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# Cascade testing effectively identifies undiagnosed sickle cell disease in The Gambia: a quality improvement project

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## ABSTRACT

**Objective** Sickle cell disease (SCD) has a high mortality during childhood in many low and middle-income countries (LMICs). Early diagnosis improves outcomes but newborn screening is not well established in LMICs. Cascade testing may be feasible and effective in identifying undiagnosed SCD and carriers of haemoglobin (Hb) S.

**Design** Quality improvement project using existing clinic and laboratory resources.

**Setting** The Haematology Clinic at the Edward Francis Small Teaching Hospital, Banjul, The Gambia.

**Participants** Families of index cases with SCD.

**Methods** Hb phenotype was determined in full or half-siblings of a SCD index case over a 6-week period using the HemoTypeSC test and confirmed by Hb electrophoresis.

**Main outcome measure** Identifying undiagnosed SCD.

**Results** Of 102 families invited, 31 (30%) attended during the study period and 53 siblings were tested. Except for one indeterminate test, HemoType SC agreed with Hb electrophoresis. Ten (19%; 95% CI 10 to 32) siblings were diagnosed with HbSS, 25 (47%; 34 to 60) as carriers (HbAS) and 18 (34%; 23 to 48) were unaffected (HbAA). Some symptoms and signs of SCD occurred significantly more frequently in HbSS than in HbAA and HbAS, but none was sufficiently common to help in identifying children for testing.

**Conclusions** Cascade testing was effective in identifying undiagnosed HbSS as well as children carrying the sickle cell gene. In routine care settings in LMICs, cascade testing facilitated by point-of-care tests may be feasible and affordable in increasing the detection of SCD and improving outcomes through earlier diagnosis.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mortality from sickle cell disease (SCD) in childhood is much higher in low- and middle-income countries (LMICs) than high-income countries.
⇒ Newborn screening for SCD would likely improve outcomes through earlier treatment but is not well-established in LMICs.

### WHAT THIS STUDY ADDS

⇒ Cascade testing of siblings of probands with SCD in The Gambia was feasible using existing resources.
⇒ Almost one in five previously undiagnosed siblings were diagnosed with SCD and half as carriers.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In the absence of well-established newborn screening, cascade testing may be feasible as part of routine care in LMICs and improve outcomes in SCD through earlier treatment and also to support genetic counselling.

## INTRODUCTION

Sickle cell anaemia (SCA or HbSS), the most common form of sickle cell disease (SCD) is an autosomal recessive disorder, caused by a mutation that codes for sickle haemoglobin (Hb) in both HBB genes. By chance, one in every four offspring of parents who are both heterozygous carriers (HbAS) will have SCA (HbSS), two will be carriers (HbAS) and one unaffected (HbAA). SCD also includes compound heterozygotes where the HbS allele is inherited with another Hb variant allele such as Hb C (Hb SC disease) or is coinherited with a β-thalassaemia allele (HbS/β-thalassaemia).[1]

It is estimated that 515 000 (95% uncertainty interval 4 25 000–6 15 000) babies were born with SCD worldwide in 2021 and of these, 405 000 (343 000–478 00) were born in sub-Saharan Africa.[2] The prevalence of SCD among newborns in The Gambia has been estimated to be between 0.8% and 1.2%.[3 4] However, the number of newborns with SCD is thought to be increasing globally due to population growth in regions with high gene frequencies and improved diagnosis.[2 5]

In SCD, red blood cells have a markedly reduced lifespan and become crescent or sickle shaped when exposed to reduced oxygen tension. Sickle-shaped red blood cells impair blood flow causing acute crises and damage to body organs. Symptoms include fatigue and limited exercise tolerance due to chronic anaemia, episodes of pain, swelling of the hands and feet (dactylitis), repeated infections, impaired vision, stroke, and stunted growth.[6]

Under-5 morality in SCA in the global north is low and most children are expected to live to adulthood.[5] In contrast, mortality among children under 5 years with SCA in sub-Saharan Africa is estimated to be up to 90% with few children surviving to adulthood.[2 7 8] SCD has been estimated to be responsible for approximately 5%–16% of under-5 deaths in this region.[9]

