regimens are also validated for co-morbid populations.

Finally, decisions about SCA management were made based on knowledge that growth and cardiac function are more normal in children with SCA who have higher hemoglobin concentrations. Typically, chronic red blood cell transfusion therapy is utilized in SCA for stroke prevention with a primary goal of maintaining Hb S <30%, which may result in a nadir Hb pre-transfusion of <8 g/dl (33). In the current case, since this degree of anemia may compromise growth and increase the risk of cardiac stress, a transfusion strategy similar to that utilized in children with beta-thalassemia major was chosen, in which total hemoglobin concentration is maintained at 9–10 g/dl to minimize anemia-related organ dysfunction (34). Chronic transfusions will cause iron overload, which over many years can increase risk of heart failure but is manageable with iron chelating drugs (34). Hydroxyurea is another option for disease-modifying therapy, but it is not recommended until age 9 months. Patients with SCA have varying response to hydroxyurea, but in general the Hb remains higher on chronic red blood cell transfusion therapy than on this medication (33). Converting to hydroxyurea therapy from transfusion therapy may be a possibility if cardiac function remains stable and his strength is improving as he gets older, with careful monitoring of cardiac and skeletal muscle function. Hematopoietic stem cell transplantation can be curative for sickle cell disease; however, it has a delicate risk/benefit balance and requires a good functional status, thus not being a feasible option for this patient.

Conclusion

We have presented a unique case of concomitant IOPD and SCA leading to complex initiation of ERT and need for aggressive transfusion support to prevent cardiomyopathy due to anemia. As more locations implement NBS for Pompe disease, it is expected that such cases will become more common, and novel protocols that take the myelotoxicity of immune tolerance induction regimens into account will become necessary.

Data availability statement

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

RS wrote the first version of the manuscript. RS, PS, JG, and PD saw the patient at presentation, made the clinical and biochemical diagnosis of Pompe disease and started immune tolerance induction, and enzyme replacement therapy. RS, KL, and HN continued to follow the patient at the genetic clinic appointments, infusions, and admissions. LM saw the patient at follow-up and counseled the family. Y-CH and MS made the molecular diagnosis and wrote the variant analysis. MH made the diagnosis of sickle cell anemia, the decision for chronic transfusion therapy, and has been following the patient throughout life. JC made all the cardiological diagnoses and has been following the patient throughout life. LV and HW have been following the patient from a critical care perspective throughout life. All other authors provided feedback on the manuscript, reviewed it, and approved the final version and the decision to submit it for publication.

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Conflict of interest

Author PD declares the following conflicts of interest: Genzyme: research support, M6P Therapeutics: research support, and Mandos Health: consulting. Author MH declares the following conflict of interest: Pfizer, Inc: spouse employment, Bluebird Bio: consulting, Forma Therapeutics: research funding, Global Blood Therapeutics: research funding and consulting.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Using dried blood spot on HemoTypeSC™, a new frontier for newborn screening for sickle cell disease in Nigeria

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Background: HemoTypeSC is a rapid, point-of-care testing (POCT) device for sickle cell disease (SCD) that traditionally uses the capillary blood from heel stick collected at the point of testing, a procedure that makes mass screening cumbersome and less cost-effective. Using dried blood spots (DBS) on HemoTypeSC could mitigate this challenge. Therefore, this study aimed to determine the feasibility of eluting blood from DBS to read on HemoTypeSC.

Methods: DBS and fresh samples from heel sticks were collected from 511 newborns at the immunization clinics of six Primary Health Centers in Abuja, Nigeria. The two samples from each newborn were analyzed using HemoType SC and then compared with the result of the isoelectric focusing (IEF) test.

Results: Of the 511 newborns, 241 were males and 270 were females. Standard HemoTypeSC (using fresh samples collected from heel sticks) and HemoTypeSC using DBS identified 404 (79.0%) HbAA, 100 (19.6%) HbAS, 6 (1.2%) HbSS, and 1 (0.2%) HbAC phenotypes. The IEF tests identified 370 (72.4%) HbAA, 133 (26.0%) HbAS, 5 (1.0%) HbSS, and 3 (0.6%) HbAC phenotypes. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of HemoTypeSC using DBS, compared to standard HemoTypeSC POCT was 100%. IEF method showed for AA, AS, AC phenotypes; sensitivity; 84.7%, 67%,100% respectively, specificity; 67.6%, 86%, 99% respectively, PPV; 91.2%, 53%, 50% respectively, NPV; 52.7%, 91%, 100% respectively. For SS phenotype, IEF showed 100% specificity, sensitivity, PPV and NPV.

Conclusion: HemoTypeSC test using dried blood spot is as accurate as the standard point-of-care HemoTypeSC test. The use of DBS on HemoTypeSC could ensure better efficiency and cost-effectiveness in mass newborn screening for SCD.

KEYWORDS

sickle cell disease, dry blood spot, newborn screening, HemoTypeSC, Hb Genotype, point-of-care-test (POCT)

1 Introduction

Sickle cell disease (SCD) is a genetic blood disorder with high prevalence in Sub-Saharan Africa (Nnodu et al., 2021). It is estimated that 3,12,000 newborns were born with sickle cell anemia globally in 2010, with 2,30,000 being born in Sub-Saharan Africa, accounting for 80 percent of the global sickle cell anaemia population (Berger et al., 2022) (Lanzkron, Patrick Carroll and Haywood, 2013). In high-income countries, the life expectancy of SCD patients has increased dramatically over the last 40 years, reaching 50 years. Whereas in Sub-Saharan Africa, most children with SCD are thought to die before reaching the age of five (Ware et al., 2017). Predictably between 2010 and 2050, the overall number of births affected by SCD will be 14,242,000. Specifically for Nigeria, the number is likely going to rise from 91,000 newborns with SCA in 2010 to 1,40,800 with SCA in 2050 (Piel et al., 2013). It is expected that large-scale universal screening stands the chance of saving up to 9,806,000 newborns with SCA globally, 85% of these newborns will be born in sub-Saharan Africa (Piel et al., 2013). SCD burden is high in Africa with especially high mortality amongst the under-fives. The prevalence of sickle cell trait in Nigeria is 25% and that of homozygous state is up to 2% in some regions. Nigeria is the country that has the highest burden of SCD (NDHS, 2018). Model estimates from the Nigeria National Demographic Survey showed that the national average under-5 mortality for children with SCD born between 2003 and 2013 was 490 per 1,000 livebirths (95% CI 270–700), 4·0 times higher (95% CI 2·1–6·0) than children with HbAA, with about 4·2% (95% CI 1·7–6·9) of national under-5 mortality attributable to excess mortality from SCD (Hsu et al., 2018) (Nnodu et al., 2021). In high-prevalence areas, there is evidence of several benefits of universal newborn screening (NBS) for SCD (Green et al., 2016).

Except for Egypt, many African nations lack a national NBS program. In the past, the Republics of Benin and Ghana were the only countries in Africa with SCD NBS programs, and even those are not at national levels despite the burden of SCD on the continent and the benefits of NBS with SCD management (Rahimy et al., 2009). Activities in the other countries include a variety of NBS pilot studies (Therrell et al., 2020).

Thus, there is a need for NBS programs to be scaled up nationally in most African countries. In Nigeria, the groundwork for a nationwide program has already been laid, but hampered by inadequate funding, high cost of reagents, and a lack of skilled manpower amongst other obstacles (Hsu et al., 2018). The fact that the bulk of the people in SSA live in rural regions and lacks access to healthcare is one of the most significant difficulties (National Population Commission (NPC) [Nigeria] and ICF, 2019). Point-of- care test (POCT) devices are reliable, easy-to-use and cheap, hence can considerably facilitate the identification of individuals with SCD in Nigeria and other countries in which the SCD prevalence is high (Nnodu et al., 2019).

A few POCT devices for SCD have recently been developed based on differential erythrocyte density (Kumar et al., 2014), differential mobility of Hb S and Hb A through filter paper (Yang et al., 2013), and a polyclonal antibody-based capture immunoassay (Kanter et al., 2015). All of these have one challenge or the other. Some of these challenges are either that the devices require apparatus as an inherent element of the technique to attain maximal specificity and sensitivity, or because of their lack of accuracy (Bond et al., 2017). A unique POCT (HemoTypeSC™ uses monoclonal antibodies (MAb) to distinguish between normal adult haemoglobin (HbA), sickle haemoglobin (HbS), and haemoglobin C (HbC) (Quinn et al., 2016). One of the first reports was in the evaluation of 100 whole blood samples from individuals with common relevant Hb phenotypes. HemoTypeSC was proven to be 100 percent accurate in identifying the proper Hb phenotype (Quinn et al., 2016). Since these antibodies are blind to haemoglobin F (HbF), they can reliably diagnose neonates with increased HbF but low levels of HbA or HbS.

In a study by Nnodu et al. (2019), the overall accuracy, specificity, and sensitivity of HemoTypeSC in identifying Hb phenotypes (AA, AS, AC, SS, SC, and CC) across multiple Nigerian primary healthcare centers in a real-life, field setting were evaluated. The results obtained in this study corroborated previously published findings and revealed a sensitivity and specificity of 100 percent for HbS and HbC, using high-performance liquid chromatography (HPLC) method as gold standard.

Dried blood spot (DBS) is a minimally invasive blood sampling technique. Blood samples are collected from the heel of newborns and applied into a cellulose or polymer card paper. The blood loaded card paper is air dried, after which it is stored in low gas-permeability plastic bags containing desiccant to reduce humidity. DBS is one of the most convenient tools for blood sample collection. Its benefits include; analytical measurements for more than 50 (Fifty) analytes, the sample has been found to be stable for a couple of months at ambient temperature or refrigeration with loss of enzymatic activity to a negligible extent, easy shipment zip-lock bags requiring no cold chain from sampling point to the laboratory and reduced risk of infection as a result of contaminated samples (Saud, 2018). Thus, this is an ideal sampling method in resource-poor settings. DBS sample has an economical preference for many clinical applications (Chace and Hannon, 2016). DBS has been used successfully on isoelectric focusing method (IEF) (Williams, 2016), and HPLC (Inusa et al., 2015).

HemoTypeSC is one of the POCT devices for SCD that has been extensively investigated and found with commendable performance characteristics. The normal HemoTypeSC procedure makes use of fresh capillary blood; hence screening has to be on the spot. Moreover, to reduce the turnaround time, two or three personnel have to be involved in the process, hence making it more cost implicative. These factors reduce the general

effectiveness of the normal HemoTypeSC™ technique for use in a mass screening settings like immunization centers in resource limited countries.

