# IMPROVING EARLY DIAGNOSIS AND REFERRALS TO LIFE-SAVING CARE FOR CHILDREN WITH CANCER IN CAMEROON

**by**

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# DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own original work, that I am the authorship owner thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

This dissertation includes four original papers published in peer-reviewed journals or books and three unpublished papers. The development and writing of the papers (published and unpublished) were the principal responsibility of myself, and for each instance where this is not the case, a declaration is included in the dissertation indicating the nature and extent of the contributions of co-authors.

Date: March 2021

# SUMMARY

Childhood cancer is curable, but survival rates in low- and middle-income countries (LMICs), especially sub-Saharan Africa, are generally low. In 2018, the International Society of Paediatric Oncology (SIOP) and the World Health Organization (WHO) launched an initiative to improve childhood cancer survival to 60% by 2030 globally. As the majority of children with cancer live in LMICs, the emphasis should be on initiatives to improve survival in these countries. This PhD dissertation has investigated the incidence of childhood cancer in Northwest Cameroon, how to improve early diagnosis of children with cancer and the role of socioeconomic support of families with a child with cancer in Cameroon. Chapter 2 of this dissertation is a literature review, documenting the management of childhood cancer in Africa for the period 2014 to 2018.

As part of a twinning programme between Stellenbosch University and the Cameroon Baptist Convention Health Services established in 2003, a hospital-based childhood cancer registry was prospectively analysed to determine the childhood cancer burden in Northwest Cameroon between 2004 and 2015 and is reported on in Chapter 3. Burkitt lymphoma was the most common diagnosis, followed by nephroblastoma and retinoblastoma, but Burkitt lymphoma diagnosis has decreased over time, probably due to the improvement in diagnosis of other childhood cancers. The registry data is useful to plan improved clinical services and may assist in future with the development of a population-based childhood cancer registry in Cameroon.

To improve early diagnosis and referral of children with suspected cancers, a nurse-led training programme was conducted in six health districts of Northwest Cameroon with the support of the Sanofi Espoir Foundation's My Child Matters programme. This low-cost training programme improved knowledge essential for early recognition of childhood cancer signs and could be replicated in other low-income settings for improved early diagnosis of childhood cancer (Chapter 4).

The next step was to investigate the destitution level through a survey of families with children with Burkitt lymphoma and the association with adherence to treatment. Destitution level (measured by socioeconomic circumstances) did not affect adherence to treatment or follow-up for these children, probably due to the charity-driven financial support with regard to accommodation, food parcels and transport funding. However, survival rate was lower for children in single-mother households, which indicated the need for a more individualised

model of support-based care for such single-parent families (Chapter 5).

As traditional and complementary medicine (T&CM) use was common in Cameroon, further investigation was carried out to determine the use first in families with children with Burkitt lymphoma and thereafter in families with children across the spectrum of cancer. The initial study was done by the health care team with potential nondisclosure bias but found significant use of T&CM (Chapter 6a). The follow-up study therefore involved interviewers not part of the health care team to minimise nondisclosure bias. The majority of families of children with cancer had used (T&CM) before diagnosis while only a quarter of families had used T&CM after diagnosis (Chapter 6b). The use of T&CM resulted in worsening cancer symptoms and was financially costly to families. Half of the parents/guardians were not willing to disclose the use of T&CM to their treating health care team.

A final step was to examine the development of paediatric oncology services in Cameroon over the last 20 years. Treatment programmes were developed largely with the help of international twinning programmes and support from charities as there was no financial support from the state (Chapter 7). Over the period, childhood cancer survival improved and staff capacity for the management of childhood cancer was established.

This dissertation has provided local evidence of successful management of childhood cancer in Cameroon with suggestions regarding feasible actions necessary to achieve 60% childhood cancer survival by 2030 in line with the WHO-SIOP initiative.

# OPSOMMING

Kinderkanker is geneesbaar, maar oorlewingsyfers in lande met lae en middelinkomste (LLMI's), veral Afrika Suid van die Sahara, is oor die algemeen laag. In 2018 het die Internasionale Vereniging vir Kinderonkologie (SIOP) en die Wêreldgesondheidsorganisasie (WGO) 'n inisiatief van stapel gestuur om die oorlewingskoers van kinderkanker teen 2030 wêreldwyd tot 60% te verbeter. Aangesien die meerderheid kinders met kanker in LLMI's woon, moet die klem val op inisiatiewe om oorlewing in dié lande te verbeter. Hierdie PhD-proefskrif ondersoek die voorkoms van kinderkanker in die Noordwes-Kameroen; hoe om vroeë diagnose van kinders met kanker te verbeter; en die rol van sosio-ekonomiese steun aan gesinne met 'n kind met kanker in die Kameroen. Hoofstuk 2 van die proefskrif gee 'n literatuuroorsig, wat die bestuur van kinderkanker in Afrika vir die tydperk 2014 tot 2018 dokumenteer.

As deel van 'n tweelingprogram tussen die Universiteit Stellenbosch en die Kameroen "Baptist Convention Health Services" wat in 2003 gevestig is, is 'n hospitaalgebaseerde kinderkankerregister prospektief ontleed om die kinderkankerlas in die Noordwes-Kameroen tussen 2004 en 2015 te bepaal, en daar word in hoofstuk 3 hieroor berig. Burkitt-limfoom was die algemeenste diagnose, gevolg deur nefroblastoom en retinoblastoom, ofskoon Burkitt-limfoomdiagnoses mettertyd afgeneem het, waarskynlik vanweë die verbetering in die diagnose van ander kinderkankers. Die registerdata is nuttig vir die beplanning van verbeterde kliniese dienste en kan in die toekoms behulpsaam wees met die ontwikkeling van 'n bevolkingsgebaseerde kinderkankerregister in die Kameroen.

Om die vroeë diagnose en verwysing van kinders met vermoedelike gevalle van kanker te verbeter, is 'n verpleegster-geleide opleidingsprogram in ses gesondheidsdistrikte van die Noordwes-Kameroen met die ondersteuning van die Sanofi Espoir-stigting se "My Child Matters"-program uitgevoer. Hierdie laekoste-opleidingsprogram het die kennis wat noodsaaklik is vir die vroeë herkenning van tekens van kinderkanker verbeter, terwyl dit in ander laeinkomste-omgewings vir 'n verbeterde vroeë diagnose van kinderkanker herhaal kan word (Hoofstuk 4).

Die volgende stap was om die armoedevlak te ondersoek aan die hand van 'n opname onder gesinne met kinders met Burkitt-limfoom, asook die verband met betrekking tot die nakoming van die behandeling. Die armoedevlak (gemeet aan sosio-ekonomiese omstandighede) het nie die nakoming van behandeling of opvolging met hierdie kinders

beïnvloed nie, waarskynlik weens die liefdadigheidsgedrewe finansiële steun met betrekking tot verblyf, kospakkies en vervoerbefondsing. Die oorlewingsyfer was egter laer vir kinders in enkelma-huishoudings, wat aandui dat ’n meer geïndividualiseerde model van steungebaseerde sorg vir sodanige enkelouergesinne nodig is (Hoofstuk 5).

Aangesien die gebruik van tradisionele en komplementêre medisyne (T&CM) algemeen in Kameroen is, is verdere ondersoek gedoen om die gebruik eerstens in gesinne met kinders met Burkitt-limfoom te bepaal en daarna in gesinne met kinders oor die hele kankerspektrum heen. Die aanvanklike studie is deur die gesondheidsorgspan met potensiële vooreerdeel ten opsigte van nie-openbaarmaking gedoen, maar beduidende gebruik van T&CM (Hoofstuk 6a) is gevind. Die opvolgstudie het gevolglik onderhoudvoerders betrek wat nie deel van die gesondheidsorgspan was nie, ten einde die vooroordeel ten opsigte van nie-openbaarmaking te verminder. Die meerderheid gesinne met kinders met kanker het T&CM voor diagnose gebruik, terwyl slegs ’n kwart van die gesinne T&CM ná diagnose gebruik het (Hoofstuk 6b). Die gebruik van T&CM het verslegtende kankersimptome tot gevolg gehad en was finansieel duur vir gesinne. Die helfte van die ouers/voogde was nie bereid om die gebruik van T&CM aan hul behandelende gesondheidsorgspan openbaar te maak nie.

’n Laaste stap was om die ontwikkeling van kinderonkologiedienste in die Kameroen oor die afgelope 20 jaar te ondersoek. Behandelingsprogramme is grotendeels met behulp van internasionale tweelingprogramme en die ondersteuning van liefdadigheidsorganisasies ontwikkel, aangesien daar geen finansiële steun van die staat was nie (Hoofstuk 7). Oor die tydperk het die oorlewing van kinderkanker verbeter en is die personeelkapasiteit vir die bestuur van kinderkanker bepaal.

Hierdie proefskrif het plaaslik bewys gelewer van die suksesvolle bestuur van kinderkanker in die Kameroen met voorstelle oor uitvoerbare aksies wat nodig is om ’n 60%-kinderkankeroorlewingskoers in ooreenstemming met die WGO-SIOP-inisiatief in 2030 te behaal.

# DEDICATION

I dedicate this dissertation to my parents Mami Mbah and Pa Mbah and to my dear wife Remmie. Their love and encouragement have been a major source of energy for my career.

