Haematological Care Priorities in Sub-Saharan Africa 2

Sickle cell disease in sub-Saharan Africa: transferable strategies for prevention and care

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Lancet Haematol 2021; 8: e744–55

Published Online September 2, 2021 https://doi.org/10.1016/S2352-3026(21)00191-5

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This is the second in a Series of four papers about haematological care in sub-Saharan Africa

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Sickle cell disease can be life-threatening or chronically debilitating for both children and adults. Worldwide, more than 300 000 children are born with sickle cell disease every year, over 75% of whom in sub-Saharan Africa. Increased awareness and early interventions, such as neonate screening and comprehensive care, have led to considerable reductions in mortality in children younger than 5 years in high-income countries. However, sickle cell disease prevention and care have largely been neglected in Africa. Without intervention, 50–90% of affected children in many sub-Saharan African countries die before their fifth birthday. Fortunately, increasing initiatives in sub-Saharan Africa are piloting interventions such as neonate screening and comprehensive care, and as mortality declines, quality of life and increased life expectancy become major targets for interventions. Hydroxyurea (hydroxycarbamide) and haematopoietic stem-cell transplantation have already been shown to be effective therapies in high-income countries, but are either not widely accessible or too expensive for most African populations. These challenges are being alleviated by numerous networks evolving through international collaborations that are positively changing the outlook of sickle cell disease management in sub-Saharan Africa. In this Series paper, we describe the epidemiology, pathophysiology, clinicobiological profile, and psychosocial effects of sickle cell disease in sub-Saharan Africa. We highlight transferable strategies already used for the successful management of the condition and key strategies and recommendations for affordable and comprehensive care on the continent.

Introduction

Sickle cell disease is a group of blood disorders characterised by the presence of sickle haemoglobin in red blood cells, and it mostly affects individuals of African descent. Sickle cell anaemia, the most severe and the commonest form of the disease in Africa, results from the inheritance of two mutated alleles encoding sickle haemoglobin. In the mutated haemoglobin subunit β gene (*HBB*), a single nucleotide change causes an amino acid change (Glu6Val) that leads to a defect in the structure of haemoglobin (haemoglobinopathy). Mutations that lead to a complete absence of haemoglobin subunit β synthesis (β^0-thalassaemia), when co-inherited with one sickle haemoglobin allele, also cause sickle cell anaemia. The co-inheritance of the sickle haemoglobin allele with other *HBB* variants (eg, haemoglobin C) results in other forms of sickle cell disease. The sickle cell mutation is now known to have originated in Africa,[1] where over 75% of the estimated 300 000 livebirths of children with sickle cell anaemia annually occur.[2] As a result of the protection that carriers of one copy of the sickle haemoglobin allele have against severe *Plasmodium falciparum* malaria, the mutation has persisted at high frequencies in Africa, where malaria caused by *P falciparum* is endemic. In addition, because of insufficient public health interventions in most African countries, such as neonate screening for sickle cell disease followed by comprehensive preventive care, 50–90% of affected children in sub-Saharan Africa are estimated to die before their fifth birthday.[3]

For more on the **Sickle In Africa Consortium** see https://www.sickleinafrica.org

Although sickle cell disease was first described more than 110 years ago, expenditure on care and research of this condition in sub-Saharan Africa has been negligible. WHO only recognised sickle cell disease as a major public health issue in the 59th World Health Assembly, in May, 2006. In the 63rd session of its General Assembly, in 2008, the UN also recognised sickle cell disease as a public health problem and June 19 was established as World Sickle Cell Awareness Day.[4] Advocacy by the American Society of Hematology resulted, in 2018, in the US Congress approving bills to strengthen global awareness and research into the disorder, such as the bill by Senators Tim Scott and Cory Booker that designated September as Sickle Cell Disease Awareness Month in the USA. The effect of these resolutions and advocacies is reflected in the momentous funding for research in sub-Saharan Africa that has led to the establishment of organisations such as the SickleGenAfrica Network, funded through the Human Heredity and Health in Africa consortium, and the Sickle In Africa Consortium (which comprises the Sickle Africa Data Coordinating Centre and the Sickle Pan-African Research Consortium), funded by the US National Heart, Lung, and Blood Institute. These initiatives are committed to translating research output into high-quality and affordable care, and to working towards a definitive cure for sickle cell disease. In this Series paper, we explore the epidemiology, clinicobiological profile, and psychosocial effects of sickle cell disease in sub-Saharan Africa, and explore key interventions, previously implemented with success, that have the potential to improve care and management of sickle cell disease in the region.

Epidemiology

Sickle cell disease and malaria endemicity

More than 110 years have elapsed since the first description of sickle cell disease in a 20-year-old African American by James B Herrick in Chicago, USA.[5] The African origin of mutated haemoglobin subunit β has been confirmed by large-scale genomic analyses, although a review, published in 2021, indicates that the correct age of the mutation and the precise location of its origin are still undetermined.[1] When Anthony C Allison and his colleagues showed, in 1954, that carrying a single allele of sickle haemoglobin (called the sickle cell trait) protects against severe *P falciparum* malaria,[6] they confirmed the evolutionary link between haemoglobin subunit β variants and malaria—the so-called malaria hypothesis that had been postulated by John BS Haldane on the basis of data on β-thalassaemia, in 1949.[7] Studies have since shown that human genetic factors are responsible for up to 25% of the interindividual differences in the clinical expression of severe malaria, and that the sickle cell trait contributes the largest proportion due to a single gene (up to 2%).[8] The sickle cell trait has been observed to reduce the risk of severe malaria caused by *P falciparum* by up to 90% in carriers, compared with individuals with a normal allele.[9,10] As a result, the sickle haemoglobin allele is highly prevalent in regions with historical malaria endemicity (figure 1A)—up to 20% in some regions; although statistical estimates have placed an upper limit at 18%.[11] Outside of Africa, the sickle haemoglobin allele is most frequent in individuals of African descent. This observation reflects the effect of migration on the spread of pathogenic mutations, for instance to the Mediterranean region (such as Padova and Monza in Italy)[12] and to the American continent (where it is absent in the native population), or in regions where malaria is endemic or was historically endemic, such as in the Indian subcontinent, the Middle East, and the Mediterranean, but where this mutation was not prevalent.[2] The expression of haemoglobin C, the second most common cause of sickle cell disease in Africa, is almost entirely restricted to west Africa, with an epicentre around Burkina Faso,[13] although changing population dynamics is resulting in a wider distribution of the variant (for instance, in the population surrounding Karachi, Pakistan).[14,15] A homozygous mutation in *HBB* is the most common cause of sickle cell disease in Africa (65–70% of cases), the compound heterozygote form with haemoglobin C is the second most common (about 30% of cases), and β^0-thalassaemia with one sickle haemoglobin allele accounts for the remaining cases of sickle cell disease in the continent.[16]

