WHO SICKLE Package of Interventions
for Sickle Cell Disease Management

Strategic Guidance Framework
Module 1

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for Sickle Cell Disease Management

Guidance framework for sickle-cell disease management in sub-Saharan Africa

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Acknowledgments

Abbreviations

AFRO	Regional office for Africa
ARISE	African Research and Innovative Initiative for Sickle Cell Education
CHEW	community health extension worker
CHW	community health worker
CoE	centre of excellence
CONSA	Consortium for Newborn Screening in Africa
CT	computed tomography
DNA	deoxyribonucleic acid
ECHO	echocardiography
ED	emergency department
EDL	essential drug list
GBD	Global Burden of Disease (study, 2021)
GI	gastrointestinal
Hb	haemoglobin
HIS	health information system
HIV	human immunodeficiency virus
IEF	isoelectric focusing
ICU	intensive care unit
IV	intravenous
IUD	intrauterine device
IVD	in vitro diagnostics
MoH	ministry of health
MRI	magnetic resonance imaging
NCD	noncommunicable disease
NGO	nongovernmental organization

PHC	primary health care
POCT	point-of-care test
RBC	red blood cell
RDT	rapid diagnostic test
SCA	sickle-cell anaemia
SCD	sickle-cell disease
SCT	sickle-cell trait
SPARCO	Sickle Pan African Research Consortium
SSA	sub-Saharan Africa
TCD	transcranial Doppler
UHC	universal health coverage
UN	United Nations
UNGA	United Nations General Assembly
WHO	World Health Organization
WHO PEN	WHO Package of Essential Noncommunicable disease interventions for primary health care in low-resource settings

Glossary

Advocacy	Demonstrating support for a cause or policy.
Alloantibody	Circulating antibody triggered by a previous antigenic challenge like transfusion of blood products.
Anglophone	English-speaking.
Antibody	A protein produced by plasma cells as a specific response to an immune challenge from a foreign protein (antigen), to which it binds.
Autosome	Any chromosome, which is not a sex chromosome.
Autosomal recessive inheritance	Genetic inheritance in which two copies of a mutated gene on autosomes are required to cause disease.
Autoantibody	An antibody produced by an organism in response to a constituent of its own tissues.
Cardiology	Relating to the diseases and abnormalities of the heart.
Chromatography	A technique for separating components of a mixture.
Circle of Willis	The arrangement of the arteries that supply different parts of the brain.
Communicable disease	An infectious disease that can be transmitted from one person to the other.
Compound heterozygote	An individual who has inherited two abnormal genes that are not identical, but cause disease.

Computed tomography scanning	A technique that uses X-rays and a computer to produce 3D images of soft tissue and bones.
Consortium	A group of two or more individuals, companies, institutions, or governments that work together to achieve a common objective.
Dactylitis	A painful inflammation of the small bones and joints of the hands and feet.
Delphi method	Used to establish consensus on one or more topics by a group of experts.
Diagnostics	Instruments or tests used in the process of establishing the diagnosis of a particular disease or illness.
Digital device	An electronic device that can create, generate, send, share, store, display or process information.
Pre-eclampsia	Hypertension in mid or late pregnancy, accompanied by protein in urine. It may progress to seizures and coma (eclampsia).
eHealth	The use of information and communication technology to support health and health care.
Electrophoresis	A technique for separating blood proteins based on their electric charge.
Endemicity	The continuous presence of a particular disease in a region or community.
Francophone	French-speaking.
Gastrointestinal	Related to the stomach and intestines.
Gene	Unit of heredity, made up of a sequence of nucleotides in DNA.
Gene therapy	Treatment of a genetic disease based on manipulation of the gene by replacing the faulty gene with a normal one or by inactivating the disease-causing gene.

Genetic counselling	Process of establishing the diagnosis of a genetic disease and communicating its implications, inheritance, clinical course, treatment, and impact on future pregnancies, family members, etc., to the patient and his or her family.
Genotype	The genetic make-up of a person especially as it relates to a particular trait.
Haplotype	A group of genetic variants or polymorphisms that are inherited together from a single parent.
Haemoglobin	The protein in red blood cells that gives them their red colour and is responsible for carrying oxygen to the tissues of the body.
Haemolysis	The breakdown of red blood cells.
Heterozygote	An individual who has inherited only one copy of a gene allele.
Homozygote	An individual who has inherited two identical alleles of a gene.
Immunization	Protection against a disease afforded by the introduction of a product of the causative organism in a person to produce antibodies to fight the disease.
Inflammation	A local response to cellular injury that is marked by capillary dilatation, leukocytic infiltration, redness, heat, pain, swelling, and often loss of function and that serves as a mechanism initiating the elimination of noxious agents and of damaged tissue. It may also be generalized as a result of other diseases including infections, connective tissue and immune-mediated diseases.
Leukocyte	Another name for a white blood cell.
Magnetic resonance imaging	A technique for producing images of the body based on a measurement of the reaction of the atomic nuclei of body tissues to high frequency waves in a magnetic field.

mHealth	Delivery of health care using mobile devises such as mobile phones, tablets, smart watches, etc.
Morbidity	Refers to any condition of ill health or how a disease causes ill-health.
Mortality	Death from any cause.
Nephrology	Study of diseases of the kidney.
Neurology	Study of diseases of the nervous system.
Noncommunicable disease	Diseases that are not contagious or spread from person to person.
Orthopaedics	Study of surgical problems of bones or joints.
Phenotype	An individual's observable characteristics resulting from his or her genotype and its interaction with the environment.
Polymerization	Any process where relatively small molecules, called monomers, chemically combine to form very larger chain-like or 3D networks (polymers).
Polymorphism	Occurs when there are two or more forms of variant DNA sequence on a gene locus in different individuals or populations.
Primary health care	Health care delivered in the community to bring care closer to the people in a comprehensive way.
Prophylaxis	A treatment or action taken to prevent a particular disease.
Pulmonology	Branch of medicine that deals with diseases of the respiratory tract.
Psychiatry	Branch of medicine that deals with the study and treatment of mental illness.
Radiology	The use of X-rays and other high-energy radiation for the diagnosis of disease.
Secondary health care	This is provided when a patient is referred from a primary health care centre to a specialist.
Spectrometry	Method of studying and measuring a specific spectrum; widely used for the spectroscopic analysis of sample materials.

Stem cell transplantation	The use of primitive or progenitor cells, usually from the bone marrow, for the treatment of illness either in the same patient (autologous) or another recipient (allogeneic).
Telemedicine	It is the use of telecommunications technology and information technologies to provide remote clinical services to patients or "healing from a distance".
Teratogenicity	The capability of producing congenital abnormalities or malformations in a developing embryo or fetus.
Tertiary health care	Specialized care offering diagnosis and treatment to patients referred from secondary care facilities. This may be in the setting of a teaching, government or private hospital.
Transcranial Doppler	A form of ultrasound technique used to study blood flow to and within the brain.

Executive summary

Problem and objectives

In the most recent Global Burden of Disease report, it was estimated that 75% of the approximately 500 000 babies born with sickle-cell disease (SCD) in 2021 were in sub-Saharan Africa (SSA). Indeed, Nigeria and the Democratic Republic of the Congo have the highest frequencies, with about 2% of newborns affected. SCD is a significant source of morbidity and mortality, with 50–90% of patients in SSA dying before their fifth birthday. On the other hand, significant strides have been made in the prevention and care of SCD patients in developed countries because of national policies and effective programmes, including newborn screening, prophylactic penicillin and expanded immunizations. In addition, transcranial Doppler imaging to identify patients at risk of stroke, readily available and safe blood transfusion services, and access to effective disease-modifying drugs (hydroxyurea and newer agents) have all contributed to more favourable outcomes for their patients. Curative modalities like stem cell transplantation and gene therapy are also becoming more accessible. Unfortunately, most of these treatments are not available in the low-income countries of SSA, where we have overwhelming numbers of patients. Although there have been recent reductions in mortality due to SCD in SSA, especially in areas with access to health care, the majority of people living with SCD live in rural, underserved areas with no access to screening or modern health care.

There are currently few organized SCD clinics in SSA offering comprehensive care. Where they exist, they are mostly in urban centres. This model denies care to the vast majority of patients, who remain undiagnosed and die from direct complications of the disease or from concomitant illnesses. It is no wonder

that the latest GBD report ranks SCD in 12th position globally as a leading cause of death in under-fives, while in SSA, it is ranked 11th, ahead of measles and malnutrition. Therefore, there is an urgent need to review management strategies for SCD in SSA. WHO AFRO, therefore, determined that clear-cut guidelines, based on the existing resources and public health programmes in affected Member States, were required to achieve maximum benefit for the effective management of SCD.

WHO AFRO convened a panel of experts in October 2022 to develop a guidance framework for SCD treatment and to define qualifying criteria for SCD treatment centres and centres of excellence in SSA. Moreover, the panel was charged with providing standardized guidance for the establishment and implementation of an integrated framework for the management of SCD, which will catalyse regional and subregional expertise in the management of the disease. It would also promote applied research through the use of innovative technology for the prevention of the disease and the care of affected patients.

Process: The panel consisted of eight African experts from various institutions, both within and outside of Africa and included five anglophones and three francophones. The first meeting defined the scope of the problem and the critical issues to address within the context of SSA. At the second meeting, each expert gave a presentation on an assigned topic of relevance to SCD in the Region. These included newborn screening, advocacy, research, transitioning from paediatric to adult care and caring for children under the age of five years, and care of pregnant women with SCD. The definitions of treatment centres and centres of excellence were then proposed, as well as how patient management in SSA should be structured to leverage existing facilities and programmes. The suggestions for the guidance framework at the third meeting were exhaustively discussed until a consensus was reached. A face-to-face meeting was held at the WHO AFRO headquarters in Brazzaville between 12 and 14 April 2023 at which all the experts and WHO public health specialists were in attendance. The various aspects of the proposed framework were reviewed, with suggestions for improvement.

Proposed management framework

PHC strategy

Primary health care is the cornerstone for providing care to persons living with noncommunicable diseases (NCDs), including those with SCD, in remote and rural communities. Thus, WHO introduced the Package of Essential NCD

interventions (WHO PEN) in 2017 and PEN-Plus in 2019. WHO PEN supports the integrated detection, diagnosis, treatment, and care of NCDs in primary health care (PHC) facilities using evidence-based algorithms and protocols for hypertension, type 2 diabetes, chronic respiratory diseases, and the referral of patients with suspected breast and cervical cancer. PEN-Plus, on the other hand, complements WHO PEN at the PHC level and strengthens the management and care of chronic and severe NCDs at district hospitals by ensuring that the capacity, infrastructure, and logistics for care are available at this level of service delivery. It is therefore proposed that SCD management in SSA be fully integrated into WHO PEN and PEN-Plus. Indeed, an SCD management algorithm for use in PHC has been produced. However, since SCD is a genetic, inherited, life-long disease, it is different from other NCDs, which tend to be prevalent in adults. Its management will therefore be across PHC and extend to secondary and tertiary health care centres.

Treatment centre

The care offered to patients will, therefore, be structured in a pyramidal fashion at three levels: the first level (Level 1) is the primary/community health care (PHC) centre; the second level (Level 2) will be at the first referral or district hospital; and the third level (Level 3) will be secondary (specialist) and tertiary health care facilities. Doctors, nurses, community health workers, and other workers at the PHC level will be trained in SCD to follow the WHO PEN SCD protocol. This provides an algorithm that allows them to identify an affected patient, screen, diagnose and counsel them, and dispense routine medications. They should be able to identify the higher referral facilities for more specialized treatment. The care given to patients with SCD will be integrated into other existing PHC services such as immunization, child care, nutrition, and antenatal programmes. The treatment centre should have a screening programme, using point-of-care testing (POCT) kits, and there should be a laboratory for basic tests. Of course, the facilities available may differ from country to country.

The second level of care will be at the first referral centre, which is the equivalent of a district hospital, where PEN-Plus should be well established. It should be able to provide care for SCD patients with acute or chronic problems that cannot be managed at Level 1. Doctors and nurses with competence in SCD must be available. Each of these centres will be responsible for the training and supervision of multiple PHC centres in their orbit in a satellite, hub-and-spoke fashion.

The third level of care is provided by secondary and tertiary health care centres that are managed by specialists in several disciplines of medicine and surgery and have sophisticated laboratories and imaging facilities. There must be demonstrable expertise in SCD and they will receive referrals from the first- and second-level tiers of care. The centre will provide continuing training to produce cadres of staff with competence in SCD at all levels of care.

All levels of care will be encouraged to have facilities for registration, preferably digital, of diagnosed patients, documenting key clinical and laboratory parameters. These registries will be linked to a nationwide database to generate data on key outcomes that will facilitate an understanding of the disease and promote research into its different aspects. Where digital devices are not available, meticulous paper records must be kept.

Each SCD care pyramid in a geopolitical area or district will constitute an SCD management unit. The units in this geographical area will be linked electronically and will pool resources. Representatives of the local government, community leaders, patients, women leaders and other stakeholders will constitute a governance body that will arrange oversight, training, awareness and advocacy, in general. They will also devise an evaluation procedure for the services in each SCD unit under their jurisdiction. The definition of a geopolitical area may be different in each country and may have different designations.

