A prospective newborn screening and treatment program for sickle cell anemia in Luanda, Angola

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Over 300,000 infants are born annually with sickle cell anemia (SCA) in sub-Saharan Africa, and >50% die young from infection or anemia, usually without diagnosis of SCA. Early identification by newborn screening (NBS), followed by simple interventions dramatically reduced the mortality of SCA in the United States, but this strategy is not yet established in Africa. We designed and implemented a proof-of-principle NBS and treatment program for SCA in Angola, with focus on capacity building and local ownership. Dried bloodspots from newborns were collected from five birthing centers. Hemoglobin identification was performed using isoelectric focusing; samples with abnormal hemoglobin patterns were analyzed by capillary electrophoresis. Infants with abnormal FS or FSC patterns were enrolled in a newborn clinic to initiate penicillin prophylaxis and receive education, pneumococcal immunization, and insecticide-treated bed nets. A total of 36,453 infants were screened with 77.31% FA, 21.03% FAS, 1.51% FS, and 0.019% FSC. A majority (54.3%) of affected infants were successfully contacted and brought to clinical care. Compliance in the newborn clinic was excellent (96.6%). Calculated first-year mortality rate for babies with SCA compares favorably to the national infant mortality rate (6.8 vs. 9.8%). The SCA burden is extremely high in Angola, but NBS is feasible. Capacity building and training provide local healthcare workers with skills needed for a functional screening program and clinic. Contact and retrieval of all affected SCA infants remains a challenge, but families are compliant with clinic appointments and treatment. Early mortality data suggest screening and early preventive care saves lives. Am. J. Hematol. 88:984–989, 2013.

Introduction

Sickle cell anemia (SCA) is an inherited and life-threatening disorder of hemoglobin affecting over 300,000 newborn infants worldwide each year [1,2]. It is estimated that at least 75% of these births occur within sub-Saharan Africa [1]. Although there are few accurate data on the true mortality of SCA in Africa, more than half of affected infants will likely die before reaching the age of 5 years [3–5]. The mortality of infants with SCA begins to increase rapidly relative to the "healthy" population after 6 months of age, when fetal hemoglobin levels decline, with reports of up to 30% mortality within the first 1–2 years of life [3]. The majority of these deaths occur before the diagnosis of SCA is made, and are most commonly due to invasive bacterial infection and sepsis from encapsulated organisms (especially pneumococcus) [6,7] or acute anemia (splenic sequestration, malaria) [8–10]. SCA thus contributes substantially to the under-5 mortality rates of many countries in sub-Saharan Africa.

In the United States and most developed countries, screening of newborns for SCA is recommended, either with a universal or targeted (at-risk) screening strategy. The goal of newborn screening (NBS) is early identification of affected infants, which allows for early care and treatment with a focus on measures that can prevent SCA-related morbidity and mortality. There is compelling evidence that the combination of NBS, parental education, prophylactic penicillin, and pneumococcal conjugate vaccination (PCV) can significantly reduce the frequency of invasive bacterial infections and decrease the under-5 mortality for children with SCA [10–15]. In the United States, all newborns are screened by heel stick procedure within the first 1–2 days of life to provide a dried bloodspot (DBS) for hemoglobin laboratory testing. All infants and families affected by SCA are then brought to clinical care within the first 2–3 months of life for parental education, initiation of prophylactic penicillin, and confirmation that the routine childhood PCV series has been initiated. This comprehensive care plan has led to a marked increase in survival for children with SCA [11,12,16,17]. It is now rare for children with SCA to die in developed countries, with a reported survival into adulthood of 94% in the United States [18] and up to 99% in England [19].