Co-inheritance of sickle cell disease and other genetic determinants of outcomes in sub-Saharan Africa

The interaction between the sickle haemoglobin allele and other red blood cell genetic variants that also confer malaria resistance—and that are also prevalent in malaria-endemic regions—has resulted in complex genetic interactions that either increase or reduce the clinical severity of sickle cell disease. For instance, individuals with the 3·7 kb deletion in α-thalassaemia, (figure 1B) which is particularly prevalent among patients with sickle cell disease in sub-Saharan Africa (compared with ethnolinguistically matched control populations), have better sickle cell disease haematological indices and lower hospitalisation rates than individuals with sickle cell disease without this deletion.[17] The G6PD deficiency variants that protect against some severe forms of malaria in sub-Saharan Africa (figure 1C) are, however, associated with an increased risk of haemolytic anaemia in sickle cell disease. The *APOL1* G1 and G2 variants that are prevalent in sub-Saharan Africa (figure 1D) because of the protection that they provide against African trypanosomiasis (sleeping sickness) are also known to predispose individuals of African ancestry—including patients with sickle cell disease—to end-stage renal disease.[18] The *HBB* gene cluster haplotypes (figure 2) that are present in all chromosomes with the sickle cell mutation are also associated with variable sickle cell

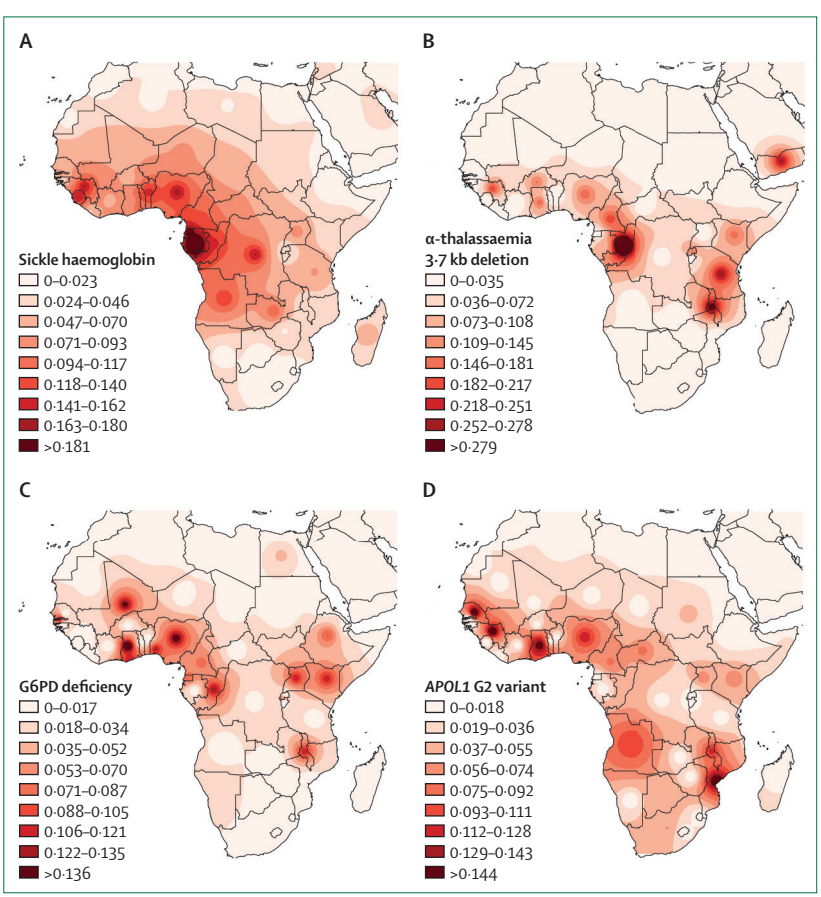
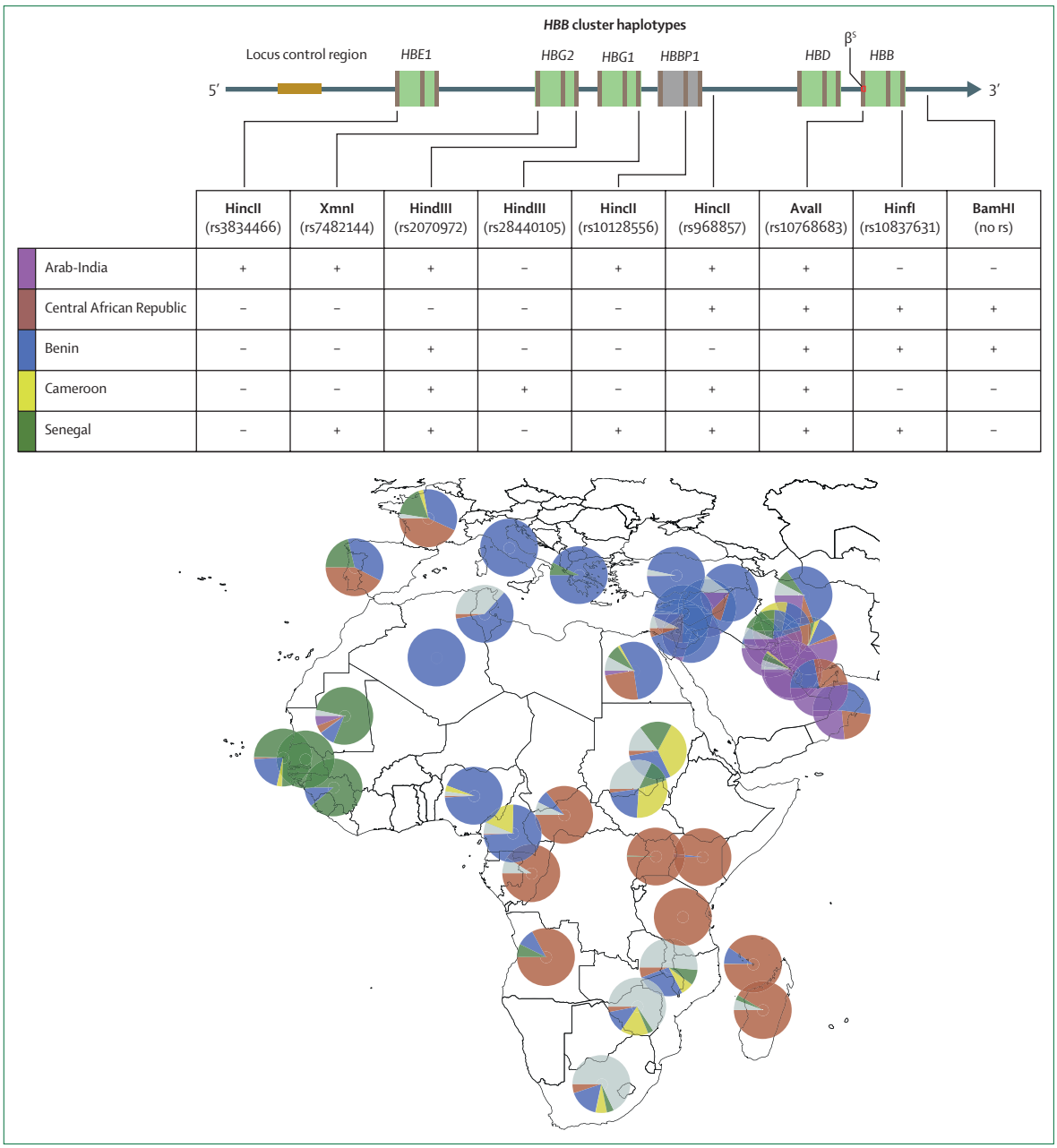