Centre of excellence

This was defined as any tertiary centre with a high level of expertise in caring for SCD patients with complex medical and surgical problems. It must have cutting-edge research facilities and linkage programmes with other centres of excellence, within and/or outside Africa. Ideally, it should have the capacity to provide all available treatments, including stem cell transplantation and gene therapy. It should also have a well-structured SCD training programme for doctors, nurses and other health care professionals. It is hoped that each subregion will eventually have at least one of such centres, which should collaborate with each other in a consortium. Cross-referral of patients will be encouraged, as necessary, to take advantage of the relative strengths of different centres. Eventually, the hope is that SCD patients will not have to be referred to centres outside of Africa for disease-modifying or curative therapies.

Integrative approach

This framework calls for the integration of SCD treatment into existing health care programmes with a view to achieving

universal health coverage in an equitable and cost-effective manner. The key programmes are WHO PEN and PEN-Plus, but there are other relevant programmes including immunization, HIV, sexual and reproductive health, maternal, newborn and child health, and blood transfusion services. In this way, scarce resources can be leveraged in a cost-effective, equitable manner. Moreover, affected patients and their families do not have to keep multiple appointments to attend the clinics.

Innovative technology

It is imperative that different available technology platforms be adopted to facilitate the operationalization of this treatment framework, especially in the centres based in rural, underserved areas, to ensure effective linkage to supervisory/referral centres. In this regard, point-of-care testing (POCT) kits and other rapid diagnostic tests (RDT) must be available. Digital devices are necessary to maintain registries that will be linked with the national databases. Telemedicine will facilitate remote consultation and supervision, while mobile technology will enhance education, surveillance, monitoring and counselling. The hope is that each PHC centre will be equipped with a renewable energy source, such as solar panels, to ensure a steady power supply. This may, indeed, be aspirational, but the absence of such technology should not delay the operationalization of the framework. Currently available facilities should be optimally utilized.

Capacity building and training

There is a dire need for expedited training of different cadres of experts in SCD-related fields to fill existing gaps, especially in data management, health care and research. All tertiary institutions and centres of excellence should have regular training programmes for medical professionals (doctors and specialists), nurses, technologists, and community health workers, as appropriate. The training should also emphasize empathy, gender sensitivity and diversity consciousness. Vulnerable groups like under-fives, adolescents and pregnant women must be recognized and cared for. SCD competence should be incorporated into the curricula of high schools, nursing, and medical schools and community health worker training colleges.

National policy

Despite the calls by the UN and WHO for affected countries to have national SCD policies, the panel noted that no country has fully complied, although it is praiseworthy that several have provided for SCD within their comprehensive NCD policies. These policies should make

provision for newborn screening, health insurance, essential drugs, education and awareness, research and funding, among others. This will go a long way toward improving the overall management and outcomes of the affected population.

Procurement of hydroxyurea and other essential devices

Hydroxyurea has made a big difference to the management of SCD both in children and adults, so much so that the NIH guidelines call for it to be offered to children with SCD from the age of 9 months, irrespective of their clinical phenotype. Unfortunately, it is still grossly underutilized in SSA because of unavailability and reluctance on the part of patients, and even some physicians. It is hoped that the barriers can be broken down and that governments in SSA would include it in their essential drugs list and negotiate, as a block, with pharmaceutical companies for discounted pricing. Local manufacturing of the drug should also be actively encouraged. The same plea goes for innovative devices such as POCT kits for screening.

Guiding principles

The operationalization of this framework will be guided by the same principles expounded for WHO PEN-Plus:
Government leadership
Universal health coverage
Equity
Evidence-based approaches and cost-effective interventions
Resource efficiency
Patient- and family-centred approaches
Collaboration between the public and private sectors
Multisectoral and multidisciplinary approaches.

Targeted audiences of this Guidance framework

This framework should be of interest to the following:

1. Policymakers at the national, State, and local government levels, especially in the ministries of health, finance, education, budget and planning.
2. State agencies in charge of public health programmes, including primary health care and the training of community health workers.
3. Local and international funding agencies, including multinational pharmaceutical companies.
4. Health care providers of all types and levels.
5. Patient support groups.
6. Religious and community leaders.
7. Genetic and premarital counsellors.
8. Anyone who wants to understand the complexity of SCD in SSA and how to deploy existing facilities and programmes for its control and management.

UNDER ARMOUR

1. Introduction

1.1 . Genetics:

Normal adult haemoglobin (HbA) is composed of two pairs of globin chains ($\alpha_2\beta_2$), with an embedded hem moiety. α-Globin chain synthesis is under the control of genes located on chromosome 16, while the β-globin gene cluster is located on chromosome 11. Inherited Hb abnormalities can be quantitative, in which there is an absence or decreased production of one of the chains, a situation described as thalassemia. On the other hand, the abnormality may be structural or qualitative, in which case there is an alteration in the normal sequence of amino acids in the polypeptide globin chain. HbS is the most common β-globin chain variant, caused by a single nucleotide (A>T) substitution in the 6th codon of the HBB gene[1]. This β^S variant is inherited in an autosomal recessive fashion. Sickle-cell anaemia (SCA) occurs when an individual has inherited two copies of the β^S gene, that is, a homozygote (HbSS). A person with only one copy of the mutated gene is a heterozygote and has sickle-cell trait (SCT).

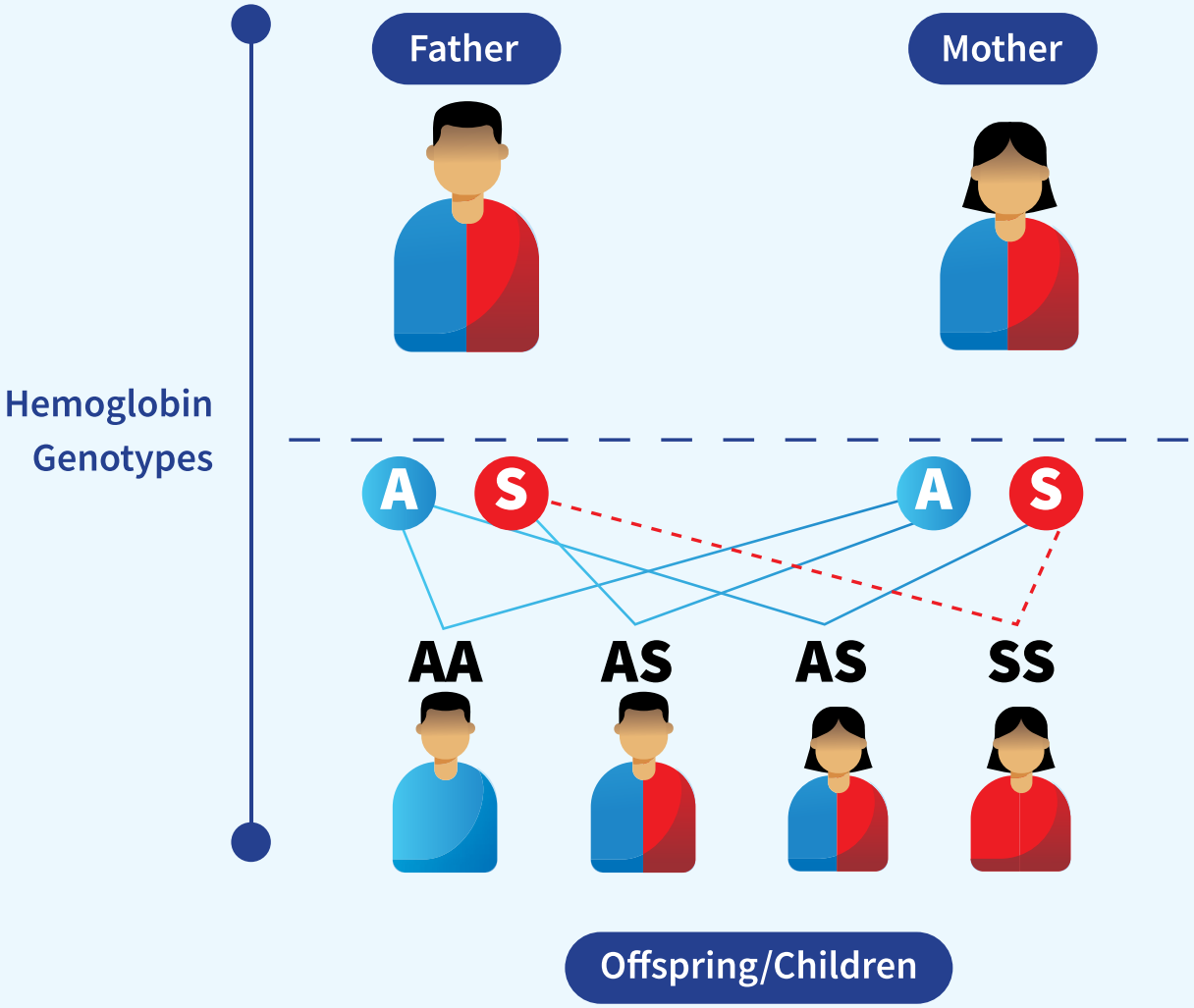

Fig. 1. Inheritance pattern of sickle-cell anaemia

When both parents carry the sickle-cell trait (AS), they have a 25% chance of having a baby without sickle-cell disease (AA) or with the disease (SS) and a 50% chance of having babies with the AS trait with every pregnancy.

There are other abnormal β-chain Hb variants that can be co-inherited with HbS and cause disease. These compound heterozygotes include HbSC, Sβ-thal, HbSO, etc. Collectively, the whole spectrum, including SCA, and the compound heterozygotes, is known as sickle-cell disease[2].

1.2 . Epidemiology:

Individuals who carry the β^S gene have relative protection against the effects of malaria[3-5] because of a lower degree of parasitaemia compared to individuals with the HbAA genotype. SCD patients, however, suffer considerably more morbidity and mortality from clinical malaria than individuals with SCT or normal Hb genotype[6,7]. The sickle gene is, therefore, most common in areas of the world with a history of malaria endemicity and sub-Saharan Africa (SSA) thus bears the brunt of the disease, with the prevalence of the trait varying from 2% to over 30% in different

countries. Of the estimated 300 000 affected children born annually worldwide, about 60% are in Africa[8, 9]. SCD is now seen in different parts of the world because of the migration of people of African ancestry to the Americas, Europe and Australia[10]F.

The β^S mutation is believed to have arisen contemporaneously in multiple centres early in the neolithic period in Africa and the Indus Valley, which correspond to the major haplotypes that have been described, including the Senegal (SEN), Benin (BEN), Bantu (BAN), Arab/India (AI), and Cameroon (CAM) haplotypes[11, 12]. SEN is most prevalent around Senegal, while BEN is seen in other parts of West Africa, North Africa, Southern Europe, and the western part of Saudi Arabia. BAN is the most common haplotype in Central and East Africa, while CAM is limited to a small area west of Nigeria, around Cameroon. However, more recent evidence suggests a unicentric origin in Africa, with eventual recombination events being responsible for the emergence of the different haplotypes[13]. These haplotypes have clinical significance in that patients with the SEN and A/I haplotypes have the highest HbF levels and the mildest phenotype; patients with Central African Republic (CAR) haplotypes have the most severe, while BEN and CAM are associated with intermediate severity[14, 15].

1.3 . Pathophysiology:

The β^S mutation leads to the substitution of glutamic acid by valine in the 6th amino acid position in the β-globin polypeptide. This causes relative insolubility of the Hb molecule especially when deoxygenated. It aggregates in rod-like polymers, which distort the shape of the red blood cells. The latter become rigid and less deformable and prone to recurrent occlusion of small blood vessels, causing the characteristic episodic pain of the disease[16]. Secondly, there is chronic haemolysis and the life span of the RBC is shortened from the usual 120 to about 30 days, causing varying degrees of anaemia.

The lysis of the RBCs releases arginase, which degrades arginine, the precursor of nitric oxide (NO), thus reducing its production. The immediate consequence of this NO scavenging is dystonia of the capillary smooth muscle, and eventual intima hyperplasia, thus contributing to vaso-occlusion and infarction in many tissues. Moreover, the free heme that is released is toxic and activates blood cellular elements including reticulocytes, neutrophils, monocytes and platelets and endothelial cells. There is also up-regulation of various cytokines and adhesion molecules. Thus, there is a myriad of pro-oxidant, pro-coagulant inflammatory pathways that are triggered, which culminate in extensive vasculopathy and worsening of vaso-occlusion. It is not surprising, therefore, that the pathological spectrum of SCD affects most organs in the body[17, 18, 19].