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# CHAPTER 1

## Introduction

Access to diagnosis and care for children with cancer is problematic in low- and middle-income countries (LMICs) (1–4). About 200 000 children below 15 years of age are probably diagnosed with cancer annually with a reported age-standardised rate of 140.6 per million person years (2,5,6). Great progress in childhood cancer treatment has been made over the past half century, with more than 80% of children being cured in high-income countries (HICs) (7). Survival rates in LMICs, however, remain low at about 25%, often due to the lack of adequate cancer care in these countries (8,9). It is therefore a global concern to ensure that these children gain access to adequate cancer care as more than 80% of children diagnosed with cancer annually live in LMICs (10). To this purpose, the motto of the International Society of Paediatric Oncology is "No child should die of cancer" (10).

About 70 000 children are diagnosed with cancer in Africa every year (11). Steliarova-Foucher et al. estimate an age-standardised incidence rate of 56.3 per million person years for children 0–14 years in sub-Saharan Africa. The most common malignancies of childhood include leukaemias, lymphomas, soft-tissue sarcomas, renal tumours, central nervous system tumours, and retinoblastoma (5). Survival rates vary across different subregions of the continent, with a reported five-year survival ranging between 5% and 70% (9). Numerous factors contribute to the relatively low survival rates for children with cancer in Africa. Late diagnosis, treatment abandonment and socioeconomic factors such as lack of affordable transport and poverty are major causes of low survival rates (12–15). Additionally, low levels of community awareness and high rates of use of traditional and complementary medicine (T&CM) also delay early detection and seeking appropriate health care (4,14,16–18). There is also a gap in access to palliative care for children with cancer in sub-Saharan Africa, resulting in reduced quality of life for these children and their families (19,20).

Experts have suggested several interventions to improve paediatric oncology care in Africa. These include interventions such as education of health care professionals and creation of community awareness regarding childhood cancer (2,15,21,22). Capacity-building projects are required to ensure that health care professionals gain expertise in the management of common childhood cancers and should include paediatricians, oncologists, nurses and palliative care experts (19). Twinning partnerships between HICs and LMICs with

involvement of nongovernmental organisations (NGOs), governments and international charities are also known to bring about significant improvement in local capacity, medicine availability and development of locally adapted treatment protocols (20–23). Establishment of population-based paediatric cancer registries is essential to ensure adequate resource allocation (8,24,25).

Childhood cancer data in Cameroon is fragmented (26). Calculations from reports of the single population-based cancer registry demonstrate an incidence of about 25 per 1 000 000 children 0–14 years, which is low in comparison to the reported incidence by Steliarova et al. (5,27). Childhood cancer treatment began in Cameroon in the early 2000s, and remarkable progress has been recorded, notably with improved outcomes for Burkitt lymphoma and Wilms tumour (28–31). Palliative care is not properly developed in the country; however, significant initiatives for childhood cancer palliative care have been initiated, which are improving the quality of life for patients (32). One major challenge for childhood cancer care in the country is low community awareness, leading to late diagnosis (33,34). Moreover, low health insurance coverage and lack of government support for childhood diseases reduce the possibility of access to cancer treatment even when treatment is available as parents cannot afford it (35).

This PhD dissertation investigated the incidence of childhood cancer in Northwest Cameroon, the outcome and costs of a capacity-building training project to improve childhood cancer diagnosis, the association between destitution and treatment adherence and survival of a childhood cancer in Cameroon, and the use of T&CM in the management of childhood cancers in Cameroon.

**Research problem statement**

Cameroon has made significant progress in paediatric health care delivery since the beginning of the 21st century. For several identifiable reasons, early diagnosis and referrals to holistic health care for children with cancer remain a major challenge in the country, leading to low survival rates. Education, proper data collection and use, collaboration with professional and funding partners nationally and internationally, and increased government support with modified cancer treatment protocols based on local resources may significantly improve delays in childhood cancer diagnosis and increase survival rates.

## Hypothesis

Null Hypothesis:

Childhood cancer health care cannot be improved in Cameroon

Alternative Hypothesis:

Childhood cancer health care can be improved in Cameroon

## Research aim

The overall aim of this research was to investigate how to improve early diagnosis, referral and management of children with cancer in Cameroon.

## Research objectives

In order to achieve the abovementioned research aim, the following objectives formed the basis of this dissertation:

i. Conduct a literature review regarding the current status of paediatric oncology in Africa, specifically Cameroon, and determine factors that can assist in successful early diagnosis, referral and management of childhood cancers in LMICs.

ii. Analyse the prevalence and distribution of cancer in children below 15 years of age in Northwest Cameroon from 2003 to 2015 to inform future planning for improving early diagnosis, referral and management.

iii. Analyse the impact and cost of a capacity-building programme for health care professionals in Northwest Cameroon to improve early diagnosis and prompt referral of childhood cancer patients.

iv. Investigate the destitution level of children below 15 years with Burkitt lymphoma and their families to determine what socioeconomic barriers parents experience that may affect adherence to treatment and outcomes.

v. Investigate the determinants, types and effects of traditional and complimentary medicines use among children below 15 years with cancer in Cameroon and its impact on early diagnosis, referral and management.

vi. Document the progress achieved in Cameroon regarding management of childhood cancers between 2000 and 2018.

## Significance of the research

Cameroon, like many other LMICs, experiences low levels of survival for children with cancer. Some of the reasons deduced for this from the literature include late diagnosis, limited capacity for treatment and supportive care, and treatment abandonment (2,21,34,36).

A few fragmented publications about specific aspects of childhood cancer in Cameroon are available, including data on the incidence of some diseases country wide or in some cities and the protocols used for certain diseases and their efficacy (26,37–39). However, no publicly available information regarding the overall situation of paediatric oncology care in Cameroon exists, which is why the first research objective was important. Cancer registration is essential to provide the information necessary for proper cancer control planning within health care systems, which was the motivation behind the second objective (24,40,41). Health care workers need capacity building to provide the necessary skills for identifying and providing curative and palliative health care to children with cancer, and therefore the third objective was to evaluate the impact and cost of a training programme provided for early diagnosis and referral of children with cancer in Northwest Cameroon (2,7). Despite the assertion in the literature that social support is required to enable childhood cancer patients to begin and complete their treatment and survival journey, there is a lack of information regarding the degree of destitution of these patients and how much support is required, which served as motivation for the fourth objective (3,7,14,20,42). International and national surveys have found that the use of T&CM is highly prevalent among children with paediatric malignancies as T&CM is an integral part of the cultural and belief system for the management of many illnesses (18,43). Given the limited data, the role of T&CM among children with cancer in Africa and Cameroon in particular is generally poorly understood, providing the motivation for the fifth objective (37).

Paediatric oncology care began in Cameroon in the year 2000 and a few programmes have been established, including the CBCHS and Stellenbosch University twinning programme. The sixth objective reviewed the published literature regarding paediatric oncology in Cameroon to identify progress made and recommendations to be made to sustainably improve paediatric oncology care delivery in the country within the context of the SIOP – WHO global initiative for childhood cancer.

## Context of the research

Cameroon is located in the Central African subregion, with a surface area of 475 440 $km^2$ with a population of 27 million, of whom 43% are under 15 years of age and the live expectancy at birth is 62.3 years (43). Cameroon possesses 90% of Africa's ecosystems including the Sahelian and Sudano type in the North, humid tropical forests in the East, Centre and South, Coastal type in the South, grass fields in the West and Mountain and Afro-mountain ecosystems. These ecosystems harbour a rich variety of plant and animal species (44). Its population is distributed between over 250 ethnic groups, whom have been suggested to originate from three of four main ethnolinguistic groups in Africa (45). The rich climatic and cultural diversity has earned Cameroon the nickname 'Africa in miniature' and endowed it with a massive ethno-pharmacopoeia(46). Cameroon is an upper middle income country with an under-five mortality of 74.8 per 1000 live births (47). The literacy rate is 77.1%, while 39% of the population live below the poverty line and malnutrition ranks 5th amongst causes of death in children below 5 years (48,49).

This research has been conducted in Northwest Cameroon where the Cameroon Baptist Convention (CBC) hospitals provide childhood cancer care to the population through an official twinning programme with Stellenbosch University, World Child Cancer and the Beryl Thyer Memorial Africa Trust, which provide funding and expertise to the CBC hospitals. Children within the scope of this study included all males and females below the age of 15 years diagnosed with cancer in Northwest Cameroon.

Data sources included publications regarding the situation of paediatric oncology in Cameroon, the rest of Africa and other developing countries, childhood cancer registries in Cameroon, and childhood cancer patients and their families. Primary data was collected from parents of patients to meet research objectives iv and v and from health care professionals to meet research objective iii while secondary data was collated and analysed to meet research objectives i, ii and vi.

The Northwest Cameroon region was used as a case study to assess the level of destitution of childhood cancer patients due to the financial and structural constraints experienced in the region. Further, due to the absence of a population-based registry, data from the CBC hospital-based registry and pathology registries was analysed to provide an indication of childhood cancer incidence by type in the country.

