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REVIEW ARTICLE

Toward the Cure of All Children With Cancer Through Collaborative Efforts: Pediatric Oncology As a Global Challenge

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ABSTRACT

Advances in the treatment of childhood cancers have resulted in part from the development of national and international collaborative initiatives that have defined biologic determinants and generated risk-adapted therapies that maximize cure while minimizing acute and long-term effects. Currently, more than 80% of children with cancer who are treated with modern multidisciplinary treatments in developed countries are cured; however, of the approximately 160,000 children and adolescents who are diagnosed with cancer every year worldwide, 80% live in low- and middle-income countries (LMICs), where access to quality care is limited and chances of cure are low. In addition, the disease burden is not fully known because of the lack of population-based cancer registries in low-resource countries. Regional and ethnic variations in the incidence of the different childhood cancers suggest unique interactions between genetic and environmental factors that could provide opportunities for etiologic research. Regional collaborative initiatives have been developed in Central and South America and the Caribbean, Africa, the Middle East, Asia, and Oceania. These initiatives integrate regional capacity building, education of health care providers, implementation of intensity-graduated treatments, and establishment of research programs that are adjusted to local capacity and local needs. Together, the existing consortia and regional networks operating in LMICs have the potential to reach out to almost 60% of all children with cancer worldwide. In summary, childhood cancer burden has been shifted toward LMICs and, for that reason, global initiatives directed at pediatric cancer care and control are needed. Regional networks aiming to build capacity while incorporating research on epidemiology, health services, and outcomes should be supported.

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INTRODUCTION

Advances in clinical and biologic characterization, the development of risk-adapted therapies, and the optimization of supportive care have resulted in a dramatic increase in the cure rates of children with cancer over the last four decades.[1,2] Collaborative work by North American and European pediatric oncology consortia have been a centerpiece in achieving these milestones. Prognostic clinical and biologic factors have been identified and treatments have been optimized, often through complex biology-based risk stratification algorithms. However, one indisputable truth defines pediatric oncology: the most important prognostic factor for a child with cancer is where he or she was born.[3] Thus, the major challenge in pediatric oncology for the next few decades will be how to translate gains achieved in higher-income settings to all children worldwide. Carefully designed initiatives, development of national and regional frameworks for collaboration, and incorporation of clinical, biomedical, and health services research are crucial to meeting this challenge.[4] We believe that regional consortia are an ideal platform and potential catalyst for development and coordination of these activities. In this article, we define why pediatric oncology is a global health problem, describe regional differences in pediatric cancer burden, and summarize the state of regional and international collaborative efforts in limited-resource settings.

PEDIATRIC ONCOLOGY AS A GLOBAL PROBLEM

As low- and middle-income countries (LMICs) continue to improve their health status, the need to develop and maintain cancer programs is becoming

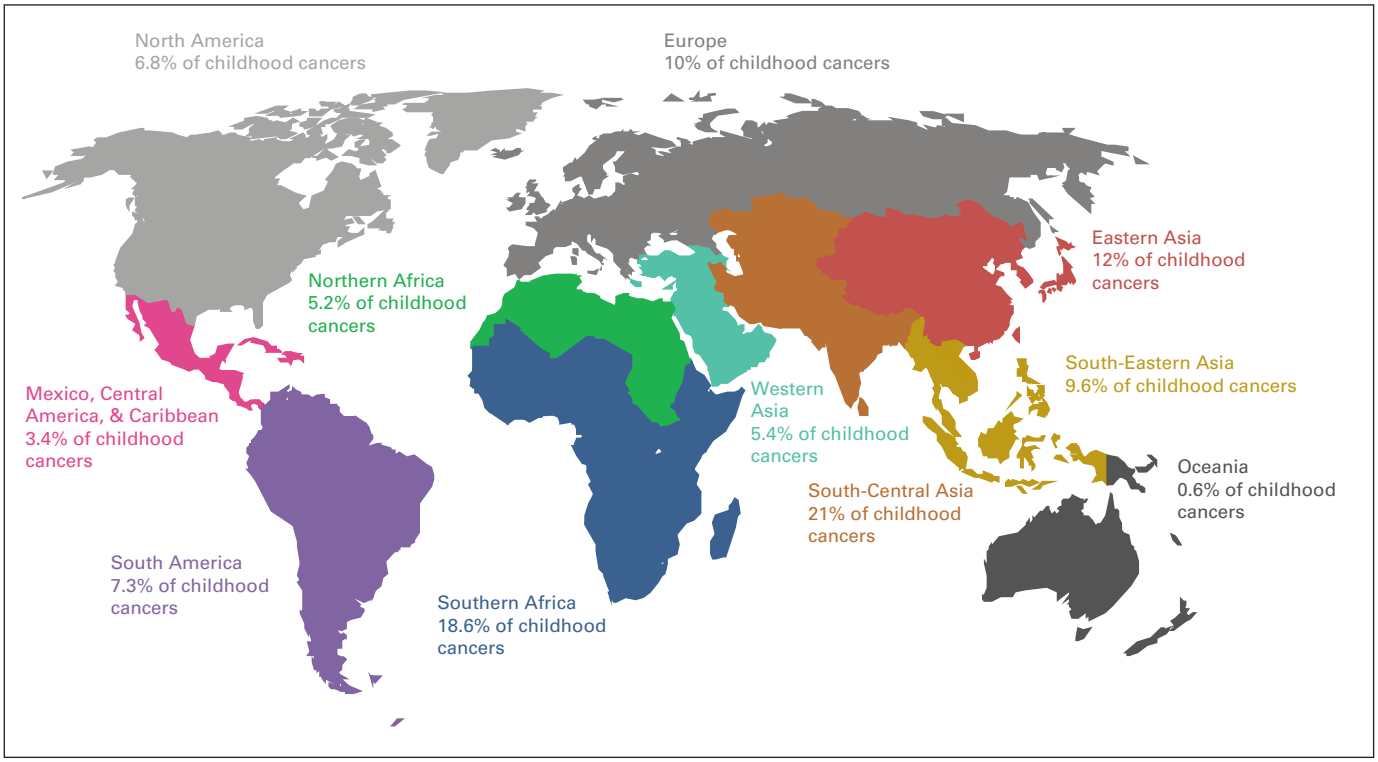

Fig 1. Global distribution of childhood cancer by region. Source: World Bank Databank[10] and GLOBOCAN 2012.[11]

imperative. Globally, the number of new cancer cases in all age groups will increase from 12.7 million in 2008 to 22.2 million by 2030. An increasing proportion of this cancer burden falls on LMICs, not only because of demographic change, but also because of a transition in risk factors resulting from globalization of economies and behaviors.[5,6] However, there is a dramatic inequity in the distribution of resources for cancer care and control worldwide. Although almost 80% of the disability-adjusted life-years lost worldwide to cancer are in LMICs, these countries have less than 5% of global resources for cancer care and control.[7] The global economic cost of new cancer cases in 2009, including medical and nonmedical costs, productivity losses, and the cost of cancer research, was estimated to be at least US$286 billion.[8] Although LMICs host more than two thirds of the world population and new cancer cases, they account for only 6.2% of the financial expenditures on cancer worldwide.[9]