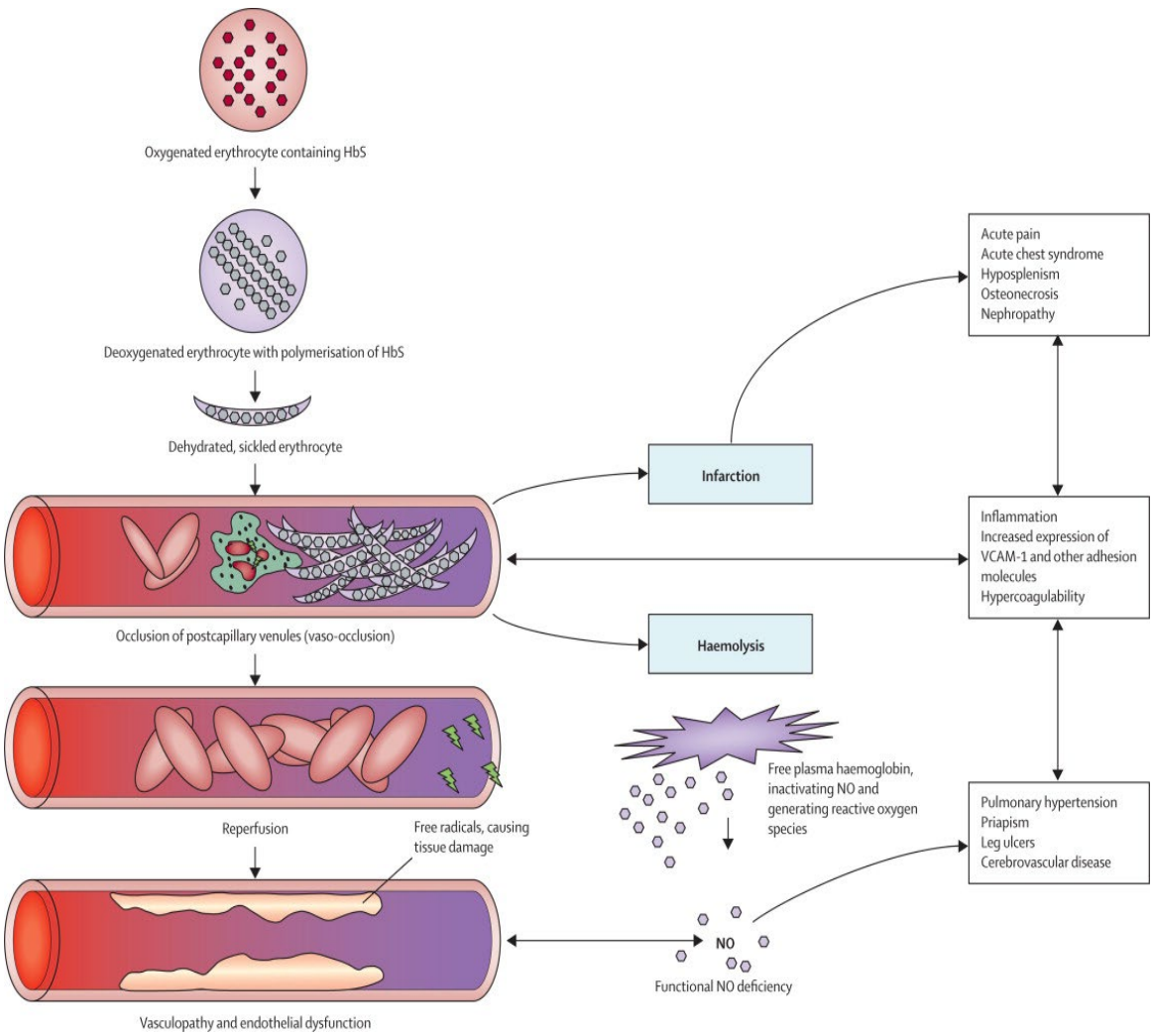

Fig. 2. Pathophysiology of sickle-cell disease

1.4 . Clinical features:

SCD is a life-long disease, whose symptoms and signs are usually evident after the sixth month of life, as fetal haemoglobin is replaced by adult haemoglobin. The earliest clinical features include pallor, jaundice, poor growth and dactylitis, which is caused by occlusion of the small capillaries in the bones of the hands and feet[20]. Thereafter, recurrent pain episodes predominate. The pain can occur anywhere in the body, but it commonly affects the limbs, abdomen and back. Splenic dysfunction occurs early in the life of the SCD patient and by the age of 2 years, most patients have functional hyposplenia in which, though the spleen may be palpable, its function is compromised. By the age of 10 years, most patients would have had auto-splenectomy because of recurrent infarction and fibrosis of the spleen. This, along with other defects in the immune system, predisposes patients with SCD, especially in childhood, to bacterial infections with encapsulated

organisms, most notably, S. pneumoniae and N. meningitides [21, 22]. Younger patients could also present with episodes of acute splenic sequestration, which though not common, can have catastrophic consequences. Acute chest syndrome, stroke, bone necrosis, and chronic leg ulcers are common in childhood. Priapism affects about 50% of males and can lead to sexual dysfunctions. In adolescent and adult patients, priapism, chronic organ damage, pulmonary hypertension and sudden death are causes of morbidity and mortality[14, 20, 23].

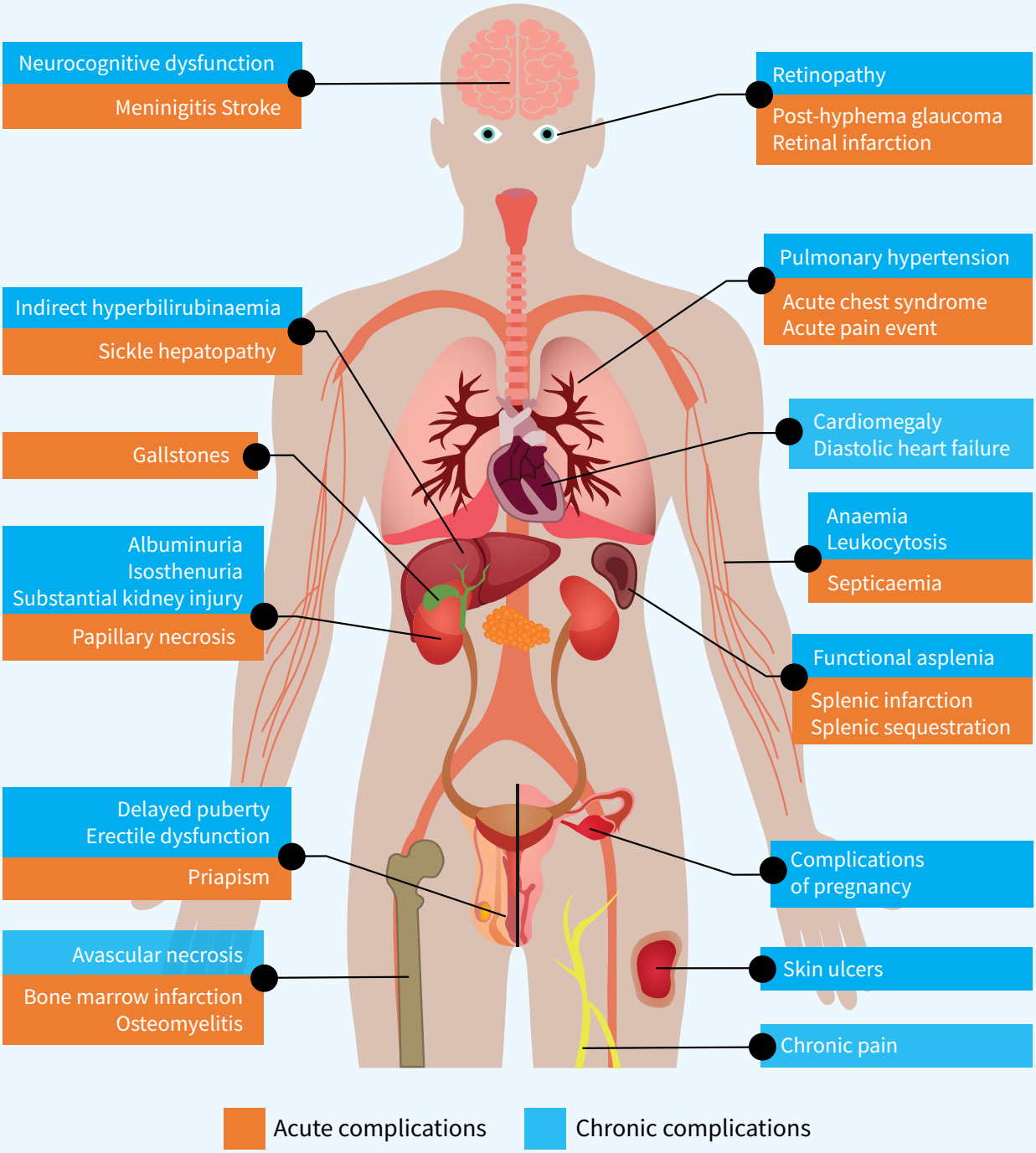

Fig. 3. Clinical complications of sickle-cell disease

1.5 . Phenotype modifiers:

Although SCD is a monogenic disease, the phenotype is highly heterogeneous, and several genetic factors modify the clinical presentation of the disease. These include:

1.5.1 . Hb genotype:

Although the homozygote, HbSS is the most common genotype encountered and the most severe phenotype, other compound heterozygotes present with significant disease. The two most common and important of these are Sβthal and HbSC. Sβ-thal is sub-classified into $S\beta^+$ or $S\beta^0$, depending on the level of β-chains produced. $S\beta^0$ has no β chains, hence no HbA and only has HbS; therefore, they are usually indistinguishable from HbSS in phenotype. Patients with $S\beta^+$thal produce reduced levels of β chains and their phenotype depends on their level of HbA. The phenotype may be as mild as in SCT but may be almost as severe as in HbSS. Fortunately, the β-thal mutation is uncommon in SSA, therefore the frequency of Sβthal is usually below 5%[24]. On the other hand, HbC is common in West Africa and HbSC is the second most common Hb genotype seen in the Region[25]. In Nigeria, 10% of SCD patients carry this genotype[24]. Phenotypically, HbSC is milder than in HbSS, but they may be more prone to end-arterial occlusion, thus retinopathy and avascular necrosis of the femoral head may be more common[26].

1.5.2 . HbF Level.

Newborns do not show symptoms of SCD because their Hb is mostly fetal. The incorporation of the g chain of HbF into the heterotetramer, $Hb\alpha_2\beta^S g$, makes the molecule more soluble and reduces polymerization. Thus, patients who have a persistent elevation of their HbF tend to be less anaemic and are spared some of the complications of the disease. It has been estimated that an HbF level above 8% is beneficial, while above20% will have significantly milder disease and above 30% is asymptomatic[27-29]. Therefore, raising HbF is a popular disease-modifying strategy in SCD. HbF expression is under the control of polymorphisms at different sites, but notably in quantitative trait loci (QTL) in the HBB on chromosome 11, the oncogene BCL11A on chromosome 2 and the HBS1L-MYB intergenic region on chromosome 6[30-32]. There is also an X-linked factor on the short arm of the X chromosome that promotes HbF expression. Thus, females tend to have a higher HbF level than males.

1.5.3 . β^S haplotypes:

These haplotypes have phenotypic implications, some of which are related to their sustained HbF levels[33]. Senegal and Arab/India haplotypes are associated with high HbF levels. These are the only two haplotypes that carry the Xmn-1 polymorphism in the HBG promoter that characterizes persistent HbF expression and are associated with a milder disease.

Indeed, the Bantu haplotype is associated with the most severe phenotype, while Benin and Cameroon are intermediate.

1.5.4 . α-Thalassemia trait:

The lower mean corpuscular haemoglobin concentration that characterizes α-thal trait leads to reduced intracellular HbS when it is co-inherited with SCD. Therefore, such patients have a decreased rate of polymerization and thus have less haemolysis and a milder phenotype. They are less likely to have splenic dysfunction, stroke or leg ulcers. However, because they have higher haematocrits, they may have higher blood viscosity and therefore be prone to end-artery occlusion complications like retinopathy and avascular necrosis of the head of the femur. The α-thal frequency is very high in SSA and varies from a low of about 4.0 to a high of over 35% in parts of Nigeria.

1.5.5 . Gender:

Since SCD is inherited in an autosomal recessive fashion, there is no gender imbalance in its incidence. However, there are some specific phenotype issues that are peculiar to female patients. As mentioned earlier, there is an X-linked polymorphism that drives HbF expression and several studies have shown that female SCD patients have a higher mean HbF than males[34-36]. El Hoss et al[35] demonstrated a genetic association of F-cell abundance with the FRMPD4 locus of the chromosome Xp22.2. Clinical studies have also demonstrated that pain episodes, cardiac complications, rates of blood transfusion and mortality are all less in female patients and this has been attributed to the higher HbF levels, although some have also implicated the influence of female hormones among adult patients[36-38]. However, a study from Jamaica showed that among adolescents, while girls performed better in knowledge scores, they did worse on QoL scores and were like the boys in severity scores[39]. On the other hand, priapism is a severe complication in males that may be associated with erectile dysfunction with attendant psychological and reproductive consequences.