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# CHAPTER 2

## Paediatric oncology care development in Africa: A narrative review of published literature from 2014 to 2018

In 2014, Kruger et al. published a review regarding paediatric oncology in Africa that identified gaps in childhood cancer care. These gaps included a lack of access to accurate cancer diagnosis, essential medicines, radiotherapy and supportive care, limited access to palliative care, and a critical need for advocacy. The aim of this narrative review was to provide an update regarding the situation of childhood cancer in Africa during the period 2014 to 2018 to assist with planning for the World Health Organization – International Society of Paediatric Oncology (WHO-SIOP) initiative to improve childhood cancer survival in Africa by 2030.

This review focussed on the published literature regarding childhood cancer in English and French between 2014 and 2018 as a follow up to the publication by Kruger et al in 2014. The articles were analysed under the following themes: awareness and education, diagnosis, epidemiology and outcomes, supportive care, adherence to cancer treatment, resources for care including cost, parent experiences, planning and programme development, twinning and regional collaboration, palliative care, and traditional and complementary medicine.

The findings revealed many improvements, varying from improving community awareness to education initiatives, improved diagnostic techniques, capacity building for health care workers and socioeconomic support for patients and families. Twinning was recognised as essential for programme development and demonstrated success in starting new programmes as well as improving existing ones. Regional collaborations for research and capacity-building programmes provided local evidence, demonstrating improved cancer care for children in the context of limited resources.

Outcomes, though fragmented and lower than what was reported in high-income countries, improved from earlier estimates of only 30% for low- and middle-income countries for childhood cancers. However, access to care remained a common problem together with the lack of universal health coverage and community support systems for children with cancer and their families. Palliative care was still lacking, but there were examples of successfully implemented training and service delivery initiatives that could be replicated.

Prioritisation of paediatric oncology by governments remains an issue. Paediatric oncology was rarely included in national cancer control plans. Good involvement was seen from non-governmental organisations working together with paediatric oncology professionals to develop health care services for children with cancer. However, for these efforts to be facilitated and sustained, government engagement is indispensable, which is a major focus of the WHO-SIOP global initiative for childhood cancer with the aim of improving childhood cancer survival to 60% by 2030.

This chapter should be read together with chapter 7, which specifically reviewed the development of paediatric oncology in Cameroon.

# Paediatric oncology care development in Africa: A narrative review of published literature from 2014 to 2018

*This chapter is publication ready and will be submitted to the Journal of Global Oncology for publication. (Impact factor 1.790) https://academic-accelerator.com/Impact-Factor-IF/Journal-of-global-oncology*

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## BACKGROUND AND AIM

Great progress in childhood cancer treatment has been made over the past half century, with more than 80% of children being cured in high-income countries (HICs) (1). However, access to diagnosis and care for children with cancer is problematic in low- and middle-income countries (LMICs) (2,3). Survival rates in LMICs remain low at about 25%, often due to the lack of adequate cancer care in these countries (4,5). In 2018, the International Society of Paediatric Oncology (SIOP) and the World Health Organization (WHO) launched the Global Initiative for Childhood Cancer with the aim of improving global survival rates for common and curable cancers to 60% by 2030 (6,7).

Steliarova-Foucher et al. estimate an age-standardised incidence rate of 56.3 per million person years for children 0–14 years in sub-Saharan Africa (8). Survival was regarded as part of the essential data for reporting by cancer registries (9). Survival rates are low due to numerous factors including late diagnosis, treatment abandonment and socioeconomic factors such as lack of affordable transport and poverty (10–13). Furthermore, low levels of community awareness (14) and high rates of use of traditional and complementary medicine (T&CM) also delay early detection and seeking appropriate health care (3,12,14–16). There is also a lack of access to palliative care for children with cancer in sub-Saharan Africa, resulting in reduced quality of life for these children and their families (17).

Experts have suggested several interventions to improve paediatric oncology care in Africa.

These include interventions such as awareness creation among health care workers and the general population; capacity-building projects for paediatric oncologists, nurses and palliative care experts; twinning partnerships between HICs and LMICs with involvement of nongovernmental organisations (NGOs), governments and international charities; and establishment of population-based paediatric cancer registries (13,14,18–22). In a situational analysis of childhood cancer in Africa, Kruger et al. identified gaps in childhood cancer care that included a lack of access to accurate cancer diagnosis, essential medicines, radiotherapy and supportive care, limited access to palliative care and a critical need for advocacy (20). The aim of this study was to identify the efforts and achievements across the African continent in the period 2014 to 2018 to assist with planning for the WHO- SIOP initiative to improve childhood cancer survival in Africa.

## METHODOLOGY

A search for published literature on childhood cancer was conducted in English and French on PubMed, Google Scholar and Science Direct for publications from 2014 to 2018. Search terms used were ‘paediatric’, ‘cancer’, ‘oncology’, ‘epidemiology’, ‘outcome’, ‘abandonment’, ‘diagnosis’ and ‘Africa’. The articles deemed eligible for inclusion had to be specific to Africa as a continent or specific to an African country, and the topic had to be specifically about paediatric oncology. Articles were identified by title and abstract, and if an article appeared to be appropriate for inclusion, the full text was retrieved for further scrutiny. Reference lists in selected articles were reviewed for other potentially eligible publications. A master list of eligible studies was created and was verified by two authors of this manuscript. Publications from LMICs were excluded if the subjects included both children and adults without a separate analysis of paediatric cases. The articles were analysed under the following themes: awareness and education, diagnosis, epidemiology and outcomes, supportive care, adherence, cost and resources for care, parent experiences, planning and programme development, twinning and regional collaboration, palliative care, and traditional and complementary medicine. The selected themes were selected to correspond with themes used by previous authors who have presented situational analyses on childhood cancer care (22,23).

### Research Design, Quality Rating, and Strength of Evidence

The Johns Hopkins Nursing Evidence-Based Practice Research Evidence Appraisal ranking was used to rate the strength and quality of evidence for the various studies (25). Level I was attributed for strength of evidence if randomized controlled trial or meta-analyses thereof,

Level II for quasi-experimental studies, Level III non-experimental, qualitative, or meta-synthesis studies; Level IV expert opinion and Level V literature reviews (25).

Thirteen of the selected publications were not research. The majority (n = 91) of the reports were quantitative non-experimental studies, with additional seven qualitative studies, two systematic reviews and one literature review.

The quality of the studies was rated as follows:

A. High: consistent results, sufficient sample size, adequate control, and definitive conclusions; consistent recommendations based on extensive literature review that includes thoughtful reference to scientific evidence or

B. Good, reasonably consistent results, sufficient sample size, some control, and fairly definitive conclusions; reasonably consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence or

C. Low/Major flaw: little evidence with inconsistent results, insufficient sample size, conclusions cannot be drawn (25).

Majority of the research articles were level III strength of evidence (96/101), two were level I and two level II. Regarding quality of evidence, most (81) of the studies were rated as good quality (B), 14 poor quality (C), and seven high quality (A).

