EuroBloodNet

Newborn Screening (NBS) for Sickle Cell Disease in Europe: recommendations

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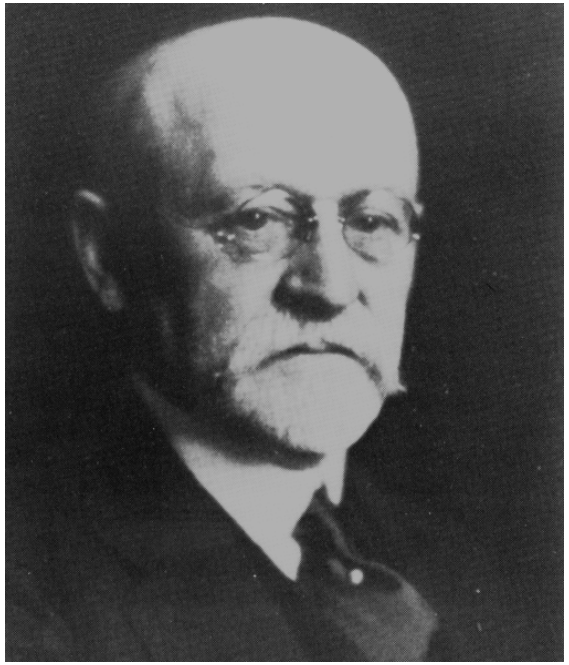
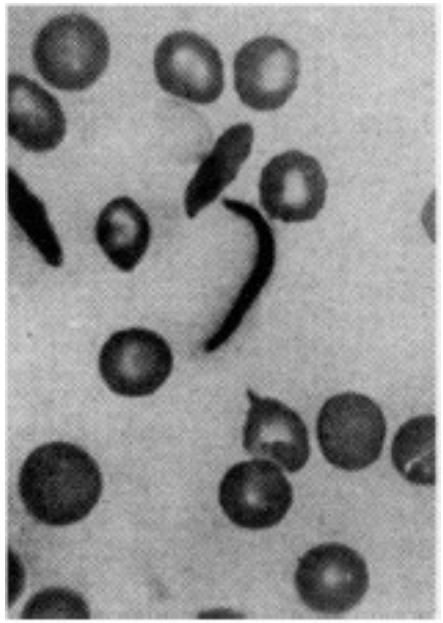
Background on Sickle Cell Disease





Peculiar Elongated and Sickle-shaped Red Blood Corpuscles in a Case of Severe Anemia[a]

James B. Herrick, M.D.

1013 State Street, Chicago, Illinois

This case is reported because of the unusual blood findings, no duplicate of which I have ever seen described. Whether the blood picture represents merely a freakish poikilocytosis or is dependent on some peculiar physical or chemical condition of the blood, or is characteristic of some particular disease, I cannot at present answer. I report some details that may seem non-essential, thinking that if a similar blood condition is found in some other case a comparison of clinical conditions may help in solving the problem.

HISTORY

The patient was an intelligent negro of 20, who had been in the United States three months, during which time he was a student in one of the professional schools in Chicago. His former residence had been Grenada, West Indies, where he had been born and brought up, one of a family of four children, all living, and all well with the exception of himself. His mother was living and in good health; his father had died of accident. At the age of 10 the patient had had yaws. This was a common disease in the locality where he lived. The lesions, as he described them, had been pustular, with formation of ulcers and scabs. On healing, scars, many of which he pointed out, were left. Some of the ulcers had been as large as a silver quarter of a dollar. The disease lasted about one year and during this time he had felt somewhat weak and indisposed. Most of the ulcers had been on the legs and the patient him-

Arch Intern Med 5: 517, **1910**

SCD Short Timeline

1910 – Dr. James B. Herrick publishes a description of sickled cells present in 20-year-old Grenadian dental student Walter Clement Noel.

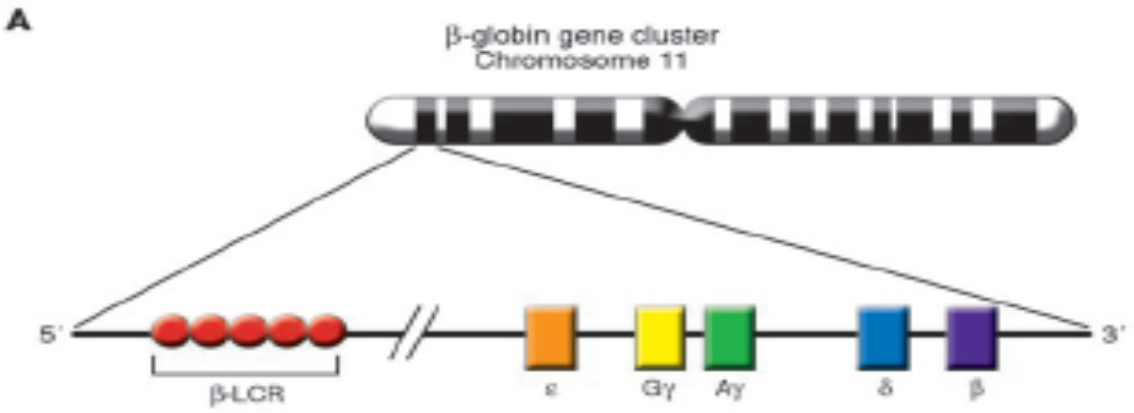
1949 – Dr. Linus Pauling and others reveal the molecular nature of SCD.

1954 – Sickle cell trait is found to protect against malaria, explaining the prevalence of SCD in regions where malaria is a leading cause of death.

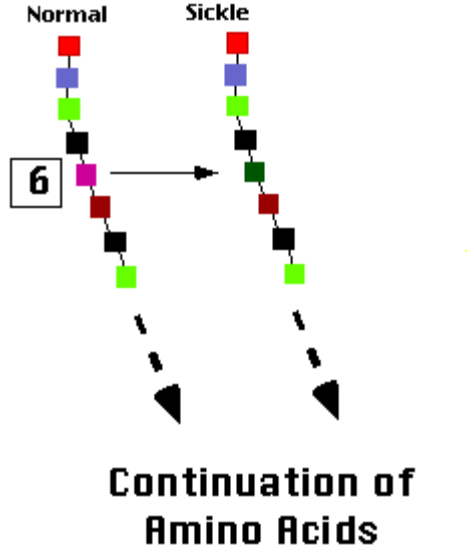
1972 – The National Sickle Cell Anemia Control Act, establishes voluntary SCD screening, counseling, public and professional education, and other key public health measures.