Using fresh capillary blood sample for running HemoTypeSC technique may not provide the required efficiency needed in a mass screening setting. Considering the afore stated challenges, Dry blood sampling may be the way forward.

Here, we tried to determine the possibility of eluting blood from DBS to read HemoType SC™ compared to the standard method of using fresh capillary blood as applied in POCT.

2 Materials and methods

This is a pilot study and the aim is to find out the possibility of eluting blood from DBS to run HemoTypeSC™ protocol and to compare the results obtained with standard HemoTypeSC™ POCT and IEF method. Newborns zero (0) to six (6) weeks of age drawn across six immunization centers in the Federal capital territory (FCT) Abuja participated in the study.

2.1 The test methods

2.1.1 HemoTypeSC™

Monoclonal antibodies (Mab) are used in the competitive lateral flow immunoassay known as HemoTypeSC™ to detect the presence of hemoglobin A, S, and C. The hemoglobin phenotypes HbAA, HbSS, HbSC, HbCC, HbAS, and HbAC are quickly detected using it (Bassimbié Kakou Danho et al., 2021). Each MAb bound just its target in a competitive enzyme-linked immunosorbent test with just 1.0% cross-reactivity. Since these antibodies are blind to haemoglobin F (HbF), it is possible to diagnose neonates with elevated HbF and low levels of HbA or HbS (Nnodu et al., 2019).

A cellulose wick, antibody-impregnated nitrocellulose, and laminated fiberglass sample pads make up test strips, which allow liquid samples to pass through the three components in a particular order. The process involved rehydrating the dried gold conjugate and dilution of the lysed blood sample using an assay solution that contained detergents and non-specific blocking reagents (Quinn et al., 2016). The presence of a line on the strips indicates the absence of the hemoglobin variant in the blood sample (Bassimbié Kakou Danho et al., 2021).

2.1.2 Isoelectric focusing

IEF employs an agarose gel that enables qualitative and semi-quantitative analysis by separating various haemoglobins from a patient sample into distinct bands based on their isoelectric point. Haemoglobins are separated on one axis using IEF gel. Visual comparison of the individual bands to the closest reference samples is a typical method of qualitatively measuring patient sample.

2.1.3 High-performance liquid chromatography

The principle of HPLC is based on the distribution of the analytes between a stationary phase such as the packing in a column and a mobile phase which is the sample or analytes which is pumped through a valve at high pressure. The interaction between the sample and the stationary phase or column depends on the chemical structure of the analyte which allow some molecules to be retained while some pass through more easily. The analyte is detected after leaving the column with the signals converted and recorded by a computer software in the form of a graph in wavelengths called a chromatograph. This method can be used to separate and quantitate haemoglobin and its variants. It is particularly sensitive to the detection Hb A2, Hb F.

Ethical clearance was obtained from Federal Capital Territory Research Ethics Committee. 511 newborns were tested at 6 immunization centers in the FCT.

The sampling was carried out between October 2021 and January 2022. Mothers of all eligible babies coming for immunization at the centers were approached for testing. Informed signed consent was obtained. The "Standard Precautions" protocol developed by the US Centers for Disease Control and Prevention was followed throughout the sample collection and testing to prevent infection when working with human blood samples (Quinn et al., 2016).

2.2 Storage, sampling and testing

The HemoTypeSC test kits containing the lateral flow assay (LFA) test strip, a transfer pipette, a sample cup, and a volumetric inoculation loop were stored at room temperature. HemoTypeSC is considered to be stable in high heat and does not require refrigeration.

Blood samples from babies 6 weeks and below were drawn by heel-prick into labeled filter paper cards unto a HemoTypeSC™ POCT Sample collection strip, supplied by Silver Lake Research Corporation. The POCT was carried out on site, while the blood spots were air dried for a minimum of 3 h at 18°C–25°C, shipped to the Centre of Excellence for Sickle Cell Disease Research and Training (CESRTA), University of Abuja Newborn Screening Laboratory and stored in gas-impermeable zipper bag, containing desiccant sachets and kept in the Refrigerator at −20°C. Iso electric focusing testing was performed at CESRTA lab using DBS. After 1 week, the dried blood sample was eluted and HemoTypeSC™ standard protocol followed to determine the test result. The tests were carried out strictly following the manufacturer's instructions and test results were

TABLE 1 Genotype and allele frequencies identified by HemoTypeSC and IEF in the 6 centers comprising University of Abuja Teaching Hospital immunization centers attached to it.

Id name	N	Genotype											
		Standard POCT HemoTypeSC				DBS HemoTypeSC AA				1 EF			
		AA	AS	AC	SS	AA	AS	AC	SS	AA	AS	AC	SS
1 UATH	167	130 (77%)	35 (20%)	1	1	130	35	1	1	111	53	2	1
2 KHC	13	11 (84%)	2	—	—	11	2	—	—	12	1	—	—
3 TUNG	25	20	5	—	—	20	5	—	—	19	5	1	—
4 ORO	15	12	3	—	—	12	3	—	—	13	2	—	—
5 GTC	263	208	50	—	5	208	50	—	5	191	68	—	4

UATH, University of Abuja Teaching Hospital; KHC, Kutunku Health Center; TUNG, Tunga Maje Primary Health Center; ORO, Orozo Primary Health Center; GTC, Gwagwalada Town Clinic; AND, Angwuan Dodo Primary Health Center.

interpreted based on a reference chart provided by the manufacturer. Clinical control samples of previously-diagnosed AA, AS, SS, and SC individuals were included with each batch of HemoTypeSC and IEF to assess the performance of these techniques. Results from HemoTypeSC standard POCT, HemoTypeSC using DBS and IEF were then compiled in a spreadsheet for analysis.

2.3 Assessment

The sensitivity, specificity, positive and negative predictive values, and overall accuracy of HemoTypeSC using DBS was compared to standard HemoTypeSC POCT and IEF were calculated. Sensitivity was defined as 100% × TP/(FN + TP) specificity as 100% × TN/(FP + TN), positive predictive value as 100% × TP/(TP + FP), negative predictive value as 100% × TN/(TN + FN) and overall accuracy as (prevalence × sensitivity)/(1—prevalence) (specificity), where TP = number of true positive events, FP = number of false positive events, and TN = number of true negative events [18].

3 Results

A number of 241 males and 270 females were screened. The HemoTypeSC standard POCT protocol tests identified 404 HbAA (79.0%), 100 HbAS (19.6%), 6 HbSS (1.2%), and 1 HbAC (0.19%).

HemoTypeSC using DBS showed the same result pattern as that done using the standard POCT protocol. The test cannot differentiate Hb SS and sickle -β^{0-} thalassemia. No HbCC or HbSC were identified. Details per center and allele frequencies are presented in Table 1. The IEF tests identified 370 HbAA (72.4%), 133 HbAS (26.0%), 5 HbSS (0.97%), and 3 HbAC (0.58%). The results of the 84 discordant samples are displayed on Tables 2, 3 gives a summary of the frequency of the various haemoglobin phenotypes. Specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of HemoTypeSC using dried blood spot, compared to standard HemoTypeSC were 100% as seen in Table 4. Isoelectric focusing (IEF) method showed; for AA, AS, AC Sensitivity; 84.7, 67, 100 respectively specificity; 67.6, 86, 99 respectively. Positive predictive value; 91.2, 53, 50 respectively. Negative predictive value; 52.7, 91, 100. For SS phenotype, IEF showed 100% specificity, sensitivity, positive predictive value and negative predictive value. Discordant results were found for a total of 84 samples. These 84 discordant samples were run with HPLC and the following results were obtained: 57 (AA), 21 (AS),1 (SS),1 (A3), 2 (ACS), 2 (DA). The discordant results were analysed by HPLC which showed that HemoTypeSC correctly identified all the HbAA, 21 of the HbAS but categorized 3 AD, 1 AC5, and 1 A3 as AS while IEF failed to identify 30 HbAA, wrongly labelling them as AS and was the only method to report 2 AC. Table 5 shows the measurement of agreement of Kappa between standard HemoTypeSC POCT and DBS HemoTypeSC and the measurement of agreement of Kappa between DBS HemoTypeSC and IEF. The table revealed Kappa value between HemoTypeSC POCT and DBS HemoTypeSC as 1.000 showing a strong agreement. The Kappa value between DBS HemoTypeSC and IEF was 0.540 showing a moderate agreement. For both measurements p-value <0.05 as seen in Table 5.

Results revealed that most of the HPLC results of the discordant samples agree with the standard POCT and DBS HemoTypeSC results and not with the IEF results thus calling into question the validity of the designation of IEF/HPLC as gold standard methods (Nnodu et al., 2019, Nnodu et al., 2020).

TABLE 2 Showing the results of the 84 discordant samples run with HPLC.

	HPLC	POCT HemoTypeSC	DBS HemoTypeSC	IEF
AA	57	57	57	27 (30)
AS	21	26	26	55 (30)
SS	1	1	1	—
AC	—	—	—	2
AD	3	—	—	—
AC5	1	—	—	—
A3	1	—	—	—
	84	84	84	84

TABLE 3 Showing the frequency distribution of the Hb phenotypes studied in the three methods used.

	(%)	(%)	IEF (%)
AA	404 (79.0)	404 (79.0)	370 (72.4)
AS	100 (19.6)	100 (19.6)	133 (26.0)
SS	6 (1.2)	6 (1.2)	5 (0.97)
AC	1 (0.19)	1 (0.19)	3 (0.58)

4 Discussion

Our findings agree with previous studies suggesting a specificity and specificity of 100% (Nnodu et al., 2019) (Olatunya et al., 2021) for HbS and HbC in ideal conditions using the standard HemoTypeSC POCT procedure. Nnodu et al., worked on 1,121 samples and compared HemoTypeSC POCT with HPLC (GOLD Standard). They got a sensitivity of; 0.989 (AA), 0.983 (AS), 1.000 (SS), 0.933 (AC), and Specificity of: 0.993 (AA), 0.992 (AS), 0.999 (SS), 1.000 (AC). Olatunya et al. (2021) in 2021 compared Cellulose Acetate Electrophoresis, HemoTypeSC POCT and HPLC methods with PCR in 158 participants. HemoTypeSC showed both a Sensitivity and Specificity of 1.00 (100%) for AA, AC, AS, SC, and SS. Using DBS to run HemoTypeSC, our study produced a result that is 100% concordant with the standard HemoTypeSC procedure. This means that DBS samples can conveniently run on HemoTypeSC and accurate results produced. SSA countries like Nigeria, with high burden of SCD are faced with challenges of lack of accessibility to healthcare facilities for large portions of their populations. In such situations, primary care must become the focal point of SCD screening and treatment, with focus on initiatives that utilize user-friendly, reasonably priced technology and engage a sizable percentage of the community). No doubt certain attributes and qualities of POCT devices for sickle cell disease screening make it very suitable for use in SSA. These qualities are; kit not requiring rigorous procedure and expensive reagents, special skills and electricity not required.

