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Prevalence of Sickle Cell Trait and Reliability of Self-Reported Status among Expectant Parents in Nigeria: Implications for Targeted Newborn Screening

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Key Words

Carrier testing · Diagnosis · Genetic screening · Newborn screening · Sickle cell disease · Sickle cell trait · Sub-Saharan Africa

Abstract

Background/Aims: Sickle cell disease (SCD) is a life-threatening, autosomal recessive blood disorder prevalent in sub-Saharan Africa. We identified the prevalence of sickle cell trait (SCT) among pregnant women and their male partners in Enugu State, Nigeria, and determined the accuracy of self-reported sickle cell status and its reliability for identifying high-risk newborns for targeted screening. ***Methods:*** We conducted a nested cohort study of expectant parents enrolled in the Healthy Beginning Initiative (HBI). The HBI is a cluster-randomized trial of a congregation-based approach designed to increase HIV testing. Participants completed a survey regarding self-awareness of their sickle cell genotype and consented to genotype screening by cellulose acetate electrophoresis. ***Results:*** SCT prevalence (HbAS) was 22% (746/3,371). Only 50% of participants provided an accurate self-report. Self-report accuracy was significantly different ($p < 0.0001$) between individuals who reported having SCT or SCD (61% accuracy) versus those who reported not having SCT or SCD (86% accuracy). Demographic variables including gender, age, household size, employment, education, and home location were significantly associated with providing an accurate self-report. ***Conclusions:*** Low numbers of accurate parental self-reports, coupled with a high SCT prevalence in Nigeria, could limit the efficacy of targeted newborn screening. However, our data indicate that it is feasible to integrate sickle cell screening for pregnant women with existing, community-based health care programs developed by the President's Emergency Plan for AIDS Relief (PEPFAR), such as the HBI. Expanding screening programs could enable the development of targeted newborn screening based on maternal genotype that could identify all newborns with SCD in resource-limited settings.

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Introduction

Sickle cell disease (SCD) is a life-threatening genetic blood disorder that affects over 6 million newborns annually [1, 2]. It is an autosomal recessive disorder most commonly caused by homozygosity for the A to T mutation in the sixth codon of the hemoglobin β-subunit (i.e. homozygosity for the S variant of hemoglobin β-subunit; SS) [3]. It can also be caused by compound heterozygosity for the S and C variants (SC) [3]. Individuals with sickle cell trait (SCT) are heterozygous for the S variant (AS) and hence are unaffected carriers.

The incidence of disease is disproportionately high in sub-Saharan Africa, where over 75% of all global SCD births occur [1]. Over 250,000 African infants, predominantly from sub-Saharan Africa, are born annually with SCD [4], and SCD is the most prevalent genetic disease in Africa [5]. Moreover, 30% of the world's annual SCD and SCT births are located in two countries, both in sub-Saharan Africa: Nigeria and the Democratic Republic of the Congo [1].

Despite the very high burden of SCD, Nigeria does not have a national newborn screening program for SCT and SCD [6]. Diagnostic screening is the key to identifying infants with SCD so that infants and families can promptly receive potentially lifesaving medical and educational interventions. Without routine newborn screening, many children are not identified early enough to receive key preventative care. Accordingly, the implementation of universal newborn SCD screening was a major factor in the significant decrease of pediatric SCD mortality in many developed countries [7–9]. The World Health Organization has recommended newborn screening as a key strategy for reducing pediatric mortality in Africa [5], where infants with SCD face an estimated 50–90% early childhood mortality rate [3]. However, newborn screening programs can be logistically and economically challenging to implement, particularly in sub-Saharan Africa where over 70% of the population have access to little or no health care infrastructure [10]. Many pilot or demonstration programs for universal newborn screening have been debuted in various resource-limited settings throughout Africa, including the Democratic Republic of Congo [11], Burkina Faso [12], Ghana [13], Nigeria [14], Angola [15], and Liberia [16]. To date, none of these countries has been able to scale the program to the national level and maintain a long-term national sickle cell newborn screening program.