1982 – 5-azacytidine is shown to elevate fetal hemoglobin levels.

1984 – Hydroxyurea demonstrates the ability to increase fetal hemoglobin levels.

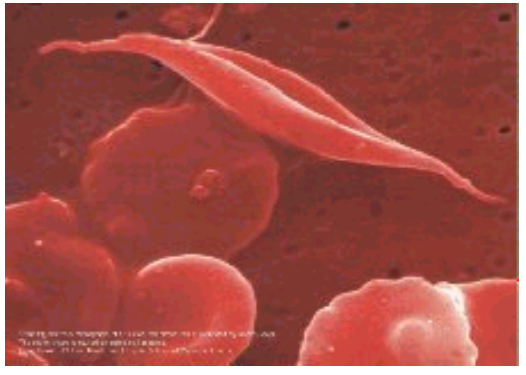


SCD is a recessive genetic disorder of hemoglobin due to a single base mutation in codon 6 of the β globin gene on chromosome 11 (HbS/HbS)



HbSS , HbSC, HbSβ° , HbSβ+, HbS/HbE, HbS/ HbPunjab

Extreme phenotypic variability
Systemic disorder



2006 The **World Health Organization** released the *"Sickle Cell Anemia" A59/9 Report*, inviting Governments and Health Ministries:

"to design, implement, reinforce in a systematic, equitable and effective manner, comprehensive national integrated programs for the prevention and management of SCD reducing morbidity and mortality"

www.who.int/gb/ebwha/pdf_files/WHA59-REC1/e/WHA59_2006_REC1-en.pdf

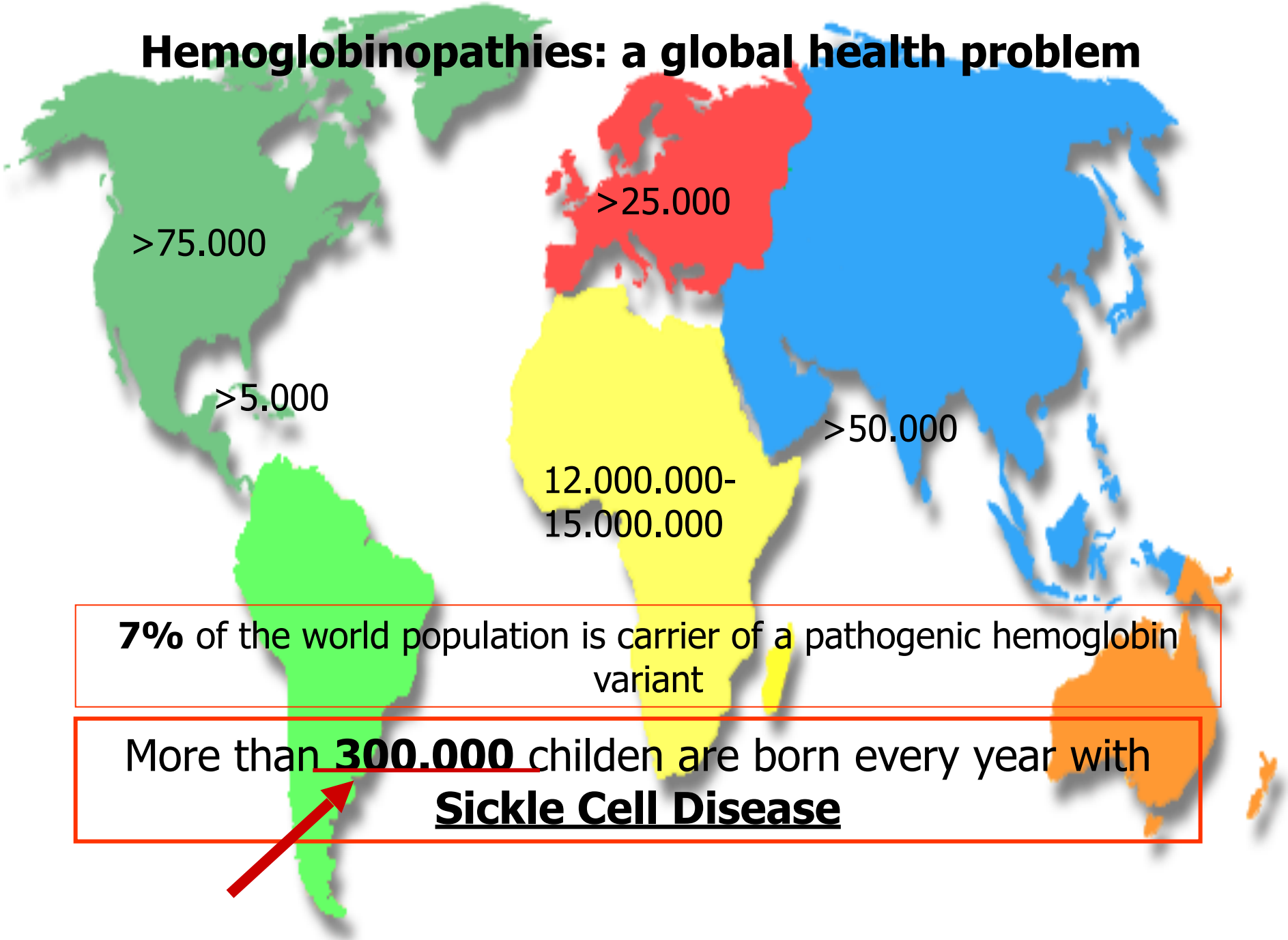
2008 The **General Assembly of the United Nations** approved the Resolution "Recognition of sickle-cell anaemia as a public health problem" (resolution A/63/L.63):

- inviting all States to "**raise global awareness on SCD**"