Collaborative efforts are needed to address these unique national and regional circumstances. Of the estimated more than 160,000 children and adolescents diagnosed with cancer every year, approximately 80% live in countries with limited resources (Fig 1). The crude numbers are sensitive to the reference population, incidence rates reported, and perspective used—economic (Table 1) versus regional (Table 2)—but the estimation of burden is consistent. The mortality rate for children younger than age 5 years (under-5 mortality rate [U5MR]) tends to be a good reflection of the strength of childhood health care delivery systems.[13] Merged data from the World Bank and GLOBOCAN show that U5MR and childhood cancer incidence are inversely correlated (Fig 2); therefore, as child health care systems improve and competing causes of mortality decrease, the number of childhood cancer cases increases. In LMICs, the expectation is that pediatric cancer cases will

Table 1. Estimated Annual Cases of Childhood Cancer Worldwide by Income Level

Income Category	Total Population*	Population Age 0-14 Years (as % of population)*	Population Age 0-14 Years	Incidence of Childhood Cancer (per million)†	Expected Childhood Cancer Cases	Percentage Living in LMIC
High	1,306,000,000	17.3	226,068,600	148	22,458	
Upper middle	2,409,000,000	21.9	527,089,200	118	62,197	
Lower middle	2,561,000,000	32.0	818,751,700	73	59,769	
Low	848,700,000	39.3	333,199,620	76	25,323	
Total	7,124,700,000	—	1,905,109,120	—	180,747	
Total for LMICs					147,289	81.5

Abbreviation: LMIC, low- and middle-income country (combination of upper middle–, lower middle–, and low-income countries).
*Source: World Bank Data by Country.[10]
†GLOBOCAN does not report incidence by World Bank Atlas Method categories. Incidence for very high, high, medium, and low human development level was used as shown for high-, upper middle–, lower middle–, and low-income countries, respectively. The total number of cases for age 0-14 years reported in GLOBOCAN 2012 for the world is 163,282. Source: International Agency for Research on Cancer: GLOBOCAN 2012.[11]

Table 2. Estimated Annual Cases of Childhood Cancer Worldwide by Region

Region	Total Population*	U5MR*	Percentage of Total Population Age 0-14 Years*	Population Age 0-14 Years†‡	Percentage of Global Population Age 0-14 Years†	Incidence of Childhood Cancer (per million)§	Childhood Cancer Cases†	
							No.	%
Europe	743,008,000	7	15.6	115,857,187	6.3	139	16,104	9.9
North America	353,860,000	7	19.0	67,220,072	3.6	165	11,091	6.8
Latin American and Caribbean	611,122,000	21	26.0	158,891,720				
Caribbean	40,972,000	34	24.9	10,195,443	0.6	79	805	0.5
Central America	164,211,000	18	29.0	47,559,950	2.6	99	4,708	2.9
South America	405,938,000	22	25.0	101,351,072	5.5	117	11,858	7.3
Africa	1,150,795,000	96	40.0	460,318,000				
Northern Africa	223,477,000	42	32.2	71,942,482	3.9	117	8,417	5.2
Eastern Africa	363,289,000	84	43.9	159,659,240	8.6	103	16,445	10.1
Middle Africa	143,590,000	113	43.0	61,788,040	3.3	78	4,819	3.0
Western Africa	338,190,000	124	43.0	145,275,339	7.9	57	8,281	5.1
Southern Africa	56,091,000	61	29.0	16,239,477	0.9	46	747	0.5
Asia	4,306,686,000	44	24.3	1,046,524,698				
Western	247,120,000	32	29.5	72,910,480	3.9	120	8,749	5.4
Eastern	1,590,701,000	17	16.7	265,708,479	14.4	74	19,662	12.1
South Central	1,831,151,000	63	29.3	536,639,626	29.0	64	34,345	21.1
South Eastern	637,714,000	31	26.6	169,424,119	9.2	92	15,587	9.6
Oceania	36,709,000	20	22.3	8,202,179	0.4	120	984	0.6
Summary	7,176,023,000	53	40.0	1,849,909,185	28.6	88	162,603	

Abbreviation: U5MR, under-5 mortality rate (ie, mortality rate for children younger than age 5 years).
*U5MR is the probability of dying between birth and exactly 5 years of age expressed per 1000 live births. See United States Census Bureau, International Programs, International Database[12] for a list of countries included in each region.
†Values obtained from calculations based on population and incidence data shown.
‡Values represent results of calculation of percentage indicated in Percentage of Total Population Age 0-14 Years column of total population included in Total Population column.
§Source: International Agency for Research on Cancer: GLOBOCAN 2012.[11]

increase by 30% by the end of this decade. Childhood cancer mortality, however, is polynomial: mortality rate estimates are low when cancer incidence and development are low, highest when development and cancer incidence are moderate, and low again when development and cancer incidence are high (Fig 2).

In LMICs, survival of children with cancer is directly proportional to several health indicators, including number of physicians and nurses per 1,000 population, annual government health care expenditure per capita, and several center-specific indicators such as human resources and level of supportive care.[14,15] Strengthening of the health care systems as a whole is required for sustainability and scale-up health interventions.

CHILDREN WITH CANCER IN LMICS

Efforts aimed at improving outcomes for pediatric cancer in LMICs must consider the unique features of the problem—the host, the diseases, and the social, economic, and cultural contexts—and how these features may vary among and within regions.[4] Examples from the perspectives of epidemiology, treatment delivery, and policy follow.