At the 59th World Health Assembly (WHA) in 2006, the World Health Organization (WHO) identified SCA as a significant public health problem in Africa that may contribute to up to 16% of under-5 mortality in some countries [20]. WHA resolution 59.20 urged African nations with high burdens of SCA to design and implement national SCA programs with a focus on widespread awareness-raising, early identification by NBS, early access to adequate preventative care, and training of medical professionals [20]. SCA has also been recognized as a significant public health problem by the United Nations [21]. In addition to designating June 19 World Sickle Cell Day [21], the United Nations has issued a call for action among African nations to address the unmet burden of SCA [22]. These efforts highlight the high mortality of children under the age of 5 years and the need for early identification and treatment

Additional Supporting Information may be found in the online version of this article.

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Conflict of interest: FA, FAS, FS are patterns of hemoglobin.

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programs, as well as the importance of developing international partnerships that allow for the development of successful national SCA educational, clinical, and research programs. These strategies work directly toward Millennium Development Goals 4 (reduce under-5 mortality) and 8 (develop a global partnership for development) [23].

Despite these direct calls for action, SCA remains largely unaddressed in sub-Saharan Africa, where the burden of disease is the greatest. Although nearly all of these countries have significant investments toward and national strategies for HIV, malaria, and tuberculosis, SCA remains below the radar of most Ministries of Health and international philanthropic agencies. It will be essential for sub-Saharan African nations to develop national sickle cell strategies focusing on early diagnosis and access to care in order to successfully reduce childhood mortality as challenged with the millennium development goals.

With the support of the Angolan Ministry of Health and the philanthropic partnership of Chevron Corporation, a prospective pilot NBS program for SCA was developed and implemented in the capital and most populous city of Luanda, Angola. We describe the early successful results of the screening and treatment program in this limited-resource setting, which was designed to reflect the priorities of increasing awareness of SCA, building local capacity with training and education, and improving SCA care and expertise using international partnerships.

Materials and Methods

Ethics

Because the NBS program was a government mandated public health initiative (such as newborn immunization or perinatal HIV therapy), informed consent was not required from the mothers before obtaining a DBS specimen from their babies. Local ethics board approval was obtained in Angola at Hospital Pediátrico David Bernardino (HPDB) and from the Baylor College of Medicine (BCM) Institutional Review Board in the United States for the analysis and reporting of these NBS pilot program data.

Program development

The First Lady of Angola and the Minister of Health requested that Chevron provide financial and logistical assistance in developing a preliminary sickle cell strategy with the Republic of Angola. Chevron is one of Angola's leading producers of petroleum and through the company's Angola Partnership Initiative, provides support for many Angola-based programs with a focus on health and education. Chevron sought the expertise of BCM and Texas Children's Hospital to assist in the development and implementation of this sickle cell program in Angola, starting with a pilot NBS program. In March 2011, a three-way agreement was signed, and plans were established to determine if a NBS and treatment program for SCA was feasible in a limited-resource setting such as Angola, with emphasis on local training and capacity building. After signing the agreement, the study was designed, the NBS laboratory was renovated and equipped, and staff were trained. Screening began in July 2011 and the data reported here include newborns screened and cared for through June 2013.

Specimen collection locations

For the pilot program, two large maternity hospitals in Luanda were selected as initial sites of blood collection from newborn infants. Maternidade Lucrécia Paim (~31,000 births per year) and Maternidade Augusto Ngangula (~21,000 births per year) are among the world's busiest maternity hospitals. Obstetrical nurses were trained in the techniques of blood collection for the NBS program, and then retrained approximately once a month. Screening was initiated first at only one hospital (Lucrécia Paim), and after the successful training of laboratory staff, Augusto Ngangula was added later as a second screening site. With further growth of the NBS program, a neighborhood health center (Centro de Saúde da Samba with ~8,000 births per year) and two smaller general hospitals with smaller maternity wards (Hospital Geral dos Cajueiros with ~8,000 births per year and Hospital Municipal de Viana-Capalanca with ~2,400 births per year) were subsequently added.

