ADVANCES VIEWPOINT

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Building capacity for pediatric hematological diseases in Sub-Saharan Africa

Lulu Chirande,[1] Ruth Namazzi,[2] Marilyn Hockenberry,[3] Peter Wasswa,[3] Sarah Kiguli,[2] Tadala Mulemba,[4] Julie M. Gastier-Foster,[5] Magdalena Lyimo,[6] Gladstone Airewele,[3] Joseph Lubega,[3] and Nmazuo Ozuah[3]

[1]Department of Pediatrics, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania; [2]Department of Pediatrics and Child Health, Makerere University College of Health Sciences, Kampala, Uganda; [3]Department of Pediatrics, Baylor College of Medicine, Houston, TX; [4]Pediatric Hematology-Oncology Program, Baylor College of Medicine Children's Foundation, Lilongwe, Malawi; [5]Department of Pathology, Baylor College of Medicine, Houston, TX; and [6]Department of Haematology and Blood Transfusion, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

The spectrum of hematological diseases in African children includes anemias, bleeding disorders, thromboses, and oncological diseases such as leukemias. Although data are limited, outcomes for these diseases are poorer in Africa. The dearth of specialists, and lack of infrastructure that supports diagnosis and management, have been identified as key barriers to improving outcomes for childhood hematological disorders in Sub-Saharan Africa (SSA). To address these, intentional capacity building efforts addressing education and training, diagnostic capacity, and access to blood products and medicines are needed. This article explores some ongoing efforts in the region aimed at fostering the capacity to identify and treat childhood hematological disorders across a breadth of initiatives targeting the critical themes of education, diagnostic support, and treatment. We also identify existing opportunities through international partnerships, to build sustainable programs that can support children with hematological diseases in SSA.

Introduction

Globally, there has been a rise in the burden of disease due to noncommunicable diseases (NCDs) in low- and middle-income countries (LMICs). This is, in part, because of effective public health strategies that have contributed to reduction in infant and childhood mortality due to infectious diseases over the past decades.[1] LMICs are experiencing an epidemiological transition from predominance of infectious diseases toward NCDs, and in Sub-Saharan Africa (SSA), the proportion of all disability-adjusted life years attributable to NCDs has increased from 19% to 30% between 1990 to 2017.[2] Hematological (inherited and acquired) diseases in children contribute to NCDs in SSA, and result in significant morbidity and mortality.[3] The precise burden of childhood hematological disorders in SSA is unknown because of lack of detection and diagnostic capacity, population-based registries, and appropriate treatment infrastructure. Building and retaining skilled workforce, strengthening existing health infrastructure and supply chain for medications, improving access to blood products, enhancing laboratory diagnostics, and ensuring sustainable funding are critical steps to improving pediatric hematology in the region.

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Burden and spectrum of pediatric hematological diseases in children in SSA

The spectrum of pediatric hematological diseases in SSA mirrors data from other regions, with a disproportionate representation of specific pathologies because of inherited ancestral, environmental, and socioeconomic influences that are unique to the region. Anemia is a global public health problem that affects ~2 billion people worldwide,[4] particularly children and woman of reproductive age. Although the prevalence varies across countries, SSA has the highest burden, with >50% of children aged <5 years being anemic.[5,6] The etiologies of anemia in African children are multifactorial, and include infection, inflammation, nutritional deficiencies, and inherited red cell disorders.[7-9] These risks often coexist, complicating diagnosis and management in settings in which diagnostic capacity and hematology expertise are less developed.