Epidemiology of Childhood Cancer

Little is known about the epidemiology of pediatric cancer in LMICs. Large portions of the world's population are not covered by cancer registries, especially those countries in which predictions indicate that the cancer burden is growing most rapidly.[16] National and regional initiatives to develop or strengthen cancer registries to serve the pediatric population are critical for measuring cancer burden in specific populations and for generating information for etiologic research. This is particularly important, given the differences in incidence rates of childhood cancers between high- and low-income countries and also among the various ethnic and racial groups within a single country.[4,17-19] Such differences may be the result of genomic determinants associated with race and ethnicity, early or delayed exposure to infectious diseases, and other environmental factors[17,18,20-22]; thus, comprehensive descriptive and molecular epidemiology studies are needed to elucidate these possible genome-environment interactions. The Global Initiative for Cancer Registry Development is addressing this gap through the establishment of six regional hubs that offer regional training, technical advice, and research support to registry staff; the focus is on empowering countries to develop cancer control plans by providing support and sharing knowledge.

Treatment of Children With Cancer in Resource-Limited Settings

Late presentation, abandonment of therapy, coexisting debilitating conditions such as malnutrition and infections, suboptimal supportive and palliative care, and inefficient health care delivery systems represent major limitations to pediatric cancer care in LMICs.[4] However, curing children with cancer in a cost-effective manner is possible, even in the most deprived settings, as shown with the successful management of Burkitt lymphoma in sub-Saharan Africa, where long-term survival of approximately 50% has been achieved with

treatment costs below US$100 per patient.[23,24] Direct translation of effective protocols in high-income countries (HICs) to children in LMICs is not possible; adaptations are necessary to address inadequate health care capacity associated with limited resources, underdeveloped health care infrastructure, scarcity of pharmaceuticals, and cultural barriers.[25] Treatment guidelines developed for countries with few resources are often based on low-intensity therapies in North America and Europe; intensity-adjusted treatment strategies are then increased gradually as safety and feasibility are documented and treatment-related mortality is decreased.[26-31] These disease-specific and level-specific guidelines have provided a starting point for developing national and regional cancer control programs as well as collaborative clinical research initiatives. In addition, the development of these guidelines may give policy makers insights into how to plan resource-appropriate cancer care and control programs at both national and regional levels.[25] Implementing these tailored approaches requires the development and validation of tier systems that accurately reflect the status of regions, countries, and pediatric oncology units of interest.[27,31]

Essential Medicines for Childhood Cancer

Among the myriad challenges to be overcome in LMICs are the availability, accessibility, and affordability of both antineoplastic and supportive care drugs.[4] Thirty years ago, the WHO established a list of medications deemed essential for the general population.[32] This list has been updated and is now reviewed every 2 years.[33,34] The Model List includes only 14 antineoplastic drugs, including four corticosteroids (Appendix Table A1, online only).[36] Independently, the Essential Medicines Working Group of the International Society of Pediatric Oncology (SIOP) has proposed a notable expansion of antineoplastic and supportive care drugs with a focus on LMICs. Agents included in the SIOP list are bleomycin, carboplatin, cisplatin, dacarbazine, etoposide, hydroxyurea, ifosfamide, and vinblastine, all of which are included in current standard treatment protocols. Within the past year, the Union for International Cancer Control has collaborated with the WHO to promote further additions to the Model List with input from the SIOP Working Group.

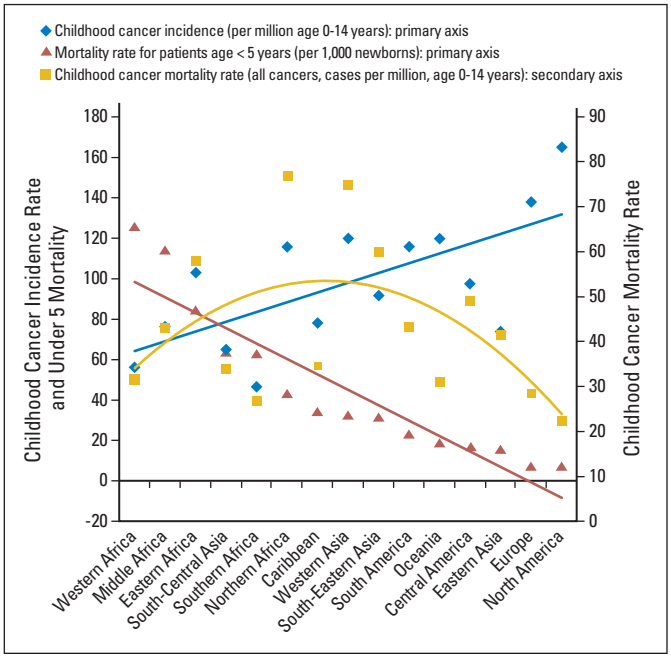

Fig 2. The mortality rate for children younger than age 5 years (under-5 mortality rate [U5MR]), childhood cancer incidence, and childhood all-cancer mortality by region. U5MR and cancer incidence show opposite linear trends: as U5MR decreases, cancer incidence increases ($r^2 = -0.617$). Sources: World Bank Databank for U5MR[10] and GLOBOCAN 2012[11] for age-specific (0 to 14 years old) cancer incidence and mortality.

REGIONAL DIFFERENCES IN THE PEDIATRIC CANCER BURDEN AND DEVELOPMENT OF COLLABORATIVE EFFORTS IN LIMITED-RESOURCE SETTINGS

Although they are significant, the many challenges that LMICs face in the diagnosis and treatment of children with cancer represent a unique opportunity for the development of focused initiatives adjusted to the particularities of each region.