Targeted newborn screening, in which testing is limited to infants deemed at high risk based on parental sickle cell status (as determined by voluntary self-report or laboratory testing), could be a useful alternative to universal newborn screening in resource-limited settings. Notably, a targeted newborn screening program for SCD was successfully implemented and maintained long-term (≥16 years) in the Republic of Benin [17]. In addition, utilizing existing public health programs and infrastructure by incorporating newborn screening into established infant welfare clinics [18] would also decrease cost and increase program sustainability. Similarly, tailoring programs to increase community acceptance could increase the number of parents who consent to screening of their newborn and commit to a comprehensive care regimen [14]. It has been noted that cultural sensitivity and thoughtful adaptation of newborn SCD screening programs to the needs of diverse local communities in sub-Saharan Africa will be a key part of any screening program's success [19].

As a first step towards the development of a newborn screening program relevant to the specific needs of Nigeria, we sought to determine (a) the population prevalence of SCT among pregnant women and their male partners in Enugu State, southeastern Nigeria, and (b) the extent and accuracy of parental self-reported sickle cell genotype. We conducted a nested cohort study by integrating sickle cell screening within an existing and community-accepted HIV testing infrastructure, the Healthy Beginning Initiative (HBI). The HBI is a cluster-randomized trial designed to increase HIV testing of pregnant women and their male partners [20]. It is a congregation-based program in Enugu State, southeastern Nigeria, which was created with heavy participation and leadership from the local community.

Methods

Study Design and Setting

This cohort study was nested within the HBI. The HBI is a large, cluster-randomized, controlled study designed to determine the effectiveness of a congregation-based intervention in increasing HIV testing among pregnant women and their male partners in southeastern Nigeria. The study design details of the HBI have been described previously [20]. In summary, 40 churches were selected from 40 communities across seven local government areas in Enugu State, southeastern Nigeria. Sample collection was done randomly as detailed in [20] and was designed to be representative for the population to minimize selection bias and increase generalizability. Church-organized prayer sessions for pregnant women were used to recruit participants early in their pregnancy. Integrated, on-site tests for HIV, hepatitis B, and sickle cell genotype were implemented during church-organized baby showers to reduce stigma associated with HIV-only testing. Church-organized baby receptions were

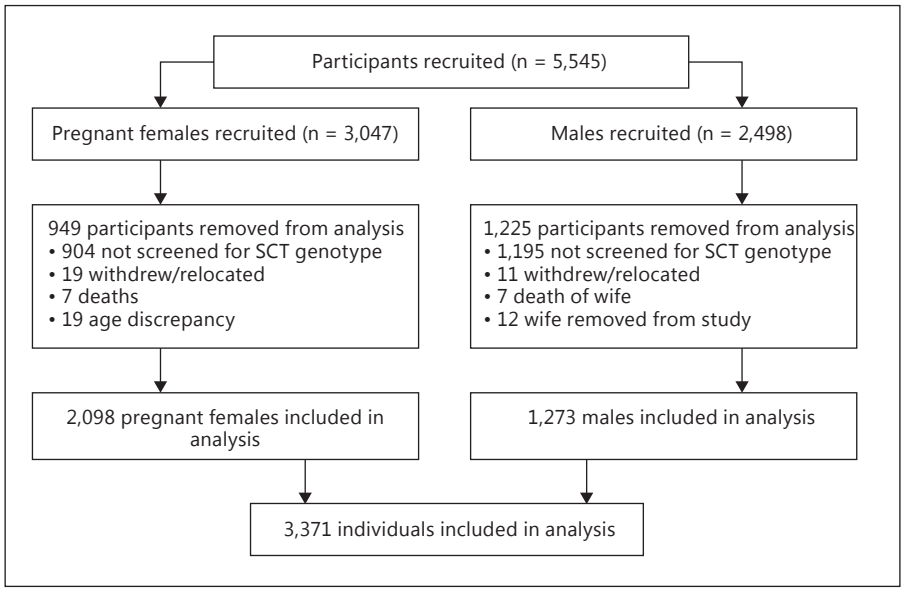

Fig. 1. Flow chart of participants included in the data analysis. Participants included males and females recruited by the HBI program in Enugu, Nigeria.

used for postdelivery follow-up and linkage to care. Recruitment occurred between January 20, 2013 and August 31, 2013, and follow-up was completed by August 31, 2014. The study follow-up period was 9 months after the last pregnant woman had been recruited, with participant contact (baby receptions) held every 3 months.

