Implementing newborn screening for sickle cell disease as part of immunisation programmes in Nigeria: a feasibility study.

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Summary

Background Sickle cell disease (SCD) is highly prevalent in Sub-Saharan Africa (SSA), where it accounts for significant morbidity and mortality. Newborn screening (NBS) is paramount in early diagnosis and enrolment of affected children in a comprehensive care programme. This strategy has so far been greatly impaired in resource-poor countries because screening methods were technologically and financially intensive. Hence the need for affordable, reliable and accurate methods. This study aimed to test the feasibility of implementing a screening programme, using innovative point-of-care test (POCT) devices, into existing immunisation programmes in primary healthcare settings.

Methods Building on a routine immunization programme, existing facilities and staff, we have carried out systematic screening of newborns and infants using new POCT devices in five primary healthcare centres in Gwagwalada Area Council, Abuja, Nigeria. We compared two different POCT devices, SickleSCAN and HemoTypeSC, and compared the results to those obtained with high performance liquid chromatography (HPLC).

Findings A total of 3,603 consecutive newborns and babies under 9 months of age were screened over a period of two years, allowing to identify 51 HbSS (1.4%), 4 HbSC (0.1%), 740 HbAS (20.5%), and 34 HbAC (0.9%). The POCT devices were easy to use by local doctors, nurses and community health workers, and the head-to-head test showed concordance between the three methods in screening 313 newborns, with specificity and sensitivity of 100%.

Interpretation Our study demonstrates that i) POCTs are reliable and accurate in NBS for SCD, and ii) the integration of NBS into existing PHC immunisation programmes is feasible and can rapidly be implemented with limited resources. This feasibility study bodes well for the care of patients with SCD in resource-poor countries.

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Introduction

Sickle cell disease (SCD) is a globally distributed genetic blood disorder of high prevalence in sub-Saharan Africa (SSA).(1) SCD is caused by the inheritance of an abnormal beta-globin allele carrying the sickle mutation on the HBB gene (c.20A>T; p.Glu6-Val). Nigeria has the highest birth prevalence of SCD in the world with an estimated 150,000 annual births of babies with sickle cell anaemia, the most common form of SCD.(2) Children with SCD have repeated episodes of painful crisis, anaemia and increased susceptibility to infections, with an estimated 50%-90% dying before five years of age.(3, 4) According to WHO estimates, SCD may account for up to 15% of mortality in children under five in Africa,(3) imposing heavy psychological, mental and financial burden on affected individuals and their families. Mortality and morbidity can be substantially reduced by early diagnosis and supportive care.(5) With access to penicillin prophylaxis, hydroxyurea treatment and chronic transfusion programmes for those at risk of stroke, the outlook for individuals with SCD has substantially improved in most countries over the last decades.(6, 7, 8 , 9) These interventions, along with pneumococcal vaccines (10) which are often available as part of national immunisation programmes, rehydration and health education, have been shown to be effective and feasible for children with SCD even in resource limited settings.(11)

Successful implementation to improve the outcome of SCD patients requires whole programmes of screening, education, follow-up, and management.(12-14) Babies with SCD need to be identified at birth or shortly afterwards by primary screening and confirmatory testing, Pre- and post-natal education and counselling needs to be available to parents and relatives. Regular follow-ups to monitor disease progression and treatment adherence are essential to prevent severe chronic complications.(11, 15, 16)

A number of pilot programmes for newborn screening (NBS) have been carried out across Africa but these have so far been relatively small and mostly hospital based (17) with few exceptions.(18, 19) Although some studies have suggested that such programmes are cost-effective, particularly when the incidence rate of SCD is exceeding 0.2-0.3%,(20) this largely depends on the affordability and accessibility of the tests, care and follow-up. In particular, implementing NBS where the HbS gene is rare presents particular challenges.(21) Furthermore, early detection by NBS requires a supportive and functional public health infrastructure to be administered.(21, 22)