- defined the **19th of June** of every year as the "Sickle Cell Day"

www.un.org/News/Press/docs/2008/ga10803.doc.htm

Hemoglobinopathies: a global health problem



7% of the world population is carrier of a pathogenic hemoglobin variant

More than **300.000** childen are born every year with **Sickle Cell Disease**

Aliyu ZY, et al. Am J Hematol 2007

Modella B et al. Bulletin of the World Health Organization 2008;86:480–487

Global increase of migrants with the Sickle cell gene

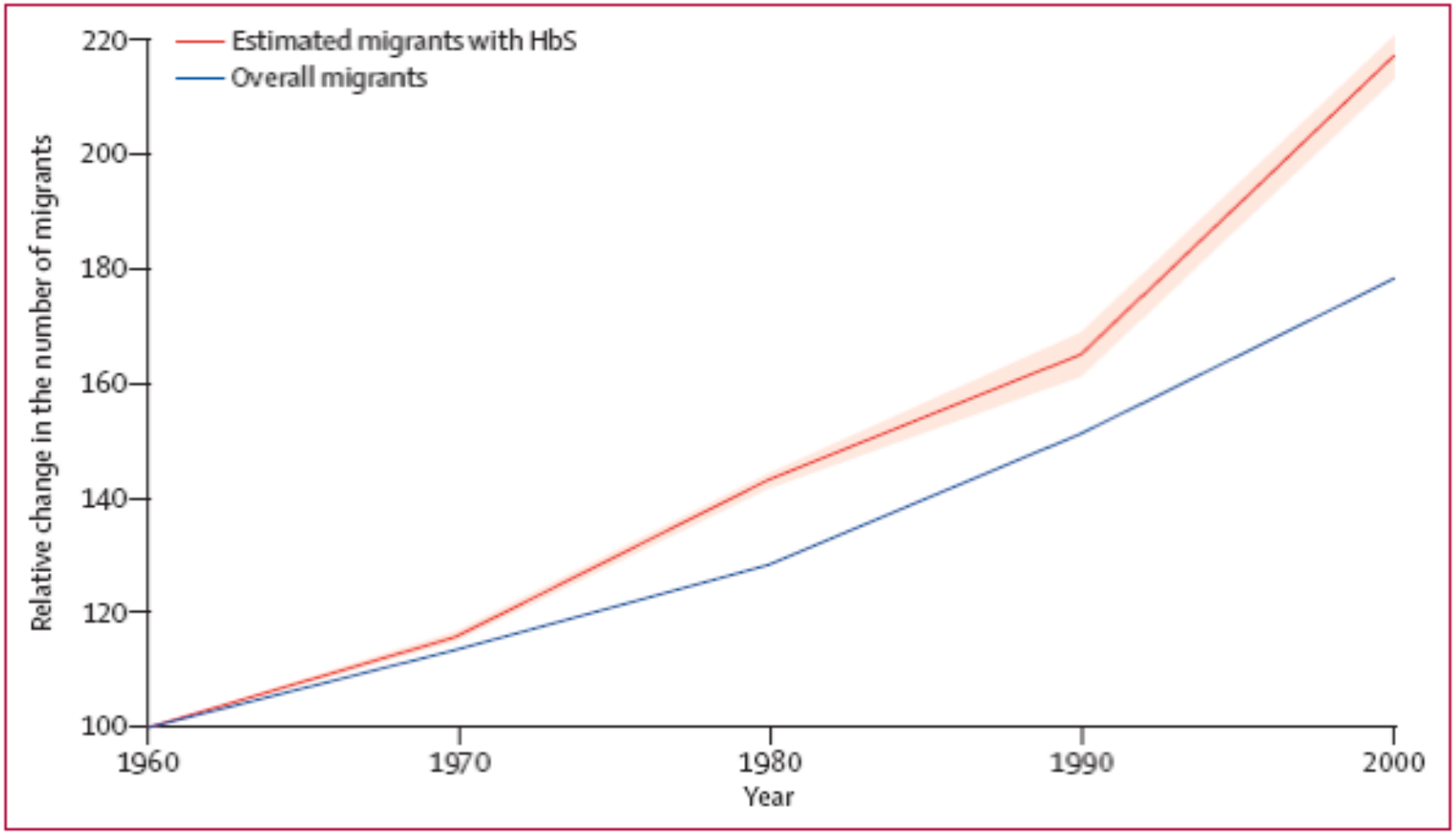
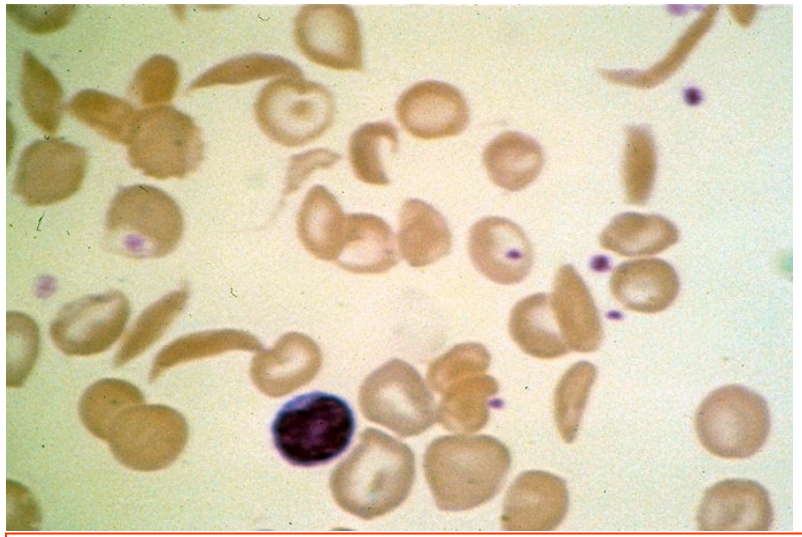


Figure 1: Global trends in the number of international migrants and estimated migrants with HbS compared with the 1960s level

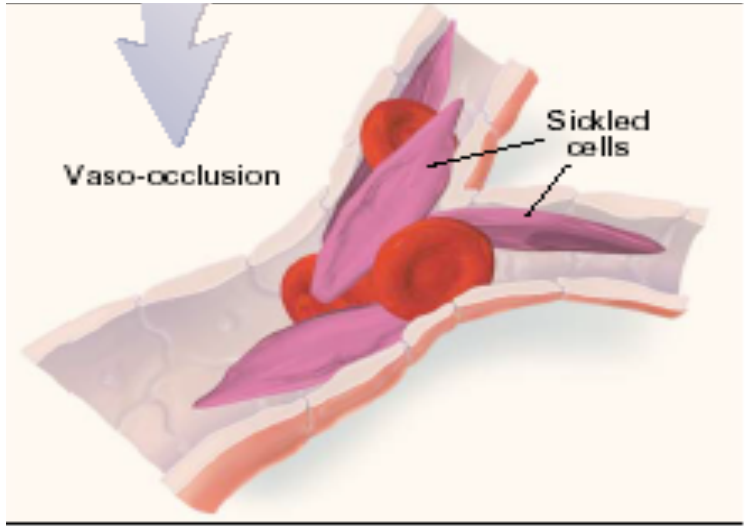
Global migration and the changing distribution of sickle haemoglobin: a quantitative study of temporal trends between 1960 and 2000