Data Collection

Between March 2013 and August 2013, two church-based volunteer health advisors who could read and write in English were selected from each participating church and trained on basic research methodology, including how to obtain informed consent and complete the survey instrument. HBI-trained research coordinators, with the assistance of the volunteer health advisors, conducted an investigator-assisted, cross-sectional survey of HBI participants to collect data on self-reported awareness of sickle cell genotype. Pregnant women and their male partners who signed consent to participate in the HBI were independently approached to participate in the cross-sectional survey and to complete a 41-item questionnaire containing two specific questions on SCT: (a) 'Are you aware of your SCT status?' and (b) 'If yes, what is your genotype?'. The survey instrument was piloted and validated among 25 postpartum women in the same community. Participants were then offered screening for sickle cell genotype as part of the integrated laboratory testing. This study was approved by the Institutional Review Board of the University of Nevada, Reno and the Nigerian National Health Research Ethics Committee.

Laboratory Procedure

Sickle cell screening was conducted by cellulose acetate electrophoresis modified from Evans [21]. For confirmation, each test was performed twice.

Statistical Analysis

Analyses included descriptive statistics for social demographic distributions and genotype prevalence among participants. χ^2 tests were conducted to determine whether the accuracy of sickle cell status self-reports was significantly different between different groups of participants. A binary logit logistic analysis with Fisher's scoring was used to determine by an odds ratio (OR) assessment whether certain demographic variables were significantly associated with the ability to provide an accurate sickle cell status self-report. Analyses were performed with Statistical Analysis System (SAS) version 9.4. The log-likelihood ratio full-enumeration exact test ('HWxtest' package in R, version 3.3.1) was used to determine whether there was a significant difference ($p < 0.05$) between the number of observed SS individuals and the number of SS individuals expected, assuming Hardy-Weinberg equilibrium (HWE) [22].

Role of the Funding Source

The HBI was funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Institute of Mental Health (NIMH) and the President's Emergency Plan for AIDS Relief (PEPFAR). Additional support for this study was provided by the HealthySunrise Foundation, the TEND Foundation, and the Mapuije Foundation. These funding agencies played no role in the study conception, design, data collection, data analysis, data interpretation, or writing of the report.

Results

From January to August 2013, we approached and enrolled 3,047 pregnant women and 2,498 male partners participating in the HBI. At completion, 45 women and 30 men had withdrawn, relocated, or died or had been removed from the study. A total of 69% of women (2,098/3,047) and 51% of males (1,273/2,498) completed both the questionnaire regarding self-awareness of their sickle cell status and laboratory screening for sickle cell genotype (fig. 1).

Table 1. Laboratory-determined sickle cell genotype versus self-reported status

Genotype	Self-reported status				No self-report	Total
	AA	AS	SS	other		
AA	**1,465**	143	2	4	1,003	2,617
AS	235	**232**	2	1	276	746
SS	3	0	**0**	0	1	4
AC	1	0	0	**0**	3	4
Total	1,704	375	4	5	1,283	3,371

Participant genotype was determined by cellulose acetate electrophoresis on hemolysate from venous blood samples. Bold figures indicate individuals who correctly self-reported their sickle cell status.

Cohort Demographics

The men and women in our study were predominantly 25–35 years old, married, and had completed their secondary education (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000448914). The majority of the study population lived in rural areas, with 27% living >10 km from the nearest health care facility (894/3,328 reports; 43 did not report), and the remainder were equally divided among those who lived 5–10 km and those who lived 0–5 km from the nearest health care facility (online suppl. table 1). Households with 3–6 people accounted for 70% of study participants (2,342/3,333 reports; 38 did not report) (online suppl. table 1).

Prevalence of SCT and SCD among Expectant Parents

The prevalence of SCT, as defined by heterozygosity for the S variant of hemoglobin β-subunit (AS), was 22% among our participants (746/3,371) (table 1). SCT prevalence was similar among female and male participants (21 and 23%, respectively; online suppl. tables 2 and 3). Heterozygosity for the C variant of hemoglobin β-subunit was rare, as is expected for southeastern Nigeria [23]; only 4 of the 3,371 study participants were genotyped as AC (table 1). No individuals were compound heterozygous for the hemoglobin S and C variants.