Traditional diagnostic methods for SCD include cellulose acetate electrophoresis, isoelectric focusing (IEF),(23, 24) tandem mass spectrometry, and high-performance liquid chromatography (HPLC). Each of these methods has important limitations for scaling up to a wide-reaching national programme in low-income settings. The challenges of screening for SCD with traditional diagnostic methods in Africa are well illustrated by the laudable initiative from the Nigerian Federal Ministry of Health to establish six special Millennium Development Goals (MDG) Sickle Cell Centres (SCC) across Nigeria between 2011-2012 (**Figure 1A**). Each SCC was equipped with a Bio-Rad HPLC machine. A national protocol for NBS for SCD based

on the MDG SCC was developed to guide the screening efforts countrywide. By 2017, the number of newborns screened were less than 2,000 in total across the six sites. The main challenges encountered were the lack of a specific budgetary allocation, inadequately trained personnel, expired reagents, the limited availability of consumables, the absence of mechanisms to collect samples from babies on a regular basis, and erratic power supply.

Inexpensive, easy-to-use tests, able to differentiate common haemoglobin phenotypes in newborns, which can be performed in remote sites, have recently been developed. These point-of-care tests (POCTs) are based on different diagnostic principles such as erythrocyte density, the differential mobility of HbS and HbA through filter paper and antibody-based immunoassay. Two of the frontline POCTs that have been validated are SickleSCAN (BioMedomics Inc., Morrisville, USA) and HemoTypeSC (Silver Lake Research Corporation, Azusa, USA). They have shown high degree of sensitivity, specificity and accuracy as screening tests, both in laboratories and in the field.(25, 26) They are easy to use as only a heel prick is required to obtain blood for testing. Neither POCT requires electricity or batteries, so they can be used in primary healthcare centres (PHCs).

Our aims were i) to demonstrate the feasibility of a bottom-up approach to implement routine screening, detection and follow-up of babies with SCD in PHCs alongside an immunisation programme, and ii) to assess the reliability and ease-of-use of the two POCTs currently available in PHCs.

Research in context

Evidence before this study

There is strong evidence globally that early diagnosis for sickle cell disease, combined with a series of basic interventions (including penicillin prophylaxis, pneumococcal vaccinations and hydroxyurea), can substantially increase the survival, reduce the morbidity and improve the quality of life of those affected. Nevertheless, apart from Ghana and India, newborn screening (NBS) for sickle cell disease (SCD) in countries of high prevalence for the disease remains limited. The recent development of several affordable and accurate point-of-care screening tests (POCTs) has been described as an additional key element to access rural areas with limited health infrastructures. We undertook a search of the literature using the following search terms: “sickle cell disease” AND “newborn screening” AND “Africa” in Pubmed. The search, conducted on March 15, 2020, returned only 47 articles, of which 9 were excluded as they focused on non-African countries. All references were published in the last 20 years. 62% (29 out of 47) of references retrieved were published after 2016. Out of the 38 publications included, eight were reviews. Seven references focused on point-of care testing devices. None of the studies incorporated newborn screening for SCD into existing immunisation programmes.

Added value of this study

We demonstrated the feasibility of implementing a NBS programme for SCD based on easy-to-use POCTs in multiple primary care settings, alongside an immunisation programme in an area of high prevalence, without substantial investment in equipment or staff.

Implications of all the available evidence

Our study provides further evidence of the feasibility of the implementation of NBS to reduce the burden of SCD in Africa countries. Although POCTs provide an affordable, reliable and easy-to-use method to screen for SCD, ensuring i) the earliest diagnosis possible; ii) the highest level of patient follow-up; and iii) the accessibility to treatments, including penicillin prophylaxis, pneumococcal vaccinations and hydroxyurea locally, and to effective prevention tools (e.g. transcranial Doppler for risk of stroke) regionally, all remain priorities to reduce the mortality and morbidity of SCD across sub-Saharan Africa and other countries of high prevalence.