Specimen collection procedures

In the short interval between birth and discharge from the maternity hospital (typically 4–12 hr), a heel stick procedure was performed using a BD Microtainer® Contact-Activated Lancet (Becton, Dickinson and Company) to fill two bloodspots on a custom-designed Whatman screening card (GE Healthcare, Supporting Information Fig. S1). Individual screening cards can be distinguished and identified by a unique barcode that links the DBS used for laboratory testing with the contact and demographic information in the electronic database. Identifying information was collected for the screening card from the medical chart and from the mother, including the mother's and father's name, their contact telephone numbers, home address and location of the local health center where the baby will receive routine childhood vaccines and follow-up care. Additional information about the birth (gender, weight) was also collected. A detachable portion of the card with the unique identifying barcode was provided to the mother. Bloodspots were dried and placed in a plastic bag for storage until specimen pickup, typically within 1–2 days of sample collection.

Laboratory techniques

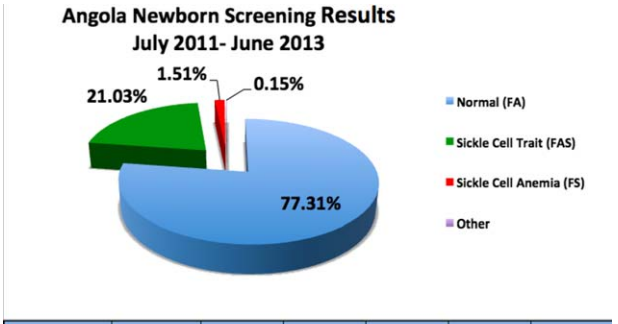
After DBS collection and transport, all specimens were initially tested by isoelectric focusing (IEF, RESOLVE® neonatal hemoglobin system, PerkinElmer, Inc.) within 1–2 days of arrival in the NBS laboratory at HPDB, the only dedicated pediatric hospital in Angola. The DBS samples were scanned using an automated barcode reader and 3.2 mm punches were captured in a 96-well microtitration plate using the automatic Wallac DBS Puncher. Controls with a combination pattern of hemoglobin (Hb) A, F, S, and C were added every 12 wells, and, therefore, a total of 76 unique DBS samples were run on each gel according to the manufacturer's recommendations (Supporting Information Fig. S2). After the IEF process was completed, the samples were scored first by the laboratory technician, according to the presence of HbF (both acetylated and nonacetylated bands), HbA, and HbS. Hemoglobin patterns predominantly included the normal FA pattern, an abnormal FAS pattern consistent with sickle cell trait, and an abnormal FS pattern consistent with SCA (Supporting Information Fig. S2). There was not a specific attempt to quantify HbS in respect to HbA, and thus, this technique could potentially have difficulty distinguishing FAS (HbS trait) and FSA (HbS/Beta-(+) thalassemia), although the IEF technique appears robust enough to distinguish these two conditions. The laboratory supervisor subsequently scored each gel independently to ensure accuracy of results. Any result with an indeterminate or unsatisfactory pattern was repeated on IEF in order to obtain a clear result. All IEF results with an FAS, FS, or other abnormal hemoglobin pattern, or in the rare instance of an indeterminate result, were selected for repeat analysis by capillary electrophoresis (CE). All CE analyses were performed using the CAPILLARYS 2 NEONAT FAST® system (Sebia, Inc.) according to the manufacturer's instructions.

Newborn sickle cell clinic

Families of all newborns with an FS or FSC result were contacted at ~6–8 weeks of age, typically by telephone, to request a repeat sample for confirmatory testing and enrollment in the newborn sickle cell clinic. During the first clinic visit, all newborns received a first dose of the 13-valent pneumococcal conjugate vaccine (PCV-13, Pfizer, Inc.) and an insecticide-treated mosquito bed net (PermaNet® 2.0, impregnated with deltamethrin at 55 mg/m^2, Vestergaard-Frandsden, Switzerland) for malaria prophylaxis, and initiated Penicillin prophylaxis (125 mg by mouth twice daily). These items were purchased solely for the newborn SCA clinic and were provided at no cost to the families. The mothers were instructed to break the 250-mg Penicillin tablet in half and crush the 1/2 tablet in liquid (typically milk, water, or juice).