1.6 . Reproductive issues:

SCD has impacts on both male and female reproductive functions as part of the disease complications. There is usually a delay in menarche in females; the pattern of menstruation is usually normal although the cycle may be shorter and the flow prolonged and increased, while dysmenorrhoea is more common and severe[40-42]. There is no consensus whether fertility is compromised in women with SCD[43] and rates of unplanned pregnancy have been reportedly high. Therefore, female patients of reproductive age should be adequately counselled

about reproductive choices. Combined hormonal contraceptives, especially those containing oestrogen, may not be ideal because of the risk of increased period pain and thrombotic events[44, 45]. The use of progesterone-only contraceptives has been associated with less pain and thrombotic events[46, 47]. The current recommendation is that the benefit of combined injectable contraceptives, low-dose, combined hormonal contraceptives, and IUDs outweigh the risks associated with the increased morbidity and mortality associated with pregnancy[48].

1.6.1 . Pregnancy:

Pregnancy and delivery present high risks of severe morbidity and mortality for the mother and baby[49]. The pregnant woman with SCD has a background of marginal organ function due to the disease and on top of that, the increased cardiovascular stress, exacerbated anaemia, compromised pulmonary function because of pre-existent vasculopathy, hormonal changes and the increasing uterine size further complicate the outlook. Moreover, the developing placenta may be impacted by intravascular sickling, endothelial damage, vascular occlusion, and inflammation leading to placental dysfunction affecting fetal well-being[50]. Apart from mortality, the mother is therefore predisposed to hypertension syndromes (pre-eclampsia and eclampsia), venous thromboembolism, hepatic dysfunction, increased pain episodes, and worsening anaemia, which may lead to high-output cardiac failure. The fetal complications include fetal and neonatal deaths, prematurity, intrauterine growth restrictions and small for gestational age[49]. In a study from Lagos, Nigeria, Ogedengbe and Akinyanju[51] reported perinatal mortality rates of 233 and 111 per 1000 and maternal mortality rates of 129 and 111 per 1000 deliveries in HbSS and HbSC patients respectively. In a study of women with HbSC in pregnancy in Ibadan, Nigeria, anaemia was reported at 51.2%, bacterial infection at 22.0%, bone pain crisis at 7.3% and pre-eclampsia at 2.4%[52]. Intrapartum complications included anaemia (29.2%), bone pain crisis (12.2%) and pseudotoxaemia (4.9%).

All pregnancies in women with SCD should be supervised and managed by a multidisciplinary team, which must include an SCD expert and an obstetrician familiar with high-risk pregnancies[49, 53]. Other specialists to consider are neonatologists, anaesthetists, blood transfusion specialists, pain management experts and others, including cardiologists, haematologists, internists, as needed. The patients must be monitored closely with individualized plans and watched for SCD complications, pre-eclampsia and fetal growth.

1.6.2 . Male hypogonadism:

Up to 24% of men with SCD may have hypogonadism, characterized by low testosterone, erectile dysfunction, infertility, and poor libido. While some of the sexual dysfunction may be secondary to priapism, there is also a suggestion that hypothalamic-pituitary dysfunction may occur[54, 55]. Hydroxyurea, which is an effective drug that reduces the frequency of pain episodes, acute chest syndrome and reduces inflammation in SCD patients[56-58], may be associated with transient gonadal dysfunction in male patients. However, recurrent vaso-occlusion by itself can also cause gonadal dysfunction. Indeed, Sahoo et al[59], reported from a prospective study, that among male patients not receiving hydroxyurea, 18% developed oligospermia and 4% had azoospermia, while among patients on hydroxyurea, the figures were 20% and 10% respectively. However, the seminal fluid abnormalities reverted to normal within 3 months of stopping the drug in 73% of affected patients. These results were similar to what was reported in male transgenic mice[60].

1.7 . Mortality:

The SCD survival rate has increased steadily in high-income countries since the introduction of newborn screening, penicillin prophylaxis, hydroxyurea, transcranial Doppler and primary prevention of stroke, and access to curative therapies like stem cell transplantation. Over 90% of US newborns with the disease now survive to adulthood and the lifespan is between 40 and 50 years[61]. On the contrary, patients in low-resource countries of SSA are diagnosed late or not at all and must contend with other adversities like infections, malaria, inaccessibility to care and poor nutrition. Hence it is no surprise that SCD mortality is highest in this Region. Nonetheless, SCD is ranked 12th among the leading 20 causes of mortality[62] in under-fives globally and 11th in SSA.

There are no large prospective community-based studies of SCD mortality in SSA. It had been estimated that 50–90% of patients died before their fifth birthday[63], but this appears to be improving, especially in urban areas. Nnodu et al[64] found that between 2003 and 2013, mortality for under-five SCD patients in Nigeria was 490 per 100 000 live births, which was still 4.0 times higher than for children with HbAA. They also reported that about 4.2% of national under-five mortality was attributable to SCD. Ranque et al[65] reported the following rates: 15.3% for children younger than 1 year; 36.4% for those younger than 5 years; and 43.3% for those younger than10 years of child mortality attributable to SCD in five francophone SSA countries (Burkina

Faso, Democratic Republic of the Congo, Senegal, Côte d'Ivoire, and Mali). None of these studies reported any difference in disease prevalence and mortality patterns among males and females.

1.8 . Management:

Being a genetic, lifelong disease, the management of SCD requires age-related structuring as appropriate. The ASH/NIH guidelines call for early diagnosis, preferably through newborn screening and enrolment of affected patients in a comprehensive care clinic[66-68]. The latter serves as a "medical home" where the management is a partnership between the patient, the haematologist and the primary care physician, along with other staff, the number and qualification of whom depend on the number of patients seen and personnel availability. These should include nurses, pharmacists, social workers, and psychologists. A multidisciplinary approach should be adopted in which the patient can be seen by other specialists, as necessary, including pulmonologists, cardiologists, neurologists, nephrologists, ophthalmologists, gynaecologists/obstetricians, urologists, orthopaedic surgeons, etc.

At the time of diagnosis, the family is counselled about the genetic basis of the disease, its clinical features, complications, and available treatments. Early institution of prophylactic antibiotics [69-71], and expanded immunization to include Strep pneumococcus[72, 73], Hemophilus influenzae b, and meningococcal vaccines are recommended. Routine drugs, including folic acid, vitamin D and malaria chemoprophylaxis (in endemic areas) are given.

1.8.1 . Health maintenance and surveillance.

SCD patients are seen in the clinic every two to three months at which time, age-appropriate counselling is reinforced and baseline laboratory studies are obtained. Complete blood count, reticulocytes, serum bilirubin and lactate dehydrogenase (LDH) are useful markers of haemolysis. Routine drugs, folic acid, and penicillin up to the age of 5 years are recommended. Annual TCD screening is started at the age of 2 years, up to 16 years, to identify patients at risk of stroke. Patients at risk are started on a chronic blood transfusion programme or hydroxyurea therapy where transfusion is not available. Screening for renal function with urinalysis and retinopathy is started at 10 years of age. Patients are checked for other chronic complications as necessary, but there are no strict recommendations about when or if it is necessary to screen asymptomatic patients for pulmonary hypertension and chronic lung disease.

There are some common acute presentations of SCD that warrant prompt, effective management to relieve patient suffering and prevent tissue and organ damage. The most common is recurrent pain and the management goal is to relieve pain as soon as possible, but within 30–60 minutes of presentation in the emergency room. Mild to moderate cases can be managed at home. The pharmaceutical options include non-steroidal anti-inflammatory drugs and opioids. There are standard protocols for the dosage, mode of administration and other considerations.

Patients with chronic pain require individualized attention to rule out a secondary cause like avascular bone necrosis, which may need to be addressed, or neuropathic pain, which may respond to gabapentin. Other useful nonpharmacological interventions include massage, acupuncture, and cognitive behaviour therapy.

A diagnosis of acute chest syndrome should be considered in the patient presenting with chest pain, shortness of breath and new infiltrates on chest radiography. They may have cough, fever, and hypoxaemia. The management consists of incentive spirometry, appropriate antimicrobials, supplemental oxygen, and blood transfusion (top-up or exchange as appropriate). Severe cases may need ventilatory support.

Regional, national, and institutional guidelines are encouraged for the management of different presentations and complications of SCD, which take local preferences, resources, and other specific local/national and regional issues into consideration.

1.8.2 . Disease-modifying drugs:

There are several approved disease-modifying drugs that are indicated for the management of SCD, while many others are in clinical trials. The first approved and most used of these is hydroxyurea, which is an antimetabolite[57, 74-77] that increases the synthesis of fetal haemoglobin, reduces the expression of adhesion molecules on blood cells leading to decreased cellular adhesions and inflammation, generates nitric oxide and increases the hydration of the RBCs[78-81]. It suppresses neutrophils and platelet production, which in turn helps in reducing inflammation and cell adhesion. It significantly decreases the frequency of pain and acute chest syndrome episodes and lessens the severity of anaemia. It also decreases the velocity of blood through the cerebral arteries in the Circle of Willis. It is therefore useful in the primary prevention of stroke, especially in low-resource countries, where access to safe blood transfusions may be limited[82-84]. It is indicated in patients with a severe phenotype, but indeed, the current recommendation is that it should be offered to all SCD patients from the age of 9 months to reduce eventual end-organ damage, even when they are asymptomatic.

Other newer agents that show efficacy and are approved for treatment of SCD include L-glutamine, which is an amino acid supplement with strong anti-inflammatory properties. It reduces the frequency of pain and acute chest syndrome episodes in SCD patients[85-88].

Crizanlizumab is a humanized monoclonal antibody that binds to P-selectin and blocks its interaction with the P-selectin glycoprotein ligand[86, 89, 90]. It reduces the annual rate of pain episodes by 30–50%. Although approved by the United States Food and Drug Administration (FDA), a global clinical trial was recently completed, and results are pending (NCT03814746).

Voxelotor is an HbS polymerization inhibitor, which reversibly binds to haemoglobin to stabilize the oxygenated haemoglobin state. It reduces red cell sickling and blood viscosity while extending RBC half-life, reducing anaemia and haemolysis in vitro[86, 91-93].

1.8.3 . Curative therapies:

The available curative therapies are stem cell transplantation and gene therapy. The former is available for patients with HLA-matched siblings who do not have SCD (but can be a carrier of SCD) as stem cell donors. However, haploidentical transplants (with a best-matched parent or a sibling) are being increasingly performed with good results using the non-myeloablative conditioning regimens that are now available[94-97]. Gene therapy is also showing considerable promise using gene editing with the CRISPR-Cas9 to knock out BCL11A gene locus in HSCs, which are then re-injected into the patient or gene addition, which entails the introduction of an anti-sickling Hb through a lentivirus vector[98-101]. Both these therapies are resource-intensive and associated with acute and long-term toxicities.

1.8.4 . Current SCD management practice in SSA:

Most SCD patients in SSA reside in rural areas with poor access to medical care. Most of these countries still do not have national SCD policies or screening programmes. Therefore, patients are usually seen in tertiary and secondary health care centres after presenting with acute or chronic complications of the disease. The implication is that most patients are left undiagnosed and untreated, hence the overwhelming mortality associated with the disease in SSA.

In a study carried out across Nigeria in 2011, the Nigerian SCD Network identified 18 clinics based in 11 leading centres in the country[102]. They were all in major

urban centres and the number of patients being followed in each centre varied from 15 to 11 000, with an average of 1317. While all the centres dispensed folic acid and antimalarials, only eight provided penicillin prophylaxis and eight prescribed hydroxyurea to patients who could afford it. Pneumococcal vaccines were not routinely administered in any centre, although some of the paediatric clinics advised patients who could afford them to do so privately. While all had facilities for complete blood count and Hb electrophoresis, only three had high-performance liquid chromatography machines installed, but none was being routinely used. Nine institutions had computed tomography, six had MRI and three had transcranial Doppler facilities. No centre had ongoing newborn screening.

Another study of blood transfusion practice in Nigeria identified severe challenges[103]. Out of 31 hospitals that ran SCD clinics, 24 (78%) were unable to transfuse patients regularly due to blood scarcity. Packed red blood cells were available only in 14 (45%) hospitals, while only one provided leucocyte depletion. Most centres screened donor blood for HIV, hepatitis B and C. However, extended phenotyping and alloantibody screening were not available in any centre. No centre had apheresis machines and only 25% offered chronic transfusion therapy by top-up or manual exchange transfusion.

The burden of SCD in rural communities of Nigeria is illustrated by the experience of an NGO, Service to Humanity, which was founded by the Katsina State Governor's wife in 2010. The State is mostly rural, and she established the NGO initially to cater to women's empowerment. She was convinced to add SCD to their initiatives and thus commenced massive awareness drives in one of the local government areas. They started with 40 patients, providing primary care, education, and routine drugs like folic acid and antimalarials. The enrolment grew rapidly, and the services were extended to two other contiguous local government areas. Between 2011 and 2015, the total number of registered patients grew from 6000 to over 18 000! They held a clinic once a month at which 200 to 300 patients would show up. There was only one doctor and a couple of trained nurses to attend to the patients. Obviously, good care could not be provided under such circumstances. These overwhelming numbers were obtained without community screening, thus illustrating the massive burden of the problem in rural areas and portending what to expect when screening becomes widely available. Service to Humanity was discontinued in 2015 when the Governor's tenure was over, and funds were no longer available! This illustrates the issue of lack of sustainability and the need to have a more stable, well-supported model of care

for these patients. However, this example also highlights the importance and effectiveness of community engagement.

