**TITLE**:

Newborn Screening for Sickle Cell Disease: An innovative pilot program to improve child survival in Dar-es-Salaam, Tanzania.

**Running title**: NBS for sickle cell disease to improve child survival in Tanzania

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**ABSTRACT**

**Background**: Sickle cell disease (SCD) is a recognized cause of childhood mortality. Tanzania has the fifth highest incidence of SCD (with estimated 11,000 SCD annual births) worldwide. Although, newborn screening (NBS) for SCD and comprehensive healthcare has been shown to reduce U5 mortality to up to 94% in high-income countries such as USA, no country in Africa has maintained NBS for SCD as a national health program. The aims of this program was to establish and evaluate NBS-SCD as a health intervention in Tanzania and to determine the birth prevalence of SCD.

**Methods**: Muhimbili University of Health and Allied Sciences (MUHAS) conducted NBS for SCD, from January 2015 through November 2016. Dried blood spot (DBS) were collected and tested for SCD using Isoelectric focusing (IEF).

**Results**: Screening was conducted on 3981 newborns. Thirty one, (0.8%) babies had SCD, 505 (12.6%) had sickle cell trait, and 26 (0.7%) other haemoglobinopathies. Twenty-eight (90.3%) of the 31 newborns with SCD have been enrolled for comprehensive healthcare.

**Conclusion**: This is the first report on NBS as a health program for SCD in Tanzania. The SCD birth prevalence 8 per 1000 births is of public health significance. It is therefore important to conduct NBS for SCD with enrollment into comprehensive care program.

**KEYWORDS**: COMPREHENSIVE CARE, NEWBORN SCREENING, SICKLE CELL DISEASE.

**Introduction:**

Sickle cell disease (SCD) refers to a group of inherited red blood cell disorders that occur due to mutations in beta globin genes . One of which is invariably haemoglobin S (Hb S), a variant produced as a result of a glutamic acid to valine substitution at position 6 of beta globin chain, the underlying mutation being HBB:c.20A>T. HbS, is prone to polymerization, disrupting red blood cell shape, function and life span. Individuals who are heterozygous for Hb S, (sickle cell trait) are usually asymptomatic while those who are homozygous have SCD. SCD can also occur when Hb S is co-inherited with beta thalassaemia and other haemoglobin variants such as Hb C. However homozygous Hb S and co-inheritance with beta zero thalassaemia result in the most severe forms. SCD is characterized by chronic hemolytic anemia and recurrent vaso-occlusions, which lead to painful crises, the hallmark of the disease.

Worldwide it is estimated that over 300,000 babies are born annually with SCD and that these numbers will increase from 305,800 in 2010 to 404,200 in 2050.1 Most of these babies are born in sub Saharan Africa and India2–4where SCD contributes significantly to early childhood mortality and morbidity.5,6 In 2006, World Health Organisation (WHO) in its 59th health assembly, identified SCD as a significant public health burden in Africa.7,8Tanzania is estimated to rank 5th after Nigeria, Democratic Republic of Congo, India and Angola in countries with the highest SCD birth prevalence.3 Up to 11,000 SCD births occur annually in Tanzania and without proper diagnosis and management, 50% or more of these babies will die before 18 years, with highest mortality in the Under-five (U5) age group.6 The high SCD prevalence is also reflected by the high proportion of individuals who are carriers of the sickle cell gene, sickle cell trait (SCT) (13-20%)6 which is more profound in areas including the Eastern coast and the North West region around Lake Victoria9. In recognition of this condition, the country has included SCD as a disease of public health priority in the National Non Communicable Disease Strategy.10

The mortality and morbidity associated with SCD can be reduced by early preventive measures including newborn screening coupled with comprehensive care and educative programs for affected families. There is significant evidence from high-income countries of increased survival for individuals with SCD following early diagnosis by NBS and comprehensive care.11–14 In Africa; although there have been different initiatives for NBS-SCD in Ghana, Nigeria, Angola and Uganda,15–18 no country has successfully established NBS-SCD as a universal national health intervention. Ghana has the largest and the most extensive initiatives. In 2015, Tanzania through Muhimbili University of Health and Allied Sciences (MUHAS) implemented a pilot NBS for SCD program in Dar es Salaam, Tanzania. The aims of this pilot programme were to establish and evaluate NBS-SCD as a health intervention in Tanzania and determine the birth prevalence of SCD. The innovation of this programme was based on utilizing expertise and resources from existing public health programme in Tanzania such as Management and Development for Health (MDH), Comprehensive Community Based Rehabilitation in Tanzania (CCBRT) and Ifakara Health Institute (IHI).