The 84 Discordant results were run with HPLC which showed that HemoTypeSC correctly identified all the HbAA, 21 of the HbAS but categorised 3 AD, 1 AC5, and 1 A3 as AS. The results obtained by HPLC tally more with HemoTypeSC than with IEF as can be seen from Table 2; HPLC recorded 57 AA and HemoTpyeSC recorded 57 by both DBS and POCT methods, IEF recorded 27. HPLC recorded 21 AS with 5 variants; HemoTypeSC recorded 26 AS while IEF had 55 AS. From the results by the three methods, the ones by IEF seem as the outlier. Obviously using HPLC as gold standard, and referring to Table 3, IEF mis-identified 33 babies who had other phenotypes as having sickle cell trait.

There are still gaps in effective application of POCT in real life mass screening settings like immunization centers. As new knowledge is explored and meaningful collaborations developed, a situation arises when a battery of tests needs to be conducted as is applicable in the advanced countries, the use of these devices as POCT will not suffice, hence the application of DBS on such devices as HemoTypeSC will bridge these gaps.

4.1 Using dried blood spots on HemoTypeSC

Using DBS on HemoTypeSC has the potential of making the move of scaling up efforts to adopt early diagnosis, penicillin prophylaxis and hydroxyurea therapy, to forestall under5 mortality in SSA a reality. High level of discordance was discovered when DBS HemoTypeSC™ and IEF were compared on same subjects (16.4%). Among the 84 discordant samples, the AA and AS phenotype results by HPLC were in agreement with the standard HemoTypeSC POCT result. Only one positive AS sampled agreed with IEF. This goes to reveal the challenge associated with the high technicality involved with IEF and we infer that the IEF run in the Low- and

TABLE 4 Performance characteristics of DBS/POCT HemoTypeSC compared to IEF.

	Pheno-method TN type		FP	FN	TP	Sensitivity	Specificity	PPV	NPV
AA	STD HemoTypeSC/DBS HemoTypeSC	107	0	0	404	1.000	1.000	1.000	1.000
	IEF	81	60	26	344	0.930	0.574	0.850	0.757
AS	STD HemoTypeSC/DBS HemoTypeSC	411	0	0	100	1.000	1.000	1.000	1.000
	IEF	352	26	59	74	0.556	0.931	0.740	0.810
SS	STD HemoTypeSC/DBS HemoTypeSC	505	0	0	6	1.000	1.000	1.000	1.000
	IEF	505	1	0	5	1.000	0.998	1.000	0.996
AC	STD HemoTypeSC/DBS HemoTypeSC	510	0	0	1	1.000	1.000	1.000	1.000
	IEF	508	2	0	1	1.000	0.996	0.330	1.000

STD HemoTypeSC, Standard HemoTypeSC.

TABLE 5 Cohen's Kappa Statistics showing the level of agreement of Kappa between DBS HemoTypeSC/Standard HemoTypeSC and DBS HemoTypeSC/IEF.

Symmetric measures

			Value	Asymptotic standardized error[a]	Approximate T[b]	Approximate significance
Measurement of agreement	Kappa	Standard HemoTypeSC POCT/DBS HemoTypeSC	1.000	0.000	24.009	0.000
	—	DBS HemoTypeSC/IEF	0.540	0.042	13.184	0.000
No of valid ases			511			

[a]Asymptomatic standardized error.
[b]Approximate T.

middle-income countries may not be as efficient as those in the developed or high-income countries IEF method is the gold standard for newborn screening, the inconsistency observed in this study between IEF results and HPLC might be due to technical challenges facing the use of IEF in resource poor settings. Since DBS is utilized in other public health initiatives like HIV screening (Sikombe Id et al., 2019), it is possible that samples from early newborn diagnosis might be quickly and affordably tested for sickle hemoglobin using this technique. Sickle SCAN which is also is a rapid, qualitative, point-of-care lateral flow immunoassay for the identification of AS, AC, SS/Sβ^0thal, SC, and CC/Cβ (Nguyen-Khoa et al., 2018). The limitation HemoTypeSC has is that, it does not detect or identify the β^0 Thal phenotype.

The prevalence for SCD in this study HemoTypeSC both STD POCT and DBS was 1.2% and by IEF was 0.97%. This is within range of the reported prevalence of 1.4% and 1.2% from the same environment by Nnodu et al., 2020 and the 2018 NDHS. About 10 mothers declined their babies being screened for various reasons. Averagely, we can say that the screening apathy was due to lack of proper understanding of the importance of NBS. We suggest a more educational approach to tackle this problem. Other studies with similar sample sizes, came up with similar results, for instance; A study conducted in two selected primary health care centres in Shomolu local government area (LGA) in Lagos, Nigeria involving Two hundred and ninety-one mother-infant pairs presenting for the first or second immunization visit presented similar results. In this study, the haemoglobin genotype of mother-infant pairs was determined using the HemoTypeSC rapid test kit. Confirmation for the infants' Hb genotype was carried out using HPLC. A SCD prevalence of the infant cohort was 0.8% not up to the proposed 2% for Nigeria (Oluwole et al., 2020). In a study conducted in Democratic Republic of Congo

448 children less than 5 years of age were screened. Among this number 12.7% were homozygous (SS) (Aimé et al., 2022). In the NDHS, there were areas of SCD prevalence up to 2% but that was not representative of the whole country.

5 Conclusion

HemoTypeSC test using dried blood spot is as accurate as the standard point-of-care HemoTypeSC test as can be seen from Table 5, with a Kappa value of 1.00. The use of DBS on HemoTypeSC could ensure better efficiency and cost-effectiveness in mass newborn screening for SCD. It can also provide an opportunity to leverage other public health programs such as the early infant diagnosis of HIV which utilize DBS to screen for SCD thus integrating the programs to expand SCD NBS services.

Data availability statement

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Federal Capital Territory Health Research Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

ON provided the conception, design and supervision for this work, CO carried out the study, wrote the first draft of the manuscript, CO and RC performed the statistical analysis, HI, ON, and SA read and revised the first manuscript, CO and ON revised the manuscript and responded to the reviewers comments.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Establishing a database for sickle cell disease patient mapping and survival tracking: The sickle pan-african research consortium Nigeria example

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Background: The Sickle Pan-African Research Consortium (SPARCO) and Sickle Africa Data Coordinating Center (SADaCC) were set up with funding from the US National Institute of Health (NIH) for physicians, scientists, patients, support groups, and statisticians to collaborate to reduce the high disease burden and alleviate the impact of Sickle Cell Disease (SCD) in Africa. For 5 years, SPARCO and SADaCC have been collecting basic clinical and demographic data from Nigeria, Tanzania, and Ghana. The resulting database will support analyses to estimate significant clinical events and provide directions for targeting interventions and assessing their impacts.

Method: The Nigerian study sited at Centre of Excellence for Sickle Cell Disease Research and Training (CESRTA), University of Abuja, adopted REDCap for online database management. The case report form (CRF) was adapted from 1,400 data elements adopted by SPARCO sites. It captures 215 data elements of interest across sub-sites, i.e., demographic, social, diagnostic, clinical, laboratory, imaging, and others. These were harmonized using the SADaCC data dictionary. REDCap was installed on University of Abuja cloud server at https://www.redcap.uniabuja.edu.ng. Data collected at the sites are sent to CESRTA for collation, cleaning and uploading to the database.

Results: 7,767 people living with sickle cell disease were enrolled at 25 health institutions across the six zones in Nigeria with 5,295 having had at least one follow-up visit with their clinical data updated. They range from 44 to 1,180 from 3 centers from South East, 4 from South, 5 from South West, 8 from North Central, 4 in North West and 3 in the North East. North West has registered 1,383 patients, representing 17.8%; North East, 359 (4.6%); North Central, 2,947 (37.9%); South West, 1,609 (20.7%); South, 442 (5.7%) and South East, 1,027 patients (13.2%).

Conclusion: The database is being used to support studies including analysis of clinical phenotypes of SCD in Nigeria, and evaluation of Hydroxyurea use in SCD. Reports undergoing review in journals have relied on the ease of data access in REDCap. The database is regularly updated by batch and individual record uploads while we are utilizing REDCap's in-built functions to generate simple statistic.

KEYWORDS

database, REDCap, sickle cell disease, SPARCO, Nigeria, registry

Introduction

Sickle cell disease (SCD) is an inherited blood disorder arising from mutations in the gene coding for the β globin chain of haemoglobin. This leads to pathogenetic processes culminating in vessel occlusion and progressive ischemia and tissue necrosis. The disease is inherited in a simple Mendelian pattern (Piel et al., 2013) and affects more than 5 million people in Sub-Saharan Africa (SSA). About 150,000 children are born with this condition annually in this region. The incidence of SCD in Nigeria varies from 2% to 3% as reported by various investigators in the different regions of the Country (Grosse et al., 2011).

The disease is marked by acute exacerbations of pain and anemia warranting frequent hospital or clinic admissions and blood transfusion. Chronic complications such as osteonecrosis, leg ulcers, pulmonary hypertension and renal failure may occur. This requires the presence of appropriately trained medical personnel to provide care at various levels of healthcare. This has huge implications on the health economics and fiscal deployment in both adults and children (Baker et al., 2015). There are approximately 111.91 cases of homozygous S (SS) per 100,000 newborns globally, while Africa has a rate of 1,125.49 (Wastnedge et al., 2018). The disease burden of people living with SCD is currently estimated to be approximately 250 million people worldwide, with the majority living in the rural areas of Sub-Saharan Africa (SSA) and with limited access to health care.

The socio-economic impact of the disease on affected persons and families is massive with frequent morbidity associated with a high mortality rate (Olatunya et al., 2015; Nnodu et al., 2021). Health budgeting and intervention planning requires a good estimate of disease burden and patient mapping in order to effectively link patients to care and track other occurrences of significant disease-related events.