Methods

Study design and participants

This prospective cohort study was carried out between July 14, 2017 and September 3, 2019 within the Gwagwalada Area Council, Federal Capital Territory, Nigeria (Ethics approval UATH/HREC/469). Five PHCs were involved (**Figure 1B**). Steps undertaken to set up the NBS and select participating PHCs are described in the appendix (**p 2**). All newborns and infants up to nine months of age presenting to the immunisation clinics at the five PHCs and for which written informed parental consent was given (**appendix p 3**) were included in the study. Mothers whose babies had not been screened, were counselled and given the opportunity to participate. Basic demographic information and contact details were recorded at enrolment.

Procedures

A schematic of the number of individuals screened and followed-up throughout the study is presented in **Figure 2**.

All the study participants were screened for SCD using HemoTypeSC due to the lower cost of this POCT compared to SickleSCAN (**Table 1**). Blood was drawn from each newborn by heel-prick and approximately one microliter was absorbed into the HemoTypeSC absorbent pad for testing, according to manufacturer's instruction (**appendix p 4-5**).

Additional blood spots on filter paper cards (supplied by the Association of Public Health Laboratories) were collected from each consecutive baby found to have SCD. The blood spots were air dried and each shipped within a week of collection to the Federal Medical Centre Keffi NBS Screening Laboratory for North Central Nigeria. Confirmatory testing was performed by HPLC testing using the Bio-Rad machine according to standard protocols.

We tested a subset of 313 newborns and infants with both SickleSCAN and HemoTypeSC to compare the two POCTs against the gold standard HPLC (25). **Table 1** describes the features of the two POCTs in terms of test principle, manufacturer, sampling technique, turnaround time, ease of sample reading, post result conservation, sensitivity, specificity and overall diagnostic accuracy, cost and availability. Results from both POCTs could be captured in the field with a mobile phone camera for a second opinion.

Results were delivered to the parents by the study nurse who performed post-screening counselling. The babies received pneumococcal and other vaccines as part of the National Program on Immunisations at each participating PHC (Supplementary Table S2). Follow-up visits were scheduled every 3 months after screening. Dedicated pharmacists maintained a register of screen-detected babies and supplied folic acid and oral penicillin. Hydroxyurea could not be administered as part of this study. The need to adhere to prescribed medication regimens in order to reduce complications was highlighted during the first visit. Since the majority of the participating babies were unable to swallow tablets, parents/guardians were asked to dissolve penicillin V or folic acid tablets in a 10ml container before administration.

For breastfed babies, it was advised that breast milk could be used as a diluent. At each visit, parents/guardians were encouraged to adhere to the medication regimen and not to share medications with other family members and friends.

To support affected families, registration and first consultation fees were paid for babies of consenting parents at the University of Abuja Teaching Hospital from the Doris Duke Charitable Foundation grant.

Throughout the study, the supervising physicians and the In-Charges at the PHCs gave a brief talk on SCD and NBS to mothers presented for immunisations. The dedicated research nurse navigated the parents of screened babies to the paediatric sickle cell programme for comprehensive care. The programme has educational materials that highlight health promotion habits and alert parents to danger signs such as fever, persistent headache, abdominal pain, vomiting and diarrhoea, the features of severe anaemia and chest pain with breathlessness. Further genetic counselling was offered to parents of newborns who were not interested in the follow up programme or who withdrew consent during the study.

Statistical analysis

We calculated the proportion of individuals with sickle cell anaemia (HbSS), sickle cell trait (HbAS), haemoglobin SC-disease (HbSC) and without abnormal haemoglobin variants (HbAA) amongst the total number of newborns and infants screened. 95% confidence intervals based on a Fisher Exact test were used to reflect the uncertainty related to the sample size, rather than the accuracy of the POCT.