Figure 1: **Frequencies of the sickle haemoglobin allele and other gene variants in Africa**
Data shown are allele frequencies per 100 individuals in the general population. Adapted from Esoh and Wonkam.[1] (A) Distribution of the sickle haemoglobin allele. (B) Distribution of the 3·7 kb deletion in α-thalassaemia variant. (C) Distribution of G6PD deficiency. (D) Distribution of the *APOL1* G2 variant.



	HincII (rs3834466)	XmnI (rs7482144)	HindIII (rs2070972)	HindIII (rs28440105)	HincII (rs10128556)	HincII (rs968857)	AvaII (rs10768683)	HinfI (rs10837631)	BamHI (no rs)
Arab-India	+	+	+	–	+	+	+	–	–
Central African Republic	–	–	–	–	–	+	+	+	+
Benin	–	–	+	–	–	–	+	+	+
Cameroon	–	–	+	+	–	+	+	–	–
Senegal	–	+	+	–	+	+	+	+	–

Figure 2: **Distribution of mutated *HBB* gene cluster haplotypes in regional variants**
The placement of pie charts across the map represents the differential proportions of *HBB* gene cluster haplotypes in countries for which data are available. Some countries have multiple pie charts representing different studies from which data were extracted, whereas for some other countries no data are publicly available.

disease clinical severity: the Arab-India, Senegal, and Benin haplotypes are associated with less severe sickle cell disease clinical outcomes, whereas the Cameroon and Central African Republic haplotypes are associated with poorer outcomes.[19] However, one study based on sequence data rather than restriction site data found sub-structuring among the haplotypes that might have confounded their association with sickle cell disease clinical severity in some populations,[20] implying that further research is needed to understand the exact role of the different haplotypes in the clinical outcomes of sickle cell disease.

The strongest known modifier of clinical outcome of sickle cell disease is, however, the concentration of fetal haemoglobin—a highly heritable trait—in adult blood. Three major loci have been identified to influence fetal haemoglobin concentrations: *Xmn*I-*HBG2* (rs7482144), located at 11p15.4, *BCL11A* (rs1427407), located at 2p16.1,

and *HBS1L-MYB* (rs66650371), located at 6q24.[21] Polymorphisms in these loci are associated with variable concentrations of fetal haemoglobin (1–30%) in adults. Functionally relevant variants have been proposed for each of the loci: the *Xmn*I restriction variant at *HBG2* (frequent in populations in the Middle East), the *BCL11A* variant (the most influential fetal haemoglobin modifying locus in Africa), and the 3 bp deletion at *HBS1L-MYB*. *BCL11A* is a transcriptional repressor of fetal haemoglobin, with a well characterised fetal haemoglobin-silencing role in adults,[21] and is therefore the target of hydroxyurea (hydroxycarbamide), the drug most widely used to treat sickle cell disease.[22] Other loci recently associated with fetal haemoglobin concentrations include *BCL2L1* (20q11.21),[23] which is yet to be found in Africa, and *FRMPD4* (Xp22.2) among Tanzanian patients with sickle cell disease.[24] Most studies on fetal haemoglobin-promoting loci have been based on non-African populations, and explain up to 50% of variation in fetal haemoglobin concentrations, which means that much is yet to be discovered about other potential influencing loci in sub-Saharan African populations. In 2020, a whole-exome sequencing study of samples from Cameroonian patients with sickle cell disease uncovered variants in multiple genes, such as *CLCN6*, *SERPINC1*, *ATP2B4*, and *OGDHL*, that are linked to improved survival without complications requiring therapy.[25] Variants in other genes (eg, *COL11A1*, *ABCC1*, *INSR*, and *ATP2B4*) have been associated with an increased susceptibility to stroke in patients with sickle cell disease.[25] For comprehensive care to be achieved, the genetic factors that predispose some individuals to variable clinical outcomes should also be considered. African populations have the highest amounts of genetic diversity and often have more extreme disease phenotypes, so genetic studies on these populations could have a substantially greater sensitivity for disease-associated variants on the continent.