The picture presented above on the situation in Nigeria is probably representative of what obtains in other SSA countries, although there have been pockets of encouraging improvements, but a lot remains to be done to take care of most patients in an equitable fashion. Previous work from the Republic of Benin has shown that the quality of life and survival can be significantly enhanced with improvements in basic comprehensive care, including health education and awareness, hygiene, nutrition support, malaria prophylaxis, penicillin prophylaxis, and routine drugs like folic acid[104], which can be based in the PHC setting.

1.9 . WHO and United Nations initiatives on SCD:

In 2006, WHO, at its Fifty-ninth Health Assembly (resolution WHA59.20)[105], documented the morbidity and mortality associated with SCD, and the implications for affected countries and asked for the establishment of dedicated treatment centres. In 2008, the United Nations General Assembly declared SCD a public health problem and urged all affected Member States to establish national programmes.[106] It again emphasized the need for specialized centres for the treatment of the disease and to facilitate access to treatment. In 2010, WHO AFRO developed an SCD strategy for the WHO African Region and identified some priority interventions that should be adapted to local settings.[107] For the purpose of the guidance framework and in light of the current management status of SCD in the Region, the most important interventions are:

- Advocacy for resource mobilization and increased awareness
- Partnership/integration with existing programmes and social impact
- Capacity building to provide skilled personnel in the areas of genetic counselling, diagnosis, and management
- Supportive activities for vulnerable groups – children under five years, adolescents, and pregnant women
- Early identification and screening
- Comprehensive health care management for SCD patients of all ages
- Research promotion.

Since primary health care centres are the closest health facilities to most patients with noncommunicable diseases (NCDs), especially in resource-poor countries, WHO launched the Package of Essential NCD interventions (WHO PEN) in 2020 and the PEN-Plus regional strategy in 2022.[108, 109] These efforts support the integrated

detection, diagnosis, treatment, and care of NCDs in primary health care centres using evidence-based algorithms and protocols. The package was well-developed for hypertension, type II diabetes, and chronic respiratory diseases. More recently, an SCD PEN has been developed but is still to be ratified.

An assessment of the implementation of the WHO regional SCD strategy in 26 Member States was carried out in 2020. While the report noted varying levels of progress in some of the expected outcomes, there was a marked shortfall in other areas, especially in newborn screening and early diagnosis, availability of services at the district and subdistrict levels, and access to medicines and medical equipment. Poor budgetary allocation for the prevention and control of SCD and poor integration of SCD into existing public health programmes like HIV and reproductive, maternal, newborn and child health (RMNCH), were also reported. There is a lack of accurate and reliable data on SCD, probably because of the absence of national-level newborn screening and surveillance programmes, as well as the lack of registries.

WHO has begun the process of developing clinical care guidelines for the management of children and adolescents with SCD. It will include recommendations for diagnostic and long-term management. Operationalization of the recommendations will have implications for the organization of health care delivery and health system investments needed for providing quality health care to children and adolescents with SCD.

2. Aims and objectives

The overall goal of this framework is to contribute to the reduction of the burden of SCD in the African Region, and the main objectives are to:

- provide standardized guidance for the establishment and operationalization of an integrated framework for the management of SCD
- catalyse the growth of regional and subregional expertise in the management of SCD
- provide a platform for the development and application of research and innovative technologies for the prevention, management and care of SCD, including surveillance and support services.

The guiding principles for the achievement of these goals will be “the greatest good for the greatest numbers, that is, leave no one behind”. There must be equitable distribution of opportunities with universal access to care and novel therapies, regardless of gender, geographical origin, socioeconomic status, etc. In particular, vulnerable and marginalized groups must be identified and catered to.

3. Suggested model of SCD management

The burden of SCD in SSA is such that current models, where the care of the patients is limited to secondary and tertiary health care centres, get easily overwhelmed by the large numbers of patients, while still not being accessible to patients in rural areas. This is more so because skilled personnel, technical diagnostic equipment and various therapeutic modalities are in short supply. As early infancy screening identifies more affected patients, the problems will become even more pronounced. Hence, the strategy for providing care for the majority of the patients has to be in the primary health care (PHC) setting, based on the principles enunciated in the Declaration of Astana[110]. In the context of SCD management, the following are the pertinent principles:

- PHC will be implemented in accordance with national legislation, contexts and priorities
- There should be national investment in PHC to strengthen health systems
- Capacity and infrastructure should be enhanced for primary care, which is the first point of contact with health services

- Care must be accessible, equitable, safe, of high quality, comprehensive, efficient, acceptable, and affordable, and delivered continuously and integrated into existing services that are people-centred and gender-sensitive
- An effort will be made to avoid fragmentation and ensure a functional referral system between the primary and other levels of care.

While it is proposed that SCD management be fully integrated into existing PHC services, special training is required for the personnel in these centres. Apart from core competence in SCD, the training should emphasize the principles of equity, diversity and gender sensitivity, with recognition of vulnerable and marginalized groups. The health surveillance and monitoring of these patients need to document several laboratory and clinical parameters and various outcomes, as these are particularly useful in guiding their management. They would also facilitate an understanding of the natural history of the disease in the local environment. Therefore, there must be intensive training of the available staff in the primary health care facilities, to acquire competency in diagnosis, prevention, and early detection of complications of SCD, with training, monitoring, and supervision to be provided by neighbouring secondary and/or tertiary centres in an organized fashion. A distinct referral pathway must be established. This is also advocated for in the recently published Lancet Commission article on sickle-cell disease.[111]

Every patient diagnosed with SCD should have reasonable access to a treatment centre so they can receive care as quickly as possible. This would, of course, vary from place to place depending on the topography, season, road network, and available means of transportation. Therefore, an identified patient should be registered for care at the nearest centre to him or her, irrespective of whether it is a primary, secondary, or tertiary centre. The expected services at each level of care are outlined below. As much as possible, a newly diagnosed patient should be registered in the same clinic where the diagnosis was made, except there is a more accessible centre closer to where the patient resides. Each patient will carry a health card with details of their Hb genotype, residential address, and other demographic and basic treatment details, including an immunization record. Children will also have a growth chart attached to their cards. The card will be updated at each clinic visit.

SCD care should be integrated into any existing or established health care initiatives in the locality, be they designated HIV, maternal/child health programmes, immunization, etc., to maximize the benefit from existing facilities for the greatest number of clients.

3.1. Community mobilization and awareness drives:

Affected communities in SSA have been aware of SCD in some form or other for millennia, even before the first description of the disease in the literature by Herrick in 1910. They had names for the disease that reflected its pain and agony. Since the scientific basis of the disease was beyond their understanding, several myths developed to explain why affected children die early in life. Among the Yoruba of Nigeria, the children were referred to as "abiku", while the Igbo called them "ogbanje", literally meaning that the children were destined to die young to torment their families because of some ancestral curse. Moreover, the concept of inheritance of genetic diseases does not align with the native understanding of disease causation, which may interfere with their acceptance of interventions. Therefore, there are several barriers to break down to obtain the active support of the local community and guarantee their participation and investment in the relevant health initiatives. For this reason, it is imperative that the introduction of a new initiative, as is being proposed, be preceded by massive mobilization of the local community and awareness drives, with the involvement of all stakeholders.

These drives must precede the establishment of an SCD treatment centre in any community and should be coordinated by knowledgeable medical teams that are trained in SCD. The stakeholders in the community that must be targeted for participation include the following:

- SCD patients and patient support groups
- Local chiefs and community elders
- Religious leaders
- Local government officials
- PHC workers
- Media practitioners
- Teachers and students
- Local artists, celebrities, sports stars, etc.

3.2. SCD treatment centre:

This is defined as a centre with personnel who have undergone training in SCD and that has facilities and amenities to offer comprehensive care to patients with SCD, depending on and according to the level (primary, secondary, or tertiary) of care provided. The services expected at each level and the minimum criteria for designating the level of care are detailed below.

It should be borne in mind that while primary health care is provided in each country in SSA, the operationalization, governance, nomenclature of different cadres of workers, available facilities, etc. differ from one Member State to another. This framework is thus a guide to be adapted to local circumstances as is reasonable and appropriate. The care offered to SCD patients will be dictated by the available services and expertise.

3.2.1. First level of care

Base: This first level of care will be based in the community, the home and the PHC facility. Some privately owned clinics or hospitals may also be able to offer primary care for SCD.

Expected services:

Community/home:

- Counselling
- Hygiene
- Nutrition
- Self-care
- Health monitoring and surveillance.

PHC level:

- Neonate/infant programme
  - Diagnostic screening
  - Genetic counselling
  - Immunization
  - Nutrition and breastfeeding promotion
- Under-fives and older children:
  - Immunization
  - Counselling
  - Health monitoring and surveillance
  - Self-care
- Adolescents and adults:
  - Counselling
  - Self-care
  - Premarital screening services to be provided
  - Sexual and reproductive health
  - Health monitoring and surveillance

- Pregnant women
  - Counselling and screening of all pregnant women for Hb genotype
  - Women with HbS should be registered for treatment and their partners screened for their Hb genotypes
  - Antenatal care should be provided for pregnant patients, but delivery should be in a secondary and/or tertiary centre.

Personnel:

The PHC staffing structure varies from country to country, but usually it includes nurses and/or community health officers (CHO), community extension workers (CHEW), the number of which will depend on the population served. Some may have one or more physicians and other allied professionals, such as pharmacists, medical laboratory technicians, etc.

The centre will be linked to a neighbouring district hospital, secondary or tertiary centre, which will oversee the training and supervision of the PHC level. All PHC-level staff will receive training with a module that can be adapted from existing materials, to achieve competence in SCD. They will be trained to use the WHO PEN SCD protocol. They must be able to identify patients requiring a referral for specialist care.

Facilities:

The centre should have facilities for the following services or programmes into which SCD management will be integrated, although as the number of affected patients increases, it may be necessary to start a stand-alone SCD clinic:

- Diagnosis
- Counselling
- Patient and family education
- Under-five welfare
- Nutrition advice/support
- Immunization
- Prenatal/antenatal services
- Simple electronic devices to maintain a registry of SCD patients diagnosed and being followed, which will be linked to the local and national databases.

Laboratory and equipment:

- Hb, haematocrit, malaria smear/ malaria RDTs
- Urinalysis/urine dipstick
- Pregnancy test
- HbS screening, preferably by point-of-care testing (POCT/sickle RDTs).

Care provided:

Routine medicines and vaccines:

- Folic acid, malaria chemoprophylaxis and barrier protection, and penicillin prophylaxis. Apart from the routine vaccines, patients with SCD should receive pneumococcal and meningococcal vaccines.
- Pain management: Analgesics, including opioids in centres with a physician.
- Disease-modifying medicines: Hydroxyurea can and should be used but provision must be made for laboratory monitoring for side effects, even if the patient has to be referred to another centre for this purpose.
- IV infusions for rehydration.
- Oxygen supply.
- Blood transfusion, where available.
- Follow the WHO SCD/NCD PEN protocols and know when to refer a patient to a secondary or tertiary centre.

Care coordination: The resident or visiting medical officer will monitor the care provided and update the level of training of the staff. Telemedicine capability should be encouraged so that virtual consultations can be done as necessary.

3.2.2. Second level of care

Base: This will be based in a secondary health care facility, that is, a general, district, or private hospital, depending on the available personnel, facilities, and amenities.

Expected services:

- All the services offered in the PHC, as stated above, should be available as appropriate;
- PEN-Plus programme;
- More specialized care;
- Emergency services;
- Blood transfusion;
- Maternity for antenatal care and deliveries;
- Advanced imaging studies (TCD, Cardiac ECHO);
- Transition programme. An appropriate supervised programme to introduce adolescents to the adult care services should be in place.

Personnel: In addition to other general staff in accordance with ministry of health regulations, there should be:

- Medical specialists in paediatrics, internal medicine, haematology, family medicine, anaesthesiology, surgery, or related specialties with competence in SCD. Virtual consultation with tertiary and primary centres should be available.

- Trained nurses and social workers.
- Genetic counsellors.
- Pharmacists.
- Laboratory technicians.

Facilities: The centre must be able to provide care for patients along the following lines:

- Management of acute and chronic manifestations of SCD.
- Blood transfusion.
- Pain management, including opioids.
- Hydroxyurea.
- Psychosocial/counselling support.
- Intensive care/high-dependency unit.
- Day-case room, separate from an emergency department (ED) for blood transfusion and IV fluids, as necessary.
- Surgical intervention for cholecystectomy, splenectomy, etc.
- A registry of all SCD patients diagnosed and being followed in the facility has to be kept using appropriate digital devices. This registry will be linked to the national database. Where these are not available, paper records should be meticulously kept. A data manager should be designated to coordinate data collection.