Iron deficiency anemia is the most common nutritional anemia among children in Africa.[5] Poor dietary intake, especially in most staple diets taken in SSA, low absorption because of high phytate levels in the diets, and chronic blood loss from intestinal worms and chronic inflammation contribute to the high prevalence.[10,11] Inherited disorders of hemoglobin and glucose-6-phosphate dehydrogenase deficiency are among the top 5 most common genetic hematological disorders that affect red cells. Hemoglobinopathies such as sickle cell disease (SCD) and thalassemia account for 6.4% of mortalities in children in Africa.[12] SCD is the most prevalent inherited hematological disorder in the world. Over 400 000 children are born with SCD every year, and ~8 million people live with the disease worldwide.[13] Of children born with SCD each year, 80% are in SSA. Nigeria, Democratic Republic of Congo, Tanzania, Angola, and Uganda are among the top 5 countries with the highest burden of SCD.[14,15] Access to evidence-based clinical care, early diagnosis through newborn screening, and comprehensive care for SCD remains a challenge in most parts of SSA, and the outcomes remain poor, with 40% to 90% of children dying before age 5 years.[16,17] This contrasts sharply with high-income countries (HICs), in which >50% of patients live well into the fifth decade.[18,19] Most HICs have routine newborn screening and evidence-based interventions to prevent the complications of SCD. Glucose-6-phosphate dehydrogenase deficiency is the most common red blood cell enzymopathy worldwide and is highly prevalent in malaria-endemic Africa.[20] Diagnosis requires quantitative spectrophotometric analysis or, more commonly, a rapid fluorescent spot test detecting the generation of reduced NADP from NAD phosphate, neither of which is widely available in SSA. Immune-mediated hemolytic anemias, and bleeding disorders such as hemophilia occur but remain largely underdiagnosed because of insufficient laboratory infrastructure for diagnosis.

Cancer is a major cause of childhood mortality in HICs, and increasingly in SSA as well. Hematological malignancies (leukemia and lymphoma) are the most common pediatric cancers worldwide including in SSA, comprising ~40% of malignancies. Recent data from a multicenter cohort of 1399 children diagnosed with cancer at 2 of the largest tertiary hospitals (Mulago National Referral Hospital and Mbarara Regional Referral Hospital in Uganda; Figure 1) suggest that leukemia and lymphoma contribute to ~50% of all pediatric cancers. In striking contrast to 80% to 90% long-term survival in HICs, survival for pediatric hematological malignancies remains dismal in SSA, as low as 30%.[21-24] In several treatment facilities in SSA, hematological malignancies such as acute myeloid leukemia are treated with a palliative intent, with or without chemotherapy because of inadequate supportive care, and high treatment-related mortalities. These enormous disparities in outcomes of pediatric hematological disease underscore the urgent need to develop clinical, educational, and research capacity to improve outcomes of blood disorders in SSA. We review strategies and initiatives to build the capacity for managing these conditions in SSA.

Initiatives to address disparities in outcomes for pediatric hematological diseases in SSA through education

Lack of a skilled workforce, including clinical and diagnostic capacity, contribute to the dismal outcomes for pediatric hematological diseases in SSA. In the majority of countries in SSA, the World Health Organization (WHO) minimum target of 1 hematologist per 100 000 is not met.[25] For example, in Uganda, a country of 47 million people, there was no trained pediatric hematologist until 2018. The majority of countries in SSA have only few pathologists, transfusion specialists, radiologists, critical care physicians, and pediatric nurses to support specialized pediatric hematology care. Development of graduate medical education programs within SSA is ideal because it can tailor training to local disease epidemiology and health system context, as well as minimize brain drain to HIC. There are some examples of such innovative education and training programs helping to address the gap of lack of skilled specialized workforce for pediatric hematology in SSA.

PHO fellowship training programs in SSA. Texas Children's Global Hematology-Oncology-Pediatric-Excellence (Global HOPE) program (United States), partnered with Makerere University College of Health Sciences and Mulago National Referral Hospital (both in Uganda) to establish the pediatric hematology-oncology (PHO) training fellowship program at Makerere University, to address the lack of trained workforce in the region.[26] Global HOPE funds this training program. The purpose of this program was to build a critical mass of locally trained PHO specialists that would foster further development and sustainability of the field. The training curriculum was developed using graduate curriculum guidelines of Makerere University and Baylor College of Medicine (BCM) and accredited by the Uganda Medical and Dental Practitioners Council. Trainees in this 2-year fellowship, acquire skills in 5 core competencies: evidence-based clinical care in PHO, procedural and diagnostic skills, communication and professionalism, leadership and advocacy for PHO, and research skills. The fellowship program uses a combination of traditional on-site clinical training by PHO faculty and innovative educational platforms, including >40 custom didactic web-based lectures, video teleconferencing, and mobile internet-based education. Highly experienced pediatric hematologists-oncologists from BCM, with prior experience of training and living in SSA or LMICs, participate in all aspects of training, including on-site bedside training, online clinical consultation and didactic education, and mentoring of local junior faculty. The curriculum covers all childhood cancers and blood disorders, with specific emphasis on local disease patterns and