Prevalence of sickle cell disease in sub-Saharan Africa

The prevalence of sickle cell disease in sub-Saharan Africa is largely driven by the prevalence of the sickle cell trait, haemoglobin C, and β^0-thalassaemia. The best measure of the prevalence of sickle cell disease in a population would be the total number of affected births per 1000 livebirths (birth prevalence). Such estimates have been possible to obtain in high-income countries in which universal neonate screening has been implemented. Making such estimates in specific African countries, where neonate screening has been piloted as a sickle cell disease management strategy, has only become possible with the establishment of sickle cell disease treatment centres across the continent (figure 3A). Generally, most national sickle cell disease prevalence rates do not exceed 2% (appendix 2, p 2). However, birth prevalence rates greater than 3% have been reported in places such as Shirati, Tanzania (3·9%),[26] suggesting that there might be more such cases in specific geographical regions in sub-Saharan Africa—especially in rural areas, where awareness of sickle cell disease is typically low. In 2019, in Nigeria, where up to 20 children with sickle cell disease are born per 1000 livebirths annually,[27] a National Demographic and Health Survey showed that 10% of children with ages between 6 months and 5 years who had severe anaemia also had sickle cell anaemia.[28] This finding stresses the need for countries to invest in epidemiological surveys of the prevalence of the important *HBB* variants in sub-Saharan Africa; sickle haemoglobin, haemoglobin C, and β-thalassaemia. Increased investment in epidemiological surveys of all variants will enable the identification and prioritisation of regions with the highest need for crucial interventions. For example, demographic projections show that, by 2050, the prevalence of sickle cell disease will increase by about 100 000 neonates globally, and that Nigeria and the Democratic Republic of the Congo will be the countries most in need of interventions.[29] Therefore, the prompt rollout of intervention strategies such as universal, or at least large-scale, neonate screening in these countries is particularly imperative. A survey of children aged 16–17 years in Bahrain showed that health education, carrier screening, and premarital genetic counselling are the best ways to reduce the prevalence of inherited blood disorders, including sickle cell disease.[30]

Diagnosis of sickle cell disease and neonate screening in sub-Saharan Africa

The three laboratory tests most commonly used for the diagnosis of sickle cell disease are haemoglobin electrophoresis, isoelectric focusing, and high-performance liquid chromatography. A screening test is typically done first in a clinical setting, and is followed by a confirmatory test with any of the three aforementioned techniques. A sickle cell solubility test, which involves treating a thin blood film with metabisulfite or sodium dithionate under hypoxic conditions and observing for sickling under a light microscope, has been the major screening technique used over the years, and a positive result can suggest either sickle cell anaemia or the sickle cell trait.[31] Rapid, inexpensive, and sensitive immunoassay-based point-of-care tests, such as Sickle SCAN[32] and HemoTypeSC,[33] have also been developed and found to have high sensitivity and specificity in sub-Saharan African settings.[33,34] These tests could propel the implementation of neonate screening programmes, which have already been piloted in several sub-Saharan African countries, across the entire region. In Nigeria, for instance, a study that assessed the feasibility of implementing point-of-care tests as part of immunisation programmes found that the tests had specificity (100%) and sensitivity (100%) similar to the gold standard (high-performance liquid chromatography).[34] The currently available point-of-care tests are affordable—eg, the HemoTypeSC costs less than US$ 2 per test—and can therefore be adopted by, and scaled up in, most sub-Saharan African countries. These low prices

See Online for appendix 2

Panel 1: **Challenges and recommendations for sickle cell disease research in sub-Saharan Africa**

- Challenges to care of sickle cell disease in sub-Saharan Africa
- Malaria endemicity, which increases the risk of anaemia and splenic dysfunction
- Absence of a universal health-care scheme in many countries, limiting access to proper sickle cell disease management
- Scarcity of penicillin prophylaxis and comprehensive immunisation programmes against pneumococcal infection and other preventable infectious diseases
- Inadequate blood supply and poor management of complications related to blood transfusion
- Inaccessibility of hydroxyurea (hydroxycarbamide) and haematopoietic stem-cell transplantation in most sub-Saharan African countries

Strategies to improve care

- Implement a neonate screening programme for an early diagnosis and management of sickle cell disease
- Establish premarital testing and genetic counselling clinics to reduce the prevalence of sickle cell disease and assist families in making decisions related to reproductive options
- Ensure the continuous professional development of clinicians on the diagnosis and management of sickle cell disease
- Improve infrastructures in health-care facilities, create haematology services, and train more qualified specialists
- Increase public awareness of sickle cell disease to mitigate stigma and negative thoughts surrounding the condition, and thus reduce the psychological effects of sickle cell disease

Research recommendations

- Assess the prevalence and incidence of sickle cell disease and other haemoglobinopathies in sub-Saharan Africa
- Use whole-genome sequencing analysis to identify genetic modifiers of sickle cell disease
- Identify environmental factors and other comorbidities affecting the clinical outcomes of sickle cell disease
- Assess the co-morbidity of nephropathy caused by mutated *APOL1* in patients with sickle cell disease in trypanosomiasis-endemic regions
- Explore the use of artemisinin combination therapy regimens as prophylaxis for patients with sickle cell disease, and its potential benefit on complications of the disease

might curtail the challenges of financial cost and logistical burden of laboratory diagnostic tests in neonate screening programmes, and can result in substantial coverage of neonate screening, including in remote areas. Therefore, universal neonate screening might be achievable in sub-Saharan Africa, provided that other challenges (panel 1) are addressed—such as increasing the number of sickle cell disease clinics offering point-of-care tests, improving accessibility to such clinics, training personnel with the necessary skills to handle point-of-care tests and individual results, and offering genetic counselling to patients with positive results. Appropriate feedback of sickle cell disease neonate screening test results is essential to parental wellbeing.[35] Genetic counselling targeting individuals with the sickle cell trait will be particularly helpful in raising awareness of reproductive options, the potential implications of having a child with sickle cell disease, and the benefits of early intervention. In addition, systems for follow-up of screen-detected babies should be put in place; for example, through the integration of neonate screening programmes in immunisation campaigns, or via prospective cohort studies, such as previously done in Kenya (panel 2).[36]

Mortality and life expectancy of patients with sickle cell disease in sub-Saharan Africa

The recessive sickle haemoglobin allele is estimated to have a lethality of 80% in malaria-endemic regions, meaning that, without therapeutic interventions, 80% of all children born with sickle cell anaemia will die of the disease before the age of 5 years if the disease is not diagnosed and managed immediately.[37] In high-income settings, such as the USA and Europe, universal neonate screening, prophylactic penicillin, and pneumococcal vaccination have drastically reduced childhood mortality rates for sickle cell disease. As sickle cell disease becomes more of a chronic disease in adults in these countries, other interventions such as hydroxyurea, blood transfusion, haematopoietic stem-cell transplantation (HSCT), and transcranial doppler screening to detect risk of stroke, among others, have considerably increased the life expectancy of patients with sickle cell disease to more than 50 years (although the life expectancy of people with the disease is still about 20 years shorter than that of unaffected individuals). In sub-Saharan Africa, where early detection of sickle cell disease and initiation of prophylactic penicillin and pneumococcal vaccination, among other interventions, have been scarce, and where the high burden of infectious diseases (such as malaria) and respiratory diseases contributes to childhood mortality, 150 000–300 000 children with sickle cell disease die before the age of 5 years every year.[3] Because these numbers are mostly estimates, studies to establish the exact mortality rates of sickle cell disease should be done across sub-Saharan Africa. The few reports of sickle cell disease mortality in sub-Saharan Africa have found mortality rates in children younger than 5 years to be between 2%[38] and 16%.[9]