Laboratory and equipment

- Specialized laboratory
  - Haematology
    - Electronic cell counters (manual or electronic differential counts) and microscope
    - Electrophoresis/high-performance liquid chromatography (HPLC)/ isoelectric focusing (IEF) or capillary electrophoresis/point-of-care testing (POCT) kits
    - Blood transfusion service
      - Grouping (ABO & Rh) and cross-matching
  - Microbiology/parasitology
    - Culture and sensitivity
    - Stool for ova and parasites
- Blood chemistry
    - Electrolytes and urea
    - Renal function tests
    - Serum lipids
    - Liver function tests
- Imaging
  - Ultrasound and transcranial doppler (TCD)
  - Radiology
  - X-ray.

Care coordination:
One of the haematologists or any other competent physician/paediatrician in the facility will head the SCD team and will be responsible for monitoring care, training personnel, and running an outreach programme covering the PHC facilities in the catchment area.

3.2.3. Third level of care

Base: This will be based in a tertiary referral, teaching, general, private hospital or equivalent, that meets the criteria outlined below.

Expected services:

- All the services listed for the first and second levels of care must be available
- Care of acute and chronic complications
- Care of patients with complex presentations
- Receiving referrals from the secondary care level
- Supervision of the transition of adolescents to the adult service.

Personnel:

- In addition to other general staff as per ministry of health guidelines, there must be:
  - Medical specialists in haematology, internal medicine, family medicine, surgery, paediatrics and other related subspecialties as enumerated below:
    - An accredited/recognized internship/residency training programme
    - Complement of trained nurses and social workers
    - Pharmacist.
  - An SCD team, headed by a specialist/consultant will oversee:
    - Provision of health care for affected patients
    - Training of personnel and capacity building
    - Outreach programme
      - Arrange community awareness and educational programmes
      - Liaise with patient groups, policy-makers, and other stakeholders, with active participation of women and gender experts

- Arrange regular training, supervisory and monitoring visits to PHC and secondary health care facilities in their orbit. Virtual consultation should also be in place.

- Availability of other subspecialties, including:
  - General surgery
  - Orthopaedic surgery
  - Plastic surgery
  - Pulmonology
  - Nephrology
  - Urology
  - Dentistry
  - ENT
  - Ophthalmology
  - Neurology
  - Radiology
  - TCD, X-ray, CT and MRI
  - ICU
  - Cardiology (echocardiography)
  - Gastrointestinal (GI)
  - Infectious diseases
  - Psychiatry or psychology.

Facilities: Same as for second-level care, but in addition, it is recommended that the following be available:

- Newborn screening programme capability
- A dedicated day-care centre, separate from the general emergency department, to receive acutely ill SCD patients for IV infusion, opioid analgesics and/or blood transfusion
- ICU or critical care facilities
- Blood transfusion services
  - Extended RBC phenotyping
  - Screening for transfusion-transmitted infectious agents
  - Alloantibody and autoantibody identification
  - Leukocyte-depleted (filtered) red cells
  - Monitoring iron overload
  - Exchange transfusion capability
- Robust health information system (HIS) with a good registry of SCD patients, including patients being followed at the first and second levels of care. The data will be linked to the national database. A data manager should be available to coordinate the collection and collation of data.

Coordination of care: This will be the purview of the SCD management team that will monitor, evaluate, and ensure health care and continuing medical education for the whole staff.

4. SCD Management Unit – Integration of the three levels of care

As outlined earlier, the management pyramid is structured such that a tertiary centre is at the apex, with a primary health care centre at the base, and a secondary centre in the middle (see Figure 1). Each pyramid will function as an integrated SCD management unit. The number of centres in each unit and the number of units in a particular locality will be determined by accessibility, the SCD density in the area, and the availability of personnel and other facilities.

A tertiary treatment centre shall have an SCD team that is headed by a trained medical specialist and shall include a nurse, pharmacist, and other relevant individuals depending on available personnel. They will maintain overall control of the management unit, overseeing training and treatment protocols. They will also receive complex cases referred for management. Depending on the number of centres in a distinct geopolitical area (district, region or however designated), a tertiary centre may also be linked to more than one secondary centre.

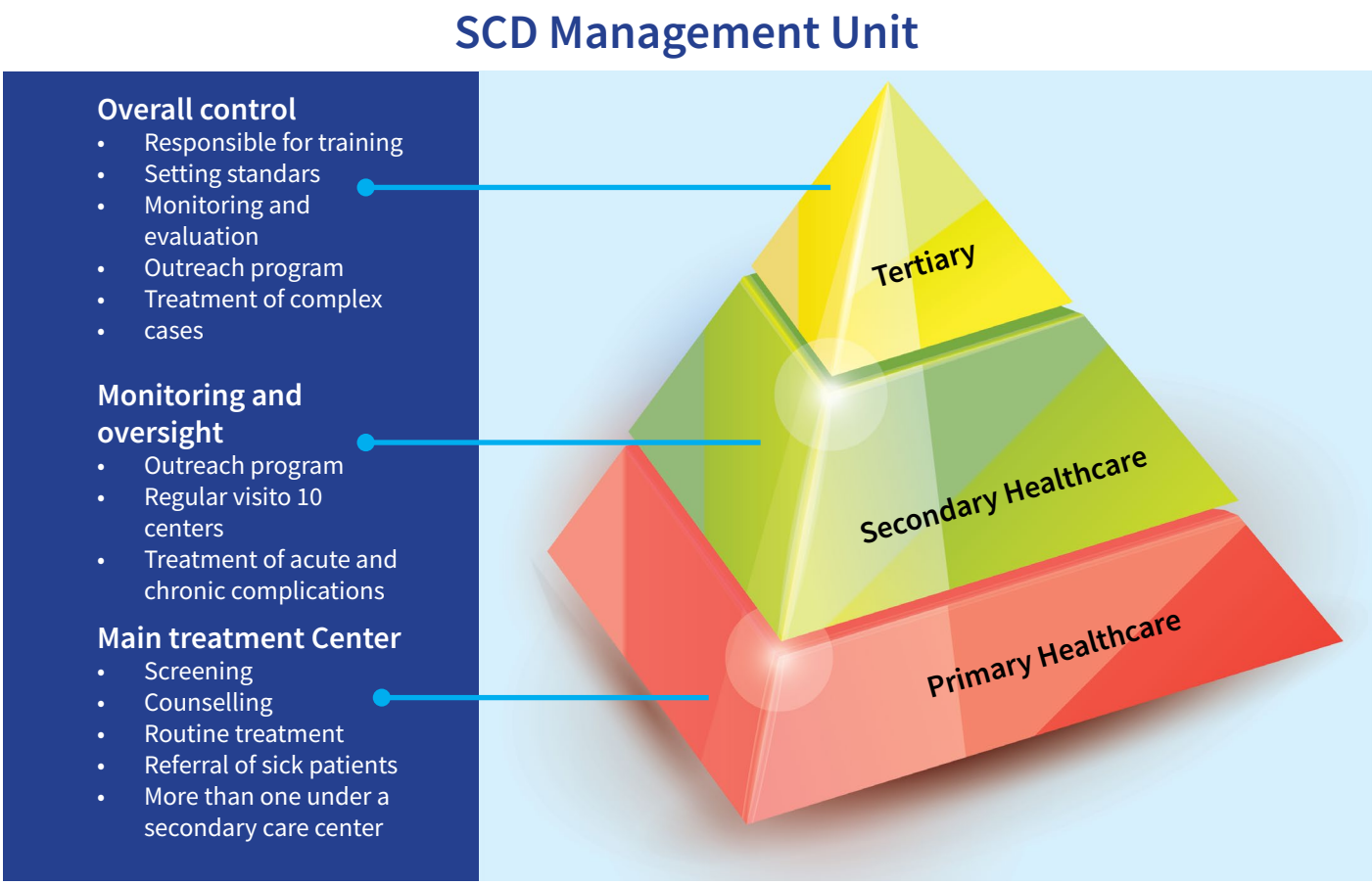

Fig. 4. The Pyramidal management unit

A secondary centre will be a hub, linked to two or more satellite primary health centres (Figure 2). An SCD team, like that in a tertiary centre, will provide training, supervision, and evaluation of the primary centres in its orbit. There will be an outreach programme in which a doctor from the centre visits and runs a clinic in each of the PHC centres on a regular basis. This may be facilitated by telemedicine (virtual consultation), mHealth, eHealth and other available electronic or digital devices. The outreach programme will also involve regular community awareness drives.

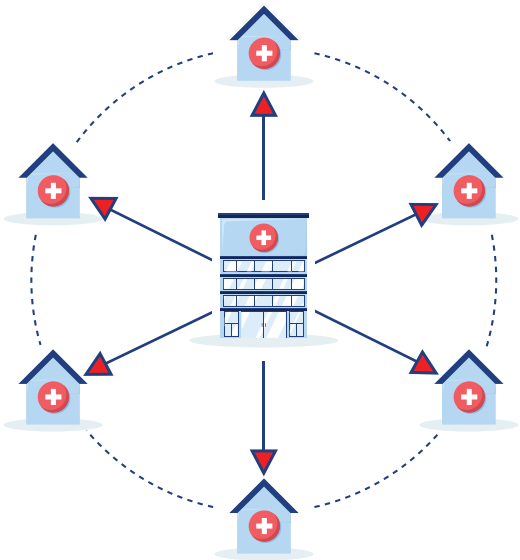

Fig. 5. The hub-and-spoke structure showing that a secondary health care centre can have more than two satellite primary health care centres

There will be an upward referral pathway from the primary to secondary and then to tertiary centres for patients that require specialist care, while supervision and monitoring will be in the opposite direction (see Figure 3).

There must be robust recordkeeping or a health information system (HIS) in place in each unit and at every level. This has to be digitized, using available eHealth, mHealth and other devices. All the SCD patients diagnosed and followed up at each level of care must be entered into a registry, which will eventually be fed into the national database. However, wherever a digital device is unavailable, paper records should be kept meticulously,

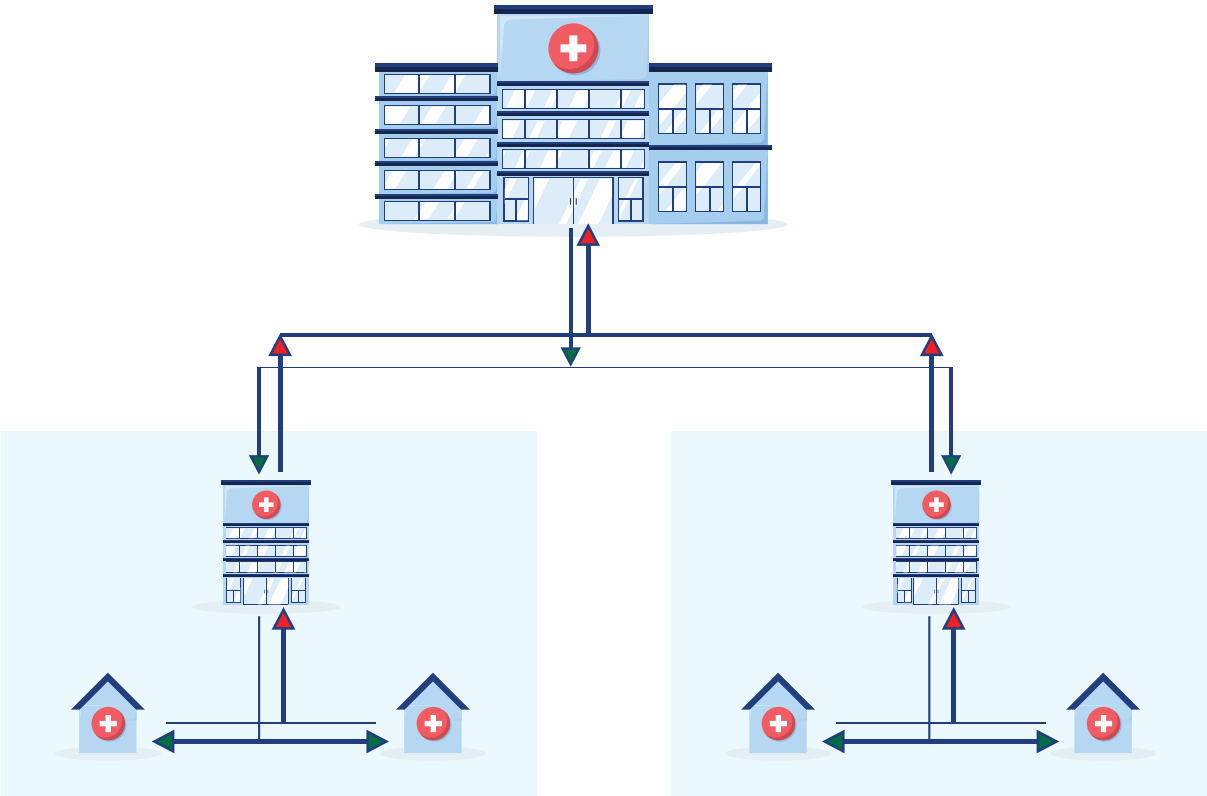

Fig. 6. Integration of the centres showing upward referral (red lines) and downward supervision (blue lines).

