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Perspective

A call to standardize the definition of countries with a high-burden of sickle cell disease

Amelia Seabold, MCP[1,*], Igor Rudan, PhD[1,2], Jemma M. Houghton, MSc[1], Lulu Chirande, MD[3], Anna Schuh, MD PhD[4], Helene-Mari van der Westhuizen, MD PhD[1]

[1]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford OX26GG, United Kingdom
[2]Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh EH164UX, United Kingdom
[3]Department of Paediatrics and Child Health, Muhimbili University of Health and Allied Sciences, Dar es Salaam 11101, Tanzania
[4]Department of Oncology, University of Oxford, Oxford OX37DQ, United Kingdom

*Amelia Seabold, MCP, Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 6GG, United Kingdom (amelia.seabold@gtc.ox.ac.uk).

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INTRODUCTION

Sickle cell disease (SCD) is the most common monogenic disease in the world.[1] Over 90% of SCD cases occur in low- and middle-income countries (LMICs), with sub-Saharan-Africa accounting for 75% of the global burden.[2,3]

In high-income countries (HICs), more than 90% of children born with SCD live to adulthood.[4,5] By contrast, estimates suggest that 50-90% of children born with SCD in LMICs die before their fifth birthday.[6] Disparities in SCD mortality and morbidity based on a country's income point to a problem of equity in the diagnosis and treatment of SCD.

Unfortunately, there is a significant lack of accurate epidemiologic data on SCD in many LMICs. Such data is integral to understanding the real burden of disease, yet most data repositories consist of estimates due to incomplete surveillance and registry data, with country level data in LMICs often extrapolated from one hospital or region.[7] While there have been country-level SCD initiatives[8-10] for improving data collection, collaboration, newborn screening, and care, as well as regional and global ones, such as SickleInAfrica[11] and the Global Sickle Cell Disease Network,[12] these require additional infrastructure and funding to build on the initial work.[13] We urgently call for more robust and precise data on SCD incidence, prevalence, and mortality to guide these efforts.

Why do we need to define high-burden countries for SCD?

There is currently no classification system for stratifying countries by their burden of SCD. A definition for a high-burden country would be beneficial to globally identify the settings where more targeted approaches to managing SCD are needed and would assist LMIC governments with balancing fiscal health priorities. Given that the World Health Organization (WHO) estimates that SCD contributes to 7.3% of under-5 mortality in Africa and leads to chronic complications worldwide such as frequent hospitalizations, pain crises, acute chest syndrome, and organ failure, SCD urgently needs global advocacy and greater resource allocation.[14-16] We identify six potential benefits of developing such a high-burden definition (Table 1).

What metrics should we use to define SCD burden?

We propose that SCD cases per 100 000 livebirths and total SCD cases should be used to define and stratify countries into different burden statuses. Using cases per 100 000 people would be appropriate if there was an accessible cure for SCD; however, most SCD patients do not currently have access to curative therapies such as stem cell transplant or gene therapy and using cases per 100 000 people might obscure SCD deaths at a young age. SCD cases per livebirths allow us to see how common SCD is in the newborn population, while total cases account for people of all ages, including those migrating between countries.

A worked example using global burden of disease data

We acknowledge that surveillance data for SCD, particularly in LMICs, is incomplete; we have chosen to use the Global Burden of Disease (GBD) data to illustrate our burden definition since it is an accessible resource that has a focused dataset on SCD, and the WHO uses this data for their SCD Fact Sheet.[17] We are open to discussion on triangulating multiple data sources to increase our definition's applicability.

According to the GBD, there is a strong correlation between SCD cases per 100 000 livebirths and SCD cases per

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Table 1. Identification of 6 potential benefits from defining what a high-burden country is as related to SCD.

Focus external and internal funding	High-burden countries should be investing more national resources in comprehensive screening and treatment of SCD. There is a lack of reliable data on how much external funding for SCD research is being channeled to high-burden countries, but burden stratification could give external funders a clear picture of where funding can have the biggest impact.
Create global targets to allow comparison	Targets such as "% *of children screened*" or "% *of children enrolled in care*" can be developed on a global scale as opposed to each country using different metrics to track progress. This would allow comparison between different settings.
Innovation fit for setting	Innovations that are designed for SCD screening and care need to be made with consideration for the specific contexts of high-burden countries so that they are useful where the need is greatest.
Access to technology	Access to new technologies/therapies for high-burden countries must be embedded in these technologies' development and market plans. This classification will help to focus on where access is most needed.
Shared learning	High-burden countries can convene for shared learning on implementing screening and care programs, and on managing large populations with SCD. Practically, many SCD conferences are held in Europe and North America each year, while shifting these to high-burden countries could focus efforts on where there is the greatest need, further engage governments in strengthening SCD care, and build capacity to address SCD in these countries.
Track changes over time	Changes in SCD case numbers might start occurring over time as climate change pushes malaria-carrying mosquitoes into new environments, leading to carriers of the sickle cell trait having a survival advantage. People could migrate by choice or force. Tracking these changes over time could help match screening and care programs to settings where there is need.