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The improved outcomes in high-income countries are likely partly due to early diagnosis facilitated by newborn screening and early institution of active management.[5 10] However, despite the much greater disease burden, few low and middle-income countries (LMICs) have established newborn screening due to cost and complexity.[10] Cascade testing involves detecting a genetic variant and/or a disease phenotype in the family members of a proband or index case.[11] Given the limited numbers requiring testing and the existing contact between families and hospital clinics, cascade testing may be feasible as part of routine care in resource-limited settings.

We evaluated cascade testing in siblings of SCD index cases under our care. The main aim was to determine the frequency of undiagnosed SCD among siblings of the proband. We also aimed to determine the proportion of siblings who had already been tested, whether medical history, symptoms and signs would be helpful in identifying siblings for testing, and to determine the frequency of carriers (HbAS) among siblings.

## METHODS

The project was undertaken at the weekly Haematology clinic, Edward Francis Small Teaching Hospital (EFSTH), Banjul, The Gambia. EFSTH is the main referral hospital in The Gambia serving the hospital catchment area and also receiving referrals from health facilities throughout the country. Current practice is that testing of siblings of children with SCD is undertaken if requested by parents/carers.

Parents/carers were invited by health staff either during a clinic or by phone call (phone numbers extracted from clinic records) to bring half and full siblings age <16 years of index cases attending the clinic for testing. Siblings were encouraged to attend whether or not they had been tested previously. Before testing, the possible outcomes (ie, SCD, sickle-cell carrier or normal) and the potential benefits of early diagnosis in SCD and knowledge of their status in carriers were explained, and verbal consent for testing secured.

In siblings who attended clinic, information regarding demographic variables, the occurrence of symptoms consistent with SCD (eg, bone pain) and whether any previous diagnostic tests had been done was collected onto a standard form (online supplemental figure 1). All siblings were examined by clinic staff for signs consistent with SCD and weight and height were recorded. Length/height-for-age z score and, in children less than 5 years, weight-for-length/height z score was determined using WHO Child Growth Standards.[12] In children 5 years or older, body mass index (BMI) was classified according to US Centre of Disease Control and Prevention criteria.[13] Family socioeconomic status (SES) was classified according to Majumder.[14] However, family income was excluded because many parents/carers were engaged in non-contracted or temporary employment and did not possess bank accounts or statements. As a result, many parents/carers could not provide a reliable estimate of the family income. The maximum score was reduced from 29 to 17; families scoring 9 or higher were classified as high SES and families scoring 8 or below as low SES.

A finger-prick blood sample was collected into EDTA. Hb phenotype was determined using the HemoTypeSC rapid diagnostic test (Silver Lake Research Corporation, USA) and confirmed by Hb electrophoresis (Helena Biosciences, UK). HemoType SC was not routinely available for diagnosis at EFSTH but was procured for this study. Hb concentration was measured using the HemoCue Hb301 system (Radiometer, UK).