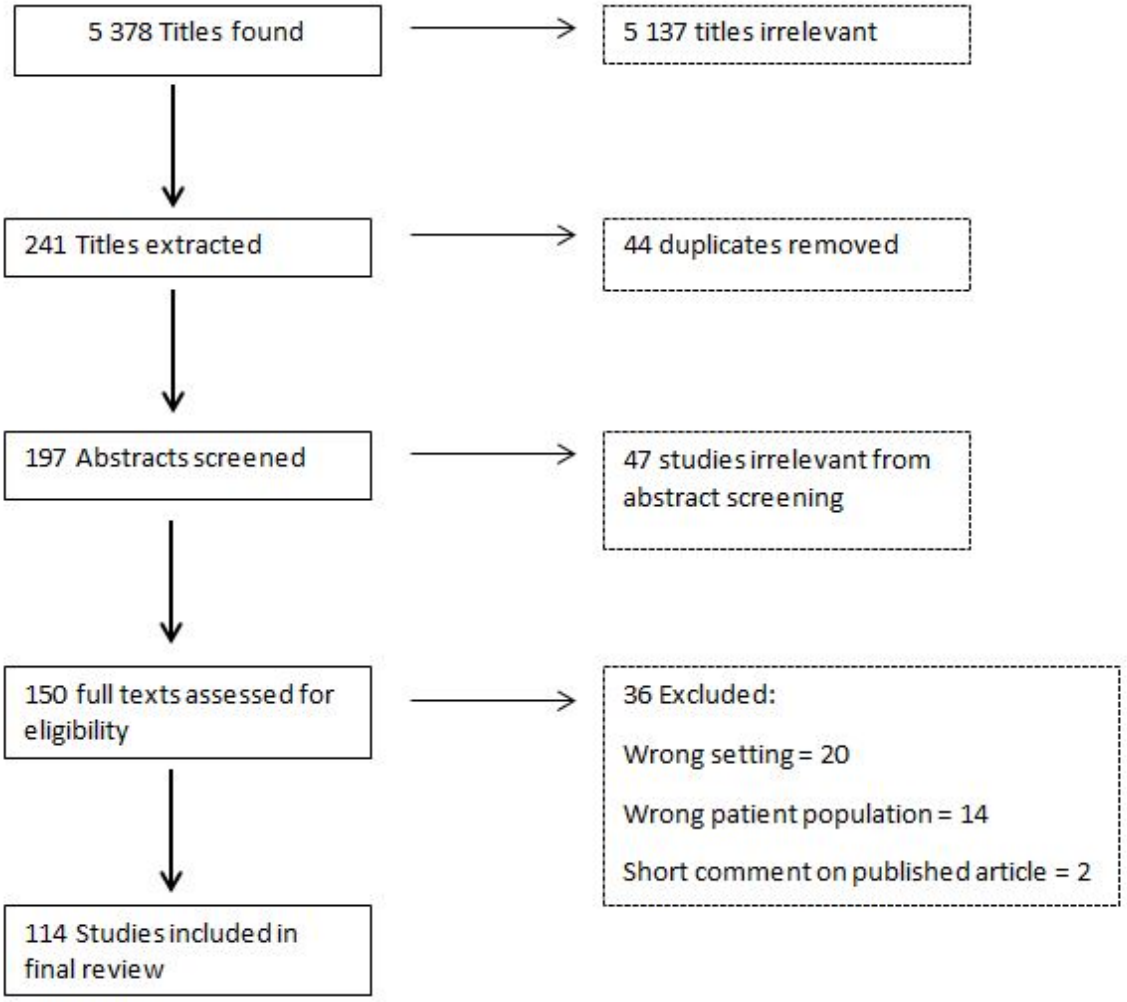
## RESULTS

### Article selection

*Selection process and geographic representation*

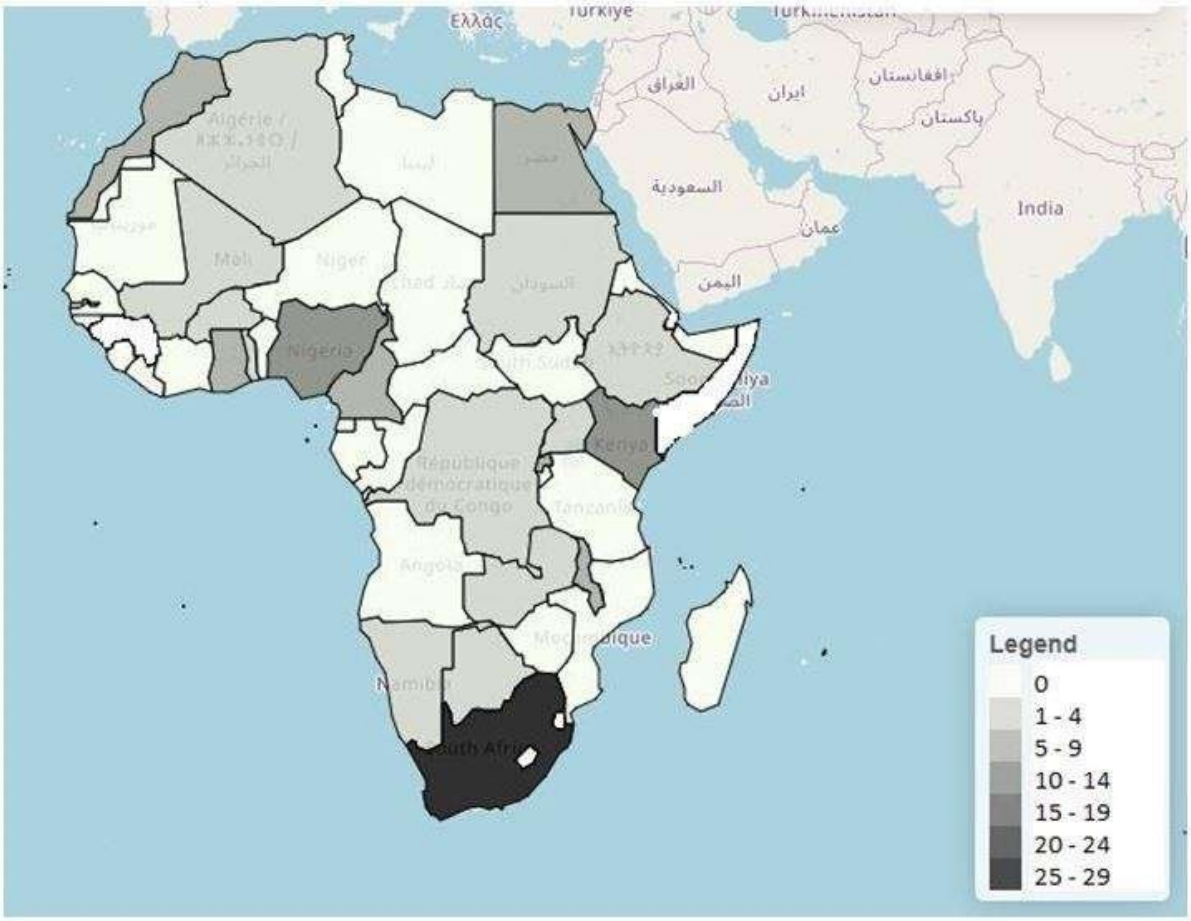
A total of 5 378 titles were found, with 241 extracted from title screening and 44 duplicates removed. The remaining 197 abstracts were screened, and 47 were found to be irrelevant to the study. Of 150 publications, another 20 publications were excluded as the setting was not specific to Africa, 14 were excluded for including no children as subjects and 2 were excluded for being short commentaries, leaving 114 to be reviewed (Figure 1).

**Figure 1: Number of included and excluded publications on childhood cancer in Africa for 2014 to 2018 from literature search**




Publications were from 19 African countries, and 12 involved multiple countries. Using the African Union divisions of the African region (24), 36 publications were from the Southern subregion, 23 were from the Western subregion, 22 were from the Eastern subregion, 13 were from the Northern subregion, 8 were from the Central subregion and 12 involved multiple subregions. Most (n = 106) of the articles were in English, and 8 were in French (Figure 2).

**Figure 2: Geographic distribution of the included publications on paediatric oncology from African countries 2014–2018**




**Awareness and education**

A low level of awareness about childhood cancer in the community was a common problem in Africa (10,19). Slone et al. trained 362 health care workers in Botswana at a cost of US$11,2 per trainee and obtained a 46.8% increase in their ability to refer a child with cancer to the national paediatric oncology hospital (26). The majority of medical students from a single university in South Africa (70.2%) recognised at least 60% of childhood cancer signs from a list of 20, and 44.1% of them correctly identified over 75% of the 20 clinical signs (27). Central nervous system tumour signs were the least recognised while lumps, fever, bleeding, easy bruising and loss of appetite were among the most recognised signs. The authors recommended increased exposure to paediatric oncology training for medical students and ongoing awareness programmes for early referrals. El-Malawany et al. called for increased awareness of the occurrence of non-Burkitt lymphomas in Southern Africa and

pointed out a need for improvement in diagnostic capacity (28).

**Diagnosis**

Delay in diagnosis remained a major concern in Africa that negatively impacted outcome. Reports documented up to 4.6 months mean delay from onset of disease to consultation for all diagnoses in Togo and up to 10 months for retinoblastoma in Morocco (29,30). A report from Kenya indicated that reasons for delay in diagnosis included travel costs, hospitalisation costs, distance from health care clinics and loss of daily wages (31). Health care system delays also played a role with long hospital stays at primary- and/or secondary-level hospitals prior to cancer diagnosis (31,32). In Morocco, delays among retinoblastoma patients were mostly due to fear of enucleation, limited access to specialised care and lack of money (30). Media campaigns, incorporation of retinoblastoma in national immunisation campaigns and appropriate counselling of parents on the need for regular follow-up with ophthalmologists were suggested as interventions to improve early recognition of childhood cancer (30).

Limited capacity for diagnosis remains a challenge for the continent (2,33). Imaging-guided biopsies were seen to provide reliable diagnostic material for paediatric malignancies as they were quick to conduct, cheap, safe and less invasive (34). Ultrasound could be adequate for diagnosis of retinoblastoma (35). Diagnosis for Burkitt lymphoma could be done with fine-needle aspiration microscopy assisted by ultrasound imaging and sometimes computerised tomography or magnetic resonance imaging if available (33).

**Cancer registration and epidemiology**

Cancer registration was deemed essential for improving paediatric oncology services (20,36). According to Renner et al., there was a need for good-quality clinical data to improve childhood cancer control in LMICs, which included proper data collection and analysis to assess the impact of awareness programmes and the outcome of treatment protocols (37). The success of the regional collaborative project on Wilms tumour was attributed to careful and inclusive planning with meticulous data collection (38). Childhood cancer ranged from 1.4% to 10% of all cancers nationally (36). Nephroblastoma was the most common solid tumour across the continent and comprised up to 10% of all cases (36).

*Southern Africa*

Kaposi sarcoma was the most common childhood cancer in Mozambique and the second most common in Zambia and Malawi (36). The overall age-specific incidence rate for childhood

cancer was 45.2 per million in South Africa over a 21-year period (1987–2007), with the most common diagnoses being leukaemia, lymphoma, central nervous system neoplasms, neuroblastoma and retinoblastoma. This was confirmed by Stones et al. for two local childhood cancer treatment centres (39,40). Children below 15 years made up 9.5% of all cancer cases in Blantyre, Malawi, between 2008 and 2010 with Burkitt lymphoma, Wilms tumour, Kaposi sarcoma and retinoblastoma the common childhood cancers (41). At Windhoek Central Hospital in Namibia, the common childhood cancer diagnoses were leukaemia and retinoblastoma, followed by lymphoma, brain tumours and bone tumours (22).