Sickle cell education and management

The sickle cell clinic was operated by an Angolan staff, including a patient educator, doctors, and nurses. These providers had preexisting sickle cell education, but were provided further education about the special care of infants with SCA focusing on how to provide appropriate parental education and how to prevent life-threatening complications within the first few years of life. This trained Angolan team performed the patient care and education described here. The first visit to the newborn sickle cell clinic included comprehensive sickle cell education, including education about inheritance patterns and the importance of vaccination, penicillin prophylaxis and the prevention of malaria infection. A picture-based sickle cell educational brochure was provided to each family to help educate other family members at home. Routine



Total Samples	FA	FAS	FS	FSC	FAC	Other
36,453	28,182	7,666	550	7	21	27

Figure 1. Newborn screening results. To date, 36,453 infants have been screened with 21.03% of infants demonstrating the FAS hemoglobin pattern consistent with sickle cell trait and 1.51% of infants with an FS pattern consistent with SCA. Hemoglobin C was rare and only seven infants demonstrated the heterozygous hemoglobin FSC pattern. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

clinical care occurred every 2 months for the first 6 months (aligned with PCV-13 schedule) and every 3 months thereafter. Patients who did not come to scheduled clinic visits were contacted and scheduled for a subsequent date. Ongoing sickle cell education occurred over the first year, particularly the management of fever and repeated instructions about splenic palpation. Febrile events were described as emergencies, and parents were instructed to always seek medical care when their child was febrile. The location and technique for palpation of the spleen was performed and reinforced with each visit. Signs and symptoms of acute splenic sequestration were reviewed (pallor, lethargy, splenomegaly), and parents were instructed to seek emergency medical care if they noticed any of these symptoms. If care was sought in the community, the clinic staff instructed parents to describing the diagnosis of SCA to the community provider and to emphasize the need for prioritized care for their child. Parents were encouraged to bring other family members to subsequent clinic visits so that education can be provided to all care providers.

Data management

Data from the NBS card were entered into a unique and custom designed internet-based electronic data capture (EDC) system with servers located at BCM in Houston, Texas. This EDC system has separate forms for demographic information, laboratory results and follow-up data and has the capacity to generate real-time reports for all data entered (e.g., screening results by IEF or CE with graphical display as in Fig. 1, total numbers of babies screened by week or month by collection site, list of names, and contact information for FS babies who are greater than 8 weeks who require follow-up, and babies who are overdue for their next pneumococcal vaccine).

Results

Demographic information from maternity sites

In the first 23 months of the pilot program, a total of 36,453 NBS cards were collected and analyzed. Accurate birth data were not available from maternity sites, but based upon prior yearly reports, it is estimated that during this pilot phase, over 85–90% of babies born at the smaller maternity sites were tested, but only 50–70% of babies born at the two larger maternity centers had a DBS collected. The monthly collection rates have increased with time due to improved education and nurse awareness. The average birth weight (mean $\pm$ 1 SD) for the entire cohort of babies was 3,201 $\pm$ 526 g. Birth weights were not significantly different for infants with different hemoglobin patterns. Initially, telephone numbers were poorly documented with only 51.7% of DBS cards in the first 3 months having at least one telephone number listed. With increased nursing education at the collection sites and emphasis on the importance of telephone numbers for retrieval of affected infants, the fraction of infants with documented telephone numbers increased significantly over time. In the past 12 months of the program, 80.5% of NBS cards had at least one telephone number documented.

Newborn screening results

Since initiation of the NBS program in July 2011, all 36,453 DBS collections have yielded interpretable laboratory results. Using a combination of primary IEF screening and CE confirmation, a total of 28,181 infants (77.31%) had a normal FA pattern, while 7,666 (21.03%) had FAS pattern (sickle cell trait), and 550 (1.51%) had FS pattern (consistent with SCA, Fig. 1). Only 55 samples (0.15%) produced a NBS result other than these expected three results, including 21 FAC (Hemoglobin C trait) and seven FSC (Hemoglobin SC disease). A fast band consistent with alpha thalassemia trait was frequently noted but was neither quantitated nor recorded during this pilot phase.