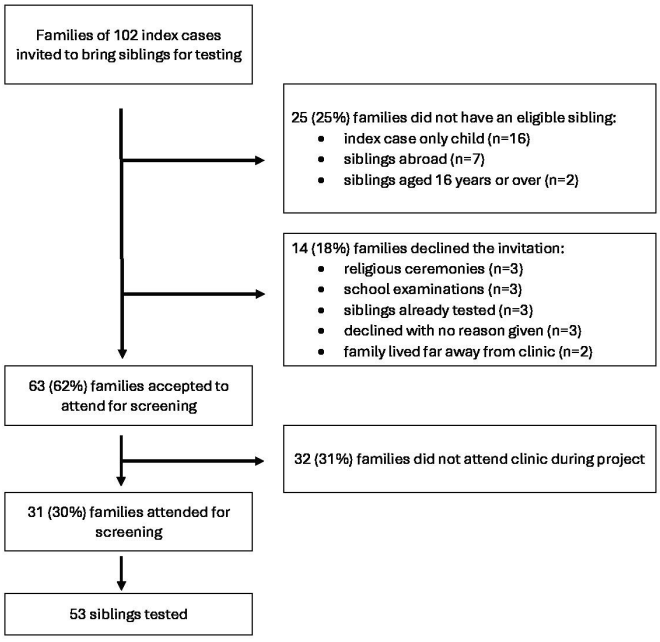


**Figure 1** Flow diagram.

Test results were reported to the child and parents/carers during a follow-up clinic visit. All children were provided with a card bearing their details and test results in a plastic folder (online supplemental figure 2). The results were also recorded in case records, where available. All siblings and their parents/carers were informed that the form completed for cascade testing including their personal identifier details (online supplemental figure 1) and test results would be held long term in the EFSTH laboratory.

Children diagnosed with SCD were invited to enrol in the clinic and begin management consistent with international guidelines including prevention of bacterial infections (pneumococcal, meningococcal and *Hemophilus influenza* type B immunisations and daily oral penicillin usually to age 5 years) and malaria (chemoprophylaxis and use of insecticide-treated bed nets during the rainy season) and folate supplements. Hydroxyurea was also available.[15] Carriers were informed of their status by trained clinic staff and the implications for future childbearing discussed.[15]

Data are presented as proportions and means (SD). The 95% CI for a proportion was calculated by the modified Wald method (https://www.graphpad.com/quickcalcs/ConfInterval1.cfm). The frequency of variables from the clinical history, symptoms and signs were compared according to Hb phenotype using the $\chi^2$ test (IBM SPSS Statistics V.29.0.1.1.(244)).

## RESULTS

Over a 6-week period between 7 June and 20 July 2023, 102 families with a child with SCD were invited to bring siblings to the clinic for testing. All index cases had been diagnosed with SCA (HbSS). Twenty-five (25%) families did not have an eligible sibling for testing (figure 1). Fourteen (18%) families declined the invitation. Of these, the timing was inconvenient for six families, siblings had already been tested and did not want retesting in three families, two lived far from the clinic and, of the 77 families with a sibling eligible for testing, only three (3.9%) declined without giving a reason. Among the 63 (62%) families who agreed to testing, 32 (51%) did not attend clinic during the project.

**Table 1** Demographic and clinical characteristics according to haemoglobin phenotype

| Variable | | Haemoglobin phenotype | | | |
|---|---|---|---|---|---|
| | | HbAA | HbAS | HbSS | |
| | | N=18 | N=25 | N=10 | |
| | | Number (%) | Number (%) | Number (%) | $\chi^2$ (P value) |
| Age (years) | < 5 | 5 (29) | 9 (36) | 4 (40) | 3.6 (0.5) |
| | 5–9 | 8 (44) | 5 (20) | 2 (20) | |
| | 10–16 | 5 (28) | 11 (44) | 4 (40) | |
| Sex | Female | 12 (67) | 11 (44) | 4 (40) | 2.7 (0.3) |
| Socioeconomic status | Low | 6 (33) | 10 (40) | 3 (30) | 0.39 (0.8) |
| Length/height-for-age z score | ≥–2 | 15 (83) | 23 (92) | 9 (90) | 1.4 (0.8) |
| | >-3 to <-2 | 2 (11) | 1 (4.0) | 1 (10) | |
| | <= –3 | 1 (5.6) | 1 (4.0) | 0 (0) | |
| Weight-for-length/height z score* (<5 years) N=18 | ≥–2 | 5 (100) | 6 (67) | 2 (50) | 6.5 (0.2) |
| | >-3 to <-2 | 0 (0) | 1 (11) | 2 (50) | |
| | <= –3 | 0 (0) | 2 (22) | 0 (0) | |
| BMI for age (>5 years) N=35 | Underweight | 2 (11) | 10 (40) | 2 (20) | 6.8 (0.03) |
| | Healthy | 11 (61) | 6 (24) | 4 (40) | |
| History | | | | | |
| Anaemia | | 3 (16) | 3 (12) | 4 (40) | 3.8 (0.2) |
| Bone pain | | 2 (11) | 4 (16) | 5 (50) | 6.6 (0.04) |
| Infections | | 2 (11) | 4 (16) | 3 (30) | 1.7 (0.4) |
| Impaired vision | | 4 (22) | 1 (4.0) | 2 (20) | 3.5 (0.2) |
| Blood transfusions | | 0 (0) | 0 (0) | 2 (20) | 8.9 (0.01) |
| Persistent/recurrent jaundice | | 1 (5.6) | 0 (0) | 3 (30) | 9.4 (0.009) |
| Painful swelling of appendages | | 1 (5.6) | 0 (0) | 4 (40) | 14 (<0.001) |
| Clinical signs | | | | | |
| Compatible facies | | 1 (5.6) | 1 (4.0) | 1 (10) | 0.48 (0.8) |
| Current dactylitis | | 1 (5.6) | 0 (0.0) | 0 (0.0) | 2.0 (0.4) |
| Palmar pallor | | 0 (0.0) | 2 (8.0) | 2 (20) | 3.7 (0.2) |
| Hepatomegaly | | 1 (5.6) | 0 (0.0) | 0 (0.0) | 2.0 (0.4) |