Africa and the Middle East

Africa, home to approximately 15% of the world's population and 25% of the world's children (500 million) is the most deprived continent, with notoriously deficient health care systems and competing health care needs that limit the development of cancer control programs (Table 2). The North Africa region is similar to the Middle East and/or Western Asia in terms of socioeconomic and cultural frameworks, and thus, they are discussed together. The young population in this region is expanding, with more than one third of the population consisting of individuals younger than age 15 years. North Africa and Western Asia account for approximately 10% of worldwide childhood cancer (Fig 1 and Table 2). Over the years, child health has improved and U5MR has decreased to its current level of below 40 per 1,000 live births. However, over the last two decades, unstable political situations, wars, and forced human displacements have had a deleterious impact on the health care systems of the region.[37] Nevertheless, cooperative initiatives have established a new ground for regional support and development. The Middle East Cancer Consortium, an initiative sponsored by the US National Cancer Institute, was established in 1996 through an official agreement of the ministries of health of Cyprus, Egypt, Israel, Jordan, and the Palestinian Authority; Turkey joined the Consortium in 2004. The major activities of Middle East Cancer Consortium include the Cancer Registry Project and the Palliative Care Project, which notably includes cross-border collaborations between Arabs and Israelis.[38] The pediatric-focused Middle East Childhood Cancer Alliance established in 2000 comprises member institutions from 16 countries in the Middle East and North Africa. The Middle East Childhood Cancer Alliance reported its first prospective study (CALLME1) to assess the feasibility of and establish mechanisms for collaborative data collection and management in the Middle East and to collect prospective data on childhood acute lymphoblastic leukemia (ALL).[39] Pediatric oncologists from 22 countries in the Middle East and Mediterranean region established the Pediatric Oncology East and Mediterranean (POEM) Group (Fig 3 and Appendix Table A2, online only). Current priorities of POEM are to assess the needs in the different countries, establish robust registries and data management procedures, provide quality training to pediatric oncology professionals, install infection control and supportive care guidelines, secure access to care for all patients, and develop and apply resource-appropriate evidence-based guidelines. The group

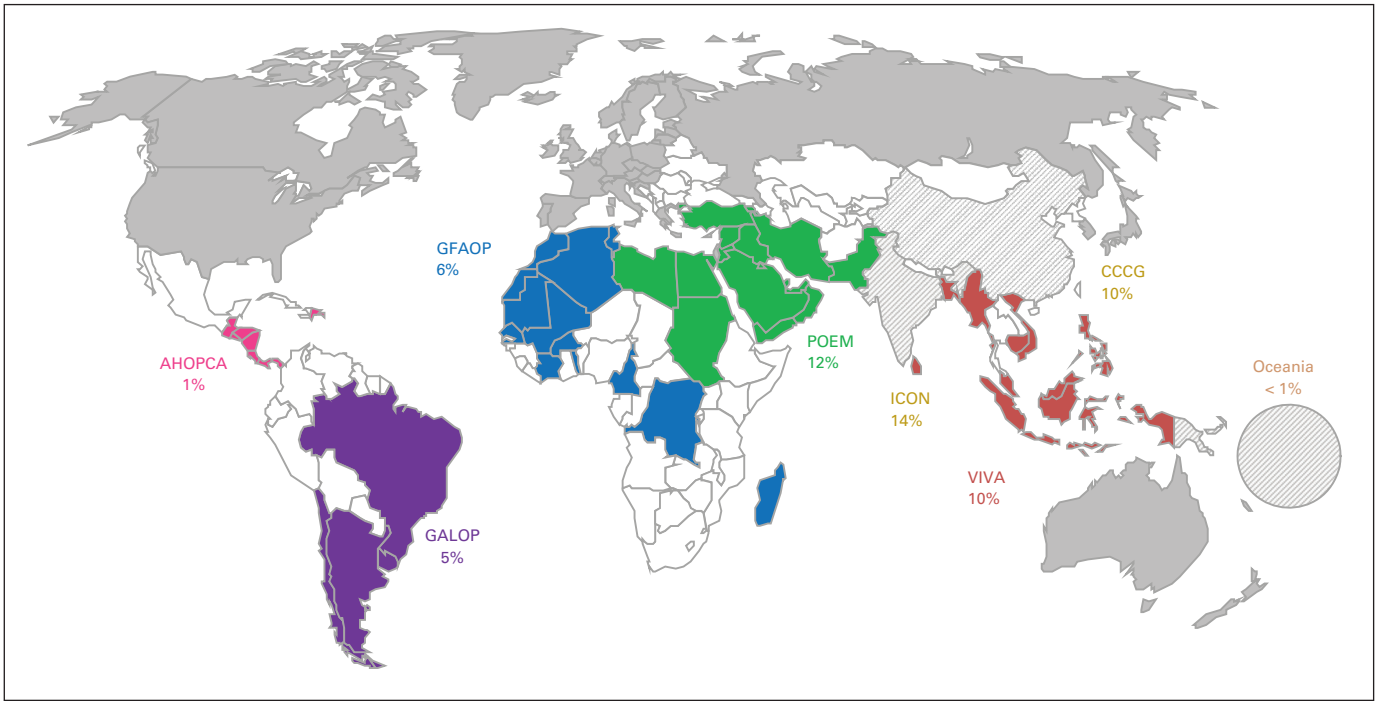

Fig 3. Regional collaborative efforts identified the expected proportion of childhood cancer covered by each consortium (total, 58.5%). The Chinese Childhood Cancer Group (CCCG) and India's Indian Cooperative Oncology Network (ICON) are included, despite being national rather than international consortia, based on the size of the population they cover. India is also a member of Pediatric Oncology East and Mediterranean (POEM) Group, but case contribution is included only once (for ICON). Algeria, Morocco, and Tunisia are members of the Franco-African Group of Pediatric Oncology (GFAOP) and POEM; their case contribution is included only once (for POEM). Source: World Bank Databank[10] and GLOBOCAN 2012.[11] AHOPCA, Central American Association of Pediatric Hematology and Oncology; GALOP, Latin American Pediatric Oncology Group; VIVA, VIVA Foundation for Children with Cancer in Singapore.

is also working on standardization for quality control and accreditation, public awareness and prevention, strategic public policy, and advocacy with local governments and communities.