An extensive database is also necessary for effective and comprehensive documentation of the natural course of the disease and its complications in the different unique socio-cultural backgrounds found in Africa. The establishment and maintenance of a simple database would provide real time as well as retrospective information on the clinical state of patients across the country. This will also offer a platform for the estimation of significant clinical events including frequency of vaso occlusive crisis, transfusion needs, frequency of complications, pattern of drug prescription as well as survival. These will provide direction targeting interventions and assessing impact of such interventions.

The Sickle Pan-African Research Consortium (SPARCO) and Sickle Africa Data Coordinating Center (SADaCC) consists of physicians, scientists, patients support groups and statisticians who work together to reduce the disease burden and alleviate the impact of disease. These primary objectives are to be achieved by establishing a research database, carrying out research aimed at alleviating disease burden and reducing its impact on already affected persons. SPARCO and SADaCC have over the past 5 years accumulated and synchronized basic clinical and demographic data from Nigeria, Tanzania and Ghana. Challenges abound in a resource-limited setting but the benefits are enormous with regards to limiting waste and–optimizing care.

Databases and other computer based systems

Databases were designed for persistent and integrated storage of data, allowing concurrent access to it by many users. They are collections of records related by referential integrity. Thus, a database is an organized collection of structured data meant to serve many applications with minimum redundancy (Elmasri

and Navathe, 2017). Database technology helps to alleviate many of the problems associated with conventional file organization methods, including data duplication, inflexibility and difficulties associated with online access by users.

Databases, in greatly aiding the availability and searchability of data, have become and indispensable tool for research in medical and other fields. For example, well-designed biological databases have become a powerful tool in biological research (Dong et al., 2015). Also, it is now well established that keeping electronic medical records leads to dramatic improvements in the level of care provided by health institutions. This was shown in a 2006 study on electronic medical records (Akor et al., 2018). The study showed, among others, that EMR facilitates easy access to medication administration records, sharing of consultation reports, and decreased transit time of test results by reducing the time taken to deliver paper versions.

Other developments in computing and computer technologies that have benefitted medical research include Data/text mining, Computer modeling. Medical imaging/ anomaly detection and Machine learning. Applications of these techniques have been discussed in the literature (Hand et al., 2001; Lei and Karniadakis, 2013; Solanki, 2014; Khalaf et al., 2016). The use of Pattern Recognition techniques in medicine have also been studied (Benamrane et al., 2005; Bacardit et al., 2014). An interesting case of the application of text and data mining in SCD research is the development of an information exploration system, Dragon Exploration System for SCD (DESSCD), which aims to promote the easy exploration of SCD related data. The system processed 419,612 MEDLINE abstracts retrieved from a PubMed query using SCD-related keywords. The processed SCD-related data was then made available *via* the DESSCD web query interface that enables information retrieval using specified concepts, keywords and phrases, and the generation of inferred association networks and hypotheses (Essack, 2013).

REDCap and electronic data capture

One tool currently used by researchers in many countries to manage research data collections is the Research Electronic Data Capture (REDCap) application. REDCap is a mature, secure web application designed to support data capture and managing online databases. While REDCap can be used to collect virtually any type of data, it is specifically geared to support data capture for research studies. The application allows users to build and manage online surveys and databases quickly and securely, and is currently in production use or development build-status for more than 290,000 projects with over 398,000 users spanning numerous research focus areas across the consortium (Harris et al., 2019).

There are many other Electronic Data Capture software that are being used in medical research; some of these are Catalyst Web Tools, OpenClinica, IBM Clinical Development and Videoc; REDCap has been found to compare well with some of these other systems (Franklin et al., 2011). It has even been suggested that the strength of REDCap as it pertains to its use in medical research is that it is primarily a clinical research database built by clinical researchers specifically for clinical research (Patridge and Bardyn, 2018). REDCap is a secondary survey tool that provides an easy-to-use interface and several desirable features for data collection, management, analysis, and reporting (Harris et al., 2009; Harris et al., 2019).

Projects are self-sufficient and workflow-based; the focus is on collecting data and exporting it to statistical programs and other data analysis software. REDCap is designed to provide a secure environment so that research teams can collect and store highly sensitive information. It is a flexible tool that can run on multiple operating systems such as Linux, UNIX, Windows, and Mac. We deployed REDCap at CESRTA, with an administrator and 4 data clerks who manage the recording of data into the database. The administrator for the system is a certified cloud infrastructure engineer from the University of Abuja's IT unit. The Principal Investigator (PI) and Data Manager were also assigned administrator roles. The users are verified members of the research team; the Site Lead determines the level of access and privileges granted to each user by the administrators.

Methodology

The study site was based in the Centre of Excellence for Sickle Cell Disease Research and Training (CESRTA), University of Abuja. The subjects are patients recruited into various research projects at CESRTA (https://cesrta.uniabuja.edu.ng/). Data was collected from consenting patients attending sickle cell clinics using case report forms (CRFs) designed for the project after ethical approval. The soft copy of the CRFs were produced on Excel sheets and shared with all the collaborating sites in Nigeria. This was preceded by a meeting of all the site leads who are doctors who run the adult and paediatric sickle cell clinics all over Nigeria and were available to be part of SPARCO. In these meetings data managers/collectors were trained on how to fill the CRFs and also to input the data electronically. The data collected with the Excel sheet are regularly sent for central collation at CESRTA where it is then batch uploaded into the REDCap database.

There are two studies currently ongoing on the REDCAP platform, 1) the SPARCO description of phenotype and 2) the survival study from the newborn screening. For the SPARCO phenotype study, we had a local care report form which was used to collect full demographic and clinical data from patients attending the SCD clinics at SPARCO centers across the country. This was then used to develop the CRF for enrollment of patients into the SPARCO registry. The hard copy CRF forms were deployed to the SPARCO Nigeria Sites for patient enrollment. Site leads were brought to

CESRTA for a data management workshop and training on the use of REDCap. Feedback was received and used to modify the first CRF, standardizing it and making it possible to separate features of past medical history, presenting symptoms and monitor follow-up data. The CRF was designed to achieve full clinical phenotyping and to obtain laboratory information as they become available. It included demographic, social, diagnostic, clinical, laboratory, imaging, and research data elements, all totaling 125 variables ("field name"), to be included in the database. These variables were harmonized using the SADaCC data dictionary; trainings were also conducted by the Big Data Analytics team in order to assist the team members harmonize the data elements in line with the SCD Ontology. Before implementation in REDCap. REDCap was installed on the University of Abuja dedicated cloud server by the University's server Administrator/Webmaster at https://www.redcap.uniabuja.edu.ng alongside requisite applications such as MySQL database server and PHP. An Administrator, who can add users to the software and assign them permissions, was then designated. Users can create new projects or be assigned roles by project owners.

Creating a new project is done at the +New Project tab after logging in to REDCap. When a user creates a new project, the project is automatically set in development status, allowing the user to edit the project and test it before uploading real data. Once a project has moved to production status, it can no longer be edited.

The REDCap administrator created a project for our site with the record auto-numbering feature enabled. After thoroughly testing the project setup and being found satisfactory, it was moved to Production Status, which made it available online for duly authorized users.

Data tables were created in the Project to adequately represent all the data being gathered. Such Tables included: Basic demographics of the screened population, results of screening, contact numbers, exact location, names of schools and nearest primary health care centres. For those with sickle haemoglobin, SS or SC, only basic patient data (demographics), routine clinic visits, acute care visits, hospital admissions and laboratory studies are collected. Each table was developed with relevant data elements suggested by the requirements analysis and was translated into user interface forms and field-tested at the data collection sites. Changes were made in the design of the Tables based on the results of the field test. All these were created on the REDCap project with appropriate form interfaces for data capture. At CESRTA, the data collected from the screening points were initially prepared in MS Excel worksheets and uploaded in comma-separated (csv) format following the Data Dictionary template. The use of mobile devices were later introduced, allowing for secure on-site clinical use as well as the collection and transmission of research data to the online project. In addition, individual data records are sometimes entered directly as the need arises. All the submitted data are subjected to quality checks by the data management team.

Results

Data was obtained from 27 centers made up of 25 tertiary health institutions, 2 secondary and one private hospital currently engaged in SPARCO Nigeria patient enrollment. Table 1 shows the centres across the country that are currently enrolling patients on the SPARCO platform.

A total of 7,767 people living with SCD have been enrolled into the SPARCO Nigeria data platform and another 5,295 have had at least one follow up visit with their clinical data updated. This represents an estimated 0.001% of the entire population of sickle cell patients in Nigeria. The number of recruited patients range from 44 to 1,180 and included 3 centers from South East, 4 from South, 5 from South West, 8 from North Central, 4 in North West and 3 in the North East. As at the time of this report, the North West had registered 1,383 patients, representing 17.8%, North East, 359 patients (4.6%), North Central, 2,947 patients (37.9%), South West, 1,609 patients (20.7%), South, 442 patients (5.7%) and South East, 1,027 patients (13.2%). This is shown in Figure 1.

From the basic analysis done on the data with the REDCap analysis tools, the following were observed:

Age: the age of patients' ranges from 0 to 64 years, with a mean value of 16.58 and median value of 16 years

Gender: 48.9% of the patients are Males, while 51.1% are Females. This displayed in Figure 2.

Genotype: the distribution of the patients by genotype is as follows, and is displayed in Figure 3.

HbSS—96.9%
HbSBThal—0.2%
HbSC—2.9%, and
HbAS—0%

It could also be observed that, though the data was collected at 27 centres from across the country, all the States of the Nigerian Federation were represented in the data set. The database could thus be said to be generally representative of the Nigerian population.

Discussion

Using REDCap features as described, we had designed data tables to store all the data elements defined in the Nigeria-specific Case Reporting Form (CRF) and SPARCO data dictionary. The online availability of the REDCap database makes it convenient for the Team members to access the database for data research, insertion, updates, viewing and reporting according to the access privileges of each member. This has been demonstrated by a preliminary analysis of the clinical phenotypes of SCD in Nigeria which was published (Isa et al., 2020) and a study on the evaluation of Hydroxyurea use in SCD (Chianumba et al., 2022). Other completed studies with submitted manuscripts undergoing review in different journals have relied heavily on the ease of access to data in the REDCap project. Data

TABLE 1 Enrolment by SPARCO centers across Nigeria.