To check the consistency of the prevalence data from our local screening programme, we compared them with data from the 2018 Nigerian Demographic and Health Survey (DHS) (27) The Nigerian DHS is a nationally representative sample survey providing up-to-date information on a range of demographic and health indicators. Genotyping for SCD of children 6-59 months old was performed in 14,000 out of the 42,000 households included in the survey. We compared our study results to those from the overall 11,243 children and the 687 children 6-8-month-old surveyed by the DHS, using a two-proportion z-test, with a p-value cut off of 0.05. All statistical analyses were performed in *R 3.6.2*.

Role of the funding sources

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Building on the immunisation services in PHCs, a total number of 3,603 consecutive newborns and babies under 9 months of age were screened from July 14, 2017 to September 3, 2019. Data collected suggested that 297 of 400 mothers surveyed (74.2%) delivered their babies within PHCs while 25.8% delivered outside health facilities. All but two mothers (99.5%) were in favour of NBS. The newborns screened comprised 1,807 (50.2%) males and 1,796 (49.8%) females. The ages, sex, ethnic group distribution and screening results of the babies tested are presented in **Table 2**.

None of the POCT devices used in this study provided invalid results. The Hb genotype results from this HemoTypeSC screening were: 2,774 (77.0%) for Hb AA, 740 (20.5%) Hb AS, 34 (0.9%) Hb AC, 51 (1.4%) Hb SS and 4 (0.1%) Hb SC. The total of babies with SCD was therefore 55 (1.5%), corresponding to 1 in 65 babies.

Of these 55 babies, 41 (74.5%) were enrolled for medications (**Figure 2**). Thirty-six (87.8%) of these 41 babies completed three visits over nine months for free folic acid and oral penicillin at the pharmacy. Two babies (3.63%) died. One was due to death from severe anaemia when the mother was transferred to another city. The other baby whose parents were initially in denial of the positive results, developed dactylitis and an acute febrile illness and died upon late presentation to hospital. Three (5.45%) babies were lost to follow up as the house addresses given could not be traced. The parents of seven babies (11.8%) were not interested when contacted. Two of the participants' parents withdrew their consent (4.8%) as they insisted that their babies were in perfect health. Three of the participants' parents (7.3%) did not return after the first visit and could not be reached by telephone. However, only 29 parents (52.7%) accepted follow up in the paediatric sickle cell programme of the teaching hospital. The median period of follow-up for the 36 newborns who completed the three visits was 226 days (IQR: 198-357).

The comparison of SickleSCAN and HemoTypeSC with HPLC revealed fully consistent results (**appendix p 6**)**.** There was complete concordance of results by all three methods for Hb AA Hb AC, Hb AS and Hb SS.

The proportion of HbSS children individuals observed in our study (1.4%, 95%CI: 1.08%-1.86%) was consistent with the data from the 2018 Nigerian DHS for children 6-8 months old (z-score: 0.87, p-value: 0.17) but statistically significantly higher than in the overall sample of 6-59 month old children (z-score: 2.68, p-value<0.01) (**Table 3**).

Discussion

In this feasibility study, we demonstrated that, by building on existing immunisation programmes, NBS for SCD using POCTs can be scaled up in local PHCs with limited additional human and financial resources for the detection and follow up of babies with SCD in low-resource settings. Through the screening of 3,603 consecutive newborns, we identified 55 cases of SCD and followed up 41 of them for 9 months. The observed prevalence of 1.4% for HbSS and 20.5% for sickle cell trait is somewhat lower than figures which have been used for years as representative of our populations but mostly in line with the DHS report of 2018. The higher prevalence of HbSS in our study compared to the overall data from the 2018 Nigeria DHS may be a reflection of early childhood mortality due to SCD. Further work to account for differences in prevalence between ethnic groups should be conducted.

NBS for SCD in African countries using traditional methods has so far been limited, with the exception of Ghana.(18, 28, 29) These efforts have not progressed beyond small pilot projects in local hospitals and regions, partly due to practical and financial constraints to set up and access evidence based interventions for the early diagnosis and management of SCD.