The largest proportion of the African population lives in sub-Saharan countries where life expectancy is low. According to GLOBOCAN 2012, approximately 6% of the world's total new cancer cases at all ages and more than 20% of childhood cancer cases occur in Africa (Table 2).[40] With current rates of population growth and improvements in the control of communicable diseases, the number of new cancer cases in Africa will increase by 70% between 2012 and 2030, yet less than half of sub-Saharan African countries have an operational policy, strategy, or action plan for cancer control.[41] Several international organizations are collaborating to build capacity for sustainable cancer research programs in the region. For example, the International Network for Cancer Treatment and Research cancer registry program is coordinating an African Cancer Registry Network and working to improve the performance of existing registries. The African Cancer Registry Network is acting as a consortium that is building several regional hubs as part of the International Agency for Research on Cancer Global Initiative for Cancer Registry Development.[42]

More than 40% of the population in sub-Saharan Africa is younger than age 15 years; an estimated 40,000 new cases of pediatric cancers are expected to occur annually, representing approximately 20% of the world's total number (Fig 1 and Table 2). Although the region has the world's highest U5MR, with a regional average of 110 per 1000 live births per year, 90% of sub-Saharan countries have had faster decreases in child mortality from 2000 to 2013 than from 1990 to 2000, which will lead to a steady increase in the number of childhood cancers in the next decades.[13] Thus, pediatric cancers constitute a larger fraction of the cancer burden in Africa than in many other parts of the globe; in some African regions, pediatric cancers account for 6% of all cases, whereas in developed countries this proportion is less than 1%.[43]

The Franco-African Group of Pediatric Oncology was founded in the year 2000 under the mentorship of the Institute Gustave-Roussy to advance pediatric oncology in Africa through twinning partnerships and the development of a cooperative group structure; this consortium comprises fifteen pilot units in 12 countries, and more than 1,000 children are treated annually in the Franco-African Group of Pediatric Oncology pilot units in sub-Saharan Africa, with a steady increase in patient numbers (Fig 3 and Appendix Table A2). An African School of Pediatric Oncology has recently been established in Marrakesh, Morocco, to increase the number of trained physicians.[44] In most pilot units, one or two physicians have had training in pediatric oncology and all of them are involved in clinical research. Other collaborative regional efforts are ongoing in sub-Saharan Africa, including a prospective collaborative project on Wilms tumor.[45] Finally, pediatric oncology programs in South Africa are engaged in developing regional capacity and in establishing new collaborative networks to improve cancer care and control.[41,46]

Asia

Asia, the most populous continent, has the largest share of the global cancer burden (48%), a proportion that is expected to increase in the next decade[40]; however, cancer control programs are still in their infancy in most of the region.[47] Huge disparities in economy and

infrastructure exist between countries and even among different regions in some large countries.[27,48] However, significant progress has been made in the development of regional initiatives in cancer care and control. The resource-stratified guidelines for cancer care and control programs and disease-specific treatments developed by the Asian Oncology Summit series of workshops are the best example of regionally focused initiatives with the potential for developing cooperative clinical research programs.[25,27,31]

Approximately one fourth of the Asian population is younger than age 15 years, with 80,000 pediatric cancer cases expected to occur in the region annually, representing almost 50% of all childhood cancers worldwide (Fig 1 and Table 2). The regional U5MR ranges from less than three per 1,000 live births per year (high-income Asian Pacific countries) to 99 per 1,000 live births per year (Afghanistan), with rapidly declining rates over the last decade.[13] Thus, the number of pediatric cancer cases is expected to increase significantly, further shifting the world's childhood cancer burden to this region. The status of pediatric oncology reflects the diversity of resources available. Although countries such as Japan, South Korea, and Singapore have well-established pediatric oncology programs, most programs in South-Central Asia and South-Eastern Asia are less than a decade old, and they focus on basic needs, education, and the application of simple protocols.[27] In South-Eastern Asia, there are several initiatives to develop regional capacity and establish a framework for cooperative group structures. The VIVA Foundation for Children with Cancer in Singapore together with the National University of Singapore and St Jude Children's Research Hospital (SJCRH) started an annual workshop and forum in 2007 for pediatric oncologists from 14 countries in South and South-Eastern Asia. The workshops have focused on management of leukemia and solid tumors, supportive care in resource-limited settings, and presentation of local epidemiologic data, treatment results, and initiatives to combat common problems such as abandonment of therapy. A core group of oncologists from various countries in the region has developed a cohesive consortium that is currently planning common studies and region-wide initiatives in cancer registration, palliative care, ALL, and retinoblastoma (Fig 3 and Appendix Table A2). Collaborative efforts such as the Malaysia-Singapore ALL Study Group have demonstrated great potential in the region and are developing clinical and translational research efforts targeted at local populations and adjusted to existing resources.[49,50]

South-Central Asia and the Indian subcontinent present a slightly different scenario. The overall cancer mortality rate in India is close to 70%, which is likely similar to the rate in the pediatric population.[51,52] Although the lack of resources to pay for treatment is one of the factors that result in poor cancer survival in India, initiatives such as the National Health Mission and the Rashtriya Swasthya Bima Yojna, which offer free treatment to economically challenged patients, are expected to ameliorate some of those limitations.[51] In 2009, more than 50% of medical colleges in India did not have facilities or expertise for treating children with cancer.[53] However, great efforts have been made to establish collaborative prospective studies, such as the modified MCP-841 ALL protocol, which resulted in an increase of survival rates from 20% to 60%.[54] The recent development of the Indian Cooperative Oncology Network (ICON) has fostered regional medical and pediatric oncology initiatives. The Indian National Pediatric Oncology Group focuses on the development of cost-effective and logistically feasible protocols. The Jiv Daya Foundation recently launched the Indian Pediatric Oncology Initiative to support childhood cancer units across the country and the development of the Web-based India Pediatric Oncology Database, a secure database designed to create hospital-based registries and facilitate clinical research. The India Pediatric Oncology Database, in collaboration with ICON and Indian National Pediatric Oncology Group may serve as a platform for collaborative pediatric oncology trials in India.[55] The pan-India Indian Childhood Collaborative Leukaemia Group protocol for childhood ALL is the first step in this direction, with an expected accrual of 2,200 children.[51,52]

In China, there are approximately 45,000 children with newly diagnosed cancer every year, including 10,000 to 12,000 with ALL. China has a largely privatized health care system, and the majority of rural residents are uninsured.[48] Until recently, only approximately 10% of children with cancer received adequate treatment because of the lack of health insurance and inability to pay[56]; therefore, cancer has become a major cause of childhood death in China. In 2004, a standardized, cost-efficient protocol was developed jointly by the Shanghai Children's Medical Center, the Beijing Children's Hospital, and SJCRH to treat underprivileged children with low- and intermediate-risk ALL with the support of a charitable foundation. In 2009, the effectiveness and affordability of the clinical trial were reported,[57] which drew the attention of China's leadership. In 2010, China's Ministry of Health initiated a pilot project that provided governmental funding for treatment of all children with ALL.[58] This initiative has been extended to other cancers and thus has an impact on many more patients. With the drastic increase in the number of patients who have access to treatment and unprecedented opportunity for clinical and translational research, Shanghai Children's Medical Center in collaboration with SJCRH formed a national childhood ALL study group in 2014 with 20 major participating hospitals and medical centers across China.

