

# Time to Invest in Sickle Cell Anemia as a Global Health Priority

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More than 500 children with sickle cell anemia (SCA) die every single day because of lack of access to early diagnosis and associated treatment, yet SCA remains an invisible global health problem.

Over the last several decades, unprecedented improvements in the survival of children across the world have been accomplished through strategic collaboration among global health leaders and funding agencies by targeting specific preventable and treatable conditions associated with high early mortality.<sup>1</sup> The Millennium Development Goal (MDG) program has been remarkable, and through MDG 4, the number of deaths in children <5 years of age has declined from 12.7 million in 1990 to nearly 6 million in 2015. Despite the historical and paradigm-shifting successes of the MDG program, much work remains to be done. Although the MDG era has resulted in many global health improvements, the progress has been somewhat uneven because global health funding has largely focused on a small number of infectious diseases, such as HIV/AIDS, tuberculosis, polio, and malaria.<sup>2</sup> The successful efforts in these areas have demonstrated that focused and goal-oriented global health strategies can result in dramatic improvements from a baseline situation that may appear dire. As we transition

from the MDGs to the Sustainable Development Goals (SDGs), we must learn from the successes of the MDG era while focusing on diversification of the global health agenda beyond just a few specific health conditions.

With the transition to the SDGs, noncommunicable diseases (NCDs) have risen to the forefront of the global health agenda. In an effort to include children in the global NCD initiative, the American Academy of Pediatrics has become a leader in NCD Child, a global alliance focused on NCDs in children and adolescents. The NCD Child Initiative importantly recognizes the necessity of including children in the NCD discussion, but, as is the case for most NCD campaigns, specifically identifies cancer, heart disease, and diabetes as the highest priorities.<sup>3</sup> Despite the fact that SCA affects millions of people worldwide, SCA is being prioritized below many NCDs that are much less common and more difficult to treat in low-resource settings, such as childhood cancer. The explicit inclusion of SCA in both the SCA and SDG strategic plans is justified given the global burden and previous invisibility of this important disease. The objective of this article is to provide convincing evidence that SCA should be considered a priority when developing strategies to improve the health of children across the world.



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## THE GLOBAL BURDEN OF SCA

SCA is a common, inherited disorder of hemoglobin affecting >300 000 infants globally each year.<sup>4</sup> For the 1% to 2% of these births that occur in high resource settings, SCA is identified early through newborn screening (NBS) programs and early-life threatening complications are avoided through early access to care. In countries with established NBS and treatment programs, death during childhood is a rare event with >90% of children with SCA surviving to adulthood.<sup>5,6</sup> This is in stark contrast to children in low-resource settings where a majority of SCA births occur. Of the estimated 312 000 annual homozygous hemoglobin SS births, >90% occur in low-resource settings, with an estimated 238 000 annual births in sub-Saharan Africa and >46 000 in India.<sup>4</sup> The incidence of SCA is likely ~1% to 2% among newborns across the sub-Saharan region, with the highest number of births in the most populous countries of the Democratic Republic of Congo and Nigeria. In these settings, estimates suggest that up to 90% of infants with SCA will die before their fifth birthday.<sup>7</sup> These children are not screened at birth, and most will die before a diagnosis can be made from unrecognized splenic sequestration, overwhelming pneumococcal sepsis, or severe malaria. The World Health Organization suggests that SCA may contribute to up to 5% of deaths of children <5 years old on the African continent and up to 16% in some high-prevalence countries,<sup>8</sup> which is comparable to the cited contributions of other well-recognized and well-funded global health problems, including HIV/AIDS (4%), measles (1%), and meningitis (3%).<sup>9</sup> Unfortunately, because of the lack of awareness and recognition of the problem by both the public and local health ministries, SCA remains a largely invisible global health issue.