An overall mortality in children younger than 5 years of 16% reported in Benin was reduced by 10 times after neonate screening and follow-up programmes were piloted in the country.[39] Mortality rates of 9·8% (Angola),[40] 5·8% (Kenya),[36] and 1·9% (Tanzania)[38] have also been reported. The implication of these high childhood

Panel 2: **Proposed guidelines for the care of patients with sickle cell disease in sub-Saharan Africa**

- Newborn infants with a positive screening result should be seen by a paediatrician to confirm the result, and families should be referred to a genetic counsellor if available
- Penicillin prophylaxis should be prescribed by the age of 90 days and continued throughout childhood
- Ensure immunisation against pneumococcal, meningococcal, salmonella, hepatitis A, and hepatitis B infections
- Ensure malaria prophylaxis, folic acid supply, and adequate hydration for all patients with sickle cell disease
- Patients with acute fever should be offered a malaria screening test and cultures of blood, urine, and other possible site of infections (eg, joints) if applicable
- In case of suspected bacterial infection, propose an antibiotic regimen in collaboration with a microbiologist if possible, and ensure pneumococcus infection is covered
- An annual transcranial doppler scan should be done from the age of 2 years where feasible, and hydroxyurea (hydroxycarbamide) should be prescribed in case of abnormal transcranial doppler velocity (mean velocities >200 cm/s) to detect stroke risk
- Patients with neurological signs and symptoms should be referred to a specialist (paediatrician or neurologist) and be offered a brain MRI or CT scan, if possible, to detect stroke
- Ensure a regular psychological assessment of patients and parents or legal guardians, and consider referral to a specialist (psychologist or psychiatrist) in case of depression, anxiety, or both
- Patients with recurrent episodes of pain should be prescribed hydroxyurea and have a specialist consultation (with a paediatrician or haematologist) if available
- Acute splenic sequestration and transient red cell aplasia should be suspected in case of acute fall in haemoglobin concentration (>3 g/dL below the steady state), and patients should be cared for by a specialist if available
- Acute blood transfusion should be proposed in case of acute or severe anaemia
- The presence of acute chest syndrome, characterised by chest pain, fever, abnormal chest examination, and new pulmonary infiltrates on the chest x-ray, should be assessed
- The treatment of acute chest syndrome should include oxygen delivery, intravenous fluids, analgesics, antibiotics (which should cover pneumococcus), physiotherapy, and acute blood transfusion
- Consider regular transfusions for the secondary prevention of stroke and in case of recurrent acute chest syndrome episodes not prevented by hydroxyurea, and prescribe iron-chelating agents
- Avascular necrosis should be considered in patients with sickle cell disease presenting with either sudden onset or progressive joint pain, and a plain x-ray should be done
- Patients should be monitored at least annually for symptoms or signs of renal disease (eg, haematuria), hypertension, and presence or progression of albuminuria, proteinuria, and declining renal function; evidence of nephropathy should motivate input from a nephrologist

mortality rates due to sickle cell disease in sub-Saharan Africa is that most affected neonates are at high risk of death in settings where disease awareness is low and access to health care is limited or non-existent. These high rates are also the rationale for the establishment of more specialised sickle cell disease clinics across the continent and for the expansion of accessibility to such clinics to patients with sickle cell disease.

Pathophysiology

Haemoglobin polymerisation triggers the downstream complications of sickle cell disease,[41] of which vascular occlusion and haemolysis are the two most important pathophysiological events (appendix 2, p 3). Haemoglobin polymerisation is mediated by a high concentration of sickle haemoglobin and low oxygen tension in red blood cells, and causes red blood cell sickling and premature breakdown.[42] This breakdown results in the release of haemoglobin, which depletes nitric oxide, leading to vasoconstriction, increased expression of endothelial cell adhesion molecules, and increased platelet inactivation. In addition, arginase 1 is released as a result of red blood cell destruction, leading to the depletion of L-arginine (the substrate of nitric oxide synthesis). These events lead to repeated tissue ischaemia (ischaemia–reperfusion) and hypoxia, which causes oxidative stress. Increased platelet and white blood cell (neutrophils and monocytes) counts incite inflammatory responses. The major factors affecting haemoglobin polymerisation include a high intracellular concentration of sickle haemoglobin relative to other haemoglobins (particularly fetal haemoglobin, which helps to prevent haemoglobin polymerisation), duration of low oxygen tension, and pH.[41] The vaso-occlusive events and haemolysis that follow haemoglobin polymerisation are the hallmarks of sickle cell disease.[16] Notable processes triggered by these events include increased activity of pro-inflammatory pathways, increased expression of endothelial cell adhesion molecules (eg, P-selectin and E-selectin), reduced nitric oxide bioavailability, and increased neutrophil, monocyte, and platelet counts. The understanding and targeting of these major pathophysiological pathways have led to the discovery of several therapeutics targets.[16] For instance, in November, 2019, the drug crizanlizumab, an anti-P-selectin molecule, was approved by the US Food and Drug Administration (FDA) to treat vaso-occlusive crisis in patients with sickle cell disease aged 16 years or older.[43] The drug was shown to be safe and effective in the USA, Brazil, and Jamaica,[43] and has now been planned for trials in Ghana and Kenya.[44] L-glutamine, an agent that reduces the redox potential and

oxidative stress in sickle red blood cells, was also approved by the FDA in July, 2017, for the treatment of vaso-occlusive crises, acute chest syndrome, and hospitalisation of patients with sickle cell disease.[45] Before these drugs were approved, hydroxyurea, an anti-sickling agent, was the only FDA-approved therapy for sickle cell disease, for its ability to prevent haemoglobin polymerisation through a mechanism of action not yet known.[22] Several other strategies targeting various pathophysiological pathways, such as agents targeting inflammatory and haemoglobin polymerisation pathways, are currently being tested in clinical trials.[16] Continued research is therefore important to delineate more pathophysiological pathways that might uncover novel therapeutic targets.