Estimates of SCD prevalence due to hemoglobin S homozygosity are commonly calculated from the observed frequency of the S allele in a study population and by assuming HWE [1]. Accordingly, the prevalence of SCD due to hemoglobin S homozygosity in our study population is expected to be 1% (42/3,371 participants). However, only 4 participants in this study were homozygous for hemoglobin S, which equates to an SCD prevalence of 0.1% (table 1). This 10-fold deviation between the expected and observed SCD prevalence is significantly different (log-likelihood ratio full-enumeration exact test, $p = 0.000000$).

Reliability of Self-Reported Sickle Cell Genotype among Expectant Parents

We found that 62% of participants (2,088/3,371) stated that they were aware of their sickle cell status. A greater proportion of females (69%; 1,447/2,098) than males (50%; 641/1,273) stated that they knew their sickle cell status. Furthermore, among all females and males who reported their sickle cell status, 81% were correct (1,697/2,088), as determined by laboratory testing for hemoglobin A, S, and C (see Methods and table 1). The accuracy of female self-reports on sickle cell status was similar to that of male self-reports (online suppl. tables 2 and 3).

The proportion of participants who accurately self-reported their status varied depending on the genotype that the individual self-reported. We found that 86% of all female and male participants who self-reported their genotype as AA, which is the most common genotype, were correct (1,465/1,704). However, only 61% (235/384) of those who reported being a non-AA genotype (i.e. AS or 'other') were correct (table 1). This phenomenon was similar for both females and males (online suppl. tables 2 and 3). Furthermore, none of the 9 individuals who reported SS or 'other' were correct; 6 of these 9 individuals were actually AA, and the remaining 3 were AS (table 1). The difference in accuracy between all individuals (females and males) who self-reported having SCD or SCT (i.e. SS, AS, or AC) and all individuals who reported being unaffected (i.e. AA) was significant (χ^2 analysis, $p < 0.0001$; online suppl. table 4).

When including participants who were not aware of their sickle cell genotype, only 50% of all participants were able to provide an accurate sickle cell status self-report (table 2). However, only 11% (239/2,088) of all participants who said they were aware of their sickle cell status were wrong in a manner that would have endangered the ability of a targeted screening based on parental self-reported status to identify infants with SCD (i.e. parent self-reported as AA when she or he was actually AS, AC, or SS) (table 1). This proportion was similar among female and male participants (11 vs. 13%; online suppl. tables 2 and 3).

Table 2. Demographic distribution of participants based on self-reported status

Demographic variable	Participant response	Correct self-report (%)	Incorrect or no self-report (%)	Total
Gender	female	1,184 (56)	914 (44)	2,098
	male	513 (40)	760 (60)	1,273
	total	1,697	1,674	3,371
Age, years	16–24.9	239 (49)	252 (51)	491
	25–34.9	902 (53)	787 (47)	1,689
	≥35	546 (47)	608 (53)	1,154
	total[a]	1,687	1,647	3,334
Marital status	married	1,645 (51)	1,589 (49)	3,234
	divorced	1 (100)	0 (0)	1
	separated	3 (30)	7 (70)	10
	single	48 (38)	78 (62)	126
	total	1,697	1,674	3,371
Education level	none/primary	369 (33)	735 (67)	1,104
	secondary	953 (55)	791 (45)	1,744
	tertiary	370 (75)	123 (25)	493
	total[b]	1,692	1,649	3,341
Employment	full-time	810 (54)	690 (46)	1,500
	part-time	380 (47)	435 (53)	815
	unemployed	490 (49)	502 (51)	992
	total[c]	1,680	1,627	3,307
Household size	≤2	279 (54)	236 (46)	515
	3–6	1,210 (52)	1,132 (48)	2,342
	≥7	198 (42)	278 (58)	476
	total[d]	1,687	1,646	3,333
Distance to health care facility	0–5 km	585 (49)	609 (51)	1,194
	>5–10 km	641 (52)	599 (48)	1,240
	>10–15 km	291 (50)	287 (50)	578
	>15 km	168 (53)	148 (47)	316
	total[e]	1,685	1,643	3,328
Area	rural	1,116 (45)	1,338 (55)	2,454
	urban	576 (65)	310 (35)	886
	total[f]	1,692	1,648	3,340

[a] 37 participants did not provide age. [b] 30 participants did not provide education status. [c] 64 participants did not provide employment status. [d] 38 participants did not provide household size. [e] 43 participants did not provide distance to health care facility. [f] 31 participants did not provide household area descriptor.