Piel et al. Lancet 2014

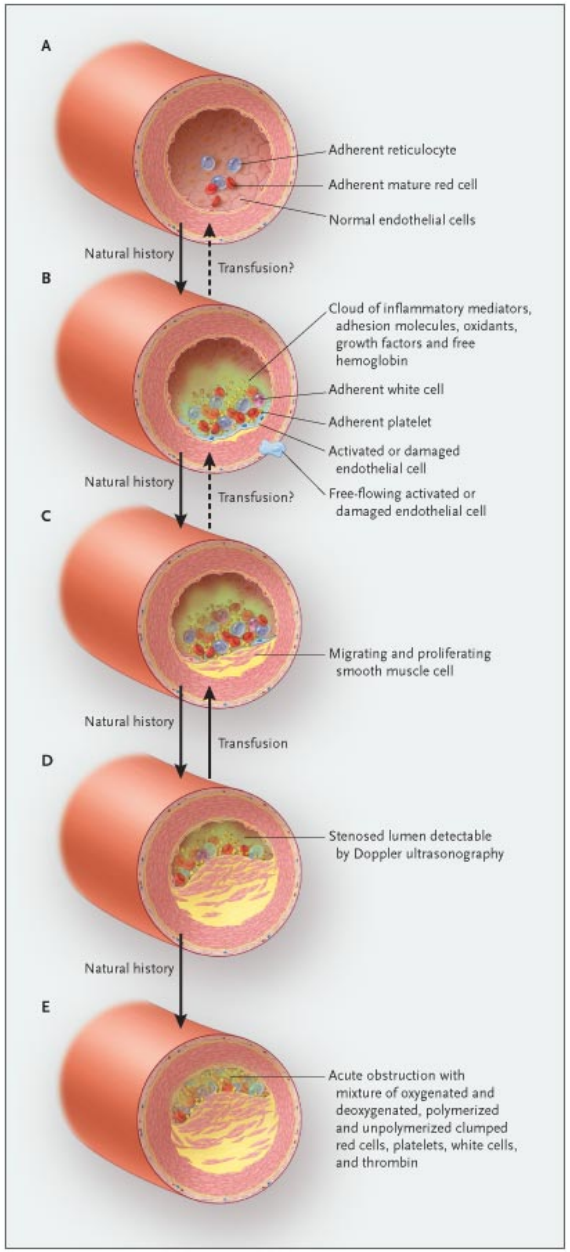
SCD: pathophysiology



Chronic hemolytic anemia



Vaso-occlusion

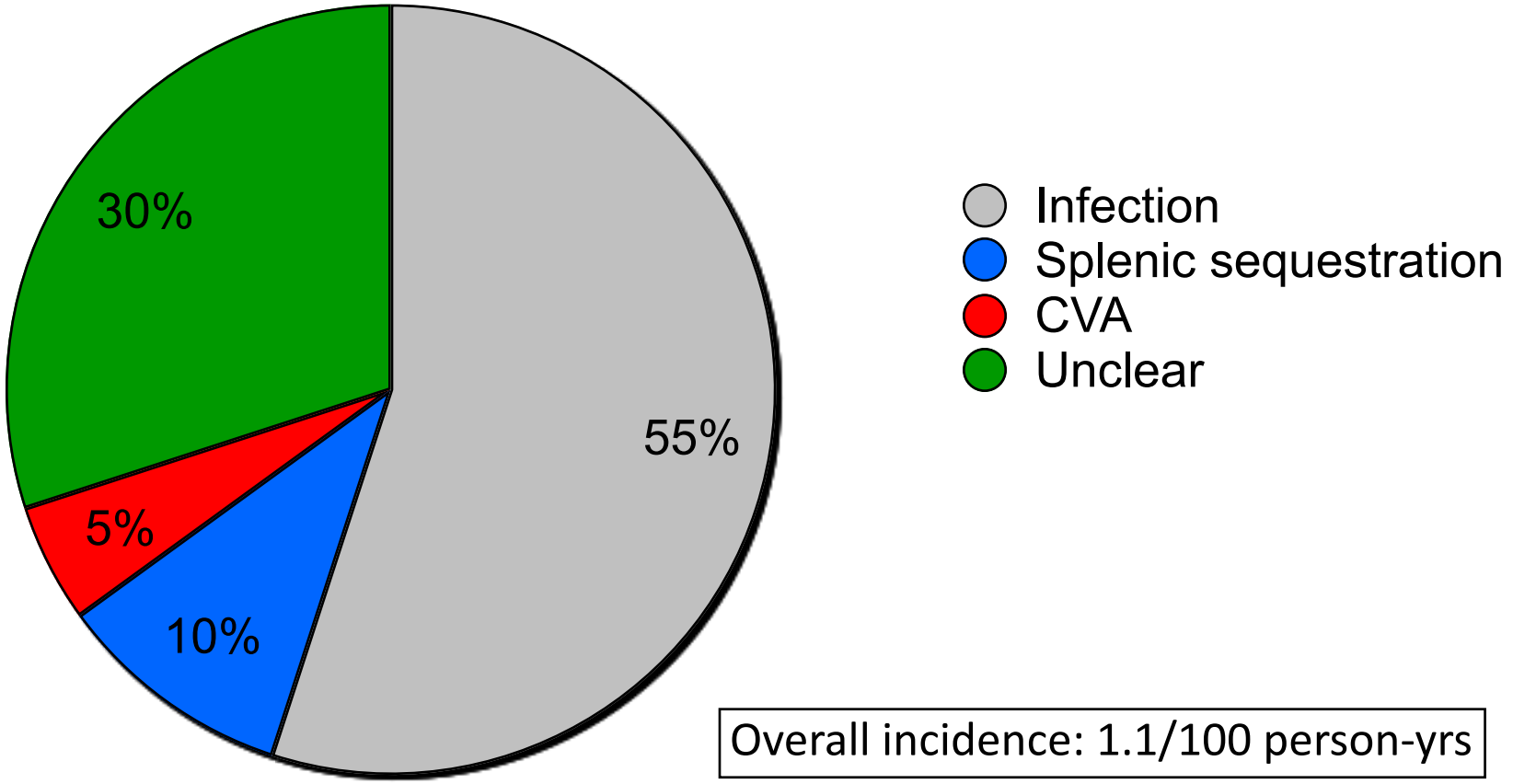


Vasculopathy

Causes of death in SCD-SS (0-10 aa)

In **USA** life expectancy for children with SCD (Hb SS) was 7 years in 1974 and is now 55 years.