Comparison of laboratory techniques

Compared to the 100% result rate of IEF, interpretable results were obtained for only 4,018 of 4,759 (84.4%) of samples tested by the CE technique. The remaining 15.6% of samples (mostly within the first 3 months of CE training period) did not produce a result due to hemoglobin degradation, inadequate blood spotting technique, mechanical failure, or unclear technical issues. For specimens with a result by both IEF and CE, concordance was greater than 99.8%. Of the nine samples with discordant results, six samples were suggestive of FAS by IEF but FS by CE and three were suggestive of FS by IEF and FAS by CE. Five of these nine babies with initially discordant results returned for a repeat confirmatory sample. Initial IEF result was correct in four of these five cases with only one FAS baby incorrectly scored as FS by initial IEF. This misdiagnosis by IEF was due to very small quantity of blood collected and the very faint HbA band was not well visualized and was thus initially scored FS. Two babies have not yet returned for a confirmatory sample and the other two babies died in the neonatal period and were not available for repeat testing.

Clinic follow-up

Families of infants with an FS or FSC screening result were notified by phone to initiate care and treatment, ideally by age 8 weeks. In the newborn SCA clinic at HPDB, infants received penicillin prophylaxis and PCV-13 pneumococcal immunization, while parents received sickle cell education and were provided insecticide-treated bed nets for malaria protection. To date, 505 of 557 FS or FSC babies have been eligible for clinic (at least 8 weeks old) and 274 (54.3%) of these families have been successful contacted. Of these 274 infants, 10 returned for a confirmatory test that indicated an FAS pattern consistent with sickle cell trait, 11 infants were dead upon contact (most having died within the first month of life due to prematurity or congenital abnormalities), two infants had moved from Angola, and five families refused care, most commonly due to reasons of faith. One of the families that directly refused care initially at 6 weeks of age and repeatedly upon successive contact reported that the child died acutely at 12 months of age following an acute febrile illness. Nine of the 11 babies had died before the time of contact died at the maternity hospital due to “asphyxia” within the first 48 hr of life, one died due to complications of cleft lip and palate within the first month of life and one died acutely within the first week of life due to congenital hydrocephalus.

A total of 244 infants were confirmed to have SCA upon confirmatory testing in the clinic and continued with follow-up care. A total of 819 doses of PCV-13 have been provided as