*Eastern Africa*

Kaposi sarcoma was the most common childhood cancer in Uganda, while it was Burkitt lymphoma in Kenya (39). Population-based childhood cancer registries in Zimbabwe, Uganda and Kenya indicated that the most common childhood cancers were Kaposi sarcoma, nephroblastoma, retinoblastoma, acute lymphoblastic leukaemia, Burkitt lymphoma and Hodgkin lymphoma (42). In Ethiopia, 275 out of 8 539 reported cancer cases from 2012 to 2015 were children below 15 years. Leukaemia was the most common paediatric cancer (30%), followed by nephroblastoma, retinoblastoma, bone and cartilage cancer and rhabdomyosarcoma (43). The annual number of childhood cancer admissions had increased at the National Cancer Institute of Sudan from 42 in 1999–2005 to 75 in 2006–2010 and 106 in 2011–2015, with leukaemia and lymphoma as the most common childhood cancers (44).

*Northern Africa*

Leukaemia, lymphoma, brain tumours and nephroblastoma were the most common childhood cancers reported in Algeria. Median survival for all patients was 2.7 years with a 57% cure rate reported for lymphomas and nephroblastoma (45).

*Western Africa*

The most common childhood cancer was non-Hodgkin lymphoma in West Africa (36). The most common paediatric solid tumours in Togo were nephroblastoma, teratoma and osteosarcoma (29). In Ghana, the most common childhood cancers were lymphomas, namely Burkitt lymphoma , non-Hodgkin lymphoma and Hodgkin lymphoma, followed by leukaemia, nephroblastoma and retinoblastoma, while in Mali the most common childhood cancers were non-Hodgkin lymphoma, retinoblastoma, nephroblastoma, acute lymphoblastic leukaemia and Hodgkin lymphoma (46). Paediatric cancer comprised 7% of all paediatric admissions in Zaria, Nigeria, with retinoblastoma being the most common followed by

Burkitt lymphoma. A single hospital report from University of Uyo Teaching Hospital in Nigeria reported the most common diagnoses to be lymphomas, nephroblastoma, retinoblastoma, acute leukaemias and osteosarcomas (47). Babatunde et al. noticed a decrease in the proportion of lymphomas, especially Burkitt lymphoma, in Ibadan, Nigeria, with an increase in retinoblastoma and leukaemias, a change attributed to increased access to specialist ophthalmology care (48,49).

**Survival**

A number of publications reported survival of paediatric cancers in different parts of Africa. A publication by population-based childhood cancer registries in Zimbabwe, Uganda and Kenya reported great discrepancies regarding three-year overall survival with survival in Zimbabwe for acute lymphoblastic leukaemia around 27.8% versus 68.4% in Kenya. The one-year overall survival for non-Hodgkin lymphoma (excluding Burkitt lymphoma) was 37.8% in Zimbabwe while the one-year overall survival for Burkitt lymphoma was 57.3% in Uganda versus 89.5% in Kenya. Retinoblastoma had a better one-year overall survival in Kenya (83.3%) than in Zimbabwe (64.6%) and Uganda (41.7%). The three-year overall survival for nephroblastoma was reported as 38.7% in Zimbabwe, which was better than in Uganda (15.8%) and Kenya (22.9%) (42). A study from Lilongwe, Malawi, reported the one-year overall survival for the four most common childhood cancers as 54% despite resource challenges (50).

In Egypt, 58% of children with cancer were alive after five years, and 10% were lost to follow-up. The only demographic characteristic that significantly affected survival was the mother's level of education. The authors believe that provision of transportation between hospital and home was essential for adherence to treatment and improved survival rates (51). Stem cell transplantation was available in South Africa with an overall survival of 57% obtained for children with haematological malignancies in South Africa (52).

Improved cancer registration led to improved childhood cancer epidemiological and outcome data across the continent, which was previously rare to obtain in Africa (20). A summary of the main disease-specific epidemiology and outcome report is provided in Table 1. Seven publications regarding lymphomas reported good survival for Burkitt lymphoma and Hodgkin lymphoma in Malawi, Ghana and Egypt (53–59). There was only one leukaemia publication from Malawi, which described progress with health care delivery for leukaemia and other haematological malignancies across Africa (33). Four publications reported good survival for

nephroblastoma from Kenya, Rwanda, Ghana, Uganda and Cameroon (60–63) while improved outcome for retinoblastoma was reported in South Africa, Mali and Uganda (64–67). There was also good outcome for Kaposi sarcoma in Malawi and rhabdomyosarcoma in South Africa (68,69).

**Table 1: Disease-specific epidemiological and outcome reports**

| Disease | Country | Author | Year | Sample size (n) | Survival rate | Duration of follow-up | Comments |
|---|---|---|---|---|---|---|---|
| Lymphoma | South Africa | Padayachee et al. (54) | 2018 | 52 | 54% | 96 months | Classic Hodgkin lymphoma had excellent prognosis. Non-Hodgkin lymphoma had poorer survival due to more advanced disease. However, no survival difference was observed for HIV+ and HIV-patients with non-Hodgkin lymphoma on highly active antiretroviral therapy. |
| Hodgkin lymphoma | Egypt | Sherief et al. (55) | 2015 | 59 | 95.1% | 39.8 months | The outcomes were good and similar to international studies with no association with pathological subtype. |
| | South Africa | Geel et al. (56) | 2017 | 294 | 79% | 5 years | Survival was satisfactory for an LMIC. |
| Burkitt lymphoma | South Africa | Stefan & Lutchman (53) | 2014 | 51 | 65% | 5 years | Disease stage was significantly associated with survival. |
| | Malawi | Molyneux et al. (57) | 2017 | 58 | 100% for Stage 1, 56.2% for | 12 months | Addition of anthracycline to the Burkitt lymphoma modified treatment protocol improved outcome and was deliverable in |

| Disease | Country | Author | Year | Sample size (n) | Survival rate | Duration of follow-up | Comments |
|---|---|---|---|---|---|---|---|
| | | | | | Stage 2 and 66.3% for Stage 3/4 | | resource-poor settings. |
| | Ghana | Offor et al. (58) | 2018 | 173 | N/A | N/A | The epidemiology changed as the children presented mainly with primary abdominal tumours. Treatment abandonment and treatment delay due to financial constraints led to poor outcome. |
| Non-Hodgkin lymphoma | Democratic Republic of Congo | Budiongo et al. (59) | 2015 | 38 | Only one patient was alive, 22 were lost to follow-up and 40 died. | Unspecified | The study found a higher proportion of children with B-cell non-Hodgkin lymphoma and with bcl-2 expression. Most presented with advanced disease (82.5%). |
| Leukaemia | Africa | Molyneux et al. (33) | 2017 | N/A | N/A | N/A | This was a review of paediatric haematological cancers in Africa. Especially lymphomas were common with evidence of |

| Disease | Country | Author | Year | Sample size (n) | Survival rate | Duration of follow-up | Comments |
|---|---|---|---|---|---|---|---|
| | | | | | | | improved outcome in Africa. |
| Nephroblastoma | Kenya | Njuguna et al. (61) | 2016 | 39 | 41% | 3 years | Stage was significantly associated with survival. |
| | Rwanda | Shyirambere et al. (62) | 2016 | 53 | 56.60% | 299 days | Nephroblastoma was successfully treated in a resource-limited setting. Modified treatment protocols would reduce toxicity. |
| | Ghana, Uganda, Malawi, Cameroon and Ethiopia | Paintsil et al. (70) | 2015 | 176 | 39% | End of treatment | Incomplete treatment and death during treatment were the most important causes of treatment failure. |
| | Ghana, Malawi, Cameroon and Kenya | Israels et al. (60) | 2018 | 122 | 68% | End of treatment | Through collaboration with low-cost interventions, the team could decrease treatment abandonment and increase survival. |
| Retinoblastoma | South Africa | Goolam et al. (64) | 2018 | 245 | 57.7% | 5 years | Late presentation and treatment refusal were major barriers to curative treatment. |
| | South Africa | Kruger et al. (20) | 2014 | 124 | 50% for 1993–2000 | 5 years | Late diagnosis with advanced disease was the major reason for poor outcome while |

| Disease | Country | Author | Year | Sample size (n) | Survival rate | Duration of follow-up | Comments |
|---|---|---|---|---|---|---|---|
| | | | | | versus 68% for 2001–2008 | | survival improved between two consecutive time periods. |
| | Uganda | Waddell et al. (65) | 2015 | 89 | 65% | 2 years | Survival improved with the combination of surgery and chemotherapy given by nonspecialist health care workers. |
| | Mali | Traore et al. (66) | 2018 | 88 | 73% overall survival and 59% event-free survival | 3.7 years | Median delay to diagnosis was 4.5 months for intra-ocular forms and 8 months for intra-orbital forms. Delayed enucleation and treatment abandonment negatively affected survival. |
| Neuroblastoma | South Africa | Hadley & Van Heerden (71) | 2017 | 45 | 4% | 3 years | Neuroblastoma is rare in Africa and usually presents with high-risk disease with poor survival. |
| Kaposi sarcoma | Malawi | Mittermayer-Vassallo (68) | 2016 | 20 | 63% | 1 year | HIV-seronegative children with Kaposi sarcoma were more common in Malawi while it differed from Kaposi sarcoma in adults and HIV-seropositive children. The |

| Disease | Country | Author | Year | Sample size (n) | Survival rate | Duration of follow-up | Comments |
|---|---|---|---|---|---|---|---|
| | | | | | | | disease is potentially curable. |
| | | The Pediatric AIDS-Defining Cancer Project Working Group (72) | 2016 | N/A | N/A | N/A | The incidence of Kaposi sarcoma in children below 16 years on antiretroviral treatment was highest in Eastern Africa, followed by Southern Africa. |
| Rhabdomyosarcoma | South Africa | Hendricks et al. (69) | 2017 | 75 | 58.7% overall survival (80% for limited disease) | 5 years | Advanced disease had poorer outcome versus good outcome in limited disease. |
| | Nigeria | Raphael et al. (73) | 2015 | 52 | N/A | N/A | The most common soft-tissue sarcoma was embryonal rhabdomyosarcoma. |
| Central nervous system tumours | Nigeria | Ogun et al. (74) | 2016 | 77 | N/A | N/A | Improved diagnostic resources improved the diagnosis of central nervous system tumours. |