## THE DIAGNOSIS OF SCA IS NOT DIFFICULT OR EXPENSIVE

SCA is an ideal condition to screen for at birth, because detection can be made using relatively simple and inexpensive laboratory techniques. Although not technically difficult or expensive, most SCA diagnostics require specialized laboratory equipment, and the result is not available at the point of care (POC). For NBS in Africa, where many families do not have easily identifiable or permanent addresses, it is challenging to locate families of affected babies to provide the diagnosis and to establish care.<sup>10</sup> An accurate, rapid, and inexpensive POC test for SCA is essential to make screening more widespread and efficient. There are a number of prototypes that are currently being developed and validated, and it appears that POC testing for SCA will soon become widely available.<sup>11–16</sup> Once simple and inexpensive POC tests become available, they will be highly useful for both NBS and public awareness campaigns to empower adolescents and young adults with both the knowledge and implications of their “sickle status” to make informed reproductive decisions. Although it is somewhat controversial in many geographic regions, genetic counseling should also be a priority, as neonatal screening programs may be able to reduce morbidity and mortality associated with SCA, but it cannot reduce the actual number of SCA births. It will be critical to perform pilot and implementation research studies in high-prevalence and low-resource settings to evaluate the feasibility, cost-effectiveness, and benefits of large-scale screening.

## INEXPENSIVE LIFE-SAVING TREATMENTS ARE AVAILABLE

Although there is no easy cure for SCA, there are several interventions that have been proven

to significantly reduce morbidity and mortality, particularly during early childhood. Early initiation of prophylactic penicillin and provision of pneumococcal vaccination significantly reduces the risk of invasive and life-threatening pneumococcal infections.<sup>17,18</sup> Parental education about SCA, focused on the identification of early signs and symptoms of serious complications, such as fever and splenomegaly, has been shown to have a direct effect on reducing mortality.<sup>19</sup> With improved survival, it will be important to provide disease-modifying therapy to reduce the acute and chronic complications of SCA, as untreated SCA is associated with significant reductions in both the quality and length of life. Hydroxyurea, a once daily oral medication, has been proven to be a safe and effective medication for the treatment of SCA. In addition to proven laboratory and clinical benefits, there is a growing literature to suggest that hydroxyurea therapy is also associated with reduction in mortality.<sup>20–23</sup> Because of provider inexperience, cost, and concerns due to its historical use as a chemotherapeutic agent, the use of hydroxyurea has been limited almost exclusively to the United States and Europe. Ongoing prospective research studies are evaluating the safety, feasibility, and benefits of hydroxyurea therapy to develop locally relevant treatment guidelines.<sup>24</sup> These pilot research studies must include or be followed-up by implementation research investigating the feasibility, safety, benefits, and cost-effectiveness of large-scale hydroxyurea use.

## BUILDING ON DEVELOPED INFRASTRUCTURE

To build successful NBS and treatment programs for SCA, there has to be some reliance on existing health infrastructure. It is not

practical or necessary to build these programs entirely from scratch. The prevention of mother-to-child transmission programs that exist in nearly every African country require many layers of infrastructure, from screening pregnant women to testing and providing treatment to affected infants. If this infrastructure is already in place in individual countries with a high burden of SCA, it should be leveraged to develop and expand treatment programs for conditions like SCA. The recently published Uganda Sickle Surveillance (US3) study is the first of its kind to leverage infrastructure from an HIV program for SCA; dried bloodspots collected from HIV-exposed infants were also tested for the presence of sickle cell trait or disease.<sup>25</sup> Vaccination programs are another tremendous health effort that has been successfully rolled out in nearly all countries in the world. Although universal vaccination is not without significant challenges, childhood vaccination rates exceed 80% to 90% in many countries,<sup>26</sup> and this early access point to newborns may provide another opportunity where SCA diagnostics may be implemented, particularly for the large number of children born outside of a hospital. Instead of traditional NBS at the time of birth, perhaps sickle cell testing can be performed with the first routine immunizations.

## CONCLUSIONS

SCA is a significant and under-recognized global health problem, and with new SDG efforts focused on ending preventable deaths of newborns and children <5 years of age, it is essential to specifically include SCA in that effort. With increased availability of POC diagnostics and inexpensive and highly effective treatments, such as hydroxyurea, simple efforts can result in millions of lives saved. As pediatricians, we have the

unique opportunity to be leaders in improving the health of children not only in our local practices, but also across the world. Increasing the visibility and advocacy for less commonly recognized childhood health conditions, such as SCA, can lead to important changes and provides an opportunity to save millions of lives.

## ABBREVIATIONS

MDG: Millennium Development Goal  
 NBS: newborn screening  
 NCD: noncommunicable disease  
 POC: point of care  
 SCA: sickle cell anemia  
 SDG: Sustainable Development Goal

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