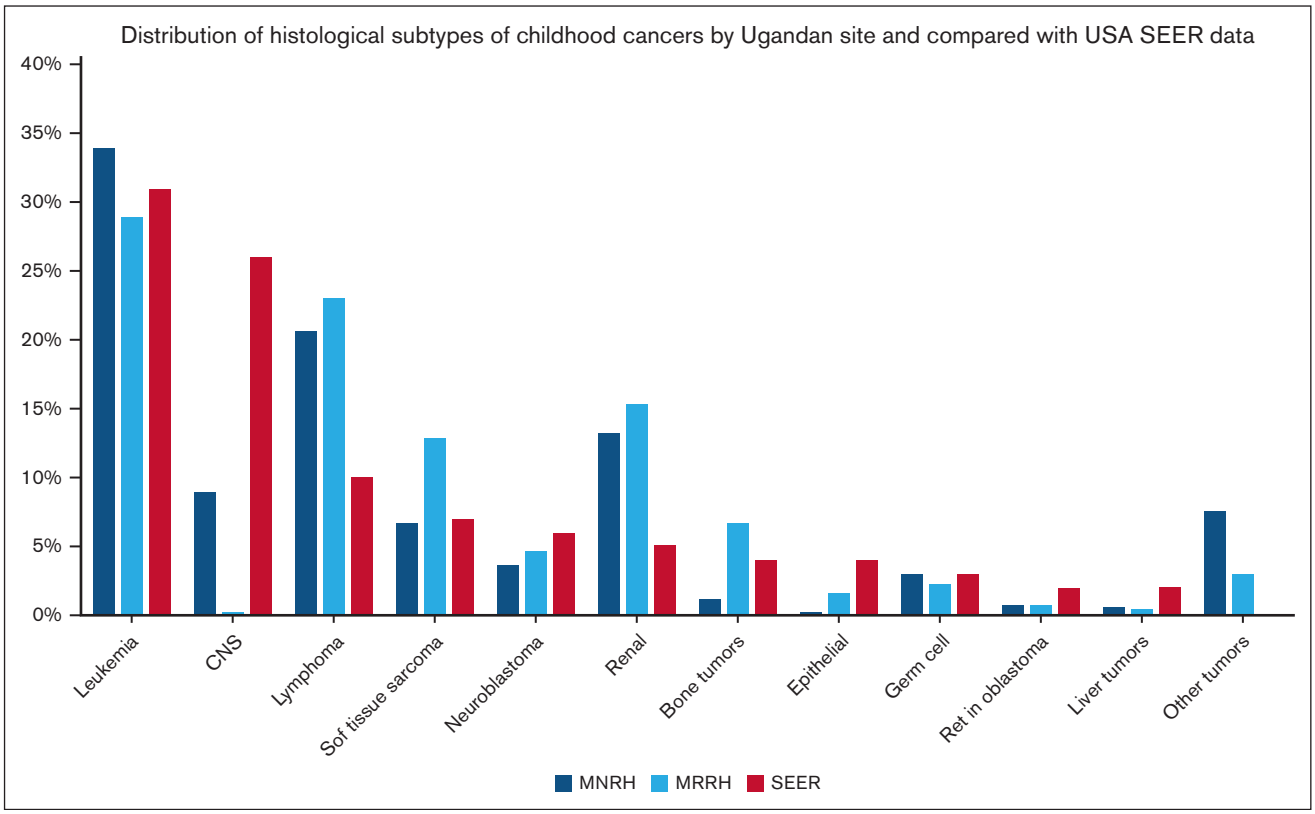

Figure 1. Contribution of leukemia and lymphoma to childhood cancers at 2 hospitals in Uganda, compared with data from the SEER program of the US National Cancer Institute. CNS, central nervous system; MNRH, Mulago National Referral Hospital; MRRH, Mbarara Regional Referral Hospital; SEER, Surveillance, Epidemiology, and End Results.

problems, available resources, and patient referral patterns. Fellows participate in weekly multidisciplinary conferences (leukemia, lymphoma, and SCD) that are led by onsite PHO experts in Uganda Fig. 2. Faculty and trainees from related specialties within and outside the department of pediatrics of Makerere University's College of Health Sciences participate in these hematology multidisciplinary conferences, thereby, expanding the educational reach to all relevant health professionals and trainees at the

Figure 2. A multidisciplinary case discussion: one of the key learning avenues for the PHO fellowship programs.