CSSCD Infant Cohort Deaths
- SCD-SS



Overall incidence: 1.1/100 person-yrs

(Gill FM, et al, CSSCD: 1995 ;Lubeck D et al. JAMA Netw Open. 2019 Nov

1986 – Penicillin is noted as a preventive measure in children with SCD, to vastly reduce *Streptococcus pneumonia* infection.

1994 –

The STOP TRIAL proves that Transcranial Doppler can be used to predict stoke risk since age 2 yrs

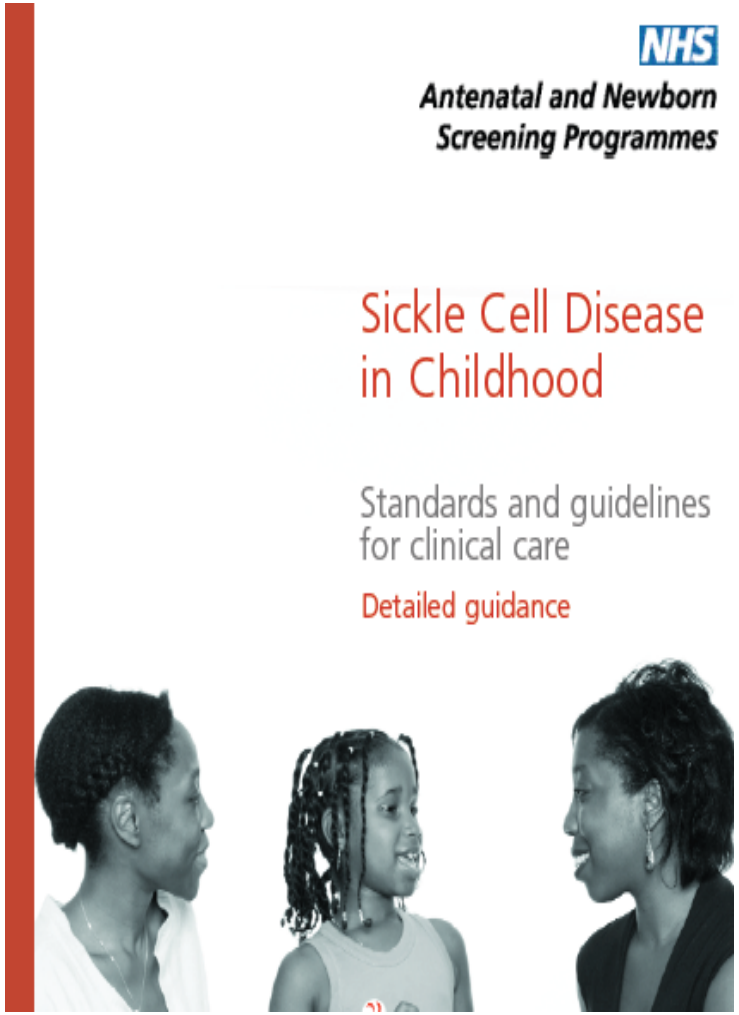
1997 – Blood transfusions demonstrate a 90 percent reduction in stroke in high-risk patients.

1998 – The FDA approves hydroxyurea for treatment of adults with SCD.

2009 – Study shows that blood stem cell transplantation can reverse SCD in adult patients.

2017 – β globin gene therapy demonstrates curative success; crizanlizumab decreases pain crises in patients; L-glutamine is approved.