Hospital name abbreviation	Institution's full name	Geopolitical zone	Number
UMTH	University of Maidugiri Teaching Hospital	North East	200
FTH, GOMBE	Federal Teaching Hospital Gombe		78
FMC Yola	Federal Medical Centre, Yola		81
BDTH	BARAU DIKKO TEACHING HOSPITAL KADUNA	North West	243
ABUTH	Ahmadu Bello University Teaching Hospital, Zaria		599
AKTH	Aminu Kano Teaching Hospital		291
FMC, BK	Federal Medical Centre, Birnin Kebbi		250
JUTH	Jos University Teaching Hospital	North Central	679
UATH	University of Abuja Teaching Hospital, Gwagwalada		1,180
FMC KEFFI	Federal Medical Centre Keffi		378
NHA, P	National Hospital Abuja		316
NGH	General Hospital Nyanya		202
NHA, A	National Hospital Abuja, Adult		99
ZMC	ZANKLI MEDICAL CENTRE, Abuja		49
MGH	Maitama General Hospital		44
UNTH	University of Nigeria Teaching Hospital, Enugu	South East	426
AEFUTHA	Federal Teaching Hospital Abakaliki		280
NAUTH	Nnamdi Azikiwe University Teaching Hospital		321
UCH	University College Hospital, Ibadan	South West	678
OAUTH, WGH	Obafemi Awolowo University Teaching Hospital, WGH		551
LASUTH	Lagos State University Teaching Hospital		101
OAUTH, C	Obafemi Awolowo University Teaching Hospital College		144
LUTH	Lagos University Teaching Hospital		135
FMC ASABA	Federal Medical Asaba	South	111
RSUTH	River State University Teaching Hospital		163
ISTH	ISTH Irrua		99
UUTH	University of Uyo Teaching Hospital		69
	Total		7,767

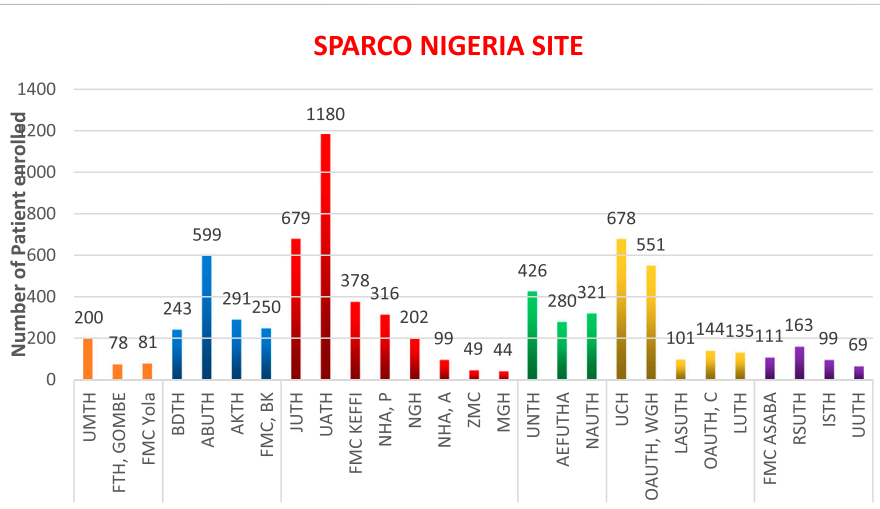

FIGURE 1
Enrolment by SPARCO Nigeria sites.

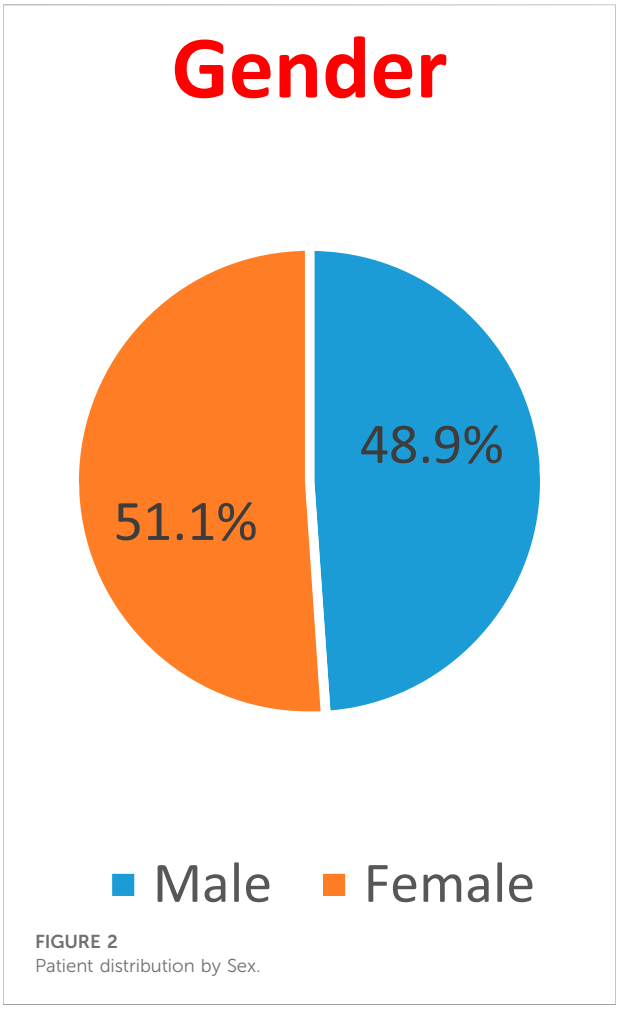

FIGURE 2
Patient distribution by Sex.

upload is also regularly done both by batch upload and individual record insertion.

Several other studies on SCD have used REDCap for data storage and management and they report on the strengths of the software, which include rapid development of forms by technical staff with limited programming skills (Patridge and Bardyn, 2018), flexibility in data entry and analysis, efficient and secure methods for data collection, ease of use and quick turnaround, and very straightforward data exports, with exported data automatically coming in SPSS, Excel/CSV, SAS, R, and STATA formats (Franklin et al., 2011). Availability of copious amounts of training materials has also been cited as an advantage (Franklin et al., 2011). Using REDCap has aided the project's data management function in a highly resourceful manner. From converting the CRF to representative data tables, and enforcing data quality and integrity, to executing data queries, REDCap provides the tools to effectively execute all desirable data management functions. We have also been able to utilize some of its in-built functions to generate some simple statistics on the data. To continually support security of the research data, and to maintain smooth data management operations, the University of Abuja REDCap instance has gone through a couple of upgrades resulting in the current version being used. This registry is an additional resource to the existing sickle cell databases in Africa and other parts of the world such as the Globin Research Network for Data and Discovery (GRNDaD), Sickle Cell Clinical Research and Intervention Program (SCCRIP), the Sickle Cell Data Collection (SCDC) program all in the United States. (Boye-Doe et al., 2020; Hankins. et al., 2018; CDC (Centers for Disease Control and Prevention), 2020). In the United Kingdom, some of the sickle cell registries include, the NHS Sickle Cell and Thalassaemia Screening Programme, National Haemoglobinopathy Register,

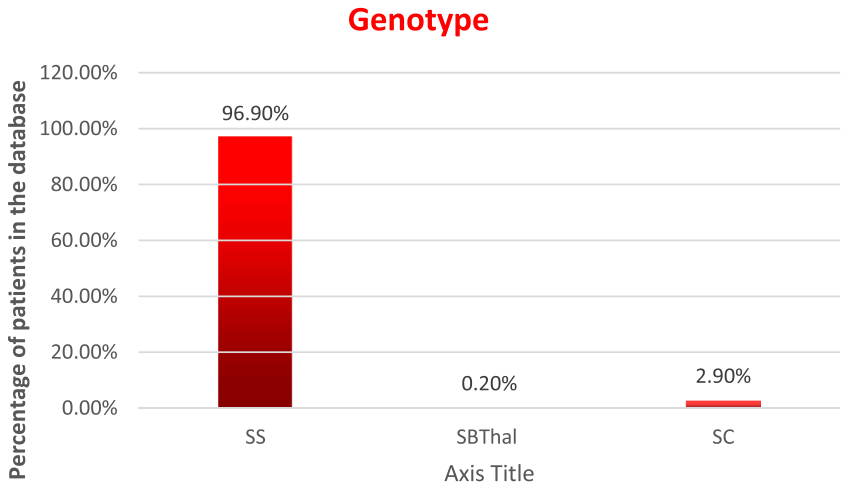

FIGURE 3
Distribution of patients by Genotype.

Screening Wales and Cardiff Sickle Cell and Thalassaemia Centre, and Paediatric and Adult Haematology Lead Republic of Ireland. (Dormandy et al., 2018). Most of these registries collect longitudinal data and are multicentred. The SCCRIP database is a single institution registry and in addition, has retrospective data. The main objective of these registries is the evaluation of outcomes of interventions and research with a view to improving the quality of life and survival of patients with SCD.

Conclusion

The initial challenge is that of getting like-minded researchers to agree with regards to the importance and value of available patient data on a particular disease. This required several correspondence and meetings and some funding. Another option is to rely on already existing networks, like SPARCO in this case.

Similar to the Tanzanian study reported in (Tluway and Makani, 2017), this work addresses the paucity of elaborate databases for many non-communicable diseases in Africa. The lack of cohesion and sustainability had hampered the availability of an online and broad-based data pool of sickle cell patients in Africa. Setting up such an online massive database is froth with several challenges that were dealt with in this manuscript. This manuscript will therefore serve as a guide for future data collection of a large pool of patients by researchers across several countries and on a variety of diseases.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

ON and OO conceptualized the article, ON and OO drafted the manuscript, RC analysed the data and AM, RC, HA, SO, ON, RS, AS, VN, JM, MJ, GM, AW, and OO all contributed. HI substantially contributed to the revision of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary Material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.1041462/full#supplementary-material

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Development of multi-level standards of care recommendations for sickle cell disease: Experience from SickleInAfrica

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Introduction: Sickle Cell Disease (SCD) causes significant morbidity and mortality particularly in sub-Saharan Africa (SSA) where it contributes to early childhood deaths. There is need to standardize treatment guidelines to help improve overall SCD patient health outcomes. We set out to review existing guidelines on SCD and to set minimum standards for management of SCD for the different referral levels of healthcare.

Methods: A standards of care working group (SoC-WG) was established to develop the SoC recommendations. About 15 available SCD management guidelines and protocols were reviewed and themes extracted from them. The first draft was on chosen themes with 64 major headings and subtopics. Using a summarised WHO levels of referral document, we were able to get six different referral levels of healthcare. The highest referral level was the tertiary facilities whilst the lowest level was the home setting. Recommendations for SCD management for the regional, district, sub-districts, health posts and CHPs compounds were also drafted.