College of Health Sciences. Other unique educational features of the program include weekly clinical video case-based teleconferences between fellows, BCM disease experts, and clinical teams in multiple affiliated countries across Africa, including Malawi, Botswana, Kenya, and Tanzania. The first year of this accredited fellowship program involves clinical immersion in inpatient and outpatient care and didactics, whereas the second year is dedicated to experience in longitudinal clinical care and didactic learning. Fellows in their second year are provided mentorship to complete scholarly work in the form of a clinical research project.

The program has since trained 24 pediatric hematologists and oncologists, representing 7 countries. These specialists have returned to 5 countries (Kenya, Tanzania, Malawi, Botswana, and South Sudan) and together they care for >2000 children with hematological malignancies annually, in addition to >10 000 children with SCD, and hundreds of children with other hematological disorders including iron deficiency anemia, hemophilia, bleeding and clotting disorders, and hemolytic anemia.

In 2020, Global HOPE supported the development of the Muhimbili University of Health and Allied Science (MUHAS) PHO fellowship in Tanzania, modeled after the fellowship in Uganda, which has trained 6 PHO specialists, adding to the growing number in East Africa. The MUHAS program is funded through support from Global HOPE, and the government of Tanzania. These programs have resulted in improved clinical outcomes. For example, in Uganda, the 1-year overall survival for acute myeloid leukemia improved to 78.6%, with remission rates of 56%.[23]

Recruitment in these programs follow local university policies and is competitive, with eligible candidates undergoing structured interviews. All available spots have been filled consistently. Financial support is available for candidates from other countries. Ongoing mentorship, institutional commitment, and support from Global HOPE ensure these trainees return after their training; 87% have returned home, and when this was not the case, it was because of extremely difficult circumstances.

Similarly, the Ethiopian program was developed in 2013 to address the dire need for PHO specialists in Ethiopia. Fellows spend 18 months onsite in Ethiopia, and a 6-month attachment at a cancer center in a middle- or high-income country.[27] The local faculty were initially supported by full-time onsite PHO experts from the Aslan Project in the United States.[28] The program has graduated >6 fellows to date, who have now taken on the leadership and advocacy of the program. The African Pediatric Fellowship Program has also supported subspecialty training in PHO at the University of Cape Town and University of Witwatersrand, both in South Africa.[29] These programs are largely successful because of the pragmatic approach in which most training is based in SSA, with support from ≥1 high-income institutions, and have become a successful model for increasing pediatric hematology specialists. They can be replicated in the rest of the SSA, and in many other LMICs, and the support can be leveraged from the growing number of PHO specialists in Africa.

PHO nursing training program. Nursing is critical to improving survival for childhood hematological diseases. A specialized nursing program soon followed the establishment of the PHO fellowship in Uganda. The goal of the nursing program was to provide specialized training for all nursing care for children with cancer and blood disorders and was particularly important because SSA experienced the growth in number of PHO centers aiming for more intense therapies with a goal of getting better cure rates, but with substantially more toxic effects. This training was developed by nursing education experts from BCM and African centers and uses a continuing professional development (CPD) approach. Each course in the CPD program is developed in the Modular Object-Oriented Dynamic Learning Environment (MOODLE) open-source education platform and downloaded onto computer notebooks. MOODLE is accessed through the internet and can also be used on mobile devices. Global HOPE funded the development of MOODLE and provided 56 computer notebooks in the initial rollout of the courses. If participants in the course do not have access to the internet but have a computer, course materials are uploaded to their computer's hard drive. This distance-based learning program supports formal training for nurses who work as full-time specialists in pediatric hematology and oncology in several countries.[30] Courses specific to hematological disorders provide a rich foundation for understanding nursing care for children with SCD, hemophilia, aplastic anemia, and other blood disorders. For sustainability, partnerships with schools of nursing have been developed to integrate PHO nursing content into the undergraduate curriculum, and several schools are working on PHO specialty tracks within their curriculum using the courses. The Global HOPE nursing course provides the foundation for the basic core curriculum for PHO nursing and is already accredited by the Uganda Nursing Council. Sixteen additional courses have been developed for continuing education credit to support advanced pediatric specialization. Examples of additional CPD courses include pediatric palliative care, pediatric pain assessment and management, pediatric wound care, quality improvement in health care, and evidence-based practice nursing.[31] Over 260 healthcare providers from 8 countries have completed the PHO nursing foundation course. Currently 1540 participants from 22 countries have enrolled in the online courses.