The successful implementation of an NBS programme for sickle cell disease in African countries relies on multiple factors including access to healthcare facilities, easy-to-use and affordable screening devices, educational material and counselling services, and appropriate follow-up and management to prevent severe chronic complications. Our study demonstrates the feasibility of implementing such a programme in PHCs by building on the infrastructure and mobilisation associated with immunisation programmes across the African continent.

This approach allowed us to reach out to the vast majority of babies born in the PHCs during the study period; the reliability of the POCT used was excellent; the costs were limited to the POCT devices and support of SCD children to attend follow-up appointments; no additional staff members were required – all of which suggest that this approach could easily and rapidly be scaled-up across Nigeria and other sub-Saharan countries. The absence of invalid POCT results may be a reflection of the high-quality of the training provided in the PHCs. Some challenges remained, such as i) the substantial delay in obtaining confirmatory testing from the MDG SCC in Keffi, and ii) the reluctance of parents – despite genetic counselling - to bring apparently healthy identified babies for routine health maintenance visits at the teaching hospital resulting in loss to follow up.

The main limitations of our study are three-fold. First, the number of newborns screened over the study period remains limited and 38% of them were older than three months. No data on the proportions of children not attending immunization clinics were available. The full schedule of vaccinations recommended by the Nigerian Federal Ministry of Health involves six visits during the first year of life, including doses delivered at birth. The NBS for SCD would therefore benefit from improvements in early access to vaccination programmes as per these recommendations. Second, a substantial number of SCD children could not be followed up

throughout the study. Alongside education campaigns on the genetic nature of SCD and its clinical manifestations, it is imperative to improve access to PHCs and to enhance the capacity of PHCs to provide routine health management of babies with SCD. Furthermore, many SCD children adequately receiving immunisation and prophylactic medication will suffer from acute pain crises, sepsis, acute splenic sequestration and other severe complications which cannot be managed by PHCs. Referral pathways to higher levels of care for treatment of emergencies and stroke prevention with Doppler scanning also need to be strengthened. Better results in follow up may be obtained if staff at PHCs are trained to carry out initial follow up by a team of house-to-house mobilisers, constituted at each facility to work within the facility catchment area. Third, evidence of the benefits of hydroxyurea to improve the prognosis of patients with sickle cell disease, including in African settings, is now very strong. It is therefore imperative to ensure that such drugs are integrated in NBS programmes.

The policy implications of this study are significant as there is now data to support the integration of NBS in immunisation programmes in PHCs, as part of universal health coverage in Nigeria, in line with the national multi-sectoral action plans for the prevention and control of non-communicable diseases (2019-2025).

Contributors

OEN was chief investigator. OEN, AS and FBP conceived and designed the study. OIO, reviewed the study design. FBP designed the statistical analysis. OEN, SA, UNA, CO, AA, GS, HAI, OO, RIC, YT and JHI recruited participants. OEN, SA, UNA, CO, AA, GS, HAI, OO, RIC, YT and JHI collected data and prepared regulatory and governance requirements. OEN, RIC, AS and FBP analysed and interpreted data. OEN, ADA and FBP wrote the manuscript. All authors reviewed and approved the manuscript.

Declaration of interests

FBP reports personal fees from bluebird bio and from Novartis outside the submitted work. All other authors declare no competing interests.

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Figures

Figure 1: Maps of A) the six Nigerian geopolitical zones and the Millennium Development Goals Sickle Cell Centres (MDG SCC) in which high-performance liquid chromatography machines were implemented in 2011-12. The Federal Capital Territory (FCT) is shown in blue. The Gwagwalada Council Area is highlighted in red; and B) the 5 primary health care centres of the Gwagwalada Council Area which participated in this screening study for sickle cell disease.