This programme adopted the NBS for SCD model from the Public Health England and customized it to fit our settings. The key issues included; location of the laboratory, Dried Blood Spot (DBS) collection and transportation, laboratory screening tests, result feedback and turnaround time. Different NBS-SCD programmes have employed different models. In most African settings where there is short interval between time of delivery and that of discharge, most NBS are built to capture babies before discharge19. However in other settings, it has proven beneficial to allow flexible capturing times up to few weeks after birth15. The type of sample collected for screening is also an important factor. Although most NBS use DBS from a heel prick, some have also tried using umblical cord samples20. Sample transportation can be a challenge especially in under developed settings. However, initiatives that have been successful have included use of postal offices and couriers. Screening test choice forms an important basis of NBS for SCD. Most African countries have employed Isoelectric focusing (IEF) as the first line and another standard test such as High Performance Liquid Chromatography (HPLC) and Capillary Electrophoresis (CE). Results feedback in most settings has utilized mobile phone communication, however this has been challenging when mothers could not provide correct numbers or did not have access to a mobile phone. The details of how our programme was conducted is described blow.

**Materials and methods**

**Study area and population**

*Study area*: This was a prospective study involving newborns at Muhimbili National Hospital (MNH) and Temeke Regional Hospital, Dar es Salaam, Tanzania from January 2015 through November 2016. MNH is the nation’s tertiary health facility and has been offering SCD services, both clinical and laboratory, for the past three decades while Temeke hospital, which is a regional hospital for the Temeke municipality in Dar es Salaam established SCD services more recently. Both MNH and Temeke hospitals, provide services for residents in Dar es Salaam and the neighboring regions.

*Study population*: This study involved women who delivered at MNH and Temeke hospitals and screening involved newborns of up to two days. Informed consent was requested from any woman who agreed to take part in the study by allowing her newborn to be screened. The study excluded all newborns with any illnesses or those whom their mothers did not agree to participate in the study. Demographic and contact details were collected prior to the collection of the blood sample using a standard profoma and later entered into project database known as MySQL (Sun Microsystems Inc, Santa Clara, California, USA).

**Health education and training**

**1. Provision of health education to mothers and training of health care workers**

*Education to pregnant women/mothers*: Trained nurses provided health education to mothers who had delivered at MNH and Temeke hospital postnatal and neonatal wards. Health education was delivered before obtaining a consent for newborn to be screened. The duration of the education ranged from 30 minutes to one hour depending on discussions/questions from the mothers. Health education on SCD was delivered through a brief talk with a group of mothers and provision of leaflets. The information included the origin of SCD, different types of sickle status including the difference between a baby who is carrier and one with SCD. Training was also provided for SCD health education including the importance of clinic visit and healthy living. The training was delivered by using the national language “Swahili” to ensure understanding. Training materials were based on existing resource developed by Sickle Cell Program of Tanzania.

*Training of health care workers***:** Training on SCD care was provided to different cadres of health workers (doctors and nurses) identified at MNH and regional hospitals including Temeke, Ilala and Amana. Areas of strengthening included; origin and inheritance of SCD, SCD screening (including the collection of dried blood spots, specifically for nurses), diagnosis, neonatal health, and SCD management. Training was scheduled for five days and training materials included brief talks, leaflets and videos, which were adopted from existing SCD resources developed by the SCP programme in Tanzania and UK partners (PHE).

**2.** **Training of laboratory technicians**

Laboratory training materials and Standard Operating Procedures were developed and used to train newly recruited NBS programme laboratory technicians as well as laboratory technicians from MUHAS and Bugando referral hospital. The initial training by our UK partners (PHE) was conducted in one week and covered the theoretical aspects of laboratory organization and management, sample collection, screening methods and result interpretation. Training was provided by manufacturers following installation of first Isoelectric focusing (IEF) and later High Performance Liquid Chromatography (HPLC). This training was conducted over two days and was facilitated by PerkinElmer and Biorad respectively, and trained the laboratory technicians on IEF and HPLC methods. In addition, the technicians underwent practical training on the use of DBS puncher user interface.

**Newborn screening for SCD**

*Enrolment into screening program*: Pregnant mothers (postnatal ward) who received SCD health education were requested to consent for their babies to be screened for SCD. Information on consenting was completed in the screening registration form together with detailed information on how to locate the mother after the screening. This included the location, street name, house number, and phone numbers of spouses, parents or most reliable individual. All babies were given unique identification numbers.

*DBS collection*: DBS sample was collected from the newborn’s heel using standard prickers. DBS collection, transportation and storage was performed according to the manufacturer’s manuals (Lasec diagnostics) and newborn screening guidelines from Clinical and laboratory standards institute (CLSI).