Training of primary health care workers to improve access to hematology care in SSA. Primary health care is a central pillar for optimal delivery of chronic care for NCDs. In SSA where the burden of pediatric hematological diseases is high, it is imperative that primary health workers are appropriately skilled in providing care for these children. Some examples include the Mali diploma in SCD training scheme, an accredited short course targeting the Francophone SSA countries[32] and aims to equip health workers to manage SCD at the primary health care level. Health care workers spend 2 weeks at a center of excellence for SCD and acquire both theoretical and practical skills in the management of SCD. Since its inception, a total of 180 primary health care workers have been trained. In Uganda, under the National Institutes of Health (NIH)-funded "Enhancing Research Capacity for Sickle Cell Disease and related NCDs across the lifespan in Uganda" (1D43TWO12466-01), 30 primary health care providers have been trained in the management of SCD in a 6-month hybrid training program. The program encompasses 5-day in-person training, monthly webinars, and mentorship from pediatric hematologists. The program has trained 30 primary health care workers who are able to diagnose and manage SCD. Similar programs can be adapted for other common hematological disorders to improve care at primary health care level, and referral to specialized units.

Improving access to diagnostics

The Lancet Commission on Diagnostics estimated that only 47% of the world population has access to diagnostic services.[33] Standard testing for hematological disease requires hemoglobin electrophoresis, high-performance liquid chromatography, immunohistochemistry, flow cytometry, peripheral blood and bone marrow aspirates, full blood counts, chemistries, and blood cultures, none of which is easily available to most populations in SSA. Even when available, the costs are too high for patients and, frequently, clinicians are forced to treat patients based on clinical suspicion. Reagent stockouts and equipment downtime (due to lack of trained personnel and resources to maintain equipment) further complicate the challenge. However, the cost of a wrong diagnosis, and consequently treatment, increases financial burden on patients and the health care system in addition to the compromised treatment outcomes.

Solutions to improve access to diagnostic services in SSA include intraregional, intracontinental, and intercontinental collaborations; advocacy for government funding; and, importantly, training of relevant specialists such as pathologists, hematologists, laboratory scientists, biomedical engineers, and technicians. For sustainability and capacity building, diagnostic tests should be performed within countries whenever possible. Point-of-care tests, suitable for some diseases, are often amendable to more remote settings and require minimal technical training. HemoTypeSC and SickleScan point-of-care tests for the diagnosis of SCD are already validated in large scale diagnostic trials and are in use in a number of countries, expanding access to SCD screening.[34,35] Establishment of regional reference laboratories, as has been done for tuberculosis, can allow for immediate access to more complex testing in the short term while serving as training centers, and catalyze establishment of laboratories in other countries.[36] Telepathology and similar platforms can be used to facilitate knowledge and skills transfer within Africa and between Africa and HICs.[37,38] Benchmarking and sharing resources with well-established and successful programs that use similar diagnostic techniques and equipment, such as flow cytometry for CD4 monitoring, can provide cost-effective solutions to some of the diagnostic challenges in resource limited settings. Furthermore, the use of automated machines is preferable to manual operations, both for scaling and accuracy. Ultimately, partnerships with companies committed to the expansion of diagnostic capabilities in LMICs using compassion pricing are critical to expanded access to diagnostics.

Subspecialty training for hematopathologists and other specialties for improved diagnostics for hematology. Improvement in pediatric hematology is dependent on hematopathology capacity. There is a dearth of pathologists, let alone hematopathologists in SSA. Educational approaches to address this dearth include a combination of formal pathology training for pathology residents, practical hematopathology sessions with fellows and other PHO health care workers, and the use of telepathology. In Uganda, a full-time onsite UK-trained hematopathologist developed training schedules that included practical and didactic sessions. Training also includes real-time clinical apprenticeship in which fellows, pathology residents, and laboratory technicians work closely with the hematopathologists to prepare, read, and interpret diagnostic tests. Alongside this, in Uganda and Malawi, Global HOPE supported the development of flow cytometry services for leukemia diagnosis. Again, using a capacity building approach, experts from the Global HOPE network worked with local faculty and laboratory technicians to set up, pilot, and interpret flow cytometry for leukemia.[39] A similar approach is being used to improve molecular testing for leukemia in the region.[40]