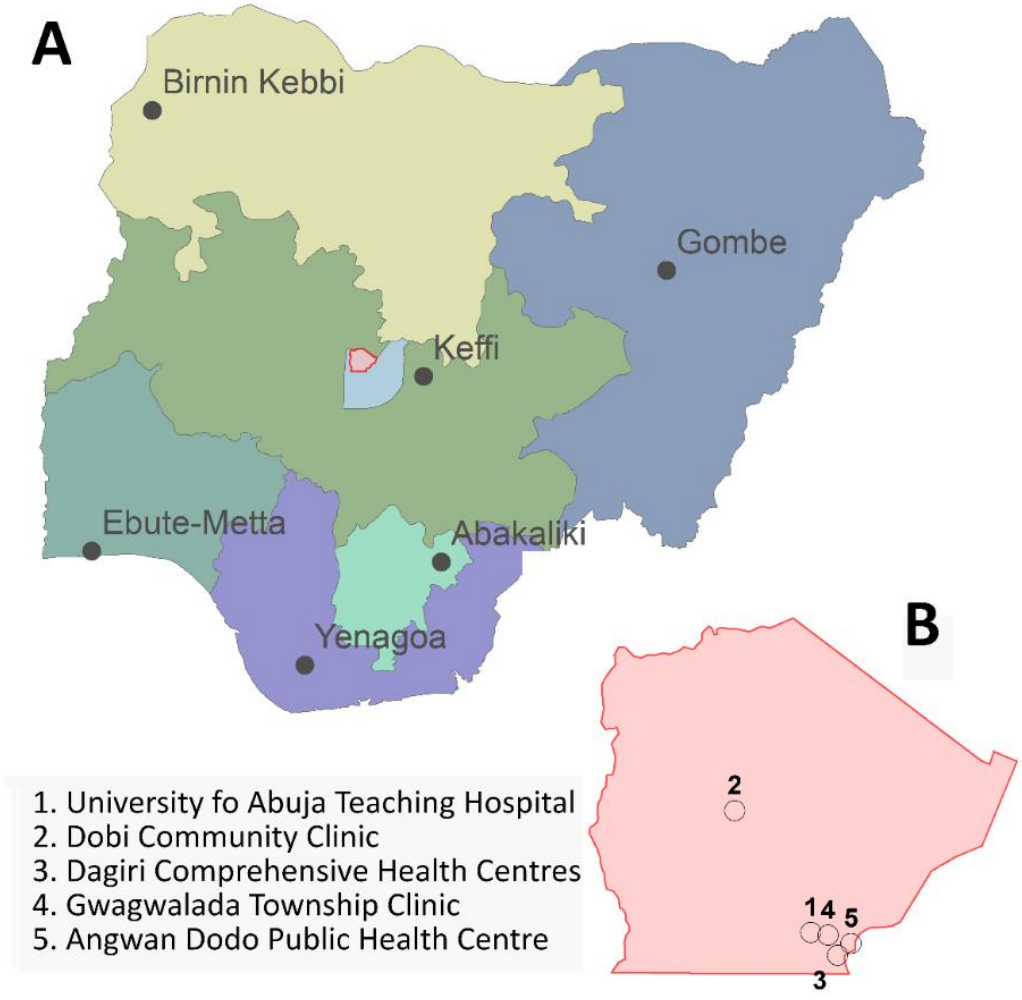