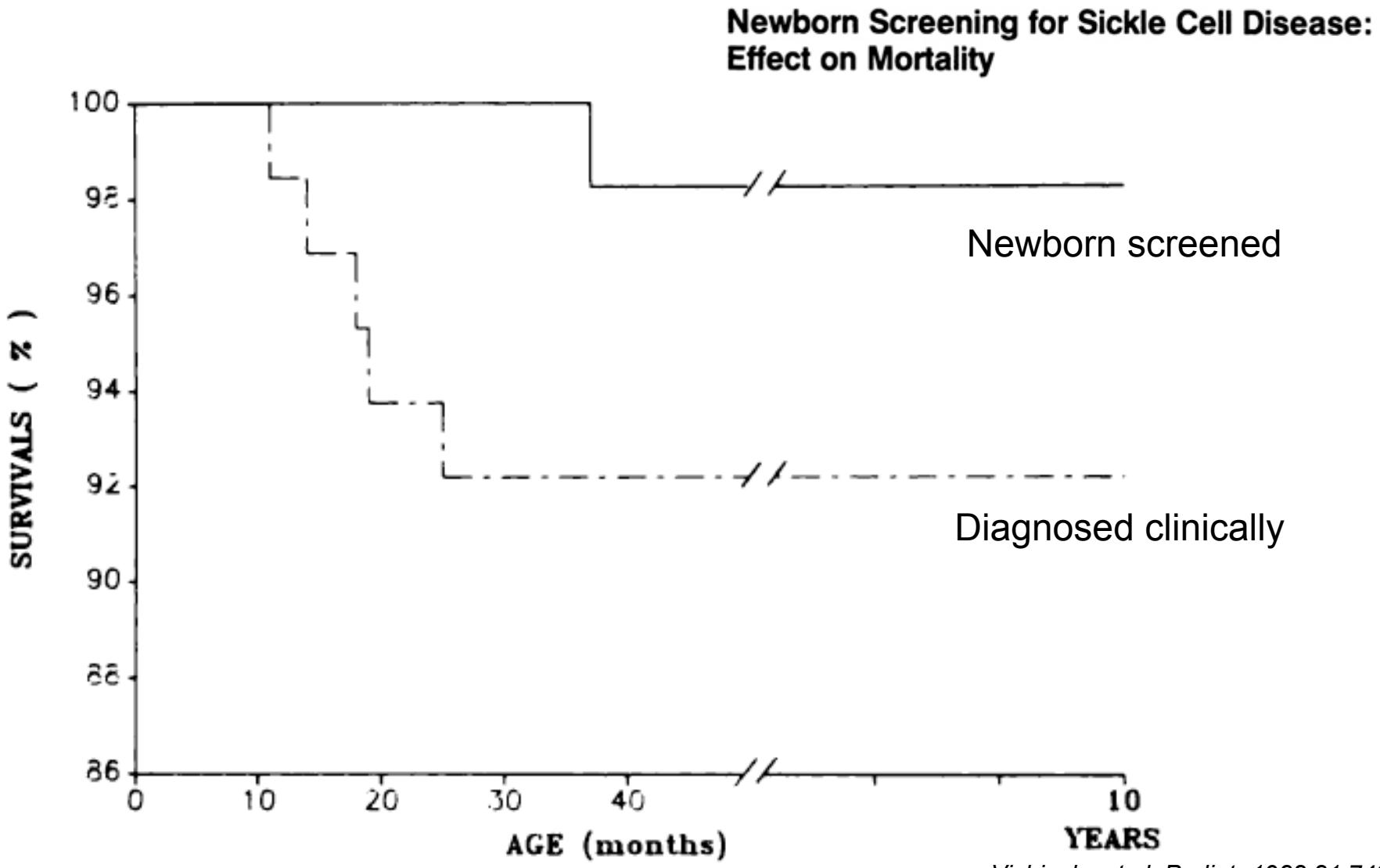
Minimal Standards of care



- Newborn Screening
- Antibiotic prophylaxis
- Vaccinations
- Transcanial Doppler Starting at age 2 (with transfusion)
- Comprehensive care
- Use of Hydroxyurea

NHS 2009

Effect of Newborn Screening on Mortality



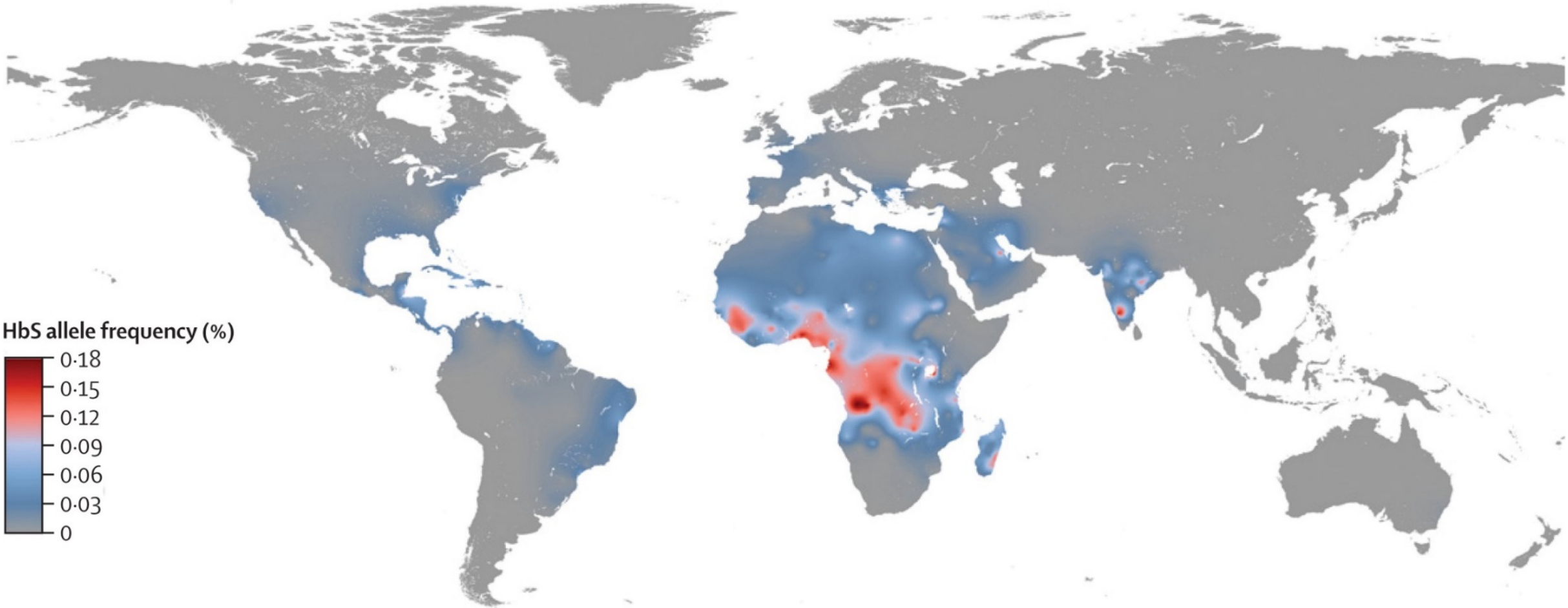
Vichinsky et al, Pediatr 1988;81;749-755

Rare Disease

UK 0.47:1000 births
Belgium 0.43:1000 births
Spain 0.03-0.18:1000 births

Common Disease

Ghana 18:1000 births
Tanzania 8:1000 births



Piel FB et al, Lancet 2013;381(9861):142-51; Le PQ et al. J. Med. Screen. 2018, 25, 57–63; Cela E et al. Pediatr Blood Cancer 2017. 64: e26322; M García-Morín et al.Annals of Hematology (2020) 99:1465–1474; Nkya S et al. Int Health. 2019;11(6):589-595; Segbefia CI et al. Pediatr Blood Cancer. 2021 Apr 23;e29068.

https://www.gov.uk/government/publications/sickle-cell-and-thalassaemia-screening-data-report-2018-to-2019

Reccomendations for Newborn Screening for SCD in Europe: Agreement through a Consensus Conference