Table 3. Certain demographic variables significantly affect the ability of participants to provide an accurate self-report of sickle cell status

Effect	OR	95% CI
Gender		
Female vs. male	0.442*	0.369–0.53
Age		
≥35 vs. 25–34.9	0.813*	0.677–0.977
16–24.9 vs. 25–34.9	1.238	0.989–1.548
Marital status		
Married vs. single	0.675	0.453–1.006
Separated vs. single	1.646	0.389–6.972
Household size		
3–6 vs. ≥7	0.78*	0.626–0.973
≤2 vs. ≥7	0.699*	0.527–0.929
Employment		
Full-time vs. unemployed	0.765*	0.637–0.919
Part-time vs. unemployed	0.945	0.772–1.157
Education		
None/primary vs. tertiary	4.033*	3.124–5.207
Secondary vs. tertiary	1.913*	1.506–2.43
Area		
Rural vs. urban	1.738*	1.455–2.075
Distance to health care facility		
0–5 vs. >5–10 km	1.052	0.886–1.248
>10–15 vs. >5–10 km	1.028	0.83–1.273
≥15 vs. 5–10 km	0.962	0.736–1.258

Logistic analysis with Fisher's scoring was used to determine the OR for the difference in the risk of participants providing an inaccurate self-report or of being unable to provide a sickle cell status self-report vs. providing an accurate self-report. An OR <1 indicates lower risk of providing an inaccurate self-report or of failing to provide a self-report.

* Significant difference between the compared demographic groups' ability to provide an accurate self-report of sickle cell status.

Influence of Demographic Variables on the Accuracy of Self-Reported Sickle Cell Status

Participant demographics were analyzed by self-report accuracy (correct self-reports versus incorrect reports or inability to provide a report) (table 2). We also performed a binary logit logistic analysis with Fisher's scoring to determine whether specific demographic variables were significantly associated with participants' ability to provide an accurate report of their sickle cell status (table 3). The largest effects in OR came from participant gender, education level, and household location. Our data indicate that females were less likely to provide an inaccurate self-report or to be unable to provide a self-report as compared to males (table 2), and this difference was statistically significant [OR 0.442; 95% confidence interval (CI) 0.369–0.53] (table 3). Similarly, participants who lived in urban areas or who had completed tertiary education were also significantly more likely to provide an accurate self-report (table 3). Smaller but still statistically significant effects in OR were seen with age, employment status, and household size. Participants older

than 35 years were significantly more likely to provide an accurate self-report than participants aged 25–34.9 years, as were participants who were employed full-time versus unemployed participants and participants from households with <7 people versus households with ≥7 people (table 3). The marital status of participants and the distance of their home to the nearest health care facility were not significantly associated with a difference in ability to provide an accurate self-report of sickle cell status (table 3).

Discussion

Building on Existing Infrastructure for HIV Testing

Substantial progress has been made in the fight against HIV infection through the partnership between the governments of the United States and Nigeria. From 2004 through 2011, the United States PEPFAR invested close to USD 2.5 billion, including USD 488 million in 2011 alone, to support Nigeria as it built the infrastructure to fight the HIV/AIDS epidemic [24]. The results of this partnership include (1) an increase in available HIV testing sites from 1,074 in 2009 to 7,075 in 2013, (2) an increase in individuals >15 years of age tested for HIV from 1.7 million in 2009 to 4.08 million in 2013, and (3) an increase in the number of pregnant women tested for HIV from 907,387 in 2010 to 1.7 million in 2013 [25]. The sickle cell screening program used in this study was built on this foundational infrastructure. To our knowledge, our study is the first to integrate sickle cell screening with HIV testing for expectant parents in Nigeria. Our data indicate that acceptance of sickle cell screening for expectant parents and their newborns is very high and that screening for expectant parents and their infants can be readily incorporated into existing community-based HIV testing programs and established public health infrastructure, such as those developed by PEPFAR, in resource-limited areas.