*SCD screening:* Screening for SCD was performed at MUHAS Haematology clinical research laboratory. 3.2 mm of the DBS was punched by an automated DBS puncher (﻿Wallac DBS Puncher) followed by analysis by Isoelectric Focusing (IEF) which was conducted according to the manufacturer’s protocol (Wallac RESOLVE® Hemoglobin System). Second testing was conducted by IEF for the samples that had abnormal results such as FAS, FS and FAV for the first test. Results were interpreted initially by a trained laboratory technician and confirmed by the laboratory manager. Confirmed results were entered into the program’s database using the unique identification number.

*Results dissemination*: Mothers or close relatives of the screened babies who had a negative screening test for SCD received a standard text message informing them of the results while those carrying a sickle gene (SCT) or those with SCD were contacted by a telephone call. Telephone calls were conducted following standard operating procedures which included information required to be passed to the responsible person and the procedure to follow in case of a failed call or unreachable numbers.

**Comprehensive SCD Healthcare**

Clinical services for SCD had been previously established at MNH and Temeke hospitals. SCD services were strengthened following training of the healthcare workers on SCD diagnosis and management. In addition, the programme provided guidelines for SCD management at outpatient clinic and during hospitalisation, with criteria for referral to MNH. Upon diagnosis of SCD, newborns were enrolled for a comprehensive health care in these two hospitals. A simple case report form (CRF) was established for each child with SCD when attending the SCD clinics. Reminders about the scheduled visits were sent by text messages to a primary and an alternative number provided during clinic visits. Active surveillance was established as a means to track SCD children who have not attended clinic after a six months period.

**Results**

**Health education and training**

*Health education for pregnant women/mothers of newborns*: About 4000 pregnant women/mothers who had delivered at MNH and Temeke hospitals received health education on SCD.

*Training of health care workers*; A total of 160 nurses and 96 health care workers from MNH, Temeke, Amana, and Mwananyamala Hospitals were trained on the origin and inheritance of SCD, SCD screening/diagnosis, neonatal health and SCD management*.* With the establishment of NBS into national policy, the training materials will be incorporated into the syllabus of midwifery training so that it is provided as part of pre-service training in nursing courses.

*Training of laboratory technicians*: A total of 16 lab technicians from Bugando hospital, MNH and MUHAS laboratories were trained to perform SCD screening using IEF and High Performance Liquid Chromatography (HPLC) methods. The laboratory technicians were selected from hospitals with either IEF or HPLC testing platforms. The training materials were submitted to the MoHCDGEC for potential revision and approval for use.

**Newborn screening for SCD**

*SCD screening*: DBS collection was conducted for 11 months (October 2015 to September 2016) following the establishment of the programme. Since this was a pilot phase and NBS is not a health policy in Tanzania, DBS collection was conducted based on the availability of resources and for a few hours in a day. MNH and Temeke hospitals have about 800 and 1000 births per month respectively. However, a total of 3981 babies were screened at MNH and Temeke hospitals, 1141 and 2840, respectively. Although screening took place in two health facilities, the catchment area included all parts of Dar es Salaam as well as peripheral areas (Table 1), 68.87% coming from Temeke municipality. Of the 3981 babies screened, 3419 (85.9%) were found to be SCD-negative (FA), 508 (12.7%) carried the sickle gene (FAS), 31 (0.8%) were found to be SCD-positive and 26 (0.7%) of babies had unidentified variants. There was an equal proportion of males (50.7%) and females (49.3%) in the babies who were screened.

*Feedback of results to the patients dissemination and enrolment into comprehensive care*: Of the 3981 screened babies, more than 80% of parents/guardians could be contacted and informed of the results, this includes parents of all babies found to be carriers and 30/31 of the parents of babies with SCD. The NBS programme followed up the 31 babies who were diagnosed with SCD at birth. And ensured that they received SCD comprehensive care. From the 31 newborns diagnosed for SCD, 28 were enrolled into comprehensive care, 2 died and 1 could not be reached. The comprehensive care for SCD included the following; i) SCD confirmation; laboratory tests for confirmation of the SCD diagnosis and full blood count. ii) Basic interventions: SCD patients received folic acid tablets (0.1-0.5mg/per day), prevention of malaria and prompt diagnosis and treatment of malaria, prevention of bacterial infection with daily oral penicillin V, (iii) Health education: health information about SCD to parents or caregivers, advice to attend outpatient clinic every 3 months and advice to seek medical care in the event of acute illness.