Table 2. A comparison of the rankings of countries by total SCD cases and SCD cases per 100 000 livebirths. The countries defined as high burden are shown. Asterisks indicate the country meets the criteria for total SCD cases and SCD cases per 100 000 livebirths.

Total SCD cases in 2021		Rank	SCD cases per 100 000 livebirths in 2021	
2 590 000	Nigeria*	1	Benin*	2560
1 280 000	India	2	Sierra Leone*	2530
655 000	Democratic Republic of the Congo*	3	Nigeria*	2290
281 000	Burkina Faso*	4	Burkina Faso*	2230
264 000	Kenya*	5	Togo*	2070
239 000	Ghana*	6	Equatorial Guinea	2060
182 000	Angola*	7	Guinea*	1870
182 000	Benin*	8	Democratic Republic of the Congo*	1610
164 000	United Republic of Tanzania*	9	Ghana*	1580
157 000	Niger*	10	Kenya*	1330
154 000	Sudan	11	Angola*	1210
129 000	Guinea*	12	Niger*	1180
126 000	Cameroon*	13	Bahrain	1040
109 000	Saudi Arabia	14	Sao Tome and Principe	1020
108 000	Sierra Leone*	15	Gabon	959
107 000	Uganda*	16	Central African Republic*	890
107 000	Egypt	17	Libya	873
82 200	Iran	18	Cameroon*	805
80 600	Togo*	19	Zambia*	746
78 300	Mali*	20	Cote d'Ivoire*	673
74 900	Cote d'Ivoire*	21	Mali*	656
60 100	Zambia*	22	United Republic of Tanzania*	617
59 800	United States of America	23	Gambia	611
45 000	Senegal*	24	Congo	601
42 800	Iraq	25	Uganda*	577
40 600	Madagascar	26	Jamaica	573
33 700	Afghanistan	27	Senegal*	557
21 200	Central African Republic*	28	Liberia	514
21 200	China	29	Haiti	505
–	–	30	Oman	503

100 000 people globally ($R = 0.986$ in 2021).[16] Despite this correlation, there was a large gap in 2021 between the rate of people born with SCD and the rate of people living with it. Some of this discrepancy is due to the fact that cases per livebirths is rising, having increased 13.6% since 2000, and therefore cases per live people is also rising, but delayed.[16] A large

Table 3. Definitions for burden categories and number of countries and territories in each category from the 204 listed in the GBD data as of 2021.

Burden designation	Cases per 100 000 livebirths	Number of countries (2021)	Total cases	Number of countries (2021)
Low	<10	94	<100	97
Lower-moderate	10–99	50	100–1999	48
Upper-moderate	100–499	30	2000–19 999	30
High	500–999	16	20 000–99 999	12
Very high	1000–1999	8	100 000–199 999	11
Severe	2000+	6	200 000+	6