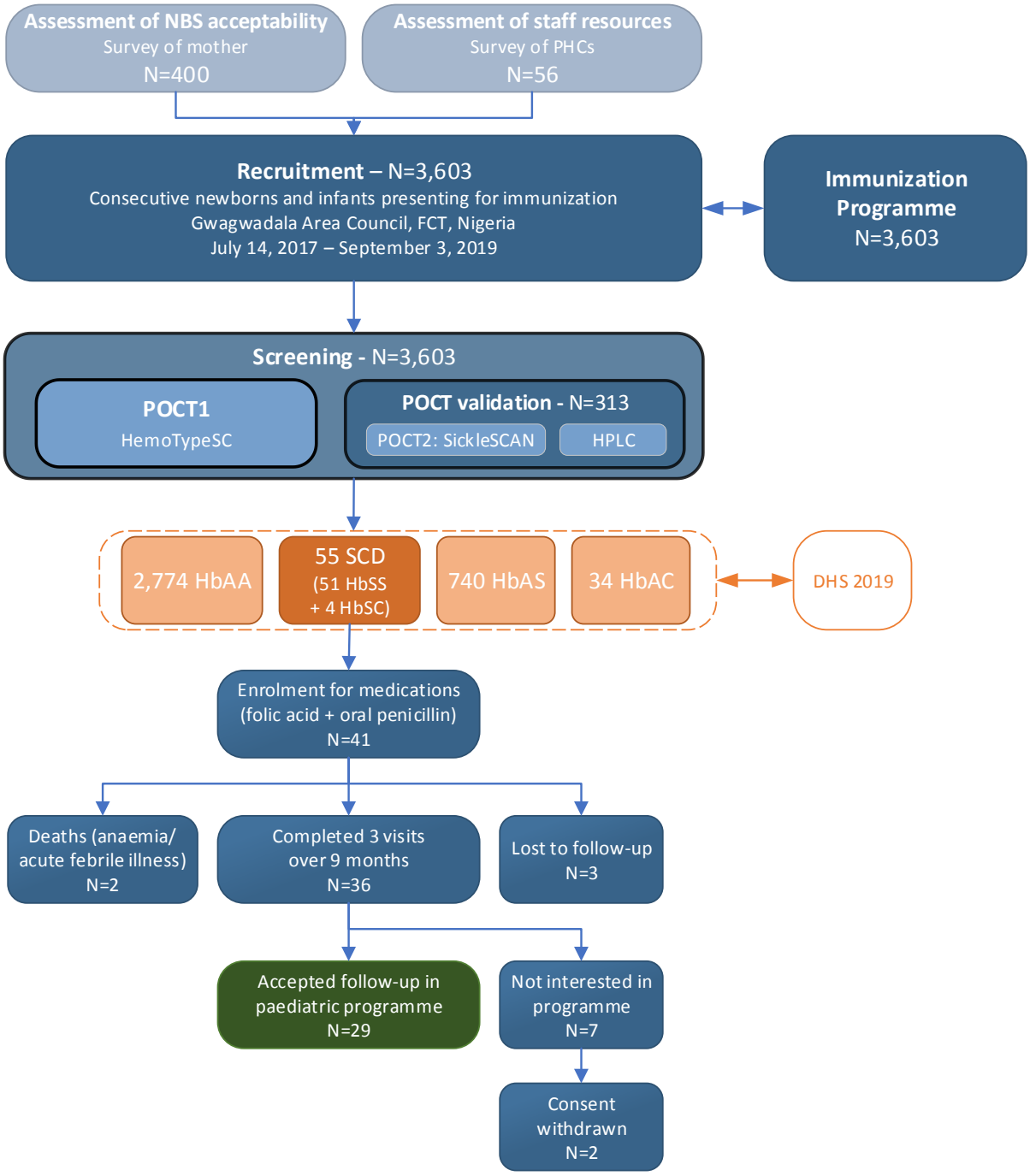