**Discussion**

Despite evident benefits of NBS for the survival and well-being of individuals with SCD in the developed countries, sub Saharan countries are failing to establish similar national NBS programmes although this region experiences the greatest burden of disease. Several African countries including Ghana, Angola, Uganda and Nigeria have embarked on initiating NBS programmes however none have been adopted as national screening programmes. Among these countries, Ghana has achieved the largest screening initiative with more than 500,000 babies screened up to 2017. However, a national screening programme has not been established. There are various reasons to the challenge of rolling out NBS services as a national programme including the challenges with the health infrastructure, disproportionately high cost of screening tests in the African setting and result feedback mechanisms.

This is the first report that documents NBS establishment as a health program for SCD in Tanzania which has the 5th highest incidence of SCD globally. The findings from this project have proven the importance of conducting NBS for SCD as a health intervention in countries with a high prevalence of SCD such as Tanzania. NBS services were initially established at MNH and thereafter Temeke hospital, with an ongoing plan to scale up to other regional hospitals. The successes and challenges that have been realized and documented in this report will be used to inform the Tanzanian government as strategies for national NBS programme are put in place.

**Health education and training:** Health education has been highlighted as an important contributor to the success of NBS-SCD initiatives 15–17. We also experienced the importance of ongoing heath education and training for the families and health care workers. As part of NBS program, health education was provided for mothers of newborns. In both MNH and Temeke hospitals education was provided in postnatal and neonatal wards. This was a limitation to the number of women who benefited from the education and it is evident that the use of antenatal clinics may increase that number. At the moment, the health system in Tanzania allows for antenatal clinics in peripheral hospitals and not in referral hospitals such as MNH and Temeke. Therefore conducting NBS for SCD in peripheral hospitals such as Temeke may both increase the number of pregnant women who receive SCD health education and the number of babies to be screened. Another limitation was the mode that was used to deliver education, brief talks and leaflets. At the time where mothers have just given birth, it is difficult to concentrate on new information and to be able to remember this afterwards. Therefore, ongoing SCD education programs in medias and at SCD clinics are important.

The program trained health workers from the selected hospitals and health care centers. The identification of health care workers was left to the hospital management in order to increase buy in and sustainability. The health care workers included doctors and nurses from obstetrics, postnatal and neonatal ward. The number of pregnant women/newborns in the wards and the time spent in that ward before discharge dictated the selection of health workers for NBS. The modality of training the healthcare workers followed the training of trainers (TOT) approach such that the subsequent training involved the trained personnel as trainers. Considering the low awareness on SCD by most health care workers in Tanzania the focus of the training was general knowledge on SCD and disease management. Interactive talks and demonstrations featuring real settings were the best delivery methods than formal talks. The main challenge with the training of health care workers is the transfer of the trainees from the designated facilities to other facilities. Therefore, well planned ongoing refresher training sessions for health care workers are required in the initial years of NBS until it is well established.

**Newborn screening for SCD**:

*SCD screening*: We observed that most (68.7%) of the babies that were screened reside in the Temeke region. The reason for this could be the high delivery capacity at Temeke hospital compared to MNH. This could also reflect differences in SCD prevalence across regions (SCD regional pockets) within Tanzania. This is similarly true for the coastal (Dar es Salaam, Pwani, Tanga) and lake Victoria (Mwanza and Mara) regions where SCD is highly prevalent.15 Although the proportion of babies screened was equal between boys and girls, the proportion of girls was much higher (71%) in the babies found to be positive for SCD. This finding will be confirmed in a larger dataset. The overall proportion of SCD (0.8%) was more than the predicted value (0.6%), this may indicate an increase in SCD prevalence in this region, or an underestimate nationally?????. In addition, the proportion of babies who are carriers of sickle cell (SCT) was high (12.5%) calling for preventive measures and genetic counseling services for this group. This frequency is in line with previous reports.6 We also observed abnormal variants (0.7%) that could not be identified by the available screening methods, highlighting the need of DNA diagnostic tests that can resolve complicated hemoglobin variants.

*Feedback of results to the patients dissemination*: Over eighty percent (>80%) of the families of the screened babies could be contacted by phone calling and provided with results information, however, some of the parents could not be contacted either due to a wrong telephone number or a misplaced/lost phone. This highlights the importance of investing in other methods such as use of global positioning system (GPS) or integrating with immunization registry which has a well established electronic system to capture and track immunizations events.

*Comprehensive care:* Out of 31 identified babies, two babies died, the verbal autopsies performed for these cases indicated that the deaths were not associated with SCD rather other causes of deaths were suspected including hypothermia and hypoglycemia. The rest of the babies were successful enrolled for comprehensive care. It is anticipated that the early enrollment into comprehensive care will translate into better health outcomes for these babies. This will be confirmed through a separate study.