Access to blood transfusion products

Hematological diseases often require transfusion of blood products. Up to 54% of blood transfusions in low-income countries go to children aged <5 years.[41] Whole-blood donation rate serves as an indicator for the availability of blood products in a country. In 2016, the WHO Global Database on Blood Safety revealed that <5 units of blood were donated per 1000 population in many African countries, far fewer than the estimated requirements of 10 units per 1000 population per year. This rate has slightly increased to 5.9 units per 1000 population as of 2022.[42] However, donations remain suboptimal primarily because of limited numbers of voluntary nonremunerated blood donations (VNRBD). Priority should be placed on efforts to increase VNRBDs.

In the addition to low proportion of VNRBD to family replacement blood donations, steady and safe supply of blood products in SSA is limited by factors such as ability to separate blood into components, high rates of transfusion-transmissible infections, lack of national blood transfusion policies, and lack of government funding. Through collaborative efforts of governments, research institutes, communities, and development partners, a number of strategies including stronger community engagement, donor education, and population sensitization can be used to improve blood safety and availability in SSA. The WHO recommends establishment of coordinated blood transfusion services and quality management, expansion of voluntary unpaid donors, and quality-assured screening of all donated blood for transfusion-transmissible infections, and rational use of blood products, as strategies to improve access to blood transfusion.[43-45]

Access to medicines for blood diseases

Hemophilia and SCD are emblematic of the peculiar challenges of accessing medicines to treat hematological diseases in SSA. Seventy five percent of patients with hemophilia live in the developing world and do not have access to routine factor products.[46] Although the incidence of hemophilia is estimated to be similar across populations in the world, the observed differences are mainly because of limited access to diagnosis as discussed above. Treatment of hemophilia with humanized or recombinant factor concentrates is relatively expensive and unaffordable for most people in SSA, hence the use of either whole blood or fresh frozen plasma is routine. A few patients benefit from factor concentrates during life-threatening bleeding events and almost none have access to prophylactic factor treatment that is recommended to prevent disabilities. Prophylactic factor treatment requires 3 to 4 IV injections per week, which, in addition to the financial burden, is met with poor compliance and challenges with venous access.[47,48] The World Federation of Hemophilia has successfully worked with LMICs to improve access to diagnosis and management of hemophilia, donation of factor concentrates, and building capacity for health care workers through training.[49-51] Recent advances in therapies (eg, emicizumab) have revolutionized care for hemophilia, and are attractive agents for use in SSA, because they circumvent some barriers to factor use such as repeated hospital visits for

infusions and venous access.[52] Certainly, a major barrier to these novel therapies is the unit cost for the drug. However, these can potentially be reduced by governments in SSA working with partners such as the World Federation of Hemophilia.

The safety and efficacy profile for hydroxyurea (HU) in SCD in SSA is proven.[53,54] Although HU is much cheaper and with less complexities in the supply chain than factor for hemophilia, access to the drug as abysmally low in SSA. Limited availability and affordability, lack of awareness and self-efficacy among health workers, patient misconceptions, and unfriendly formulations for children, all hinder wider use in SSA.[55-57] To address some of these barriers, the Republic of Tanzania piloted local manufacturing of HU and showed this to be feasible and affordable.[58] Nigeria is currently the only country in SSA that manufactures HU locally. Collaboration with pharmaceutical companies to scale up local manufacturing of HU in SSA, developing standard treatment guidelines and learning from existing and well-performing programs like procurement and supply of antiretroviral drugs can help scale up HU use.

Similarly, access to anticancer drugs for hematological malignancies remains poor in SSA.[59] Similar barriers to HU and factor exist and are further compounded by the wide variety of combination agents required for each cancer subtype, unreliable availability of the medicines in the pharmaceutical market in countries, lack of treatment protocols and policies to guide registration, and procurement of anticancer medicines in SSA.[60-62] Strategies to improve access to anticancer drugs encompass cancer drugs on the national essential drugs list,[63] increased participation in clinical trials in hematological malignancy, social impact business models, and pooled procurements.[64,65]