Important blood components measured in sickle cell disease

The components of red blood cells and their breakdown products (such as haemoglobin, haem, and lactate dehydrogenase) released after haemolysis constitute some of the haematological indices routinely measured in patients with sickle cell disease. Substances released from the liver are equally important indicators of disease severity. The liver plays a major role in the metabolism of bilirubin, an important breakdown product of haem, converting free serum bilirubin to a soluble form (conjugated bilirubin) that can be easily excreted through urine. Serum and urine bilirubin concentrations, as well as some important liver enzymes such as aspartate aminotransferase and alanine aminotransferase, are therefore routinely measured to assess the health of the liver under anaemic and oxidative stress. Haemolytic anaemia is especially severe in cases of homozygous sickle cell disease and leads to substantial reductions in haemoglobin concentrations (<7 g/dL), particularly in children younger than 5 years.[46] Haemoglobin concentrations in patients with sickle cell disease older than 5 years are typically stable.[47] In a multinational study, Inusa and colleagues[48] observed that baseline (before initiation of therapy) haemoglobin concentrations are generally lower in patients with sickle cell disease in sub-Saharan Africa than in patients living in the USA and Europe, who usually have access to better care. However, the fact that patients with sickle cell disease in sub-Saharan Africa have lower baseline haemoglobin concentrations does not necessarily mean that they need higher doses of hydroxyurea to have a proportional increase in fetal haemoglobin concentrations in comparison with patients in the USA and Europe. Furthermore, geographical heterogeneity in haematological profiles within Africa has been observed (eg, higher baseline haemolysis and total bilirubin in east African than in west African patients).[48] Low haemoglobin and high total bilirubin concentrations are typical predictors of risk of death,[38] which implies that sickle cell disease clinical outcomes might be more severe in east Africa than in west Africa. This finding would be consistent with the prevalence of the Central African Republic haplotype in east Africa, and of the Senegal and Benin haplotypes in west Africa. Regional differences in fetal haemoglobin concentrations typically disappear after hydroxyurea therapy.[49,50] In general, monitoring of blood components in sickle cell disease is crucial to determine the risk of complications (such as nephropathy) and when specific life-saving interventions, such as initiation of hydroxyurea or regular blood transfusion for stroke prevention, are needed.

Subphenotypes of sickle cell disease in sub-Saharan Africa

Sickle cell disease clinical phenotypes are highly heterogenous; some individuals can be completely asymptomatic, whereas others living in the same geographical region and under similar environmental conditions can have more severe outcomes. The clinical course of sickle cell disease typically includes a steady-state period characterised by no history of painful episodes requiring emergency procedures or hospital admissions, blood transfusions within the previous 6 months (except in case of sickle haemoglobin co-inheritance with a transfusion-dependent β^{+}-thalassaemia), or infections requiring medications such as antibiotics.[51] By implementing universal neonate screening and comprehensive care programmes in high-income countries, reduction in mortality of children younger than 5 years has transformed sickle cell disease from a life-threatening paediatric disease to a debilitating condition of adults, with chronic complications that might ultimately culminate in end-organ dysfunction.[52] Patients in sub-Saharan Africa face the particular challenges of infectious comorbidities and poor access to care, associated with poorer baseline haematological indices, and severe sickle cell disease clinical events with multiorgan damages. These challenges specific to sub-Saharan Africa mean that early detection and monitoring via follow-up programmes and early initiation of comprehensive care are essential to prevent the progression of chronic complications.

Specific environmental determinants of sickle cell disease clinical outcome in sub-Saharan Africa

Splenic dysfunctions such as autosplenectomy or hyposplenism can substantially predispose patients with sickle cell disease to infections. Bacteraemia is a major cause of pneumococcal disease in these patients, and the causative organisms in sub-Saharan African children with sickle cell anaemia are not different from those in high-income countries: *Streptococcus pneumoniae*, non-typhoidal *Salmonella* spp, *Haemophilus influenzae* type b, *Acinetobacter* spp, and *Escherichia coli*.[53,54] In addition, patients with sickle cell disease have increased susceptibility to transfusion-transmissible infections, such as HIV or *Yersinia enterocolitica* infections. Malaria also presents a particular challenge to the management of sickle cell disease in sub-Saharan Africa because it is

independently associated with severe anaemia and splenic dysfunctions that considerably worsen the clinical outcomes of patients with sickle cell disease, particularly in children younger than 5 years.[55] However, studies have reported that current antimalaria chemoprophylaxis (ie, chloroquine, mefloquine, artesunate–mefloquine, proguanil, pyrimethamine, sulfadoxine–pyrimethamine, and sulfadoxine–pyrimethamine–amodiaquine) have very little or no effect in preventing sickle cell disease complications;[56] further research is needed to assess other antimalarial drugs in this setting. Acute chest syndrome is an important cause of morbidity and mortality in children, who are particularly susceptible to bacterial and viral pneumonias. The emergence of COVID-19 was a cause for alarm because of its potential to rapidly exacerbate acute chest syndrome in patients with sickle cell disease. Data from these patients in Europe and the USA, however, indicate that COVID-19 has not been as upsetting to this group as was anticipated.[57] Although vaso-occlusive crisis was highly prevalent in patients with sickle cell disease infected by SARS-CoV-2, no proportional increase in acute chest syndrome was seen, and acute chest syndrome was not the major cause of fatality in such patients.[58] There is a paucity of information on COVID-19 and sickle cell disease in sub-Saharan Africa. Other infectious comorbidities in sub-Saharan Africa that pose a challenge to patients with sickle cell disease in the region include trypanosomiasis, for which protective genetic variants in *APOL1* have been shown to increase susceptibility to end-stage renal disease.[59] Adherence to penicillin prophylaxis has virtually eliminated pneumococcal bacteraemia in patients with sickle cell disease and has led to reductions in morbidity and mortality in high-income countries, and should be urgently and widely implemented in sub-Saharan Africa, alongside vaccination programmes against pneumococcal infections.[52] Additional considerations should be given to research on dengue fever, the prevalence of which largely overlaps with sickle cell disease, and to eventually developing and implementing policies for the incorporation of dengue vaccination in the comprehensive programmes for prevention of infectious diseases and care of patients with sickle cell disease.[60] In addition, further research is needed to assess the efficacy of other antimalarial drugs, and there is an urgent need to develop laboratories and infrastructure capacity for appropriate infection detection to improve transfusion services for patients with sickle cell disease in sub-Saharan Africa.