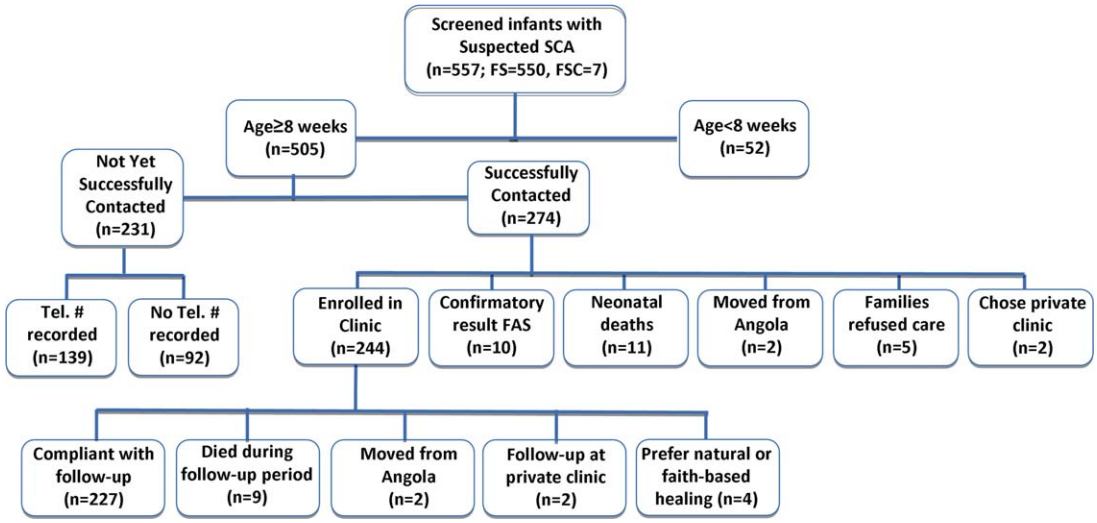


Figure 2. Retrieval efforts for infants with SCA. This illustration depicts the retrieval rate and follow-up rate of screened infants with hemoglobin patterns consistent with SCA (hemoglobin SS or hemoglobin SC disease). Follow-up remains a challenge but greater than 54% of affected infants are successfully brought into follow-up care. Once families are successfully contacted and enrolled in the newborn SCA clinic, follow-up is excellent. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE I. Timing and Details of Mortalities within Newborn SCA Cohort

Age of death (months)	PCV-13 doses	Receiving penicillin	Presenting symptoms	Medical evaluation and therapy	Place and details of death
2	1	Y	Fever	None	Home, no hospital evaluation
5	4	Y	Car accident	N/A	Car accident, died at scene
6	2	Y	Fever	Emergency department, but no evaluation	Died waiting in ED
7	2	Y	Fever/pallor/lethargy	Emergency department, but no evaluation	Died waiting in ED
7	2	Y	Fever	Emergency department; received oral antimalarial medication, no antibiotics	Died at home <24 hr after ED visit
8	3	Y	Fever	Local health center acute care, no antibiotics administered	Fever returned, died en route to ED for second time
15	4	Y	Fever/pallor/lethargy	Emergency department, received RBC transfusion, no antibiotics	Died at home <24 hr after ED visit
17	4	Y	Lethargy/pallor	Emergency department, but no evaluation	Died at home <24 hr after ED visit
19	3	Y	Fever/pallor	Community health center, no antibiotics	Died at home <24 hr after visit

per routine vaccination scheduling. All babies received their first pneumococcal immunization at the initial visit, at a median age of 65 days of age. After the first visit, a total of 433 follow-up visits have been scheduled and 416 (96%) have been maintained with nine deaths, two families electing to receive care at a local private clinic, two families that moved from Angola and four families that declined further care due to a preference for faith-based and/or traditional healing methods. Figure 2 summarizes the clinical follow-up to date for infants with SCA identified through the NBS program.

Household demographics

Families lived in the urban and poverty-stricken Luanda. The average household had 6.43 people with an average of 2.83 people sleeping in each bedroom. Only 34.2% of families reported access to water within their household.

Mortality

Only 9/244 (3.6%) of enrolled infants have died during the follow-up period. Table I details the timing and circumstances of death among these nine infants. At the first and at each subsequent clinic visit, families were educated in clinic of the warning signs of emergency complications (fever, pallor, splenomegaly), and were instructed to seek emergency care if they noted any of these warning signs. As instructed, nearly all families did seek care, but due to gaps in the medical system and lack of awareness among Angolan healthcare providers, appropriate and timely care was unfortunately not provided for these children. Table I details the reported circumstances of death for these nine infants. Using all children who have reached the age of 1 year, the calculated first-year mortality rate for all enrolled SCA babies who are at least 1 year of age (6.8%, $n = 132$) demonstrated improved survival for this high-risk population in comparison to the published national infant (<age 1 year) mortality rate of 9.8% for all Angolan infants from 2010 [24]. With the decline of HbF at ~6 months of age, it would be assumed that the mortality rate before 1 year would be elevated for children with SCA, perhaps as high as 30% [3]. It is encouraging that the care provided through this screening and treatment program result in a mortality rate for high-risk infants with SCA that is at least equal to (and perhaps better than) the mortality rate than "healthy" Angolan children before the age of 1 year.