Oceania

Oceania is characterized by its vast geography and unique, diverse mix of ethnic populations living in communities widely dispersed over large masses of land and sea. Of 18 countries and territories, only two are HICs (Australia and New Zealand); all other countries and territories are classified as small-island developing states. Australia and New Zealand are the most well-resourced countries in Oceania. Both have sophisticated publicly funded health care systems, so children and young people with cancer have benefited from the survival advances seen in Europe and North America over the last 40 years. Their 10 pediatric oncology centers are members of the Children's Oncology Group (COG) and the Australian and New Zealand Children's Hematology and Oncology Group. Membership in the COG, Australian and New Zealand Children's Hematology and Oncology Group, and various SIOP-associated collaborative clinical trials groups has ensured that children and young people in Australia and New Zealand have access to contemporary cancer care and novel emerging technology. However, the same is not true for pediatric cancer in the wider Pacific region. Across Pacific Island countries and Papua New Guinea, there is wide variation in resources and health care provision which, coupled with geographic barriers of distance and limited infrastructure, create great challenges in caring for children with cancer and underscore the need for locally adapted solutions. To address some of these issues, the New Zealand Children's Cancer Network, funded by New Zealand Aid, has developed an active twinning model that has adapted treatment regimens for selected cancers. By combining regular clinical outreach and teaching through weekly teleconferences with New

Zealand, two child health services in Fiji treat most cases of childhood cancer in their own country. Fiji is now accepting selected referrals from other Pacific countries and is providing affordable regional cancer care. A similar but more limited twinning program was recently started between Papua New Guinea and Australia.

Latin America and the Caribbean

The Latin America and Caribbean region has approximately 8% of the world's population (Table 2). The economies of Latin America and the Caribbean are growing rapidly; however, Latin America is poorly equipped to deal with the alarming increase in cancer incidence and disproportionally high mortality rates compared with other world regions. Approximately 26% of the region's population is younger than age 15 years, and the region has 17,000 cases of childhood cancer annually (Fig 1 and Table 2). The annual U5MR ranges from 12 per 1,000 live births in the more developed southern countries to 18 in Central America, 28 in the Andean countries, and 34 in the Caribbean. The rate of decline in U5MR slowed down after 2000.[13]

One of the most successful models of pediatric oncology cooperative work and research in resource-limited settings has been the Central American Association of Pediatric Hematology and Oncology (AHOPCA).[59] Twinning between 'La Mascota' Hospital in Managua, Nicaragua, and the Pediatric Clinic of the University of Milano-Bicocca in Monza, Italy, which was initiated in 1986, led to the establishment of the Monza International School of Pediatric Hematology-Oncology. The activities of Monza International School of Pediatric Hematology-Oncology culminated in the formation of AHOPCA in 1998 (Fig 3 and Appendix Table A2). The group initially focused on education and support for program building, but it has evolved into a true multidisciplinary group over the years. Support from institutions in North America (SJCRH, Children's Hospital of Colorado, Pediatric Oncology Group of Ontario, Hospital for Sick Children in Toronto, and Dana-Farber/Boston Children's Hospital) and Europe (Hospital San Gerardo, Monza, and Istituto Nazionale Tumori Milano) has helped optimize treatments and foster research capacity. AHOPCA now has a clinical research infrastructure with a shared Web-based database, data managers, and coordinators in all units. Multidisciplinary prospective protocols have been developed for most pediatric malignancies that generate evidence-based data to guide the development of programs in other resource-limited settings. The contributions to the field made by this cooperative group are highlighted by study results featured in nearly 50 peer-reviewed publications. To address knowledge deficits in pediatric specialists in the region, training programs in pediatric hematology and oncology and pediatric intensive care have been initiated in Guatemala. More recently, AHOPCA has organized a pediatric cancer epidemiology initiative with the support of Dana-Farber/Boston Children's Hospital,

Table 3. Proposed Components of Research Consortia by Their Longitudinal Experience and Research Resources

Level	I	II	III	IV
Longitudinal experience	Young consortium	Young-experienced consortium	Experienced consortium	Maximally experienced consortium
Research resources	Lower resource setting	Medium resource setting	High resource setting	Maximal resource setting
Clinical trial type	Single-arm intervention study for common and highly curable disease (ALL, BL, WT) or target disease (OS, ES)	Single-arm intervention studies for most childhood cancers Biology studies for banking or focused etiologic research	Incorporation of randomized clinical trials Few single- or multi-arm trials for relapse disease Biologic studies for expanded etiologic research	Predominance of randomized clinical trials Focus on relapsed disease, phase I/II clinical trials, and effectiveness trials Biology studies for identification of new markers
No. of studies/trials	Few (1-5)	Several (> 5)	Multiple (> 10)	Multiple (> 20)
Research infrastructure	Strong emphasis on building local capacity by: Training data managers Establishing processes for data collection, quality, safety, and analysis Nurturing local researchers Establishing ethics committees	Additional emphasis on: Increasing data quality checks, research staff, and oversight proportional to higher volume Support for development of secondary analysis and local projects	Clinicians have dedicated time to be site-specific principal investigators Clinical research staff is more experienced and independent Stable financial support has been achieved	Dedicated staff, time, and support has been secured Full set of research staff is available (CRC, CRA, CRN) Statistics core available Research has close ties to drug development and pharmaceutical companies (bench to bedside)
Informed consent	Relatively simple because studies likely reflect standard of care	Relatively simple because studies likely reflect standard of care	Increasing complexity	Increased complexity
Health systems	Intentional strengthening of health systems through: Drug procurement Access to care Quality checks Outcome assessment	Additional emphasis on: Expanding the formulary (treatment and supportive) Improving early referral Building research teams	Culture of research, quality, and safety has been achieved Clinical research is part of subspecialty training Nursing research	Clinical research is embedded within health care systems Consortium influences health care policies
Health care delivery	Intentionally improving: Standardization of care for specific diseases Evaluation of barriers to implementation Monitoring of compliance	Additional emphasis on: Standardization of care Processes and/or quality Integration and/or incorporation of subspecialists Increased access to expert care	Care teams are supported by research teams Care is multidisciplinary and interdisciplinary More supportive staff allows for more outpatient care	Cost-effective care Maximizing outpatient care Limiting impact on quality of life Accountability is high

Abbreviations: ALL, acute lymphoblastic leukemia; BL, Burkitt lymphoma; CRA, clinical research assistant; CRC, clinical research coordinator; CRN, clinical research nurse; ES, Ewing sarcoma; OS, osteosarcoma; WT, Wilms tumor.