Figure 2. Schematic of the number of individuals screened for sickle cell disease and followed-up throughout the study.



Tables

Table 1: Screening results for 313 newborns screened for sickle cell disease in the Gwagwalada Area Council, Federal Capital Territory, Nigeria and properties of two point-of-care tests: SickleSCAN and HemoTypeSC.

Name	SickleSCAN	HemoTypeSC
Screening results	• HbAA: 225 • HbSS: 6 • HbAS: 81 • HbAC: 1 Total: 313	• HbAA: 225 • HbSS: 6 • HbAS: 81 • HbAC: 1 Total: 313
Principle	Qualitative lateral flow immunoassay	Competitive enzyme-linked immunosorbent assay
Manufacturer	Biomedomics, 6 Davis Drive, Durham, NC 27709, USA	Silver Lake Research Corporation, Azusa, CA 91702 USA
Sampling technique for the test	Finger or heel prick, can also be used on venous blood	Finger or heel prick
Ease of sample reading	Straight forward. Positive results are seen as bands on the cassette. Minimal training required.	Counter intuitive, the absence of a band is the positive result. Rigorous training required.
Turnaround time	3-5 minutes	10 minutes
Kit	Cassette with tests	Dipsticks method in test tube
Storage	Up to two years at room temperature	Stable at room temperature
Post-result conservation	Bands do not fade on the cassette. Available for comparison with the result of confirmatory testing	Test strips can be mounted on paper with the results. Available for comparison with the result of confirmatory testing for a limited time as the test strip paper shows sign of fragmentation with time
Sensitivity (in field conditions)	>94.9% (Segbena *et al*, BMC Hem. 2018. 18:26)	>93.8% (Nnodu *et al*, Blood Cells Mol Dis. 2019. 78:22-28).
Specificity (in field conditions)	>99.2% (Segbena *et al*, BMC Hem. 2018. 18:26)	>99.2% (Nnodu *et al*, Blood Cells Mol Dis. 2019. 78:22-28).
Overall diagnostic accuracy	99% (Kanter *et al*. BMC Med (2015) 13:225)	>99% (Steel *et al*, Am J Hematol. 2019. 94(1):39-45); 99.1% (Nnodu *et al*, Blood Cells Mol Dis. 2019. 78:22-28).
Cost	$2.19	$1.49
Availability	Biomedomics, Inc. Registered in Europe under C€ and in the following countries: Nigeria, Ghana, Kenya, Tanzania, Kuwait, India and Brazil.	Zutron Pharmaceuticals Ltd

Table 2: Age, sex, ethnic group distribution and screening results of the 3,603 newborns screened for sickle cell disease in the Gwagwalada Area Council, Nigeria between July 2017 and September2019. The 95% confidence intervals are based on a Fisher Exact test and purely reflect uncertainty related to the sample size, rather than the accuracy of the POCT.

Description		**Number**	**Percent**	
Gender	Female	1796	49.8	
	Male	1807	50.2	
Age Category	<6 Weeks	896	24.9	
	6 Weeks - < 3 Months	1340	37.2	
	3 Months - < 6 Months	749	20.8	
	6 Months - 9 Months	618	17.2	
Ethnic Group	Hausa	447	12.4	
	Igbo	425	11.8	
	Yoruba	336	9.3	
	Ebira	228	6.3	
	Igala	218	6.1	
	Others	843	23.4	
	Not Stated	994	27.6	
Genotype	**Genotype**	**Number**	**Frequency**	**95% CI**
	AA	2774	77.0	75.59%-78.34%
	AC	34	0.9	19.25%-21.89%
	AS	740	20.5	1.08%-1.86%
	SC	4	0.1	0.67%-1.32%
	SS	51	1.4	0.03%-0.30%

Table 3: Comparison of the screening results with those of the 2018 Nigerian Demographic Health Survey (DHS).

	HbAA	**HbAS**	**HbAC**	**HbSC**	**HbSS**	**Other**	**Total**
Present study	2,774	740	34	4	51	-	3,603
	77.0%	20.5%	0.9%	0.1%	1.4%	0.0%	100.0%
DHS 2018 - 6-8 months	528	139	10	1	7	-	687
	76.9%	20.2%	1.5%	0.2%	1.0%	0.0%	100.0%
DHS 2018 - 6-59 months	8,782	2,244	182	46	103	11	11,391
	77.1%	19.7%	1.6%	0.4%	0.9%	0.1%	100.0%