Discussion

SCA represents a significant global public health problem, with hundreds of thousands of affected children dying each year from preventable causes due to lack of early identification and appropriate care. With growing public health initiatives against many well-publicized health problems in developing countries, such as HIV, malaria, malnutrition, and tuberculosis, the relative contribution of SCA to under-5 mortality in Africa will become even more pronounced [3]. With relatively simple interventions such as NBS, prophylactic penicillin, pneumococcal immunization, and early education,

the survival of African children with SCA can be markedly improved [25–27]. Given the significant contribution of SCA toward under-5 mortality, it will be critical for international philanthropic agencies and African Ministries of Health to recognize and address the problem of SCA.

NBS is a common practice for dozens of diseases in the United States but has yet to become a national standard for any sub-Saharan African countries, despite the fact that the burden of SCA is 10-fold higher than the most common inherited conditions identified through NBS programs across the developed world. Reports of NBS efforts across many African countries have previously been reported in Burkina Faso [28], Benin [29], the Democratic Republic of Congo [30], and Ghana [31]. These reports focus entirely on the incidence of SCA in these countries and do not discuss the ability or efforts to find affected infants or to describe the success or efficacy of follow-up care for screened infants with SCA. As with any screening program, follow-up care is just as important as the screening procedure and these follow-up data are critical aspects of evaluating any screening program. Our data are the first to describe the combination of NBS for SCA and the success of finding affected infants and providing and sustaining follow-up care over the first year of life.

Angola is a developing country rich in natural resources but with an unbalanced distribution of wealth, ranked 148th of 187 countries on the United Nations International Development Index, and >50% of the population lives below the international poverty line ($1.25 USD per person per day) [32]. The health care system was damaged through the 1975–2002 civil war, but now with more than 10 years of peace, the infrastructure and health statistics are steadily improving. However, Angola still has one of the world's highest infant (98 per 1,000) and under-5 (158 per 1,000) mortality rates [24]. With 795,000 births per year [24] and a documented incidence of 1.51% based upon this pilot program in Luanda, we estimate that there are over 12,000 infants with SCA born in Angola each year. Coupled with a 50–90% estimated under-5 mortality rate, there is a tremendous unrecognized burden of SCA in Angola, and the potential for great benefits using simple measures such as early identification by NBS and provision of lifesaving comprehensive care and treatment. With a 1.5% incidence of SCA among newborns and an estimated 80% mortality before 5 years of age, it is possible that up to 8% of the under-5 mortality in Angola may be attributable to SCA, making it an important comorbidity on which to focus healthcare resources.

This prospective pilot study documents an important proof of principle, namely that systematic NBS for SCA with a close and organized clinical follow-up plan is feasible in a developing country with limited health resources such as Angola. Capacity building and sickle cell education provides local healthcare workers with skills necessary to have a functional NBS program and an essential newborn SCA clinic. It is important to recognize that each step of this program was implemented by an Angolan staff, from blood collection to clinical care. Maternity nurses were trained about blood collection and were instructed to provide sickle cell education to mothers. Laboratory technicians were instructed on laboratory techniques and interpretation of results. Angolan doctors and nurses were instructed on comprehensive sickle cell care. Community efforts remain ongoing to educate the general and medical community about the importance and impact of SCA within Angola. These data confirm that the burden of SCA is extremely high in Angola. Despite the ongoing challenges of contacting and retrieving all affected infants, this pilot program demonstrates that a majority of families can be contacted and that when contacted with an explanation of the findings, families are extremely compliant with clinic appointments, treatment, and follow-up care. Early diagnosis and access to comprehensive sickle cell care appears to reduce mortality, but it is important to recognize that expansion of NBS and strengthening of healthcare systems is needed to further reduce this mortality and extend these results across the country. Our experiences with the unique three-way public-private partnership among government, industry, and academia suggest a novel means by which to approach MDG 4 and 8 for SCA and other serious diseases. SCA is becoming a more important and pressing health issue in this region and startup funds such as those provided by Chevron for this program, can help to "get the ball rolling" for the development of national sickle cell strategies, as is the plan for Angola.