Generalizability

Our cohort study was nested within the HBI study, which itself is a cluster-randomized controlled trial. Sample collection for the HBI was randomly selected as detailed in [20], and was designed to be representative for the population in southeastern Nigeria to minimize selection bias and increase generalizability. Furthermore, for the HBI and consequently this cohort study, churches were used as convenience venues in the community to identify pregnant women, implement intervention, and conduct postdelivery follow-up. This is similar to the use of CVS, Walgreens, etc. for influenza immunization in the United States [26]. These neighborhood stores are used for immunization campaigns in the United States because they are easily accessible, widely distributed, and as highly patronized as worship centers in most resource-limited settings. Accordingly, we anticipate that our findings will likely be generalizable for other resource-limited settings beyond southeastern Nigeria. We note that for these same reasons, the HBI model of patient contact via churches in southeastern Nigeria is currently being adapted for implementation in Mosques in northern Nigeria and Hindu temples in India, where these venues serve a similar function.

Discordance between SCT and SCD Prevalence

The recruitment of such a large cohort enabled us to determine the population prevalence of SCT and SCD among women of childbearing age and their male partners in southeastern Nigeria. Importantly, the high prevalence of SCT detected among Nigerians in this study is in stark contrast to the low prevalence of SCD (22 vs. 0.1%, respectively) (table 1). Moreover, the 0.1% SCD prevalence observed in our study population of expectant parents is significantly different from the 1% SCD prevalence expected for these adults, given the observed frequency of the hemoglobin S allele in our study population and assuming HWE. This 10-fold difference between observed and expected SCD prevalence suggests excess mortality for individuals with SCD within the birth cohort represented by our adult study population.

Furthermore, a recent analysis of newborn SCD screening surveys throughout Africa determined that deviations from HWE equilibrium are common [22]. Specifically, the observed prevalence of SCD in screened newborns is typically much higher than that expected based on HWE [22]. This implies that within the birth cohort represented by the adult expectant parents in our study, the 1% SCD prevalence expected based on HWE may also be an underestimate. In this case, the difference between the expected and observed SCD prevalence in our study group would be larger than 10-fold and would suggest an even more serious excess mortality rate for newborns with SCD within the birth cohort represented by our adult study population. This would be consistent with the estimated 50–90% early childhood mortality rate reported for infants with SCD in sub-Saharan Africa [3].

Extent and Accuracy of Parental Self-Reported Sickle Cell Status and Implications for Its Use in Targeted Newborn Screening

Targeted newborn screening is less expensive and labor-intensive than universal newborn screening. If effective, it could be a useful public health strategy in resource-limited settings. To be successful, targeted newborn screening based on parental self-reported sickle cell status will require expectant parents to accurately report their sickle cell status.

Individuals may not be able to report their status because they have never been tested or because they do not remember the test results. A cross-sectional survey of Ghanaian women found that only 47% of women who reported being tested for SCT also reported that they knew their test results [27]. In our study group, 69% of expectant mothers (1,447/2,098) stated that they knew their status, which implies that many more had been tested previously. Interestingly, the proportion of women who reported their status in our study is much higher than the 29% observed in a previous study of postpartum mothers in Nigeria [14]. This difference may be due to our study's larger sample size (3,371 vs. 630) or to a general increase in sickle cell testing in Nigeria since Odunvbun et al. [14] collected their data. From the perspective of developing sickle cell screening programs in resource-limited settings, we note that improvements in communication of genetic test results between patients and clinicians could increase individuals' recollection of their sickle cell status [28–30] and improve the effectiveness of targeted newborn screening based on parental self-reported status without increasing the number of adult diagnostic tests performed (i.e. without increasing the cost of the program).

Improved patient-clinician communication as well as SCT community outreach education could also be used to increase the accuracy of parental self-reported status. We found that the accuracy of parental self-reporting was significantly different when parents reported being unaffected (genotype AA) versus having SCD or SCT (non-AA genotype) ($p < 0.0001$). In our dataset, expectant parents who reported being AA were much more likely to be correct than individuals who reported having a non-AA genotype (86 vs. 61% accuracy; table 1). Similar results were recently observed for a cohort of African American adults in the United States, in which 100% of those who reported not having SCD were correct (although 12% actually had SCT), yet only 6% of those who reported having SCD were actually SS or SC (63% of these had SCT and 25% were genotype AA) [31]. Together, our results and those of Bean et al. [31] indicate that self-awareness of one's sickle cell status is a challenging problem common to both developed nations with robust medical infrastructure and resource-limited areas such as Nigeria. Furthermore, these findings also suggest that the communication of negative sickle cell test results has been more effective than the communication of positive test results (i.e. the individual has SCD or SCT).