**Supportive care**

Treatment toxicity- and supportive care-related issues remained major deciding factors for adaptation of treatment protocols for developing countries. Two studies from South Africa reported ototoxicity in association with cisplatin treatment in 80% of a cohort investigated, which was associated with age less than 10 years (75). Systematic auditory tests for children receiving cisplatin should be conducted to prevent disability.

An outbreak of nosocomial hepatitis B infection that affected 38 patients in a paediatric oncology unit at a tertiary hospital in South Africa led to major interventions, which included cessation of the use of multidose vials, strict handwashing and improved cleaning of equipment. Routine testing for hepatitis B on admission and routine antibody tests every three months with vaccination were introduced if patients had very low antibodies and proved to be effective in prevention of further infections (76). A significant number of children with cancer had no immunity to hepatitis B although vaccinated. Passive-active vaccination was advised for oncology patients in areas where hepatitis B virus exposure was significant (77).

Pain in paediatric oncology patients was mainly due to cancer, cancer treatment or invasive diagnostic and therapeutic procedures in Morocco, and treatment ranged from weak opioids to strong opioids. It was noted that effective pain management required systematic evaluation and intervention with standardised management guidelines (78). Distraction was suggested as a probable effective intervention for pain reduction in paediatric oncology patients, but the evidence was insufficient (79). Allergic reactions with L-asparaginase use were effectively alleviated with premedication and desensitisation with antihistamine in South Africa (80).

Blood stream infection prevalence was 27% in a single paediatric oncology unit in South Africa (81). The common isolates in the blood stream were gram-positive bacteria, gram-negative bacteria and fungi. The most common complications were septic shock, respiratory failure, renal failure and multiorgan failure with a case fatality rate of 2%. The highest antimicrobial resistance was ampicillin resistance for gram-positive bacteria and fluconazole resistance for fungi (81). Total white cell count and absolute monocyte count were predictive of adverse outcomes in patients with febrile neutropenia (82).

Critical appraisal of prognosis was reported as crucial for admission of the child patient to the Paediatric Intensive Care Unit (83). Tumour lysis syndrome was a common emergency, and rasburicase was shown to cost effective and efficient in preventing patients from needing renal dialysis in South Africa (84).

Nutritional support was an important component of supportive care for children with cancer as poor nutrition status as assessed by mid-upper-arm circumference was associated with increased incidence and severity of febrile neutropenia in children with nephroblastoma (85). In Cameroon, nutritional support to children with Burkitt lymphoma through food grants led to improvement of triceps skinfold and mid-upper-arm circumference measurements and was associated with less morbidity and mortality during the induction phase of treatment (86). According to Schoeman et al., a nutritional intervention plan should be developed for each child that includes the patient's caloric and nutrient requirements according to her/his nutritional status, oral or parenteral foods required, monitoring and homecare (86).

**Palliative care**

With difficult access to treatment and low rates of survival, training and innovations in palliative care delivery were suggested in several publications as a prime need for paediatric oncology in Africa (17,33,87–89). Palliative care provision was recognised in 11 out of 18 national cancer control plans in Africa (90). A trained nurse in the Stellenbosch University-Cameroon Baptist Convention Health Services twinning programme in Cameroon provided symptom control and emotional support at home and improved the quality of life for terminal patients in rural settings (91).

**Adherence**

Nonadherence and treatment abandonment remained a major factor affecting survival rates (19). In Egypt, 56% of children with acute lymphoblastic leukaemia were nonadherent to 6-MP treatment. There was a significant association between nonadherence and low socioeconomic status, low parental education level and large family of five or more children. It was recommended that counselling be reinforced on 6-MP adherence, hospital visits be reduced and improvements be made in health care provider-parent relationships (92).

Mansell et al. found that the factors associated with treatment abandonment across Africa included not being part of a research cohort, parents with only primary education, unemployed parents, long travel distances to health care facilities and no health care insurance (93). In Kenya, the most common reasons for treatment abandonment were financial difficulty, inadequate access to the national hospital insurance fund, transport issues, health care workers' inability to treat, lack of social support or pressure from the social network and no improvement in the child's condition. Access to health insurance combined with financial

and psychosocial support might reduce treatment abandonment (3,12).

Up to 73.2% of children with Burkitt lymphoma abandoned treatment in Nigeria (88,94). Late presentation and financial constraints led to poor outcomes, highlighting the need for palliative care to relieve suffering. In Zambia, less than 10% of patients completed treatment for retinoblastoma. The main hindrances to effective treatment were treatment refusal of especially enucleation, long duration of treatment, inadequate understanding of disease, outstanding pathology reports and inconsistent access to treatment (95).

**Cost of and resources for care**

Financial constraints were repeatedly identified as a major cause of low survival (17,19,93). In Rwanda, the cost of treatment of Wilms tumour ranged from US$1,831.2 to US$2,418.7 and was higher for advanced-stage disease due to longer hospital stay and intensive treatment (96). In Ghana, the annual cost of a paediatric oncology programme was US$1,7 million, amounting to US$9,781 per patient. The cost per disability-adjusted life years averted was US$1,034, which was less than Ghana's per capita income (US$1,513) and, therefore, according to the WHO-CHOICE (Choosing Interventions that are Cost-Effective) criteria very cost effective (97). In Kenya, event-free survival was higher among children with National Health Insurance Fund subscription than those without, an indication that universal health coverage would improve childhood cancer outcomes (98).

Stefan et al. reported that 16 paediatric oncologists in 38 childhood cancer treatment centres had been surveyed in Africa and that all these centres had access to haematological resources. Computerised tomography was available in 31 centres, magnetic resonance imaging in 23 centres and radiotherapy in 21 centres. Chemotherapy was free of charge in 27 centres, while in 2 centres families had to pay partially for chemotherapy. Only 12 centres had pharmacists available to prepare chemotherapy for administration. All 38 centres had access to blood banks. Palliative care was available in 27 centres with free morphine in 26 centres. Survival rates varied from 20% to 39% in 12 centres, 40% to 59% in another 12 centres and 60% and 80% in centres. Four centres reported survival rates below 20%, and no centre reported rates above 80%. Only 21 centres had a hospital-based cancer registry. Parent support groups were present in 20 centres, providing support for transportation and lodging, emotional support and volunteering (17).

The Franco-African Paediatric Oncology Group reported variable resources for diagnosis and

treatment of neuroblastoma in 2013 in Cote d'Ivoire, Democratic Republic of Congo, Togo, Burkina Fasso, Mali, Senegal, Tunisia, Madagascar, Algeria and Morocco. None of the sub-Saharan Africa centres in this report had meta-iodobenzylguanidine scans, and none had the ability to measure urinary catecholamines locally. Immunohistochemical tests were only available in the North African centres. In the sub-Saharan Africa centres, all costs of care were borne by families (99).

**Parent experiences**

Psychological support and assistance were reported as insufficient for parents of children with cancer in South Africa (100). Families experienced a high cost burden, stigmatisation and lack of social support systems in Zambia while there was a major use of alternative medical systems including T&CM and faith healing among parents (101). Some parents blamed family planning methods for their child's cancer while others reported their past health choices and inadequate nutrition of their children. Prayer and faith in God were major coping strategies for most parents (101). In South Africa, parents suggested individualised communication strategies in their preferred language with continuous assessment and reinforcement to meet their information needs (102). Other challenges for patients and caregivers included emotional issues, treatment challenges, financial difficulties, transportation issues, inadequate information, powerlessness, stigma and challenges at school (87).

Social networks are critical in shaping patients' experiences. Grandparents, friends, village communities and extended family relations were seen to have the most influence on treatment decisions in Kenya (12). Beliefs surrounding the cause and meaning of disease were a cultural construct usually resulting in the perception of cancer as witchcraft, inheritance or a curse, leading to the pursuit of alternative medical systems for health care (103). South African mothers perceived that having a child with cancer was unusual in their communities, and some wished that it had been HIV/AIDS or tuberculosis, which were well-known diseases with treatment known to the community. Having a child with cancer caused significant shifts in the mothers' responsibilities as their attention was mostly focused on the sick child, with taking care of the other children and other household responsibilities being left to the fathers or other children (100). The factors that helped to build resilience in the mothers included support from the Cancer Association of South Africa and immediate and extended family members as well as acceptance of the child's condition with belief in God as an aid in the

child's cure (100). In Kenya, parents shared their experiences with other parents in the ward as often they did not understand the doctors' vocabulary. Some families experienced isolation from their extended family members, and some were considered to be bewitched and advised to use T&CM (3).