*No child was overweight.
BMI, body mass index; Hb, haemoglobin.

Nearly all (29; 94%) of the 31 (30%) families who attended for testing lived in the western region of The Gambia; one family lived in Banjul City and one in the North Bank region. Many of the parents/carers worked as professionals or in private business (online supplemental tables 1,2). SES was assessed to be high in 21 (68%) families.

Twenty-nine families provided information on family structure and, including the index case, reported a total of 115 children. The mean number of children born to each family was 4.0 (SD=1.5; range 2–8). Three families reported that one of their children had died (mortality of 2.6%) and 40 children had already been diagnosed with SCA (including index cases). Of the families that reported family structure, 51 (71%) of the 72 surviving siblings (<16 years) in whom HbSS had not been diagnosed attended for testing. One sibling from each of the two families where family structure was unknown were also tested.

Of the 53 siblings who attended for testing, 27 (51%) were female. The mean age was 7.7 years (SD=4.8; range 6 months to 15 years); 18 children (34%) were younger than 5 years. 16 (52%) families brought one child, 8 (26%) brought two and 7 (23%) brought three children. Parents/carers reported that only 3 (5.7%) had been tested previously; of these, results were unknown in two and one child's caregiver knew the previous result but wanted to confirm the diagnosis.

There was agreement in diagnosis between HemoTypeSC and Hb electrophoresis except for one chid in whom the HemotypeSC result was equivocal but electrophoresis confirmed HbSS.

Of the 53 siblings who underwent testing, 10 (19%; 95% CI 10 to 32) were diagnosed with HbSS, 25 (47%; 34 to 60) as carriers (HbAS) and 18 (34%; 23 to 48) were unaffected (HbAA). The distribution of sex, age and SES was similar in the different Hb phenotype categories (table 1). Among the newly diagnosed SCA children, four (40%) were less than 5 years old.

Anthropometric indices were similar according to Hb phenotype, except that in children 5 years and older a higher proportion of HbAA children had a healthy BMI-for-age (table 1). No child was overweight. Among symptoms and signs, although the frequency of bone pain, previous blood transfusion, painful swelling of appendages and jaundice was significantly greater in HbSS than HbAS and HbAA, none occurred in the majority of HbSS children (table 1). No child had splenomegaly or leg ulcers. Mean (SD) Hb concentration was 13.3 g/dL (2.6) in 17 siblings with HbAA, 13.7 (2.5) in 24 HbAS and 9.1 (1.7) in 10 HbSS.

## DISCUSSION

A far as we are aware, this is the first report of cascade testing in SCD. Testing of siblings of index cases was highly effective in identifying undiagnosed SCD with almost one in five siblings diagnosed with SCA. All were invited to attend the clinic and to

start treatment. Starting treatment earlier in these children, especially in the 40% under 5 years of age, likely reduces longer term complications and early mortality.[16] In addition, and as expected, about half of siblings tested were identified as carriers and one-third as having a normal Hb phenotype (HbAA), which allowed the provision of genetic counselling, although at an early age.