Beyond the availability medications, training pharmacists on safe preparation of chemotherapy and management of PHO diseases, and robust supply chain and procurement procedures for medications are crucial to ensuring safe provision of PHO medicines. Through the Organization of Eastern Caribbean States and the Pan American Health Organization, the Caribbean and South American countries, respectively, have demonstrated that pooled procurement of childhood cancer medicines can overcome challenges of low purchasing power.[66,67]

Access to HSCT

A significant proportion of children with hematological diseases now require treatments such as hematopoietic stem cell transplantation (HSCT). These services are largely nonexistent in SSA, forcing patients to seek treatment outside the continent.[68,69] The successful cellular program in Egypt attests that HSCT is feasible in LMICs.[70] Although establishing HSCT requires costly investments in infrastructure and human resources, the costs in LMICs has been shown to be significantly lower than in HICs. For example, the average cost of HSCT in Egypt is 17 000 United States dollars, which is about 10% of the cost in the United States.[70] Muhimbili National Hospital and Benjamin Mkapa Hospital in Tanzania have partnered with institutes in India and Italy to set up HSCT programs in which the cost of the procedure is one-third of that in United States.[71] The Aga Khan Health Services are partnering with governments in Tanzania and Kenya to set up HSCT.[72] Outcomes from centers in LMICs have been comparable with those in HICs, suggesting the lower costs are likely driven by lower personnel and administrative costs, and not compromised quality.[73,74] Recognizing the financial and social challenges in SSA, building upon critical care support services and strengthening availability of blood products, investing in stem cell research and processing facilities, and taking steps toward establishing national bone marrow transplant matching registries are reasonable initial steps in preparation for full-scale HSCT services. These efforts should be complemented with training multidisciplinary teams that include infectious disease specialists, microbiologists, immunologists, laboratory scientists, and intensivists, among others. Hospital infrastructure and operations need to be strengthened to manage patients who are immunocompromised who require long-term follow-up for monitoring and management of complications such as graft-versus-host disease.

Opportunities for training research scientists in pediatric hematology. There is a need to train scientists and infrastructure for hematological research including multicenter clinical trials, and longitudinal cohort studies. Initiatives such as the Sickle Pan Africa Research Consortium, an NIH funded collaboration between 6 countries in Africa are building research capacity, skills, and locally adapted standards of care for SCD.[75,76] Notably, the Sickle Pan Africa Research Consortium is developing longitudinal databases that can be leveraged for well-designed observational studies. To foster multisite Africa-led research for other hematological disorders, and to build research capacity, similar initiatives should be developed. Funding mechanisms targeting researchers in LMICs such as the American Society of Hematology global research award, the Fogarty International Center of the NIH, and other funding bodies will be particularly important to drive these research capacity building programs. Such mechanisms should also be supported by local funding from governments in SSA and local research organizations.

Government investment is needed to sustain capacity building programs in SSA

Challenges remain as wider implementation of training programs for pediatric hematology across Africa develop. The estimated cost of training a fellow in the Ugandan program is ~$20 000 annually. Because most of current funding for these training programs are external, local commitment is necessary. The government of Tanzania, for example, provides tuition scholarships to indigenous fellows in the MUHAS program. Additionally, retaining this workforce requires governmental support for conducive work environments that encourage professional growth. Although capacity-building initiatives with high-income partners are encouraged, there is need to sustain these diagnostic and clinical infrastructure. Beyond training and retention, national budgets should include funding to support provision of required medicines and supplies, safe and efficient blood banking services, and improved laboratory capacity for comprehensive pediatric hematology services.

Conclusion

SSA has a disproportionately high burden of pediatric hematological diseases. Lack of trained health workforce, and insufficient health infrastructure that supports diagnosis and management are key barriers to improving survival of children with hematological

disorders in SSA. Collaborative efforts targeting education and training through innovative programs, strengthening of diagnostic capacity, and access to medicines through international partnerships have yielded significant results in some countries in the region and serve as a model to be replicated in others. Improving research capacity is critical to understanding the full scale of these disorders and developing locally adapted and evidence-based treatment paradigms. Ultimately, intentional support from governments in SSA, achievable through strong and continued advocacy is paramount to the sustainability of these efforts.

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ORCID profile: N.O., 0000-0001-5344-7875.

Correspondence: Nmazuo Ozuah, Texas Children's Cancer and Hematology Centers, 1102 Bates Ave, Houston, TX 77030; email: nmazuo.ozuah@bcm.edu.

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