Santa Casa Medical School (Sao Paulo), Union for International Cancer Control, International Agency for Research on Cancer, and St. Baldrick's Foundation. Population-based pediatric cancer registries have been established in El Salvador and Guatemala in 2013, and expansion is planned to Nicaragua and Honduras in 2015, which will create a Central American network of registries and an infrastructure for epidemiology research. Following the steps that AHOPCA took, the Caribbean Pediatric Cancer and Blood program coordinated by the Hospital for Sick Children aims to develop a collaborative network among six Caribbean countries that focuses on cancer registration, program building, and education.

The heterogeneity of South America is reflected in disparities in human development and access to care. Although some countries have poor infrastructure and lack key components for successful treatment of children with cancer, others have a long-standing tradition of national cooperative groups and participation in international studies. Building on this experience and with the goal of fostering regional clinical research in pediatric oncology, those countries formed the Latin American Pediatric Oncology Group (GALOP). GALOP includes 12 pediatric cancer centers from Chile (as part of the National Program for Antineoplastic Drugs for Children in Chile), six from Argentina, 24 from Brazil, and the National Pediatric Oncology Center from Uruguay. GALOP has the support of the COG for organizing its clinical research infrastructure and strategic planning (Fig 3 and Appendix Table A2). Protocols have already been developed for retinoblastoma, osteosarcoma, and Ewing sarcoma and are in the planning stages for germ cell tumors and high-risk neuroblastoma. In addition, GALOP participates as a cooperative group in the ARET0321 (Combination Chemotherapy, Autologous Stem Cell Transplant, and/or Radiation Therapy in Treating Young Patients With Extraocular Retinoblastoma) protocol of the COG. The COG-GALOP partnership can be viewed as a model of collaboration at the cooperative group level, whereby experienced cooperative groups assist in the development and growth of similar structures in more resource-limited settings.

CLINICAL RESEARCH AND CLINICAL RESEARCH INFRASTRUCTURES IN LMICS

Collaborative research through consortia or large cooperative groups has created a pathway to the major advances experienced in pediatric oncology over the last few decades.[1,2] However, less than 20% of children with cancer worldwide benefit from those large cooperative efforts, which are centered mostly in North America and Europe. By contrast, existing consortia and organized groups under development in LMICs may currently be covering more than 50% of the world's children with cancer (Fig 3 and Appendix Table A2). Strengthening those groups and fostering new regional collaborations has the potential to create new ground for collaborative research in low-resource settings. The infrastructure, organizational culture, systems, and expertise that develop as a result of sustained participation in cooperative clinical trials research may have a favorable impact on patient care and outcomes.[60] Regional collaborations can further increase the level of expertise, increase regional capacity through shared resources, and enhance the spirit of collaboration that has been key to the successes made in pediatric cancer over the last four decades.[61] Different levels of consortia could be identified, with step-wise increments in the level of complexity and range of initiatives developed (Table 3).

CONCLUSION

The shift in the pediatric cancer burden in the developing world highlights a pressing need for high-quality research to identify feasible and evidence-based therapies that are appropriate for low-resource settings.[62] Cancer care in LMICs must not be limited to copying unrealistic strategies used in HICs—it demands innovation. Thinking beyond our present standards is mandatory for generating new constraint-adapted therapeutic strategies to treat patients with cancer who live in LMICs.[63] The success of the regional initiatives suggests that enhancing regional research capacity in pediatric oncology in LMICs should be prioritized. Partnerships between institutions and cooperative groups in high- and low-resource settings provide successful models. As collaborations evolve, a clear research framework must be defined, and academic credit should be properly shared; research interventions are ethical only if the intervention under study has the potential to provide health benefits to the communities or countries in which the trials are conducted.[62]

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Toward the Cure of All Children With Cancer Through Collaborative Efforts: Pediatric Oncology As a Global Challenge

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Appendix

Table A1. WHO Essential Medicines

WHO Model List of Essential Medicines for Children (4th edition, April 2013; revised October 2013)
Asparaginase
Cyclophosphamide
Cytarabine
Dactinomycin
Daunorubicin
Dexamethasone
Doxorubicin
Hydrocortisone
Mercaptopurine
Methotrexate
Methylprednisolone
Prednisolone
Thioguanine
Vincristine

NOTE. Data source contains a core list and a complementary list of antineoplastic agents.[35]

Table A2. Proportion of Children With Cancer Covered by the International Consortia Identified and Evaluated