Overall, engagement in cascade testing among families was high. Only about 18% of eligible families declined testing and for most this was due to inconvenient timing or living far from the hospital. Also, the project period covered the Eid al-Adha national holiday. We consider that more families would likely engage in cascade testing at some point if it was routinely available and some may have attended after the project ended.

Although a history of blood transfusion and some symptoms and signs consistent with SCD were significantly more common in HbSS than HbAS or normal, none occurred in the majority of HbSS children and, therefore, these variables appear to have limited value in prioritising children for testing. In addition, these variables were similar in HbAS and HbAA children so would not be useful for identifying carriers.

We used the existing clinic and laboratory resources with support from a visiting MSC student (ED-L) to undertake this project. The point-of-care test HemoTypeSC has shown high sensitivity and specificity for the diagnosis of HbAA, HBSS and HbSC with results available within 10 min[17] and performed well in our hands. Although we did not undertake an economic analysis, we consider that including cascade testing as part of routine care would likely be feasible within existing resources for many hospital clinics. However, to optimise the clinical service and also ensure long-term record-keeping of test results, the service could be led by a dedicated, trained clinical nurse specialist working alongside existing clinic staff. Diagnosis could be based mainly on affordable point-of-care tests[17] with laboratory staff undertaking appropriate quality control and a confirmatory test to confirm the diagnosis in SCD.

Cascade testing of relatives of children diagnosed with genetic conditions was effective in programmes to identify individuals at risk of cardiovascular conditions, monogenic conditions and haematological conditions.[18] In terms of identifying carriers, cascade testing of 691 relatives of children with β-thalassaemia in Mumbai, India, identified 151 carriers. The authors concluded that targeted cascade testing was five to six times more effective at identifying carriers than untargeted population screening.[19]

Several authorities advocate for the provision of comprehensive care for SCD and highlight the critical importance of early diagnosis facilitated by newborn screening.[20] One of the 12 key recommendations of The Lancet Haematology Commission on SCD was to 'ensure that all babies worldwide can be tested by 2025 to prevent long-term complications, requiring action by governments'[5] and there are concerted efforts to establish programmes in sub-Saharan Africa.[21] However, to date, newborn screening has generally not progressed beyond the pilot stage due to the considerable challenges of establishing such programmes.[5 6 20] Our findings support the use of routine cascade testing for families as another element of comprehensive care in LMICs that do not have well-established newborn screening yet shoulder the greatest SCD burdens.

Limitations of our study included that the families who participated were nearly all from the western region of Gambia and most were of higher SES. Participation in cascade testing may differ in more remote regions and among more disadvantaged families. We did not provide travel expenses to attend clinic, but this may have increased participation. In addition, point-of-care tests are suitable for use in primary care settings which, being closer to families, may improve access to testing.

## CONCLUSION

Cascade testing was feasible using existing clinic and laboratory resources and was highly effective in identifying undiagnosed SCA and HbS carriers in a low-resource setting. In the absence of well-established neonatal screening, cascade testing of siblings of an index case should be part of standard care to improve outcomes in SCD through earlier diagnosis and to support counselling regarding future childbearing.

A concise summary of the findings and recommendations were submitted to the EFSTH Board of Directors.

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**Contributors** All authors contributed to the study's conception and design. ED-L performed data collection. AA undertook the laboratory analyses. ED-L and SJA analysed the data. EDL wrote the first draft of the report. All authors approved the final report. SJA is the guarantor.

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**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** The project was approved by the EFSTH Research Ethics Committee (EFSTH-REC-2023-042) and was considered exempt from ethical approval by the MSc Research Ethics Committee, Liverpool School of Tropical Medicine. The parents/guardians of participants gave verbal consent for testing for sickle cell disease as part of routine care.

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**Data availability statement** Data are available upon request.



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