**Development of strategy for NBS in Tanzania**:

*Scaling up*: The experience gathered from this project will be used to strengthen or scale-up NBS in Tanzania. Conducting NBS first at MNH and then Temeke hospital gave us an experience of scaling up and operating in both a national referral hospital and a regional hospital. The scaling up model has been used elsewhere, as this allows for proper establishment in one site prior to the involvement of multiple sites.21 The ultimate goal of the NBS program is to be a sustainable national health programme owned by the Government. The program has initiated discussions with the MoHCDGEC to ensure sustainability of NBS services. The approach that has proven to be sustainable for Tanzania is the integration of NBS services with existing healthcare systems in provision of health education, sample collection and results dissemination. We have identified platforms that may be best to work with, one of which is the immunization program and the utilizing NCD clinics. MoHCDGEC will be able to advise whether Non communicable diseases (NCD) or Reproductive and Child Health(RCH) or both will be the best host of NBS activities for SCD in Tanzania. The Non-Communicable diseases (NCD) strategic plan (2016-2020) (https://www.worlddiabetesfoundation.org/files/tanzania-ncd-stategic-plan-2016-2020), has the following priority areas; Community sensitization, early detection NBS, SCD screening at health facilities among newborns in high prevalence areas and provision of comprehensive care. Therefore, whether SCD screening will be done in pregnant women, newborns or as early infant diagnosis should be agreed upon.

*National initiatives*: At the national level, SCP has worked with the Government to establish a national SCD taskforce, which will work on establishing a national NBS program that will include SCD screening. The programme also supported the MoHCDGEC in the development of the first draft of "National Newborn Screening Guidelines" which includes SCD. NBS programme facilitated the convening of two consultative meetings held in July 2015 in Dar-es-Salaam and in December 2015 in Morogoro. These meetings involved 25 health professionals and policy makers from the (MoHCDGEC), Muhimbili National Hospital (MNH), Newborn Screening (NBS), and the Regional health facilities. The SCP continues to work with the ministry of health and other stakeholders to finalize the national NBS guidelines and lobby for its implementation.

*Limitations:* This program faced challenges and limitations at various levels. *One*, challenge of getting the program stakeholders and implementers buy in. This was mitigated by conducting frequent meetings to share the development and progress of the program at site, regional and national levels. *Two*, challenges of delayed procurement and high cost of laboratory equipment and reagents. Although not solved during the program, the mitigation for this is exploring different screening platforms, particularly point of care tests.

**Conclusion**

Tanzania has made a good progress on the targets for Millennium Development Goal 4 including the decline in under-five deaths from 166 in 1990 to 112 in 2005 and 67 in 2015 per 1,000 live births. In addition, infant mortality has decreased from 68 to 43 per 1,000 live births between 2005 and 2015. NBS for SCD is expected to contribute to these efforts. The importance of NBS intervention in Tanzania is supported by previous data showing increasing number of babies born with SCD in the country.1 Despite the fact that NBS requires a significant investment, the cost effectiveness of NBS across Sub-Saharan African countries is based on the high prevalence of SCD.13

The major learning is that NBS programme is needed and is practical in Tanzania. In the 11 months of piloting NBS at MNH and Temeke Hospital (October 2015 to September 2016) there was success in counseling of women at delivery, collection of blood samples from newborns, identifying newborns with SCD and introducing them to comprehensive care. The feasibility of the programme has been mainly due to the approach of selecting public hospitals and integrating NBS services in existing government RCH services.

We recommend that NBS program is approved as a national programme and be coupled with immunization program to leverage resources and increase feasibility. We recommend a stepwise scaling up from MNH and Temeke hospitals to all peripheral hospitals in Dar es Salaam and subsequently to zonal hospitals across the country.

**Author's statement**

Authors contributions: JM,JK,HM,SC,NU,AS,SR designed the study. LM, DS, JM,SN,VM,PBM,PM,IM,MN,NU,SC,GK,MA,BD,FT,ML,YD and FM implemented the study. BM and SN analysed tand interpreted the data. SN and JM drafted the manuscript and all authors contributed to the drafts of the manuscript and approved the final draft.

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**Ethical approval**: Ethical approval was granted by MUHAS research and publications committee with reference number 2017-03-22/AEC/Vol.XII/67. Verbal consent was given by the participants (mothers of the newborns) of the study which was recorded on the enrollment form. Verbal consent was formally approved by our ethics committee.

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