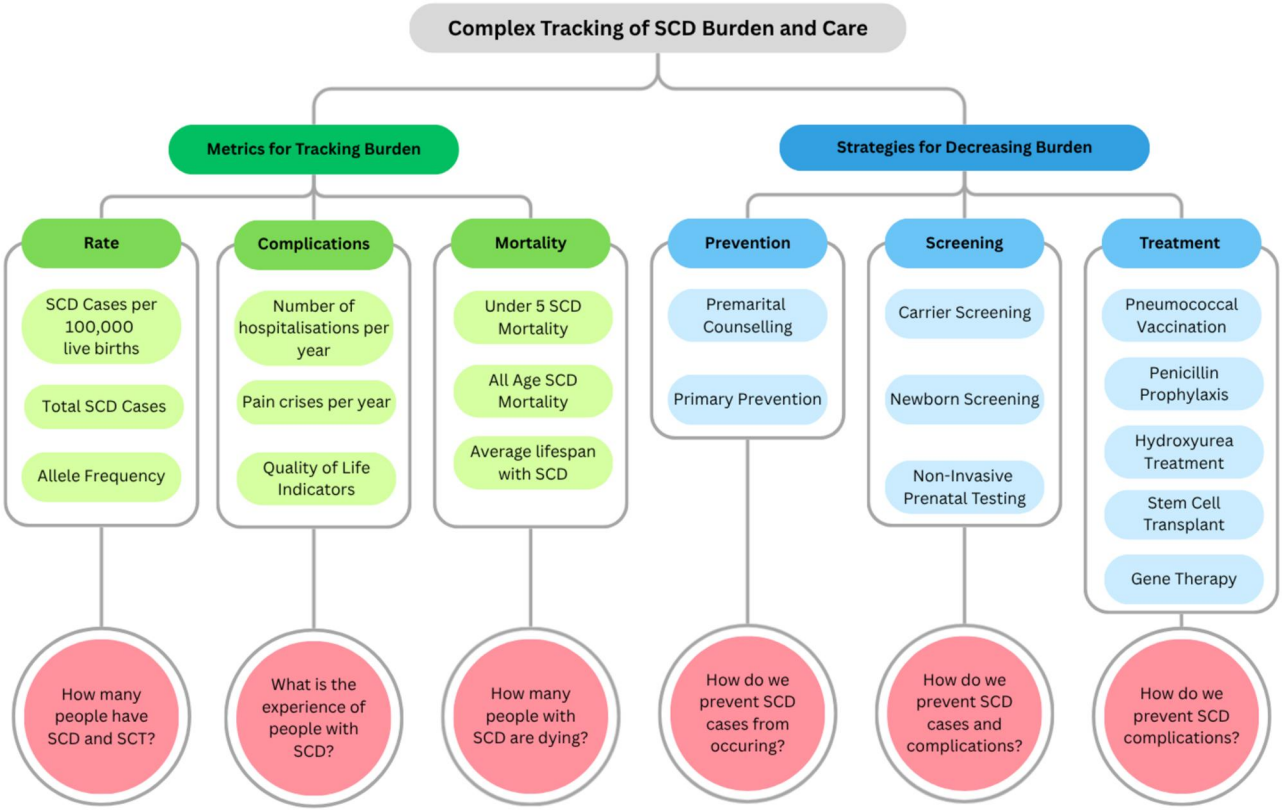

Figure 1. Metrics that can be tracked and triangulated to gain a better picture of overall improvement to care for people with SCD, as well as strategies for affecting changes to these metrics.

reason for this discrepancy is due to deaths–both caused by SCD and other factors. Cause of death data is often unreliable because there may be multiple contributing factors. While some people with SCD die of other causes, there are also many deaths attributed to other causes where the underlying and unreported cause is SCD. It is difficult to accurately estimate the SCD mortality burden and the potential effect size of increased interventions, another need for better data.

An argument against using only SCD cases per 100 000 livebirths to define burden is that certain countries with high numbers of SCD cases but larger populations will not fall into the high-burden category, which is why we are additionally including total SCD cases in our definition. This will enable the inclusion of countries with a large number of SCD cases, regardless of how much of the population is affected.

What should the high-burden threshold be?

We argue for the threshold of 500 cases per 100 000 livebirths or 20 000 total SCD cases as the definition of a high-burden country. Based on the GBD 2021 data, 40 countries meet this criterion, with 19 meeting both thresholds (see Table 2). Table 3 shows a more granular stratification. We acknowledge that classification definitions may need to change over time as global trends change and recommend revisiting in 5 years.

Additional metrics for quality of care to accompany burden definition

Primary prevention of SCD, tracked by SCD cases per 100 000 livebirths, is cost-effective and lessens health system burden; however, we need to track additional metrics to measure quality of care. We recommend the creation of a more robust framework for both tracking burden and decreasing it (see Figure 1).

We acknowledge that cause of death estimates can be inaccurate and SCD is an underlying contributor in many more deaths than is attributed to it, and therefore suggest using a combination of SCD rate, complications, and mortality for a wholistic understanding of disease burden. Screening and treatment coverage are required for improving quality care for people with SCD. Globally agreed-upon targets for these must follow a burden definiton, for example a target for number of babies screened and enrolled in care by 6 months. We acknowledge that national health system capacity will impact how well a country can handle their SCD burden. The availability of trained staff, essential medicines, diagnostics, and financing are complementary indicators to be considered in overall system readiness. We welcome further discussion and collaboration from SCD researchers across the globe to find consensus on appropriate ways to use the indicators to track improvement over time.

CONCLUSION

Our piece uses a worked example of GBD data to propose the use of 500 cases per 100 000 livebirths or 20 000 total cases as a threshold to define a country with a high burden of SCD. We justify this due to the lack of a widely available cure and suggest using additional metrics including mortality data and treatment coverage to track changes in disease management over time. In LMICs, there is a significant unmet need for accurate data and comprehensive SCD prevention and care programs. We call for regional stakeholder conversations to establish agreement on this definition, which must include representatives from countries with varied SCD burdens and different health system capacities. This could be accomplished through WHO Regional Committees, supported by conversations at local levels, such as conferences and national meetings of experts focused on SCD. Efforts to attract global resources to the areas of most need could be invigorated by international consensus among researchers, activists, and WHO on what constitutes a high-burden country for SCD.

AUTHOR CONTRIBUTIONS

Amelia Seabold (Conceptualization, Project administration, Visualization, Writing—original draft, Writing—review & editing), Igor Rudan (Conceptualization, Writing—review & editing), Jemma Houghton (Conceptualization, Visualization, Writing—review & editing), Lulu Chirande (Conceptualization, Supervision, Writing—review & editing), Anna Schuh (Conceptualization, Supervision, Writing—review & editing), and Helene-Mari van der Westhuizen (Conceptualization, Supervision, Writing—review & editing)

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CONFLICTS OF INTEREST

None declared.

DECLARATION

ChatGPT was not used in the development of this article.

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