Results: The results from this review yielded a guidelines document which had recommendations for management of SCD on 64 topics and subtopic for all the six (6) different referral levels.

Discussions: Every child with SCD need to receive comprehensive care that is coordinated at each level. This recommendation is unique in terms of the availability of recommendations for different levels of care as compared to the traditional guidelines which is more focused at the tertiary levels. Patients can access care at any of the other lower referral hospitals and be managed with recommendations that are in keeping with institutional resources at that level. When such patients need care that requires expertise that is not available at that level, the recommendations will be to refer to the appropriate referral level where those expertise are available. This encourages patients to have good clinical care

nearer their homes but also having access to specialist screening modalities and expertise at the tertiary hospitals if need be. With this, patient are not limited to a specific referral level when interventions cannot be instituted for them.

Conclusion: This SoC recommendations document is a useful material that can be used for consistent standards of treatment in SSA.

KEYWORDS

standards of care, Sickle Cell Disease, SickleInAfrica, Sickle Pan African Research Consortium (SPARCO), Sub-Saharan Africa

Introduction

Sickle Cell Disease (SCD) is a group of inherited red blood cell disorders characterized by presence of abnormal haemoglobin resulting in formation of hard and sticky C-shaped red cells (CDC, 2022). This is caused by a single base-pair point mutation in the 6th position of the beta globin chain leading to substitution of the amino acid glutamic acid to valine (GAG to GTG) (Genetic Mutation, 2022). The most common types of SCD are SCD-SS, SCD-SC and SCD-S beta thalassemia. SCD causes significant morbidity and mortality particularly in SSA. SCD is one of the leading causes of hospitalization and mortality in under-fives in Africa. The clinical manifestation of SCD are varied and due to the short life span of sickled red blood cells and their tendency to get stuck in the blood vessels and impair the blood flow. Symptoms and signs include anaemia, pain episodes, infections, stroke, and other symptoms depending on the organ involved.

Over 300,000 babies are born annually worldwide with SCD and most of them are found in low and middle income countries (LMICs). About 75% or more of these births are in Sub-Saharan Africa (SSA) (Piel et al., 2013). SCD contributes to the high health burden in SSA and to early childhood deaths if no interventions are put in place. If existing evidence-based cost-effective interventions were implemented in SSA, they could prevent about 70% of these childhood deaths. Therefore, there is need to implement strategies and treatment guidelines to help improve overall SCD patient health outcomes through standardization of quality care. A commonly used approach is the use of "Standard of Care" guidelines for healthcare professionals.

In September 2015, the National Heart, Lung and Blood Institute (NHLBI) of the National Institute of Health (NIH) of the United States of America issued a Request for Application (RFA-HL-17-006) for establishment of a "Sickle Cell Disease in Sub-Saharan Africa: Collaborative Consortium". A multinational collaboration among Muhimbili University of Health and Allied Sciences (MUHAS), Dar es Salaam, Tanzania as hub and three sites; MUHAS, Dar es Salaam, Tanzania, University of Abuja, Abuja, Nigeria and The Kwame Nkrumah University of Science and Technology, Kumasi, Ghana applied for and was awarded the grant (U24HL135881) (Yoshizawa et al., 2019).

Sickle Pan Africa Research Consortium (SPARCo) was established with a vision to transform the health of individuals with SCD in SSA through the establishment of a robust and portable framework for research and healthcare. Its first goal was to reduce morbidity and mortality in SCD in Africa through implementation research that will demonstrate the feasibility of introducing newborn screening (NBS) and providing comprehensive care to prevent, identify, treat and manage acute and chronic complications. Specific aim two of the proposal was to develop, implement and evaluate a resource-based, multi-level "Guidelines for Management of SCD in SSA". The specific objectives were as follows;

1. To review existing guidelines on SCD
2. To set minimum standards for management of SCD based on institutional and human resources
3. To field test the compiled SoC guidelines in the various countries (Makani et al., 2020).

Standard of care definition

The term "standard of care" (SoC) refers to the reasonable degree of care a person should provide to another person, typically in a professional or medical setting (Standard of Care, 2022). Medically, it refers to treatment guidelines that are accepted in the medical community as the most appropriate for the treatment of a certain disease or condition (NCI, 2011). SoC provide clinical practice guidelines which outline formal diagnostic and treatment processes that a doctor will follow in management of a patient with a specific illness. SoC are commonly developed by a medical society or organization working on the specific disease. The use of SoC has been found to improve quality of care for patients and reduce incidences of malpractice (Mccabe et al., 2009).

Importance of SoC tailored for specific levels of healthcare facilities

There are various SCD SoC guidelines worldwide (Heart and Institute, 2014; De Montalembert et al., 2011; Sicklecell Society, 2018; Wilson, 2019; MEDBOX, 2022). However, the majority of the existing guidelines are one level guidelines, developed to be used in tertiary level healthcare facilities where resources and expertise are available (Alli et al., 2014; Heart and Institute, 2014; Sicklecell Society, 2018). This is not feasible in many African settings where there are limited tertiary level healthcare facilities (see Table 1 for descriptions of classification of the different levels of healthcare facilities). Furthermore, some tertiary level healthcare facilities in Africa are not well-resourced, which results in some well-established SCD centres having to adapt existing SCD SoC based on the availability of resources. Given that anecdotal data shows that majority of patients are seen and managed at the lower level healthcare facilities before being referred to tertiary hospitals, the use of the tertiary level guidelines by the lower level healthcare facilities would be inappropriate. Although there are efforts to develop guidelines at the institutional and national levels, we decided to develop multiple

TABLE 1 Summary of WHO classification of healthcare facility levels.

Standard version	Last referral hospital (LRH)	University teaching hospital (private, government or mission); may serve as a regional centre for sickle cell Disease	Highest level of medical care available in the country or region
Limited Version 1	Secondary Referral Hospital (SRH)	Regional Hospital (private, government or mission), Community Hospital; may serve as a Regional Centre for Sickle Cell Disease	Multi-specialist intramural and extramural care and services. May also have special expertise in some particular diagnostic or treatment domain that may qualify it as the last referral for that specific subject
Limited Version 2	First Referral Hospital (FRH)	District Hospital (private, government or mission); may serve as a Sub-Regional Centre for Sickle Cell Disease	Intramural medical care of a level or complexity beyond that feasible by ambulatory care in the particular area, district, or region
Limited Version 3	Level II Health Centre	Health Centre	Ambulatory and curative services; health promotion, prevention, and education; support for Level I Health Centres; maternity and observation beds; outpatient operating room; staffed by multidisciplinary team of professional and auxiliary health workers; population served maximum 100,000
Limited Version 4	Level I Health Centre (HC I)	Dispensary, Health Post, Health Sub-center, or Community-based Health Planning and Services (CHPS) Compound (Ghana)	Limited ambulatory and curative services; community development; no beds—possibly one maternity bed; staffed by auxiliary nurse midwife; population served <10,000
Home Version	Home	Home (urban or rural)	No medical expertise; with or without electricity or refrigeration; with or without private transportation

recommendations for SoC guidelines to match the availability of facilities and expertise for different levels of healthcare facilities in SSA (Table 1).

The Sickle Cell Foundation of Ghana in 2012 were the first to develop SCD guidelines for each of the different referral levels of healthcare for Ghana. The current work adopted this multi-referral level guideline development. The Ghana guidelines recognises the disparities in the availability of resources at the different levels of healthcare facilities and incorporates it into the guidelines. These levels of healthcare was adopted from the WHO document on the levels of referral. This WHO document has five referral levels for healthcare facilities depending on resources available. The highest level of medical care available in the country comprise the tertiary level and mostly a University or teaching hospital. There was the inclusion of a 6th referral level which is the home SCD management guidelines targeted at the patient or their parents. The highest referral level is the tertiary level health facility. There are recommendations for the regional level facilities, district level facilities, health centres, health posts/dispensaries/Community-based health planning and services (CHPs) compound which is unique to Ghana and finally the home level recommendations. The highest level guideline is also denoted as the "Standard Version" for the tertiary healthcare facilities. This standard version is then also scaled down for the other lower-level health facilities. These are also denoted as limited Version 1 for the Regional hospitals, Limited Version 2 for the district hospitals, limited version 3 for the health centres and limited version 4 for the dispensary, health post or CHPs compounds. The Sickle Cell Foundation of Ghana has a unique guideline, the home management guideline as the last level.

The Sickle Pan Africa Research Consortium (SPARCO) adopted the SoC guidelines design approach developed by the Sickle Cell Foundation of Ghana. This design is especially suitable for developing countries where healthcare infrastructure and human resources are largely low with patients being managed with restricted resources. It is our expectation that the SPARCO SCD SoC recommendations will guide all cadres of healthcare providers at all the different referral levels of healthcare, therefore improving the quality of care given to individuals with SCD.

Methodology

Setting up of the working group

A standards of care working group (SoC-WG) was established to develop the SoC recommendations for use in the various referral levels of healthcare. The SoC-WG comprised of seven members who were elected from all the three sites (Ghana, Nigeria and Tanzania) in the Sickle Pan Africa Research Consortium (SPARCo). Each of the sites nominated two (2) doctors with a background in haematology to be part of the team. One member of the group who was a clinical psychologist, although not part of SPARCO, was co-opted to help with the section on psychosocial support for Sickle Cell Disease (SCD) patients as he had lots of experience with it. The chairperson of the working group was a Professor of Haematology with experience in guidelines development and the other members of the group were people who had helped with guidelines at their national levels.

Project management

A detailed work plan (Table 2) was developed according to the grant proposal and members worked according to the fixed timelines. To achieve our goals, assignments were initially discussed and distributed to members. Monthly online meetings were held and communications *via* email and WhatsApp were conducted to keep

TABLE 2 SPARCO standards of care working group: Detailed work plan.