Stephan Lobitz,[1,2] Paul Telfer,[3] Elena Cela,[4] Bichr Allaf,[5] Michael Angastiniotis,[6] Carolina Backman Johansson,[7] Catherine Badens,[8] Celeste Bento,[9] Marelle J. Bouva,[10] Duran Canatan,[11] Matthew Charlton,[12] Cathy Coppinger,[12] Yvonne Daniel,[12] Marianne de Montalembert,[13] Patrick Ducoroy,[14] Elena Dulin,[4] Ralph Fingerhut,[15] Claudia Frömmel,[16] Marina García-Morin,[4] Béatrice Gulbis,[17] Ute Holtkamp,[18] Baba Inusa,[19] John James,[20] Marina Kleanthous,[21] Jeannette Klein,[22] Joachim B. Kunz,[23] Lisa Langabeer,[24] Claudine Lapouméroulie,[25] Ana Marcao,[26] José L. Marín Soria,[27] Corrina McMahon,[24] Kwaku Ohene-Frempong,[28] Jean-Marc Périni,[29] Frédéric B. Piel,[30] Giovanna Russo,[31] Laura Sainati,[32] Markus Schmugge,[33] Allison Streetly,[34,35] Leon Tshilolo,[36] Charles Turner,[37] Donatella Venturelli,[38] Laura Vilarinho,[26] Rachel Yahyaoui,[39] and Jacques Elion,[25] Raffaella Colombatti[32] with the endorsement of EuroBloodNet, the European Reference Network in Rare Haematological Diseases

bjh research paper

Newborn screening for sickle cell disease in Europe: recommendations from a Pan-European Consensus Conference

Summary

Sickle Cell Disease (SCD) is an increasing global health problem and presents significant challenges to European health care systems. Newborn screening (NBS) for SCD enables early initiation of preventive measures and has contributed to a reduction in childhood mortality from SCD. Policies and methodologies for NBS vary in different countries, and this might have consequences for the quality of care and clinical outcomes for SCD across Europe. A two-day Pan-European consensus conference was held in Berlin in April 2017 in order to appraise the current status of NBS for SCD and to develop consensus-based statements on indications and methodology for NBS for SCD in Europe. More than 50 SCD experts from 13 European countries participated in the conference. This paper aims to summarise the discussions and present consensus recommendations which can be used to support the development of NBS programmes in European countries where they do not yet exist, and to review existing programmes.

Consensus Methodology

- Four months before the conference, clinical and laboratory experts in the field of SCD from European countries where SCD is considered a health care issue were invited to participate.

- Experts were selected by a Steering Committee on the basis of their publications and/or presentations at scientific meetings. They were joined by representatives from national scientific societies, national SCD reference centres and national NBS programmes.

- The steering committee prepared a standardized form for the presentation of each country's national data on NBS that was sent to the speakers 1 month in advance of the conference

- The committee also drafted a list of questions for consensus discussion

On the first day of the conference, key topics in epidemiology, screening and NBS techniques were reviewed. Representatives from 12 countries (Cyprus, France,Germany, Ireland, Italy, Netherlands, Portugal, Spain, Sweden, Switzerland, Turkey, UK) then reported available data on NBS for haemoglobinopathies in their countries

On the second day, consensus questions were discussed and experiences of NBS for SCD outside Europe were explored. The discussion was moderated by an independent non-European specialist (KOF) who was assisted by a patient representative (JJ)

Topics addressed in the Consensus

- Overview of **epidemiology** of SCD worldwide and in Europe
- Examples of already **established national NBS** programs: **UK** and **France**
- **Comprehensive care** in UK and France
- Review of standard and **emerging technologies** for diagnosis of SCD (POC, MS…)
- Overview of **current situation** for SCD/NBS in every European coutry (5-10’ presentation each)
- Patient’s associations perspectives

Consensus Questions 1

- **Do you agree that the number of children born with SCD is currently increasing**?
- **What are the target diseases in a newborn screening programme for haemoglobinopathies? What is the significance of thalassaemia**?
- **What is the justification of a newborn screening for SCD (and thalassemia)?**
- **Which countries/regions/cities should screen?**
  - Is there a threshold for the prevalence?
  - If yes, what is this threshold?
  - What are the minimal infrastructural and medical requirements to start NBS?
- **Who should be screened? (Basically: universal or targeted screening or selected?)**
  - In case targeted screening is considered acceptable: Which methods are recommended to identify individuals at risk?

Consensus Questions 2

- **How to handle carriers?**
  - Does carrier screening increase awareness?
  - What about costs and resources of counselling?
  - Do we need more involvement of patient organisations?
  - Are there concerns about stigmatization of carriers how to handle them?
- **Which methods are recommended/acceptable?**
- **What is the recommended procedure after a positive screening result?**
  - Re-screening from the same sample? Same method? Second-tier screening?
  - When should the family be informed?
  - Where and when should the family be referred to for confirmatory testing and which methods are recommended?
  - What about carriers?

  - **Which blood samples are recommended/acceptable for screening?**

Consensus Questions 3

- **What are the pitfalls?** (E.g. preterm newborns, transfusions etc.)
- **Which false-negative and which false-positive rate are acceptable?**
- **Are these recommendations valid for all high-resource countries or is there any dependency on specific local characteristics?**

EuroBloodNet
European Reference Network in Rare Hematological Diseases

*With the endorsment of **EuroBloodNet***

Consensus statements

1a. In Europe the burden of Sickle Cell Disease (SCD) has increased and will continue to increase.

1b. It is desirable that all European patients with SCD are enrolled onto registries, with standardized data collection and coordinated follow-up.

Consensus statements

2a. The target disease of a NBS programme for haemoglobinopathies is SCD, including all genotypes.

2b. Beta thalassaemia, whilst not a formal target disease of a NBS programme for haemoglobinopathies, should also be reported.

Consensus Statement

3. Early diagnosis by NBS, together with anti-pneumococcal penicillin prophylaxis and vaccination, coordinated follow-up and parental education, reduces morbidity and mortality from SCD in childhood.

Consensus statements

4a. The implementation of a national NBS programme for SCD should be informed by a review of national epidemiological data on SCD, but should not be based solely on a threshold birth prevalence. Where not available, these data should be collected.

4b. A NBS programme should be developed and implemented alongside a national disease management strategy.