**Planning and programme development**

Egypt had established a world-class paediatric oncology hospital with a scientific advisory board, good health care services, research facilities and an electronic medical records system supported by fundraising and establishment of international partnerships (104). Shared care networks were suggested as a practical way to organise paediatric oncology services nationally. There should be a hub site at the centre of the network with dedicated space, beds and a specialist multidisciplinary team capable of providing training (105).

A historical analysis of the Kenya National Retinoblastoma Strategy demonstrated remarkable improvement in planning, community awareness creation, family support with transportation and accommodation, pathology and clinical care training, and resource mobilisation, with a dedicated retinoblastoma-specific electronic database. Psychosocial support initiatives had also been established including a Child Life programme whereby child life leaders provided psychosocial support and medical education to patients and families. The programme's successes were attributed to the involvement of the multidisciplinary team (106).

Hampejskova et al. proposed a tool for planning human resources for retinoblastoma care following a gap analysis of retinoblastoma services in Nigeria, Uganda, Tanzania, Zambia, Gambia, Malawi, Uganda and Zimbabwe. The tool (http://www.sokidscansee.org/rb) provided estimates of total cases, enucleations, chemotherapy/radiotherapy treatments, palliative care treatments, prosthetic eyes and hospital visits (107). Digital communication could contribute to childhood cancer service improvement. While social media might assist to dispel myths, educate communities and support patients and families, data protection with confidentiality should be a major priority (108).

**Twinning and regional collaborations**

International collaboration was instrumental in establishing paediatric oncology programmes in Africa. Twinning projects were developed with colleagues from Stellenbosch University supporting projects in Malawi and Cameroon (20,109–111). The Franco-African Paediatric Oncology Group was the first group to be established as collaboration between

paediatric oncologists in France and several Franco-African countries. This group adopted the approach of capacity building and provision of material support to local teams to mitigate the challenges of limited clinical competencies, treatment abandonment and low cancer knowledge (112). Seventeen doctors as well as paediatric oncology nurses and paediatric surgeons were trained in an African paediatric oncology school(113). The regional Wilms Tumour project, including Cameroon, Malawi, Ghana, Malawi and Kenya, focused on reduction of treatment abandonment and improvement of survival as well as improvement of data management and reporting (38,63). Another major collaboration was the African Cancer Registration Network that assisted with the establishment and development of population-based cancer registries and collaborates with the International Agency for Research on Cancer (36,42).

In Rwanda, a partnership-based model was used to establish care for children with cancer at Rwinkwuvu District Hospital with consultation between home-based and United States-based physicians and pathologists, provision of free meals and travel grants to patients and establishment of palliative care and an online database (114).

A paediatric oncology programme was established in Botswana as a partnership between the government, Baylor College of Medicine and Texas Children's Hospital. The doctors and nurses were trained by United States experts, and a hospital-based registry was set up. The overall survival was 52% in the first nine years (115).

With increased recognition of paediatric oncology as a separate public health problem in Africa, specialised education, creation of cancer registries, twinning programmes between Africa and overseas partners, palliative care programmes and national cancer control plans with provisions for paediatric cancer care should be implemented (116).

**Traditional and complementary medicine**

The use of T&CM was commonly seen among patient groups and had implications for late diagnosis, treatment abandonment and ultimately survival rates (3,16,101). In Kenya, doctors insisted that parents and patients disclose T&CM use and receive guidance on safe and harmful T&CM practices (117). The majority of parents of children with Burkitt lymphoma in Cameroon (55%) consulted traditional healers before diagnosis (see Chapter 6) (15). Choice of T&CM was mostly based on belief or advice from friends and family.

## CONCLUSION

This review of published literature on childhood cancer in Africa between 2014 and 2018 showed increased reporting of paediatric oncology activities in Africa with improved outcomes. Cancer registration improved provision of information regarding epidemiology and outcome for specific diseases. Access to care remained a common problem with the lack of universal health coverage and community support systems for children with cancer and their families. Palliative care was still inadequate. The WHO-SIOP global initiative for childhood cancer should assist in advocating to African governments the importance of establishing childhood cancer services to improve survival rates to 60% by 2030.

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# CHAPTER 3

## The evolution of a hospital-based cancer registry in Northwest Cameroon from 2004 to 2015

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*Afungchwi GM, Kruger M, Wharin PD, Bardin R, Kouya FN, Hesseling PB. The Evolution of a Hospital-Based Cancer Registry in Northwest Cameroon from 2004 to 2015. Journal of Tropical Pediatrics. 2020 Oct 6.*

The study analysed the data captured in our Paediatric Oncology Networked Database for patients with cancer aged 0–15 years who had been diagnosed at two Cameroon Baptist Convention hospitals during the period 2004 to 2015.

One thousand and twenty-nine individual cases were registered. Lymphomas (mostly Burkitt lymphoma) were the most common followed by nephroblastoma, retinoblastoma and rhabdomyosarcoma. The proportion of cytologically confirmed diagnoses improved from 71.8% in the period 2004 to 2009 to 88% in 2010 to 2015.

This study demonstrated the success of a paediatric oncology tumour registry in a resource-limited setting, which might serve as a potential source of epidemiological data for planning and resource allocation. As next steps, the establishment of a national childhood cancer tumour registry and the support of the National Committee for the Fight against Cancer would be essential for success.

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Original Paper

# The Evolution of a Hospital-Based Cancer Registry in Northwest Cameroon from 2004 to 2015

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**ABSTRACT**

Effective cancer registration is required for the development of cancer management policies, but is often deficient in the developing world. In 2008 cancer registration was set up Banso Baptist Hospital and Mbingo Baptist Hospital in the Northwest region of Cameroon, using the Pediatric Oncology Networked Database (POND). The objective of this study was to analyze the POND registry data for patients with cancer aged 0–15 years for the period 2004–15. A total of 1029 malignancies were recorded in children 0–15 years in the study period. The male-to-female ratio was 1.4:1. The median age at diagnosis was 7.22 years. The most common malignancies were lymphomas followed by nephroblastoma, retinoblastoma, rhabdomyosarcoma and Kaposi sarcoma. There were more Burkitt lymphomas cases between 2004 and 2009 than between 2010 and 2015, while the number of cases rose for other diagnoses like retinoblastoma and nephroblastoma. This report has demonstrated how pediatric oncology registration can be implemented, improved and sustained in a low- and middle-income country setting with limited resources. Using the data, these hospitals can improve their treatment planning and ensure the availability of essential chemotherapy for childhood cancers.

**KEYWORDS**: cancer registry, pediatric cancer, cancer incidence, Cameroon

## INTRODUCTION

Effective cancer registration is a major challenge in Africa [1, 2] and other low- and middle-income countries (LMICs) [3]. A few African countries, such as Zimbabwe, Namibia, Kenya, Ethiopia, Nigeria, South Africa, Mali, Niger, Benin and Botswana, have shown significant improvement in childhood cancer registration [1]. Some of these registries have contributed

both to the GLOBOCAN estimates of cancer incidence worldwide [4] and the International Incidence of Childhood Cancer, Volume 3, by the International Agency for Research on Cancer (http://iicc.iarc.fr/index.php). Only 11% of the population of Africa is covered by cancer registries and often only urban centers [2].

In Africa, childhood cancers account for 4.8% of all cancers [5], compared with the 1% proportion worldwide [6]. It should be noted that children 0–15 years constitute about 40% of the total population of Africa [2]. Variations in childhood cancer incidence occur between countries and different ethnic groups. Reports on global childhood cancer incidence estimates have shown that the incidence of leukemias is several folds higher in high-income countries (HICs) than in low-income countries, whereas lymphomas and solid tumors tend to be more commonly recorded in sub-Saharan Africa [6, 7].

The childhood cancer service in the Baptist hospitals in Cameroon is a twinning project with Stellenbosch University in South Africa. The Beryl Thyer Memorial Africa Trust and the World Child Cancer UK as partners enable the provision of free cancer treatment for children aged 0–15 years, as well as expert treatment assistance and capacity building programs for local staff. Initially, the program mainly focused on the management of Burkitt lymphoma (BL), but it was subsequently extended to include the major childhood cancers, especially incorporating solid tumors [8, 9].

The objective of this study was to analyze the data captured in our twinning pediatric oncology POND registry for patients with childhood cancers under the age of 16 years for the period 2004–15.

## MATERIALS AND METHODS

The data of all childhood cancers treated at the Banso Baptist Hospital (BBH) and the Mbingo Baptist Hospital (MBH) were entered from 2008 onwards in the joint Pediatric Oncology Network Database (POND) registry, a multilingual online database developed by St Jude Children's Hospital [10].