Yr	#	Activities	Methods	Start date	End date	Responsible	Status
1	1	Set up a Care Standards Committee within SPARCO health working group					
	2	Collect and review all the SCD management guidelines and protocols available at Consortium sites					
	3	Review the latest versions of management guidelines from the US, UK, France, Brazil and Jamaica					
2	4	From reviews: develop "Common" Guidelines for Management of SCD in SSA					
	5	Set minimum standards for management of SCD based on institutional technical and human capacity for each level of healthcare					
3	6	One-year of extended field testing, including SPAN sites					
	7	Final versions of minimum standards, in English, French and Portuguese, will be disseminated mostly through the internet, hard copies in areas where internet service is poor and a Mobile application (App) version					
4	8	Set approval of the Regionalized Common guidelines from Ministry of Health, Medical and Nursing organizations, and the major healthcare institutions within the regions for incorporation into their system of implementation					
	9	A plan for continual review and modification of the Final Versions of the Regionalized Guidelines of Management of SCD in SSA will be developed					

SPARCO, Sickle Pan African Research Consortium; SCD, Sickle Cell Disease; US, United States; UK, United Kingdom; SSA, Sub-Saharan Africa

track of the work. In-person working meetings were also held during the consortium's bi-annual meetings.

A database detailing the elements of the SoC recommendations with the activities to be conducted was developed by the members of the working group. These elements were agreed upon by consensus after appraisal of the literature available. This database for the review process included the contact information for members of the SoC WG, the workplan and activity tracker for the working group members. Metrics to analyse and compare guidelines were also developed. The first task was to review all the available SCD management guidelines and protocols.

SCD guidelines review

Before the review process, several stakeholders in and outside Africa were contacted for a copy of their SCD management guidelines. The SoC WG members reviewed 15 guidelines from US, UK, France, Brazil and Jamaica and from the three sites in SPARCo and SADaCC. These guidelines were grouped into African (Alli et al., 2014; MEDBOX, 2022) and non-African guidelines (Sickle Cell Unit, 1997; Ali Susanna, 2008; Sicklecell Society, 2010; De Montalembert et al., 2011; NICE, 2012; CanHaem, 2014; Heart and Institute, 2014; Colombatti and Sainati, 2016; Sicklecell Society, 2018; Sirigaddi et al., 2018; Liem et al., 2019; Wilson, 2019). These guidelines were mostly national guidelines for the tertiary level healthcare (Table 3).

Appraisal of guidelines

The working group members were assigned sets of guidelines from the different countries other than their own country to review. They were assigned the guidelines based on their specialties and area of interests making sure that assignments were evenly distributed. From this review, sets of themes which were common in all the guidelines were documented and other themes which were deemed important but not common in all the guidelines were also extracted and agreed upon by the group. These themes were compiled into a single document and afterwards, an in-depth review was undertaken from which the detailed guidelines were written.

The themes that were chosen were grouped into the following major headings (Table 4): Diagnosis of sickle cell disease and related conditions, Health maintenance and preventive therapy, Screening for specific complications of SCD, management of acute complications of SCD, management of chronic complications of SCD and special management protocols e.g., hydration guide, analgesic therapy and their use in SCD and hydroxyurea therapy. Under these major headings were other sub topics for consideration. These sections made up 64 topics and subtopics.

Specific subtopics were then assigned to working group members to review the different guidelines and adapt them to suit our population. There was the need to develop the guidelines to also suit lower referral health facilities that also manage SCD patients. The working group adopted a classification of healthcare facilities based on the summarised

TABLE 3 Existing guidelines reviewed by the SoC working group.

African Scd General Guidelines	Non-African Scd General Guidelines
Management of Sickle Cell Disease- The United Republic of Tanzania	Management of children with Sickle Cell Disease in Europe: current situation and future perspectives. R Colombatti and L. Sainati (16)
National Guidelines for the Control and Management of Sickle Cell Disease—Federal Ministry of Health, Nigeria (10)	Sickle Cell Disease: The Clinical Care Guidelines of the Sickle Cell Unit– Watermarked Jamaica. (18)
Recommendations for the management of sickle cell disease in South Africa. Alli N.A. et al. (14)	Consensus statement on the Care of Patients with Sickle Cell Disease in Canada, CanHaem (15)
Draft Sickle Cell Management Guidelines for Ghana	• NHLBI- Evidence based management of Sickle Cell Disease—Expert Panel report 2014 (9)
	• A parent's guide to managing Sickle Cell Disease. NHS(UK) - Screening Programme-Sickle Cell and Thalassaemia (19)
	• Sickle Cell Disease in childhood. Standards and guidelines for clinical care NHS (UK)-2010 (24)
	• ENERCA Clinical recommendations for disease management and prevention of complications of sickle cell disease in children. Mariane de Montalembert, et al. (23)
	• Standards for the clinical care of adults with Sickle Cell Disease in UK. Sickle Cell Society, 2008 (20)
	• Outcomes of febrile events in pediatric patients with sickle cell anaemia. Krishnaveni Sirigaddi, Inmaculada Aban, Amelia Jantz et al. (22)
	• Standards for the clinical care of adults with Sickle Cell Disease in UK. Sickle Cell Society, 2018 (12)
	• Sickle cell acute painful episode; Management of an acute painful sickle cell episode in hospital (NICE) 2012 (21)

WHO classification to get five referral health facility levels for the recommendations (Table 1).

Consensus and preparation of final guidelines

Based on the review of the existing guidelines, the SPARCo WG developed guidelines for the management of SCD in SSA and set minimum standards for management of SCD aligned to institutional technical and human resources for each level of healthcare facility (see levels summarized in Table 1). In developing common guidelines for management of SCD in sub-Saharan Africa, the group successfully developed the first draft of the tertiary facility guidelines for management of SCD and the guidelines developed included all the thematic areas. The first drafts of the tertiary facility level guidelines also referred to as the standard version of the guidelines were internally reviewed by members of the group, and then by the consortium members before being sent out for external review. In developing the guidelines for all the other lower referral levels ie regional, district, health centres, health posts/dispensaries/CHPs level and home level, the same processes were taken but other members of the consortium from Ghana, Tanzania and Nigeria were co-opted into the working group to complete this final aspect of the work and the multi referral level SCD guidelines were compiled. They were reviewed by our senior haematologists in the group before being submitted for internal review by SPARCO hub to other consortium members and subsequently for external review. The processes for the review of the guidelines and drafting of the recommendations are represented in Figure 1.

Results

The results from this review yielded a guidelines document which had recommendations for management of SCD based on the institutional and human capacity. We developed recommendations for five different levels of healthcare and a sixth level being what has to be done in the home before patients were taken to the hospital. A total of 64 topics had recommendations written out for them (Table 4). The major themes and topics that had recommendations are as seen in Table 4. The recommendations showed what management guidelines could be instituted at each referral level with the option of referring a patient to another referral level health facility for specialist expertise. The home level guidelines focussed on what action was needed in the event of any complication at home and when the patient needed to go for screening for complications of SCD.

Tables 5, 6 are two examples out of the 64 guidelines written. These two illustrate the different recommendations for the screening of stroke and retinopathy in different levels of healthcare facilities and also in the house.

Each of the recommendations were different for the different levels of healthcare for screening of stroke (Table 5). For home-based care, the caregiver was advised to ask about the TranscranialDoppler (TCD) ultrasound screening test so that it could be written out for them by the healthcare practitioner. At the level 1 facility which is the Health posts or CHPs compound and Level 11 referral centre which is the health centre, healthcare workers (HCW) are required to refer to the tertiary centre or regional centres where TCD facilities are commonly available. The last referral hospital which are tertiary facilities mostly have TCD

TABLE 4 Major themes/topics and subtopics identified.

S/NO	Theme/Topic	Subtopics
1	Diagnosis of Sickle Cell Disease (SCD) and Related Conditions	A. Tests for hemoglobin (Hb) type using Hb separation or specific immunologic methods, and DNA-based mutation analyses for confirmation
		B. Tests to diagnose heterozygous beta thalassemia (trait) in those with "No Hb variant" visible by the Hb separation methods (Hb phenotypes FA, AF, AFA2, AA2F, AA2, A)
		C. Rapid Screening and Point of Care tests for Hb S, C, A
		D. DNA- based tests
2	Health Maintenance and Preventive Therapy	A. Organizing Clinical Care (Outpatient routine; outpatient acute; and inpatient)
		B. Infection Prevention: General
		C. Immunization
		D. Prevention of invasive pneumococcal disease (IPD)
		E. Prevention of Malaria
		F. Prevention of enteric Gram-negative organisms (*salmonella*, *E. coli*, *klebsiella*, etc)
		G. Genetic and Reproductive counselling
		H. Female reproductive health (Pregnancy, Contraception and Fertility)
		I. Male reproductive health
		J. Nutrition
		K. Growth and development monitoring in children
		L. Education and psychosocial counselling
		M. Organizing support groups
		N. Transitioning of adolescents to adult care
		O. Travel management
3	Screening for Specific Complications of Sickle Cell Disease	A. Screening for stroke risk
		B. Screening for renal disease
		C. Screening for retinopathy
		D. Screening for pulmonary disease
		E. Screening for cardiovascular disease
		F. Screening for hypertension
		G. Screening for red cell antibodies related to pregnancy
4	Management of Acute Complications of SCD	A. Acute anaemia
		B. Acute chest syndrome
		C. Acute hepatobiliary complications
		D. Acute ocular complications
		E. Acute renal failure
		F. Acute SCD pain (vaso-occulsive pain episode, VOPE, or "pain crisis)
		G. Acute splenic sequestration
		H. Acute stroke
		I. Fever and other signs of infection
		J. Osteomyelitis and septic arthritis
		K. Multisystem Organ Failure
		L. Priapism

(Continued on following page)

TABLE 4 (*Continued*) Major themes/topics and subtopics identified.

S/NO	Theme/Topic	Subtopics
5	Management of Chronic Complications of Sickle Cell Disease	A. Avascular necrosis
		B. Cardiac complications
		C. Chronic hypersplenism
		D. Chronic pain
		E. Endocrine complications
		F. Gastrointestinal complications
		G. Leg ulcers
		H. Nocturnal enuresis
		I. Ophthalmologic complications
		J. Psychological complications
		K. Renal complications
		L. Pulmonary complications
		M. Seizures under neurological complications
		N. Stuttering/Recurrent Priapism
6	Special Management Protocols	A. Analgesic Medications and their Use in Sickle Cell Disease
		B. Haematopoietic stem cell transplantation
		C. Hydration guide
		D. Hydroxyurea Therapy in Sickle Cell Disease
		E. Peri-operative care and surgery
		F. Transfusion Therapy in Sickle Cell Disease/Iron chelation
		G. Organizing SCD clinical service (outpatient routine and acute care, in patient)

facilities available and can perform TCD for children 2–16 years annually.