5. Centre of excellence

Definition:

Any tertiary centre with a high level of expertise in taking care of SCD patients with complex medical or surgical problems. The CoEs will be hubs for high-level research activities that will apply innovative technologies for the prevention, management and care of patients with SCD. The centres will be linked in a consortium for coordinated research and professional collaboration. They will generate invaluable data on different aspects of SCD in Africa and be able to complement each other in managing complex cases with their different specialized capabilities.

The evolution of CoEs could be through organic, incremental growth as the existing tertiary centres acquire more expertise and specialized programmes over time, or they could be purposely designed and built ab initio. While one may not expect governments to bear the whole cost, it is hoped that the centres would be established through public-private partnerships. Advocacy will be key in achieving the political will that will drive governments in this direction.

The centres should have state-of-the-art facilities such that a patient with SCD does not have to be referred for management outside of Africa. Each CoE should have the following, in addition to what is required for a tertiary centre:

- Health care
  - Super-specialized services including, but not limited to:
    - Exchange blood transfusion (preferably automated)
    - Hematopoietic stem cell transplantation
    - Gene therapy.
  - Specialized clinics including, but not limited to:
    - Genetic counselling
    - Mental health/psychosocial support
    - Reproductive health services
    - Cardiology
    - Orthopaedics
    - Nephrology
    - Neurology
    - ENT
    - Ophthalmology
    - Urology.
  - Outreach clinics
    - Provide specialist clinics and support to tertiary and secondary health care centres.
  - Specialized diagnostics
    - Laboratory including relevant DNA/molecular studies
    - State-of-the-art laboratory services that could provide expertise at the national/regional level
    - Imaging studies, including TCD, CT, and MRI.
  - Education and training, including but not limited to:
    - A recognized residency and/or fellowship training programme with the availability of residents/fellows with competence in SCD
    - Provision of a platform for continuing professional development (CPD) activities.
  - Research
    - Clinical and basic science: Evidence of ongoing research with internal and external collaborations
    - Translational: gene therapy through national, international or external linkage
    - Provide national or regional hubs for collating data
    - Should have data coordinators and research managers.
  - Health information systems (HIS)
    - There must be a sophisticated electronic HIS that maintains a registry of SCD patients, linked to the national database.

Operational requirements

- All the services and requirements outlined above must be supported by adequate:
  - personnel
  - facilities
  - equipment
  - funding.

Accreditation and audit

- These centres must meet international norms and accreditation standards in the relevant fields.

6. Integration into existing programmes

It is important that this framework be integrated into existing public health structures and programmes to ensure cost-effectiveness and equitable distribution of resources for the benefit of most patients. This will retain personnel and limit the number of clinic appointments that patients must keep. This is particularly important at the beginning of the programme in a particular location. However, with time, and as the numbers of patients increase, stand-alone SCD clinics may become necessary. This programme must be always patient- and family-centred. Some of the programmes, structures, institutions, and other resources into which the management of SCD patients can be integrated include the following:

- Existing public health programmes to be considered for integration
  - NCD especially WHO PEN and PEN-Plus
  - Newborn screening into immunization programmes
  - HIV and malaria programmes especially focusing on screening for pregnant women, stigma, and counselling
  - Sexual and reproductive health

- UHC
- Maternal and child care
- Blood transfusion services
- Laboratory and diagnostic services

- Technological innovation for diagnosis, treatment, referral and care coordination
  - Electronic medical health or health information systems
  - Telehealth and mobile technology health platform, for virtual consultations
  - Point-of-care diagnostics
  - Digital registries with other existing NCDs
  - DNA-based diagnostic methods

- Human resources for health
  - Community health workers
  - Primary care and family medicine physicians especially for diagnosis and treatment initiation, monitoring and follow-up
  - The available skilled medical, surgical and other subspecialties in the secondary and tertiary institutions should be leveraged in this integration
  - Allied health professionals (pharmacists, physiotherapists, etc.)
  - Traditional birth attendants
  - Traditional herbalists and religious leaders (we need to educate them)

- Advocacy groups
  - Patient support groups
  - Professional associations such as medical, haematology, orthopaedic, neurology associations, etc.
  - Networks and consortia such as CONSA, ARISE, H3Africa, Sickle In Africa, leveraging their existing guidelines/resources
  - Establishment of Pan-African SCD network

- Other sectors
  - Inclusion of SCD curriculum at all levels of education, especially
  - health care professionals in training
  - Supply chain division for medicines, vaccines and diagnostic products
  - Public-private partnerships
    - Public, that is, governmental agencies
    - Philanthropy such as NGOs or faith-based institutions
    - Private, including the pharmaceutical industry, health insurance companies, etc.
  - Continuing education or professional development
  - Health planners
  - Women and gender experts.

Referral pathways

- Leverage existing referral linkages and functional relationships across all levels of care with the patient at the centre to ensure care coordination:
  - Patient directed
  - Health care provider directed.

7. Regional evaluating teams as catalysts for developing expertise and research in SSA

The proposed structure will provide a great opportunity not only for patient-centred, equitable care but also for the accumulation of data that will be invaluable in understanding the disease in Africa. It will also catalyse planning and broad-based research in the Region. However, these goals can only be achieved if good supervisory, monitoring, and evaluation protocols are put in place. These efforts can be described at different levels:

- Management unit level: At each unit, the emphasis is on the collection of data on clinical indices and patient outcomes. The tertiary centres will supervise the secondary and primary centres in their orbits. Evaluation criteria will be developed that will be executed on a regular basis. The data collected in the local registry has to be fed into the district and, eventually, the national databases.

- District level: Depending on the number of management units, an evaluation team will be formed with representatives from each tertiary and secondary centre. There will also be external representatives, including a nurse, pharmacist, community leader, public health official, and patient. This team will be responsible for evaluating the management units in the district. However, when a particular unit is being evaluated, none of the members of the evaluating team from the unit will be involved. The team will also be responsible for assembling data from the different centres, including on the prevalence of the disease and carriers from the screening programmes. They will also follow trends in presenting clinical features, complications, and other outcomes. The criteria and frequency of evaluation are to be determined.
- State level. There should be a State SCD committee, convened by the MoH, headed by an SCD desk officer in the ministry, with representatives of important stakeholders, including care providers, district SCD evaluating teams, and patients, as members. The committee will coordinate the overall activities of the State. They will draw up criteria for evaluating the different district SCD teams. They should monitor and collate all SCD data coming from the registries in the districts.
- National level. The same structure as advocated for States will be put in place in the national or federal MoH. The committee here will collate all the data from the States into a national SCD database. This committee will drive the national SCD agenda, especially in capacity building, training, and research.
- Regional and subregional levels. The teams described for the different levels above
- will be replicated in other affected countries. A mechanism should be put in place that links the national committees of the different countries. This could be at the governmental (MoH) level or through academic/professional consortia, such as Sickle-in-Africa, SPARCO, etc. Indeed, there are many current centres of excellence that provide care for patients and carry out research on SCD. There is a need to map these as soon as possible to identify them and promote linkages.

- WHO AFRO level. The ultimate control, evaluation, and accreditation must be at the level of WHO. Therefore, as is being canvassed, the secretariat of the Global SCD Alliance should be at the WHO Regional Office, with a full-time officer, preferably an SCD expert, supported by a standing panel of experts drawn from different parts of the Region that will meet on a regular basis. This body would draw up criteria for evaluating and accrediting different centres in the Region. They will promote advocacy, management guidelines, databases and research. The body would also be in the best position to solicit funding from different international agencies, individuals, and private enterprises, including pharmaceutical companies.

8. Need for national SCD policies

8.1. Rationale:

The expert panel strongly recommends that the national governments of affected countries, which are, indeed, the most significant stakeholders, must fully commit to supporting this guidance framework for the management of SCD. They must demonstrate the political will to advance the issues that have proven to have major positive impacts on the survival and quality of life of patients with SCD and to promote them with sufficient resource mobilization. Despite the ongoing advocacy of the UN and WHO on this issue, the response from affected countries has not been encouraging. An SCD policy is still lacking in most African nations, although it is now included in many, as part of their general NCD policy. The following facts should be clearly articulated to policymakers:

(a) Governments that have dynamic, well-articulated SCD policies and demonstrate political will are better placed to attract international funding for their programmes.
(b) SCD is by far the most important genetic disease that affects people in malaria-endemic areas and is, therefore, most prevalent in SSA.

(c) SCD contributes to the overall incidence of anaemia at all ages, under-five mortality, malnutrition, infections, etc. Indeed, it is now ranked the 11th cause of under-five mortality in SSA. The recurrent acute manifestations of the disease and its chronic complications take a toll on the productivity and earning power of adults with SCD. Thus, SCD comes with a high economic cost to patients and society at large.

8.2. The national policy should address the following issues, among others:

8.2.1. Health insurance:

This is an essential component of assisting persons living with SCD to access affordable care. A programme for reimbursing expenses incurred by patients and their families should be implemented. Where there is no insurance programme, other support mechanisms should be put in place, such as a policy of subsidizing curative care or provision of free basic care.

8.2.2. Early diagnosis:

Evidence shows that the greatest factor in promoting the survival of affected patients is early diagnosis and the institution of appropriate comprehensive care. While newborn screening is the eventual goal, all opportunities should be utilized to ensure the early determination of the Hb genotypes of the majority of the population. Thus, screening can be linked to immunization, post-natal clinics, primary school entry, or any other contact between the child and a health facility, and mandatory premarital counselling.

- Screening programmes are expensive, and the governments must take the lead in executing the programme, which should eventually be universal. Until recently, the available methods required expensive equipment and reagents, highly trained personnel, and a steady supply of electricity, which are all in short supply in SSA. However, point-of-care testing kits are now available and are listed in the WHO Model List of Essential in-vitro Diagnostics (WHO EDL). These do not require electricity or extensive training to use. Several pilot studies have attested to the efficacy and reliability of the kits, even in the newborn period.

- Genetic counselling should be linked to the screening programme at all levels. A training programme should be in place to create a cadre of competent individuals who can give appropriate factual, non-directive counselling to patients and their families. Individuals with sickle-cell trait should also be properly counselled about their marital choices.

8.2.3. Essential drugs:

Each country's essential drug list should include commonly used drugs in SCD care. They should also be listed under the UHC programme. These include folic acid, antimalarial drugs, penicillin, morphine and hydroxyurea. There are also extra vaccines including pneumococcal and meningococcal, that should be on this list. There should be a clear policy on opioid analgesics so that a patient who requires them for pain control is not deprived.

8.2.4. Essential in vitro diagnostics:

Each country's essential IVD list should include recommended IVD tests for the screening, diagnosis, and general management of SCD patients. These include rapid diagnostic tests (RDT), including POCT for non-laboratory settings suitable to be used at PHC level, and other laboratory-based tests: sodium metabisulfite slide test, haemoglobin solubility and haemoglobin electrophoresis.

8.2.5. Education and awareness:

it is essential to increase local awareness of SCD with well-designed strategies to facilitate early diagnosis, the institution of care, and the elimination of the stigma associated with the disease. All strata of the community should be involved, and the media have a crucial role to play in this regard. The earlier an awareness programme is introduced in the life of an individual, the better the assimilation of the knowledge and change in attitude. Thus, it is desirable that SCD be included in primary, secondary and university education curricula, using appropriate language that avoids ambiguity but is still easily understood by the children. By the same token, this should be part of the curriculum in all community health training institutions.

8.2.6. **Funding:**

This initiative will cost a lot of money. While national governments must increase their budgetary allocations as advocated by WHO, other sources of funding should also be sought. International agencies, pharmaceutical companies, local philanthropists, and private companies should be motivated to contribute. When the current framework is adopted, funding agencies will have concrete and definitive initiatives that they can sponsor in the control and management of SCD on the African continent. In the long term, it would be ideal for SCD to be funded in the same way as infectious diseases such as malaria, HIV, and tuberculosis.

8.2.7. **Research:**

SCD interfaces with many different spheres including clinical, basic, social, and public health sciences. There is still a lot to learn about the disease, especially its natural history and impacts in Africa. There have been significant recent developments in novel therapies, with many more clinical trials under way. Stem cell transplantation and gene therapy are making big strides in SCD. Africa must be part of these efforts, including investigating indigenous traditional and herbal remedies. All aspects of therapy should be available on the continent so that patients do not have to travel out to access them. All tertiary institutions designated as SCD treatment centres, and certainly, the centres of excellence, should have ongoing high-level research programmes with regional and international collaborations. By far the most important starting point is the accumulation of data on the prevalence and phenotype of the disease.

9. Conclusion

The proposed framework will complement and be integrated into WHO PEN and PEN-Plus. Thus, the goals of the proposed SCD framework will be incorporated into the eventual targets and milestones set out in PEN-Plus.

The main priorities in the management of SCD in SSA are:

1. Sensitization and awareness drives within the community to build advocacy and eliminate erroneous beliefs, myths and stigmas.
2. Training of PHC workers and other health care professionals at all levels. An appropriate, standardized curriculum should be developed for use across the Region. The modules currently available in some anglophone and francophone countries can be adapted for this purpose after proper vetting and collation.
3. Development of supervision, monitoring and evaluation criteria for the SCD treatment centres. These criteria will be provided by secondary and/or tertiary health care centres depending on local availability. The composition of the teams and the performance landmarks will be determined and adapted to local norms and the availability of personnel.