This early phase of the Angolan sickle cell NBS program had both seen and unforeseen challenges. Attempting to implement a new procedure for maternity hospitals that are already overworked with as many as 100 babies born per day remains an ongoing challenge, but training and ongoing education have resulted in sustainably high collection. Laboratory testing by IEF was quite successful, since training of technical staff was not difficult and the IEF testing was robust and reliable. However, the two-stage approach to testing (IEF followed by CE) does not appear to be technically feasible or necessary in settings with limited resources. In countries such as Angola, with a straightforward hemoglobin distribution of F, A, and S without the presence of other rare hemoglobin variants, IEF is a reliable standalone NBS technique. Finding affected babies also remains an ongoing challenge, but with dedicated personnel and the near universal ownership of cellular telephones by Angolans, it has been possible to locate a majority of affected infants. Our program has a single social educator employed to find patients, primarily by telephone, but community resources in Angola are lacking. There is not widespread community health workers as is the case in many other African countries. If a telephone number is disconnected or incorrect, it remains difficult to contact affected infants. Several novel mechanisms have been attempted to varying degrees of success and ongoing efforts are being made within the community to mobilize resources and improve the percentage of affected infants found and brought to care.

Once enrollment in the clinic has been established, the care and treatment of newborns in the first year of life has not been challenging, but as these infants grow up and develop complications of SCA, developing a stable clinical infrastructure that provides rapid evaluation and effective treatment of emergency complications such as fever and severe anemia, as well as therapeutic options such as hydroxyurea, will be important goals. As illustrated in Table I, most of the mortalities that we experienced during this pilot phase were likely preventable if timely and appropriate care was administered in the emergency setting. As most emergency care for sickle cell-related complications occurred in the community, we do not have access to the details of these records and recognize this as a limitation of this report. The resources of this pilot program focused on the screening and treatment of newborns and the training of the sickle cell clinical staff, and had limited personnel to educate the healthcare community on a wider level (e.g., emergency department (ED) physicians, community providers). There were educational sessions given to the hospital ED and to develop emergency care, but implementation of these protocols on a wide level in a very busy ED remains an ongoing challenges. There is a developing educational plan to train healthcare providers at large to improve the management of sickle cell related

complications in the community. The few deaths that occurred in this cohort highlight the need for widespread sickle cell awareness in the medical community.

Recently published estimates suggest that the number of annual SCA births is likely to increase by up to 25% and that NBS and care programs could save the lives of nearly 10 million young children with SCA over the next several decades [33]. With this increased number of births and improved survival of infants due to screening and care programs, it will be imperative to consider the introduction of hydroxyurea to this young population, since this is the only disease-modifying therapy currently available for SCA [34–36]. Hydroxyurea is now included on the WHO model list of essential medicines for children with SCA, and represents a potential opportunity for the treatment of children with hemoglobinopathies in the global setting. With many unanswered questions about the use of hydroxyurea in this population, including feasibility (with once every 4–8 week monitoring) and safety/efficacy in a malaria-endemic region with numerous interacting exposures and comorbidities, prospective research will be needed to determine the safety and efficacy profile of hydroxyurea in a limited-resource setting like Angola.

This pilot study provides compelling data regarding the diagnosis and treatment of infants with SCA in Luanda, warranting expansion of the program to additional provinces, with an eventual national strategy for the diagnosis, care, and treatment of children with SCA throughout the entire country. It will be important to validate that our experiences in Luanda is equally feasible and effective in the more remote provinces of Angola, as the incidence of SCA, the feasibility of NBS and the efficacy of SCA care may be quite different in these less developed regions. This NBS and follow-up care and treatment program in Angola can also serve as a model for how other low-middle income countries with limited health resources can begin to respond in earnest to the WHO call for action against this growing global health problem.

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