Consensus statement

6. SCD is a genetic condition. The knowledge of the carrier state in the family provides opportunities for prevention of affected births. The carrier status (all mutations that might cause SCD) should be reported and counselling offered to carriers.
The panel acknowledges that there is virtually no other evidence for this recommendation than solely "expert opinion" and encourages future research on this question. Any national decision-making process should take this into account.

Consensus statements

5a. The panel recommends universal NBS screening for SCD in all countries participating in the conference.

5b. Targeted screening based on ethnic origins is not recommended because of the higher risk of failure to identify an affected newborn.

5c. In countries where national NBS screening for SCD is not implemented, an interim policy should be agreed for testing at-risk newborns on a case-by-case basis according to family origins.

Consensus statements

7a. High performance liquid chromatography (HPLC), capillary electrophoresis (CE), isoelectric focusing (IEF) and tandem mass spectrometry (MS/MS) are appropriate methods for NBS for SCD.

7b. New methods currently being tested should prove to be as specific and sensitive as HPLC and CE before being implemented on a larger scale.

Consensus statements

8a. A haemoglobin pattern that is in accordance with any genotype of SCD requires a re-test with a fresh punch from the same sample. If available, a different method from the first one should be used (second-tier screening). If a second alternative method is not available, a re-test with the same method is acceptable. If the re-test is positive, the newborn should be re-called for confirmatory testing.

8b. Screen-positive newborns should be referred to a paediatric haematologist for counselling and confirmatory testing by a certified laboratory. The confirmatory test result should be available by the end of the second month of life. If not available at that time, penicillin prophylaxis should be initiated and continued at least until the result is available.

8c. In NBS programmes where carrier states are reported, any haemoglobin pattern in accordance with a carrier state requires a re-test with a fresh punch from the same sample, preferably using a different method.

8d. All children with SCD should be enrolled in a comprehensive care programme. The programme should ensure equal access to high-level clinical care.

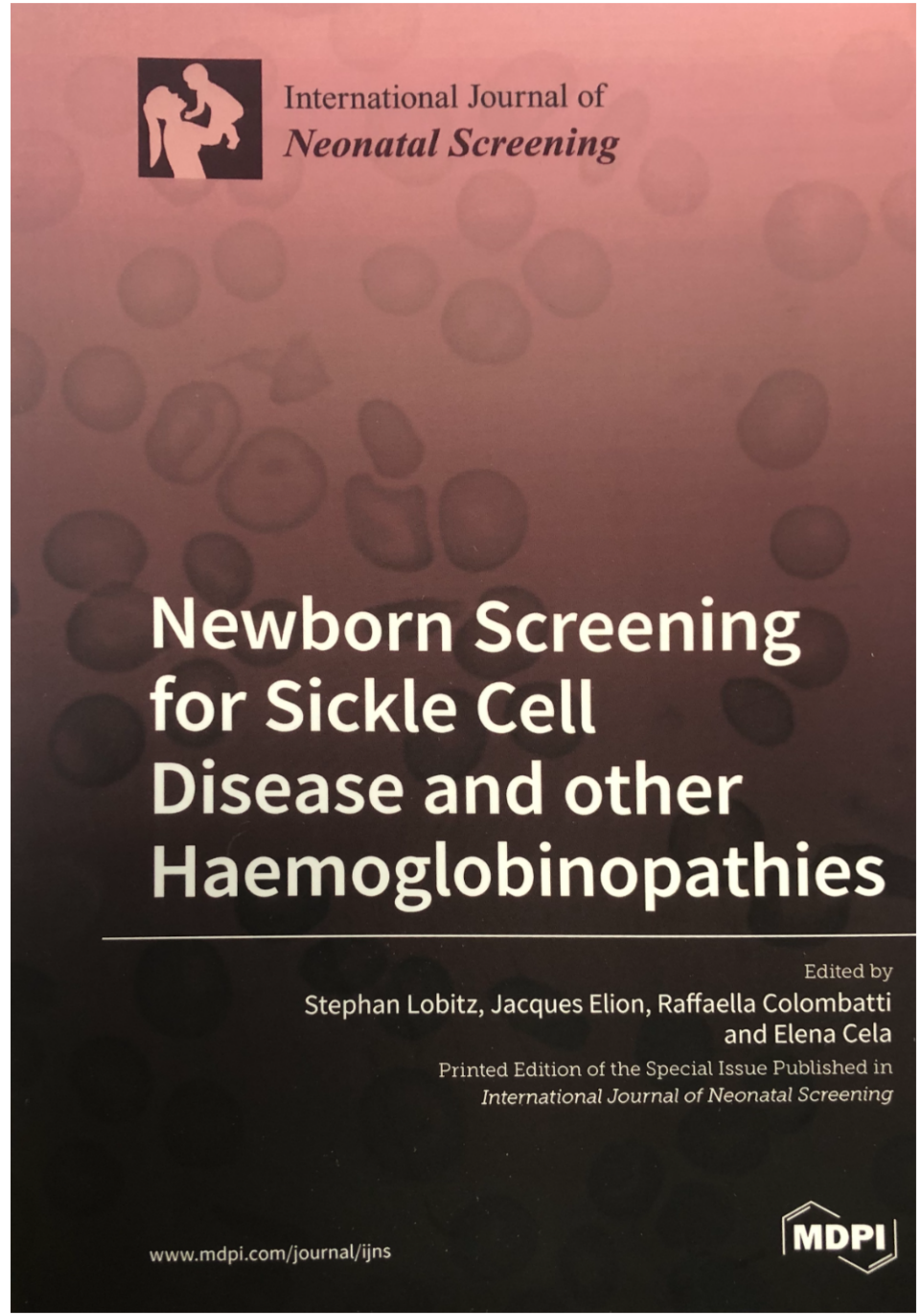
This panel recommends ***universal NBS in all countries participating in the conference, collection of data*** *on clinical outcomes through* ***setting up of registries*** *and* ***development of shared clinical protocols for comprehensive care*** *of all affected newborns.*

Raising public awareness *about SCD is recommended, as well as focused education about the condition for health care workers, allied professionals, managers and commissioners of health care systems.*

Currently, still different approaches:

National-Regional-Pilots
Universal-Targeted
Different techniques

https://www.mdpi.com/books/pdfview/book/1649




thank you
danke
謝謝
ngiyabonga
teşekkür ederim
рахмат
Баярлалаа
спасибо
gracias
merci
obrigado
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