In Table 6, the primary physician/haematologist are prompted to let the ophthalmologist do a fundoscopy for patients from age 10 at the tertiary level. In the regional hospitals where ophthalmologists are available, patients can be referred to them at the regional facility or to the tertiary hospitals for fundoscopy. Healthcare facilities at lower referral levels are recommended to refer to either the regional or tertiary facilities whilst the home guidelines will alert the parent or patient to ask about the ophthalmology review.

Discussion

It is essential that every patient with SCD receives comprehensive care that is coordinated at each level by medical experts. The availability of treatment guidelines normally leads to a harmonised way of treating patients. The existing guidelines are commonly developed for the last referral levels or tertiary facility making adaption for use by the primary healthcare very difficult. This can lead to misuse of these available guidelines. The compilation of this document brought to the forefront a harmonised way of treatment of SCD in SSA based on our resources and constraints. The lowest level of comprehensive care for patients with sickle cell disease is available at the healthposts/dispenasaries/CHPs compounds which are mainly manned by nurses and with available recommendations, they will know what can be done at their end and when to refer.

Patients can access care at any of the other lower referral healthcare facilities and be managed with recommendations that are in keeping with institutional resources at that level. When such patients need care that requires expertise that is not available at that level, the recommendations will be to refer to the appropriate referral level where those expertise are available (mainly a higher referral level facility like the regional or tertiary facility). This encourages patients to have good clinical care nearer their homes but also having access to specialist screening modalities and expertise at the tertiary hospitals if need be. With this, patients are not limited to a specific referral level when interventions cannot be instituted for them at that level of healthcare.

One of the lessons learnt during this process was the benefits of task sharing and teamwork. The SoC WG worked as a team with every member carrying out his or her writing assignment dutifully. Another benefit derived from the exercise was the mentorship from the SoC WG Chair, Professor Kwaku Ohene-Frempong to the younger members of the team. It is also noteworthy that with little or no financial resources

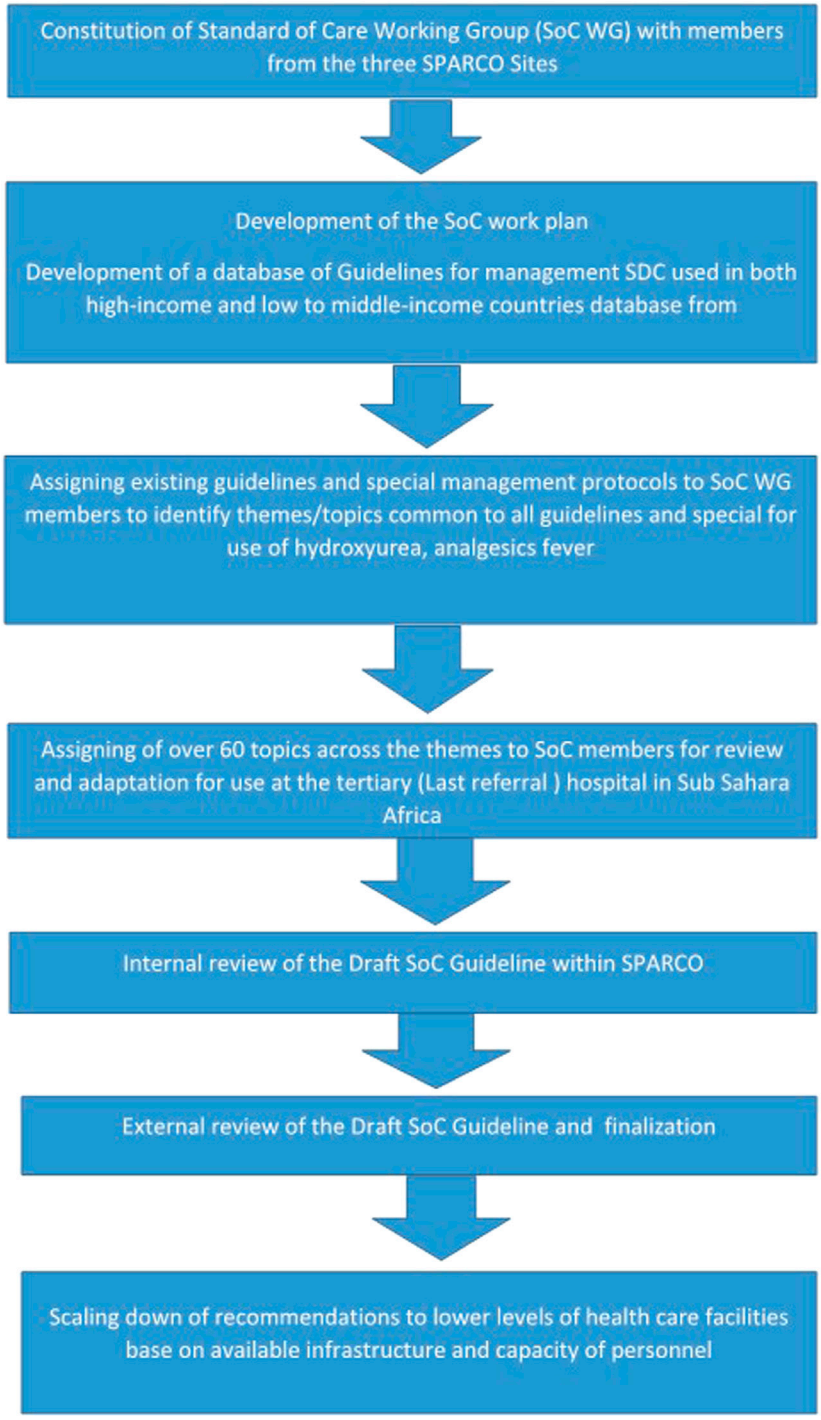

FIGURE 1
Graphical presentation of the process of development of the standard of care guidelines.

the SoC WG was able to put together this valuable SoC document which if implemented has potential to improve the care and management of SCD in sub-Saharan Africa.

It is unique in terms of the availability of recommendations for different levels of care as compared to the traditional guidelines which is more focussed at the tertiary levels. With the traditional guidelines, those in the primary healthcare settings find it difficult adapting it for their use.

Limitations

Time constraint was a challenge for both writers and reviewers as most members are very busy in other equally important duties such as clinical work and teaching at their respective institutions thus often missing timelines and delaying the process though not compromising the quality of work.

TABLE 5 Screening for stroke risk. Transcranial Doppler ultrasonography (TCD) for children at different levels of healthcare facilities.

Last referral hospital
Obtain TCD at least once annually in those with SCD-SS or SCD-Sβ^0. If TCD is not available at your facility, arrange for the child to visit a centre where it can be performed, or arrange for portable TCD screening to be performed for the child at your facility on a periodic basis
Level I Health Centre (HC I)
Refer children with SCD-SS or SCD-Sβ^0 to the secondary referral hospital (regional centre) for SCD annually for comprehensive evaluation including TCD at least once a year
First level of care (Home)
If your child has SCD-SS or SCD-Sβ^0, ask your doctor or nurse about a test called "TCD". This test detects those children who may be in danger of having a stroke

TABLE 6 Screening for retinopathy SCD disease patients for different healthcare levels.

Last referral hospital
Refer a person with SCD to an ophthalmologist for a dilated eye examination to evaluate for retinopathy beginning at age 10 years. If dilated retinal examination is normal, re-screen at 1–2-year intervals
Secondary Referral Hospital
Refer to an ophthalmologist for a dilated eye examination to evaluate for retinopathy beginning at age 10 years. If dilated retinal examination is normal, re-screen at 1–2-year intervals
Level II Health Centre
Refer to an accredited centre for dilated eye examination by ophthalmologist to evaluate for retinopathy, as part of Annual Review beginning at age 10 years
Level I Health Centre
Refer to an accredited centre for dilated eye examination by ophthalmologist to evaluate for retinopathy, as part of Annual Review beginning at age 10 years
First level of care (Home)
From age 10years and above: Ask the doctor or nurse about referral to a retina specialist eye doctor to check the eyes regularly. If the person with SCD complains about his sight or has pain in the eye, she or he should be seen by specialist eye doctor as quickly as possible

Conclusion and recommendations

This SoC recommendations for SCD is a useful material that can be used for consistent standards of treatment in SSA. We will need to create awareness and advocate for adoption and use among governments and stakeholders such as Paediatricians and Haematologists as well as other specialties involved in managing the complications of SCD.

We recommend the training of stakeholders across medical disciplines, professions and cadres on the use of the guideline and possibly incorporating it in the training curricular of nursing schools, community health workers' schools and other allied health workers. We will also recommend the distribution of both online/mobile App and both full and short (pocket) versions of the SoC recommendations for SCD and adapted in a local context for implementation in all SSA countries.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

VP, MA, and HI conceived the idea and wrote the first draft. VP, MA, HI, KA, JM, MN, VN, YO-M, FN, LC, AM, ON, AW, JM, and KO-F wrote the guidelines, contributed sections and critically reviewed the manuscript. All the authors approved the submission.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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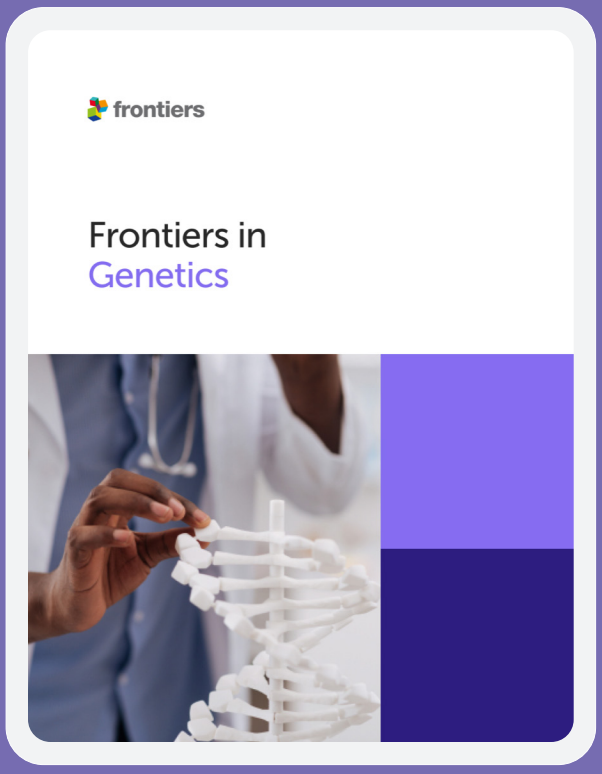

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