Our analysis of the influence of participant demographics on the accuracy of parental sickle cell self-reports identified several demographic groups that were significantly less likely to provide an accurate sickle cell self-report. Consequently, communication and education outreach efforts tailored to these subpopulations could be particularly useful. In addition, gender had a large effect on the OR, with males at significantly higher risk of failing to provide an accurate self-report. It is possible that this gender difference could be due to increased contact between females and medical staff due to pregnancy and delivery, which are events that are more likely than others to prompt discussion of sickle cell status and the pattern of SCD inheritance. Regardless, our data indicate that the inclusion of males from all demographic groups should be a high priority for future sickle cell community outreach educational efforts.

Our data indicate that 11% of all parental self-reports in our study were wrong in a manner that would have endangered the ability of a targeted newborn screening based on parental self-reported status to identify infants with SCD (i.e. the parent self-reported as AA when she or he was actually AS, AC, or SS) (online suppl. table 2 and table 1). Thus, in regions where resources are limited yet there is still sufficient public health infrastructure to track and document patient test results, we propose that instead of targeting sickle cell screening to only the infants of parents who do not report their status or who report as a non-AA genotype, the preferred screening strategy would be two-step laboratory testing of (1) first-time mothers and (2) high-risk infants, where high-risk infants would be defined as infants from laboratory-tested, non-AA genotype mothers. In such a strategy, expectant primipara women would be offered sickle cell genotype testing either prenatally or at the time of delivery. Ideally, all tested women would then receive a document with their sickle cell status and be entered into a secure maternal sickle cell genotype database. Preferably, such a database would be accessible to authorized health care providers in both urban and rural Nigerian health care clinics, since an estimated 95 million people (53% of the population) reside in rural areas [32]. Mobile phones and mobile

phone coverage are extensive throughout rural Nigeria, and a mobile phone application could be one solution that would enable authorized providers access to the data even in rural areas with frequent electricity interruptions and no ground internet infrastructure [33]. Furthermore, integrating two-step screening within an existing community-based public health infrastructure, as we did by integrating sickle cell screening as part of the HBI's HIV testing program, could increase community acceptance and parental commitment while simultaneously increasing program affordability and sustainability. We note that all women who participated in this sickle cell study, which represented 69% of the women participating in the HBI community-based HIV testing program, also gave consent for sickle cell screening of their infants, which underscores the feasibility of integrating both primipara and newborn screening for SCT with established HIV testing programs for expectant parents.

Testing all primiparas and all infants from non-AA mothers would be more logistically complex to implement than screening based simply on parental self-reported status, but it would eliminate the issue of inaccurate parental sickle cell status self-reports or the lack of parental self-reports. To limit the number of adult diagnostic tests, ideally women would be tested only once, and their genotype results would be stored for use with subsequent pregnancies. For primiparas, this strategy would require 22% more diagnostic tests (adult and newborn tests combined) than a universal newborn screening program not testing mothers. However, for second pregnancies where the maternal genotype could be retrieved from the secure database, this strategy would require only three-quarters of the total diagnostic tests of universal newborn screening (first and second pregnancy; adult and newborn tests combined), and would achieve the same SCD identification rate as universal screening. For third pregnancies, this strategy would require only 55% of the total diagnostic tests required for universal screening (first, second and third pregnancy; adult and newborn tests combined). The cost savings of implementing this strategy as compared to universal screening continue to improve with additional pregnancies. In Nigeria, the average fertility rate is 6.0 per woman [33], which makes the cost savings of this strategy versus universal newborn screening highly attractive.

In summary, we conclude that sickle cell screening of expectant parents and their infants has high public acceptability in Nigeria and can be readily integrated into the existing health care infrastructure. The high prevalence of SCT among expectant parents in Nigeria coupled with the unexpectedly low prevalence of SCD among these adults highlights the urgent need for a newborn screening system to identify infants with SCD early so that they can receive prompt, lifesaving medical care. Moreover, the high proportion of expectant parents who inaccurately report having SCT or SCD indicates the need for better community education on SCD as well as the need for any targeted newborn screening strategies to be based on parental laboratory tests. Increasing access to SCD diagnosis by implementing routine newborn screening in Nigeria and other resource-limited regions could increase the number of patients who receive timely treatment, and help decrease the devastating early mortality rate in children with SCD.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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