4. Screening. All newborns should be screened at birth or during immunization visits. School entry and premarital periods are also opportunities for screening to ensure people are aware of their Hb genotypes. This will allow for early intervention for affected patients and counselling for carriers. While diagnosis in PHC centres can be done with point-of-care devices, the positive results should be confirmed with HPLC or IEF in a secondary or tertiary centre.

5. All patients confirmed to have SCD should be followed up in a treatment centre with comprehensive care. Community health workers should verify patients' addresses for ease of follow-up.

6. All patients should have easy and affordable access to folic acid, antimalarial prophylaxis and penicillin up to the age of five years.

7. All patients in SSA should be offered hydroxyurea from about the first year of life. It is advised that the different countries negotiate as a block with the pharmaceutical companies for discounted costs of the drug to make it affordable for patients. Local manufacturing must also be encouraged without delay. A low, non-escalating dose of 10 mg/kg can be used in PHC centres. Higher doses should be restricted to centres with medical expertise and laboratory facilities to monitor toxicity with complete blood counts and blood chemistry.

8. Acutely ill patients should be promptly referred to higher-level centres for proper investigation and treatment.

Treatment options that are recommended in the secondary and tertiary treatment centres include:

1. Febrile episodes:

Patients with fever should be screened and treated for malaria and have appropriate cultures done but should be started on antibiotics while the results of cultures are being awaited.

2. Stroke prevention:

Annual screening with TCD to identify patients at risk for stroke should be commenced at 2 years of age and continue to the age of 16 years. Patients with abnormal velocities should be commenced on hydroxyurea.

3. Acute chest syndrome (ACS):

This should be suspected in a patient presenting with chest pain, fever, difficulty in breathing and showing new infiltrates on chest X-Ray. Such patients would require oxygen, intravenous fluids, antibiotics to cover pneumococcus and atypical organisms. Blood transfusion may be indicated, and chest physiotherapy and incentive spirometry are useful adjuncts.

4. aplastic crisis:

Patients presenting with aplastic crisis, hyperhaemolytic crisis, or acute splenic sequestration may all require acute blood transfusion.

5. Prevention of stroke and in recurrent ACS:

A chronic blood transfusion regimen may be considered for secondary prevention of stroke and in recurrent ACS.

6. Psychological assessment:

Efforts should be made to provide psychological assessment for patients and their caregivers, while psychiatric consultation should be sought for patients with depression, anxiety neurosis, etc.

7. Avascular epiphyseal necrosis:

Avascular epiphyseal necrosis should be suspected in patients with acute or recurrent joint pain, limping, or restricted joint movement. Imaging assessment with X-ray or MRI should be done and orthopaedic consultation sought for appropriate management.

8. Regular monitoring for renal disease:

Regular monitoring for renal disease (haematuria, hypertension, progressive proteinuria, and declining renal function) with urine microalbumin/creatinine ratio and renal function tests should be done yearly from the age of 10 years. Patients showing positive features should be seen by a nephrologist at level II or III.

9. Other complications of SCD:

Patients should be monitored for other complications of SCD like leg ulcers, priapism, retinopathy, chronic lung disease, gallstones, etc.

10. Women of reproductive:

Women of reproductive age should be adequately counselled about reproductive choices and all pregnancies must be supervised and deliveries should be in centres with specialists, for high-risk pregnancies.

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Annex 1

Process

Panel of experts

1. Professor Adekunle Adekile, of Kuwait University (Consultant and Convener)
2. Professor Baba Inusa, of St. Thomas' Hospital, London, UK
3. Professor Ibrahima Diagne, of Gaston Berger University, Saint-Louis, Senegal
4. Professor Isaac Odame, of Sick Kids Hospital, Toronto, Canada
5. Professor Julie Makani, of Muhimbili University of Health Science, Dar es Salaam, United Republic of Tanzania
6. Dr Kwaku Marfo, Ghanaian, of Novartis International, Geneva, Switzerland
7. Professor Leon Tshilolo, of CEFA-Centre Hopitalier, Monkole, Kinshasa, DRC
8. Professor Obiageli Nnodu, of the University of Abuja, Nigeria
9. Professor Eleonore Kafando, Burkina Faso
10. Professor Jean-Marie Dangou, WHO AFRO – Facilitator
11. Dr Prebo Barango, WHO AFRO – Facilitator.
12. Dr Kouamivi Agboyibor, WHO AFRO – Facilitator.

Operational procedure

Inauguration: The panel was inaugurated online on 10 October 2022, with an address by Professor Dangou, the NCD Director at WHO AFRO, outlining the terms of reference of the panel. Dr Barango then gave a presentation, highlighting the SCD initiatives of the United Nations and WHO over the years, spanning the time in 2008, when the United Nations General Assembly (UNGA) declared SCD a public health problem in affected areas, to the WHO strategy on SCD in 2010, and lately, the WHO PEN and PEN-Plus strategies. Members of the expert panel then made self-introductions, highlighting their track record in the SCD field and their hopes for the work of the panel.

First technical meeting (visionary presentations): The first meeting of the technical committee took place on 27 October 2022. It was a free-flowing session in which each expert presented his/her vision for tackling SCD in SSA and then focused on a pre-assigned relevant topic. Some of the areas covered, in an excellent and comprehensive fashion, included newborn screening, care of vulnerable groups (under-fives, pregnant women, and teenagers), the transition from paediatric to adult service, advocacy, community involvement, and research. The following is a summary of some of the presentations.

- **Newborn screening:** Dr Obiageli Nnodu presented evidence that more babies with SCD survive when they are identified at birth than those identified in early childhood, because interventions like penicillin prophylaxis and pneumococcal vaccination can be instituted as soon as the affected baby is identified. She listed the currently available diagnostic methods: electrophoresis, isoelectric focusing, high-performance liquid chromatography, mass spectrometry and molecular techniques. These are all expensive; they require highly

trained technical personnel and a stable power source. It is, therefore, not surprising that no African country has been able to sustain a newborn screening programme beyond pilot studies. The recently introduced point-of-care testing kits are cheap, exceptionally reliable and require only basic training. They can be used even in remote villages, thus ensuring universal access. Some of the kits have been validated in several field studies in some African countries. Screening has also been successfully integrated into immunization programmes, as a proof of concept.

- **Children:** This area was addressed by Professor Kunle Adekile, who noted that for a long time to come, children will continue to bear the brunt of SCD in Africa. Unfortunately, most of the children are born to poor parents residing in remote rural areas with no access to health care. There is no awareness of the disease, and affected children are only identified when they present with acute complications of the disease, including dactylitis, severe anaemia and infections, since there is no organized newborn or early infancy screening. The current model, where care is based in secondary and tertiary centres, is not serving most of these patients, and we have to resort to PHC-based care. This is like what Dr Morley did in Ilesha in the early 1950s in establishing the first under-five welfare clinic. In this model, nurses and community workers were trained to provide care and identify patients who needed to be seen by a physician. “Road-to-health” cards were designed, which tracked the child’s weight, upper arm circumference, immunizations, and any acute events, and treatment given. Fortunately, there are now point-of-care devices that can be used at the PHC level for diagnosis, and the WHO PEN programme has developed situational algorithms for CHWs to follow at PHC level for SCD management. This is the model that needs to be developed for the management of SCD in SSA.

- **Transition:** Dr Baba Inusa stressed the fact that adolescents are vulnerable, and the aim of a transition programme is to improve the effectiveness of health care for this group of patients. He listed the barriers to transition as sociocultural factors (poor self-management, low patient engagement, and lack of support), health system factors (lack of trained providers, cost of care, and poor care coordination) and faster

disease progression (emerging end-organ damage, and accumulation of comorbidities). There is a need for a balanced transition team that should include mental health professionals. Patient navigators, including CHWs and CHEWs, should be utilized to aid the process.

- **Pregnancy in patients with SCD:** Dr Leon Tshilolo noted that pregnancy in these patients is always at high risk and may be misdiagnosed because their menstrual cycles are usually irregular. There is a high risk of abortion in the first trimester and fetal death later in pregnancy, while the mothers are prone to frequent pain episodes, pre-eclampsia, and pulmonary embolism. Before conception, the husband's Hb genotype should be established, and proper genetic counselling should be done at this time. The need to interrupt the use of hydroxyurea should be discussed because this is the current recommendation, although the fear of teratogenicity with the use of hydroxyurea may be more theoretical than practical. Malaria prophylaxis, folic acid, and iron supplementation should be maintained. There should be supervised prenatal visits, preferably by a multidisciplinary team, including a haematologist and an obstetrician. Delivery should be at a secondary or tertiary level of care.

- **Advocacy for SCD:** Dr Isaac Odame addressed this topic and emphasized the need for effective advocacy as a way of giving prominence to a disease condition, attracting attention from policy-makers, and empowering affected patients. He mentioned examples of other diseases like cancer, haemophilia and HIV. SCD has peculiar challenges in that it is a genetic, complex disease that is not easy to diagnose and is clinically very heterogeneous. A successful advocate must be well-informed, persistent, and able to interact effectively with the authorities. The most important advocates are patient groups and their families, followed by the different cadres of health care providers. These two groups need to work hand in hand. Policy-makers have to be persuaded to come on board with information and evidence. This is the way to generate the political will that is needed to increase the budget for the disease. The leaders should learn that the attention they give to the disease will attract external funding for the programmes that will contribute to the care of the patients. The roles of

community leaders, traditional chiefs, religious leaders, etc. cannot be overemphasized. Training in the art of advocacy should be encouraged to produce individuals with the expertise that can work specifically to promote SCD in the community.

- **Community involvement:** Dr Ibrahima Diagne addressed this issue as an extension of Dr Odame's contribution to advocacy. The government, through the ministry of health, should prioritize SCD care and provide funding for strategic control plans. Areas of concern should be information and awareness, the equipment of health facilities, the development of management guidelines and early diagnosis. Community health workers should receive specific training on SCD. Different civil associations in the community should form partnerships to advocate for SCD. Information about the disease should be included in primary school curricula, and teachers should be trained on the needs of affected children. The main targets of care and concern should be affected children, adolescents and young adults. There should be organized information and awareness events in high schools and universities. Employers should make allowances to accommodate the needs of patients under their responsibility. All communication channels should be utilized to disseminate information about the disease, including social media, social networks, and sports and entertainment events.

- **Role of the private sector in partnering with government:** Dr Kwaku Marfo outlined the complementary roles of the private, governmental and nongovernmental sectors in promoting SCD management. Private high-end philanthropists and companies, including the pharmaceutical industry, should be motivated to fund infrastructure and capacity strengthening, especially for clinical research and the training of health care workers. The main role of government is to have the political will to prioritize SCD in financial allocation, especially in countries with high sickle-cell prevalence. They should implement national efforts to gather data for planning purposes, and establish organized, integrated systems of care. A health insurance policy is necessary to reimburse or subsidize the cost of standard interventions. NGOs should promote public awareness, drive

public policy through legislative action, and collaborate with other key stakeholders in driving cohesive advocacy.

- **Research:** Dr Julie Makani gave a presentation on research on SCD in Africa. She stressed that SCD is a multifaceted disease, that interfaces with public health science, basic science, clinical science, and social science, with their individual ramifications. We need to develop capacity in these areas. It is paramount to have a strong database, which will be achieved by local registries being fed into national and regional databases. She outlined the various opportunities available for research on the continent and the need for inclusion and equity in various programmes and clinical trials so that Africa is well represented, all the more so as it will benefit from newer treatment modalities, especially stem cell transplantation and gene therapy.

Second technical meeting (first Delphi round): The next meeting, held on 10 November 2022, was the first round of eDelphi. The convener had circulated a document with a draft framework derived from the previous discussions and suggested definitions for a treatment centre and centre of excellence, criteria for the designation, facilities, and amenities that would qualify a centre to be a primary, secondary, or tertiary health care facility for the treatment of SCD. Suggestions were also made on how the centres would be monitored and integrated. These were the points that were deliberated upon and debated at this meeting. There were robust interactions, and modifications were made.

Third technical meeting (second Delphi round): The second round of eDelphi was on 1 December 2022, at which the suggestions and corrections incorporated from the previous round were again discussed until a consensus was reached. It was then agreed that the convener should start writing the final report of the panel's work. Dr Prebo Barango and Dr Kouamivi Agboyibor, outlined the timeline going forward, and it was agreed that the panel would have a physical meeting sometime in January or February 2023 at which the report will be finalized.

Meeting with WHO AFRO experts: A meeting of the experts was held in Brazzaville with representatives of the NCD and other relevant programmes from 12 to 14 April 2023. Various inputs were obtained on the draft of the framework document. A revised copy was therefore produced and sent back to Dr Barango on 1 May 2023.

Review of the revised draft. The draft was returned on 20 May 2023, with several new comments and suggestions, including a change in the title, with implications for the terms of reference of the panel. This warranted extensive rewriting of several parts of the document. This latest revision was done, and the document sent back to Dr Barango on 27 July 2023.

World Health Organization

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