Management of sickle cell disease in sub-Saharan Africa

Effective management of sickle cell disease involves early detection with neonate screening programmes, followed by comprehensive preventive care. There are relatively few reported specialised sickle cell disease treatment centres across sub-Saharan Africa (figure 3A)[61] that offer standard-of-care treatment for sickle cell disease, including home-based care and family education on primary preventive measures, such as the recognition of when to seek medical care, how to detect an enlarged spleen, and prevention of dehydration. Hydroxycarbamide remains the most extensively tested therapeutic (with over 100 ongoing or completed trials listed in ClinicalTrials.gov), and the best known disease-modifying therapy for sickle cell disease, recommended for adults and for all children with sickle cell disease from the age of 9 months.[62] Clinical trials—notably the REACH[63] and NOHARM[64] dose-escalation studies—have shown the safety and efficacy of hydroxyurea in treating sickle cell disease in sub-Saharan Africa. A major challenge with hydroxyurea has been establishing the optimal dosing and monitoring regimens, especially given the high interpatient variability in hydroxyurea response.[65] Previous clinical trials with a fixed dose of 15–20 mg/kg per day have shown the effectiveness of hydroxyurea and that it causes only a few reversible toxicities, such as mild to moderate neutropenia followed by reticulocytopenia and then by thrombocytopenia.[65] The REACH and NOHARM trials in sub-Saharan Africa have now shown that even higher concentrations of fetal haemoglobin (>30% increase) can be observed by gradually increasing the hydroxyurea dose every 2 months until a maximum tolerated dose of about 35 mg/kg per day is reached.[64] Researchers have also developed a new pharmacokinetic-guided precision dosing method for children, which reduces the time to establish a child's maximum tolerated dose and improves fetal haemoglobin concentrations to more than 40%.[66] The potential benefit of this method is that it will substantially reduce the logistical challenges of the trial-and-error dose-escalation dosing method and of laboratory monitoring and the need for provider expertise. However, this method is yet to be tested in adult patients with sickle cell anaemia in particular, and in sub-Saharan Africa in general. Other potential challenges to hydroxyurea therapy in sub-Saharan Africa are hesitancy and low adherence to treatment outside experimental conditions. In addition, there is ongoing discussion on whether long-term hydroxyurea use increases the risk of adverse effects such as infertility.[67] However, information on this subject is scarce,[68] thus emphasising the need for longitudinal cohort studies with long-term follow-up to accompany the implementation of hydroxyurea therapy in sub-Saharan Africa.

Blood transfusion is commonly used in sub-Saharan Africa to manage acute complications of sickle cell disease such as splenic sequestration, haemolysis, and malaria-induced haemolytic anaemia. However, major challenges that hinder blood transfusion for patients with sickle cell disease in sub-Saharan Africa include inadequate blood supply, high risk of transfusion-transmitted infections such as bacterial and viral infections that are usually high in the general population, and haemolytic transfusion reactions due to the so-called innocent bystander mechanism, whereby antibodies

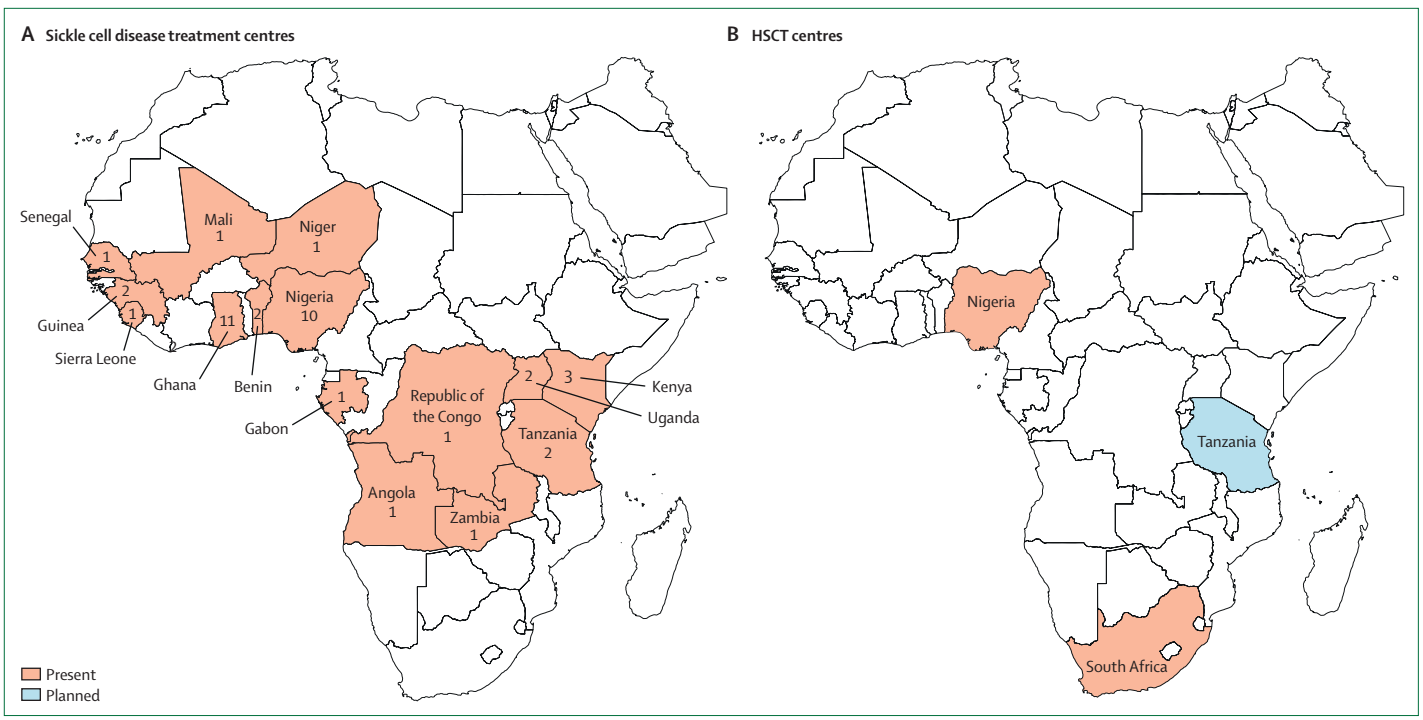


Figure 3: **Sickle cell disease treatment centres and HSCT centres in Africa**
The figures within countries show the number of reported sickle cell disease treatment centres. HSCT=haematopoietic stem-cell transplantation.

against transfused red blood cells (alloantibodies) destroy the host's own red blood cells. In addition, repeated blood transfusions can lead to iron overload. Therefore, improving the transfusion system in sub-Saharan Africa through increasing blood supply by encouraging blood donation, improving blood screening tests and donor-recipient matching, and increasing accessibility to iron-chelating agents in the case of chronic blood transfusions will greatly reduce sickle cell disease morbidity and mortality.[69] The topic of safe blood transfusion sub-Saharan Africa is covered in further detail in the fourth paper of this Series.