Country	Country Income Level in 2013*	Population Total in 2013*	Population Age 0-14 Years in 2013 (%)*	Population Age 0-14 Years in 2013	Incidence of Childhood Cancer (per million)†‡	Annual Cases per Country	Coverage by Consortium (%)
Central America (AHOPCA)							
Costa Rica	UMIC	4,872,166	23.5	1,145,730	130	149	
Dominican Republic	UMIC	10,403,761	30.2	3,141,984	73	229	
El Salvador	LMIC	6,340,454	30.0	1,899,971	69	131	
Guatemala	LMIC	15,468,203	40.4	6,253,590	59	369	
Haiti	LIC	10,317,461	35.0	3,606,615	30	108	
Honduras	LMIC	8,097,688	35.2	2,853,268	60	171	
Nicaragua	LMIC	6,080,478	32.8	1,996,346	52	104	
Panama	UMIC	3,864,170	28.3	1,094,071	74	81	
Total						1,343	0.7
South America (GALOP)							
Argentina	UMIC	41,446,246	24.2	10,044,064	144	1,446	
Brazil	UMIC	200,361,925	24.1	48,256,432	124	5,984	
Chile	HIC	17,619,708	21.1	3,715,100	156	580	
Uruguay	HIC	3,407,062	21.8	744,385	115	86	
Total						8,095	4.5
North Africa (GFAOP)							
Algeria	UMIC	39,208,194	27.8	10,890,906	141	1,536	
Burkina Faso	LIC	16,934,839	45.5	7,712,086	55	424	
Cameroon	LMIC	22,253,959	43.0	9,559,669	184	1,759	
Cote d'Ivoire	LMIC	20,316,086	41.3	8,397,252	54	453	
Democratic Republic of the Congo	LIC	67,513,677	45.0	30,400,157	58	1,763	
Madagascar	LIC	22,924,851	42.4	9,718,059	75	729	
Mali	LIC	15,301,650	47.4	7,252,347	153	1,110	
Mauritania	LIC	3,889,880	40.1	1,560,022	57	89	
Morocco	LMIC	33,008,150	27.9	9,193,815	113	1,039	
Senegal	LMIC	14,133,280	43.5	6,148,984	84	517	
Togo	LIC	6,816,982	41.8	2,852,689	65	185	
Tunisia	UMIC	10,886,500	23.2	2,526,167	102	258	
Total						9,861	5.5

(continued on following page)

Table A2. Proportion of Children With Cancer Covered by the International Consortia Identified and Evaluated (continued)

Country	Country Income Level in 2013*	Population Total in 2013*	Population Age 0-14 Years in 2013 (%)*	Population Age 0-14 Years in 2013	Incidence of Childhood Cancer (per million)†‡	Annual Cases per Country	Coverage by Consortium (%)
India (ICON)†							
India	LMIC	1,252,139,596	29.1	364,250,394	63	22,948	
Total						22,948	12.7
China (CCCG)†							
China	UMIC	1,357,380,000	18.0	244,746,591	69	16,888	
Total						16,888	9.3
Middle East (POEM)§							
Algeria	UMIC	39,208,194	27.8	10,890,906	141	—	
Armenia	LMIC	2,976,566	20.2	602,719	100	60	
Bahrain	HIC	1,332,171	21.0	279,621	119	33	
Egypt	LMIC	82,056,378	31.1	25,555,143	138	3,527	
India	LMIC	1,252,139,596	29.1	364,250,394	63	—	
Iran	UMIC	77,447,168	23.8	18,440,404	100	1,844	
Iraq	UMIC	33,417,476	40.1	13,386,280	120	1,606	
Jordan	UMIC	6,459,000	34.0	2,198,516	109	240	
Kuwait	HIC	3,368,572	24.8	834,677	141	118	
Lebanon	UMIC	4467,390	20.8	930,182	167	155	
Libya	HIC	6,201,521	29.4	1,825,865	96	175	
Morocco	LMIC	33,008,150	27.9	9,193,815	113	—	
Oman	HIC	3,632,444	23.5	852,932	93	79	
Pakistan	LMIC	182,142,594	33.8	61,609,988	74	4,559	
Saudi Arabia	HIC	28,828,870	29.0	8,369,349	113	946	
State of Palestine	LMIC	4,169,506	40.1	1,672,057	125	209	
Sudan	LMIC	37,964,306	41.2	15,635,119	73	1,141	
Syria	LMIC	22,845,550	35.1	8,016,704	110	882	
Tunisia	UMIC	10,886,500	23.2	2,526,167	102	—	
Turkey	UMIC	74,932,641	25.7	19,224,026	143	2,749	
United Arab Emirates	HIC	9,346,129	15.3	1,429,356	105	150	
Yemen	LMIC	24,407,381	40.2	9,806,195	99	971	
Total						19,445	10.8
Asia (VIVA)							
Bangladesh	LIC	156,594,962	30.0	46,976,764	42	1,973	
Cambodia	LIC	15,135,169	31.1	4,704,539	151	710	
Indonesia	LMIC	249,865,631	28.9	72,185,545	107	7,724	
Malaysia	LMIC	29,716,965	26.1	7,758,045	103	799	
Myanmar	LIC	53,259,018	24.9	13,267,065	81	1,075	
Philippines	LMIC	98,393,574	34.1	33,592,525	65	2,184	
Singapore	HIC	5,399,200	16.1	867,208	140	121	
Sri Lanka	LMIC	20,483,000	25.2	5,154,515	52	268	
Vietnam	LMIC	89,708,900	22.7	20,365,733	69	1,405	
Total						16,259	9.0
Oceania‖							
Fiji	UMIC	881,065	28.9	254,266	154	39	
Papua New Guinea	LMIC	7321,263	38.0	2,782,994	90	250	
Total						290	0.2
Total No. of children covered by these consortia						95,128	58.5
Total No. of children with cancer in the world§						162,603	

Abbreviations: AHOPCA, Central American Association of Pediatric Hematology and Oncology; CCCG, Chinese Childhood Cancer Group; GALOP, Latin American Pediatric Oncology Group; GFAOP, Franco-African Group of Pediatric Oncology; HIC, high-income country; ICON, Indian Cooperative Oncology Network; LIC, low-income country; LMIC, lower-middle-income country; POEM, Pediatric Oncology East and Mediterranean; UMIC, upper middle[en]income country; VIVA, VIVA Foundation for Children with Cancer in Singapore.

*Country income level was determined by using gross national income per capita, Atlas method (current $) values, and cutoffs from 2013, except for Libya where most recent gross national income per capita was from 2009. Source: World Bank Data by Country.[10]

†China's CCCG and India's ICON are included despite being national rather than international groups based on the size of the population they cover. India is also a member of POEM, but case contribution is included only once (for ICON).

‡All rates reported on the Web site were converted from cases/100,000 to cases/million. Source: International Agency for Research on Cancer: GLOBOCAN 2012.[11]

§Algeria, Morocco, and Tunisia are members of GFAOP and POEM; their case contribution is included only once (for POEM). Palestine is reported as "State of Palestine" in GLOBOCAN[11] and as "West Bank and Gaza" in World Bank Data.[10]

‖Source: International Agency for Research on Cancer: GLOBOCAN 2012.[11]