Allogeneic HSCT is currently the only curative measure for sickle cell disease, with a cure rate of more than 95% in HLA-matched sibling donors.[16] When done before the age of 2 years, allogeneic HSCT can completely restore marrow function in patients with sickle cell disease. Immunological reactions such as graft-versus-host disease limit the use of unrelated matched donors, but this complication could be alleviated with gene editing and autologous HSCT. In Africa, where large families are common, allogeneic HSCT might be facilitated by the availability of matched sibling donors. However, access to and the costs of HSCT are challenges in the continent. The process and techniques required for these interventions, such as harvesting haematopoietic stem cells ($CD34^+$), require specialist training that is scarce in Africa. Only two countries in sub-Saharan Africa have HSCT centres: Nigeria and South Africa;[70] Tanzania has also put forward an agenda to establish a centre[71] (figure 3B). Increasing funding by sub-Saharan African governments and international organisations is required to invest in HSCT centres and for further clinical trials in sub-Saharan Africa, which are particularly important because genetic studies on the continent are progressively identifying Africa-specific genetic factors in sickle cell disease.

The prospect of potential curative options for sickle cell disease has recently improved by a joint initiative from Novartis and the Bill and Melinda Gates Foundation to develop a single-shot gene therapy without the need to engineer cells outside the body. Considering the small number of specialised treatment centres for sickle cell disease in Africa (figure 3), the success and equability of gene therapy implementation in the continent is questionable. However, the recent, faster-than-expected development of COVID-19 vaccines by use of genomic approaches is encouraging, and accompanying equity mechanisms through international agencies such as WHO might be expected. The responsibility of implementing future gene editing and therapy for sickle cell disease in Africa will also lie with African governments and funding bodies, such as the Cure Sickle Cell Disease Initiative of the US National Institutes of Health. The time might be right to set an ambitious global genomic research programme to uncover curative options for sickle cell disease.

Psychosocial effects of sickle cell disease

The morbidity and mortality associated with sickle cell disease impose substantial psychosocial weight on

affected patients and families. The labelling of affected individuals as sicklers in settings where awareness about sickle cell disease is low often stigmatises patients, and is frequently accompanied by suicidal thoughts. Sickle cell disease in sub-Saharan Africa is also frequently associated with witchcraft and the mother is often blamed.[72] Therefore, education on sickle cell disease should not be limited to patients and their families, but be extended to the general community. Results from screening tests could be particularly burdensome to families with affected individuals. Premarital screening and genetic counselling, or prenatal screening of carrier mothers, with genetic counselling on reproductive options, could also contribute to the reduction of the morbidity and mortality due to sickle cell disease.

Conclusion and perspectives

Sickle cell disease preventive measures, including primary prevention through neonate screening and genetic counselling focused on individuals with the sickle cell trait, can greatly reduce the burden and prevalence of sickle cell disease in sub-Saharan Africa and globally. Neonate screening is currently one of the most powerful tools available for sickle cell disease management; however, its application can only be effective if associated with patient follow-up, comprehensive care, and genetic counselling of sickle cell trait carriers, as previously shown in Bahrain.[73] In addition, public awareness campaigns are important to reduce the stigma associated with the disease and to promote knowledge of warning signs that should prompt medical attention. In this Series paper, we have shown that progress in implementing neonate screening and comprehensive care in some sub-Saharan African countries has been encouraging. When the disease is detected early, family education on the management of sickle cell disease can reduce morbidity; hospital attendance for immunisation campaigns should be encouraged, and hydroxyurea therapy should be initiated in affected children as young as 9 months old. Therefore, African governments must embrace implementation of universal health care and invest in making hydroxyurea more accessible and affordable to all individuals affected by sickle cell disease. There is also an immediate need to improve Africa's blood transfusion services and to understand the socioeconomic and psychosocial effects of sickle cell disease, including when providing sickle cell disease screening test results to families. Such research projects will be best done in longitudinal cohort studies,[74] requiring the concerted effort of governments, the general public, and international collaborators. Increased research in pharmacogenetics is needed to optimise long-term treatment of chronic complications and to manage toxicities, in view of the anticipated increase in the number of patients with sickle cell disease taking hydroxyurea. As hydroxyurea dose-escalation algorithms promise to further reduce sickle cell disease morbidity and mortality, more sickle cell disease clinics in semi-urban and rural settings need to be established to reach all patients with sickle cell disease who do not have access to existing specialised treatment centres in sub-Saharan Africa. Finally, research in sub-Saharan Africa is urgently needed to establish the exact prevalence, mortality, and morbidity, environmental and genetic factors affecting clinical complications, and life expectancy of patients with sickle cell disease, to facilitate the design of future risk models and to investigate novel routes for therapeutic options with the ultimate aim of improving the clinical outcomes of patients with sickle cell disease in all parts of the world.

Search strategy and selection criteria

References for this Series paper were identified through searches of PubMed with the words "sickle cell" and one or more of the following words or phrases to build specific search strategies: "sickle mutation", "origin", "*HBB* haplotype", "morbidity", "mortality", "haematological parameter", "newborn screening", "neonatal screening", "prenatal diagnosis", "psychosocial impact", "genetic modifier", "hydroxyurea", "clinical trial", "stem-cell transplant", "pathophysiology", "treatment", "management", "transfusion", "complication", "clinical profile", "prevalence", "burden", "diagnosis", "point-of-care test", "standard-of-care", "infection", and "bacteraemia". Searches were done between May 27, 2020, and Jan 31, 2021, and broadly covered the field with specific attention to studies on transferable interventions for sickle cell disease published within the past 36 months. The final references list was generated from original articles and expert reviews or commentaries in English exclusively on specific topics relevant to the broad scope of this Review.

Contributors

KE did the literature search and drafted the manuscript. EW-T reviewed the selected references for quality and revised the manuscript. AW conceived the manuscript, supervised revisions, reviewed the literature search, and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

AW is director of the Sickle in Africa Data Coordinating Centre, based at the University of Cape Town, South Africa, and funded by the US National Institutes of Health under grant number U24HL135600–02; and is director of the Hearing Impairment Genetic Studies in Africa, funded by the US National Institutes of Health under grant number U01-HG-009716, by the African Academy of Sciences, and by the Wellcome Trust grant number H3A/18/001. KE is a student at the Sickle in Africa Data Coordinating Centre, funded by grant U24HL135600–02. EW-T is a student at the Hearing Impairment Genetic Studies in Africa, funded by grant U01-HG-009716.

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