The data for childhood cancers diagnosed prior to 2008 in children under the age of 16 years were entered retrospectively from 2004 and prospectively from 2008 onwards. Between 2004 and 2009, only one pathologist in the Northwest Region of Cameroon, located at the main urban center of the region, reviewed all specimens with a required minimum of 2 weeks to report the results for fine-needle aspiration, bone marrow aspiration or cerebrospinal fluid cytology, and about a month for histology. In 2010, a pathology service was set up at the MBH, which henceforth received all specimens from both hospitals, with an improved turnaround time, sometimes as short as 3 days. Data were verified using other sources such as hospital records, admission and discharge notes of the pediatric wards and the hospital medical records system and entered in an Excel database. As there was no access to post-mortem investigations, it was not possible to review death certificates. The POND registry collected information regarding the demographic data (age at diagnosis, gender, date of birth, region), diagnosis, histopathology, stage, treatment, date of onset of symptoms and outcome [11].

Data were extracted from POND and analyses were conducted on SPSS for Windows (IBM SPSS Statistics for Windows, version 25.0, Armonk, NY, IBM Corp.). Univariate analyses were conducted to describe patient characteristics, including region and division of permanent residence, religion, gender and age. Descriptive statistics were also analyzed for tumor types, admissions by year, method of diagnosis (cytology/histology or clinical). Measures of central tendency such as means and medians were used to describe the distribution of age and annual diagnoses. Cross tabs were used to categorize the various tumors recorded by age group, gender and year of diagnosis.

Ethics approval was obtained from the Cameroon Baptist Convention Health Services Institutional Review Board for registration of patients in the POND registry (IRB2008-4; IRB2011-7) and from the Health Research Ethics Committee of Stellenbosch University (HREC Reference no.: Sin18/08/163).

## RESULTS

### Patient characteristics

There were 1029 malignancies recorded in children 0–15 years between 2004 and 2015. Five hundred and nineteen (50.4%) were registered at BBH and 510 (49.6%) registered at MBH. The male-to-female ratio was 1.4:1 (603 males, 424 females, gender not

recorded for two cases). The median age at diagnosis was 7.22 years (IQR 5.03–9.92). The majority of patients (69.1%) came from the Northwest Region [367 (36.4%)] and West Region ($n = 329$; 32.7%); 99 (9.8%) came from the Southwest Region; 87 (8.6%) were from the Littoral; 59 (5.9%) came from the Central Region; 4 (0.4%) were from the South Region; and 2 (0.2%) came from the East Region. Ten (1%) patients came from neighboring countries: 9 (0.1%) from Nigeria and 1 (0.9%) from Equatorial Guinea (Fig. 1). The diagnosis was confirmed on histology or cytology in 79.9%, whereas 20.1% were diagnosed on clinical and ultrasound findings. The majority (88%) of diagnoses were confirmed by either histopathology or cytology for the period 2010–15, compared with only 71.8% for the period 2004–09, indicating the importance of a dedicated pathology service at the local hospitals.

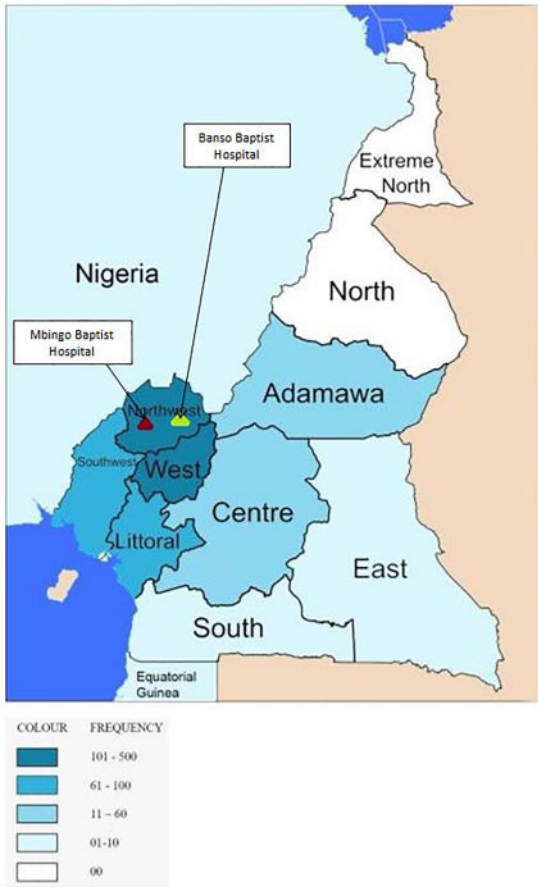


**Fig. 1.** Density map showing regions of residence for childhood cancer patients treated at the MBH and the BBH from 2004 to 2015.

The most common malignancies were lymphomas ($n = 823$; 80%) including BL, non-Hodgkin's lymphoma and Hodgkin's lymphoma, followed by Wilms' tumor ($n = 75$; 7.3%), retinoblastoma ($n = 57$; 5.5%), rhabdomyosarcoma ($n = 14$; 1.4%) and Kaposi sarcoma (KS, $n = 11$; 1.1%). Seventeen patients (1.7%) were diagnosed with acute lymphoblastic leukemia (ALL) 14 (1.4%). Other diagnoses included: pleomorphic xanthoastrocytoma (low-grade WHO (II) astrocytic neoplasm, 1); histiocytic tumor (Langerhans cell histiocytosis, 2); neuroblastoma (3); non-rhabdomyosarcoma (2); germ cell tumor (2) hepatocellular carcinoma (2); carcinoma—unspecified (1); teratoma (1); non-Wilms' renal cancer (2); neurofibroma (1); and medulloblastoma (1; Table 1).

### *Lymphomas*

The majority of lymphomas were BL ($n = 789$; 76.7%), with a male-to-female ratio of 1.4:1. The median age was 7.66 years (IQR 6–10). Five hundred and eighty-nine (80.8%) of the BL diagnoses were confirmed on the basis of cytology/histology and 200 (19.2%) based on the clinical presentation and abdominal ultrasound. There were 20 (1.9%) cases of non-Hodgkin's lymphoma (NHL) (type unspecified) with a median age of 10.07. Eleven (1.1%) cases of Hodgkin's lymphoma were recorded with a male-to-female ratio of 2.7:1 and a median age of 7, mean 7.17 (SD: 3.10).

### *Nephroblastoma*

Nephroblastoma (Wilms' tumor) was the second most common diagnosis ($n = 75$; 7.3%), with a male-to-female ratio of 1:1 and a median age of 3.5 years. The majority (73.8%) were between 0 to 4 years of age, 21.3% were 5–9 years, and 4.9% were 10–15 years. Fifty-four (93.1%) of the Wilms' tumor diagnoses were confirmed by cytology/histology, while 7% were by clinical diagnosis. Information of laterality of the tumor and congenital abnormalities were not recorded.

### *Retinoblastoma*

Retinoblastoma was the third most common tumor, comprising 57 (5.5%) of all cases. The male-to-female ratio was 1.4:1. The age range at diagnosis

**Table 1.** ***Various malignancies registered***

| Diagnosis | *n* (%) | F | M | 2004–09 | | | 2010–15 | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 0–4 years | 5–9 years | 10–15 years | 0–4 years | 5–9 years | 10–15 years |
| BL | 789 (76.7) | 323 | 465 | 50 (12.1) | 261 (63.2) | 102 (24.7) | 38 (10.2) | 211 (56.7) | 123 (33.1) |
| Wilms' tumor | 75 (7.3) | 37 | 38 | 10 (62.5) | 5 (31.3) | 1 (6.3) | 44 (74.6) | 12 (20.3) | 3 (5.1) |
| Retinoblastoma | 57 (5.5) | 23 | 33 | 1 (100) | 0 | 0 | 50 (90.9) | 5 (9.1) | 0 |
| Non-Hodgkin's lymphoma (unspecified) | 20 (1.9) | 9 | 11 | 1 (14.3) | 2 (28.6) | 4 (57.1) | 1 (8.3) | 3 (25) | 8 (66.7) |
| ALL | 14 (1.4) | 2 | 12 | 0 | 1 (100) | 0 | 2 (15.4) | 7 (53.8) | 4 (30.8) |
| Rhabdomyosarcoma | 14 (1.4) | 3 | 11 | 0 | 0 | 0 | 6 (46.2) | 1 (7.7) | 6 (46.2) |
| Hodgkin's lymphoma | 11 (1.1) | 3 | 8 | 1 (100) | 0 | 0 | 2 (20) | 6 (60) | 2 (20) |
| KS | 11 (1.1) | 1 | 10 | 1 (50) | 1 (50) | 0 | 0 | 6 (66.7) | 3 (33.3) |
| Osteosarcoma | 8 (0.8) | 6 | 2 | 0 | 0 | 1 (100) | 0 | 3 (50) | 3 (50) |
| Neuroblastoma | 3 (0.3) | 2 | 1 | 1 (50) | 0 | 1 (50) | 1 (100) | 0 | 0 |
| Lymphoblastic lymphoma | 3 (0.3) | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 3 (100) |
| Leukemia—other | 3 (0.3) | 2 | 1 | 0 | 0 | 0 | 1 (33.3) | 1 (33.3) | (133.3) |
| Other cancers | 21 (2) | 12 | 14 | 1 (12.5) | 4 (50) | 3 (37.5) | 5 (38.5) | 2 (15.4) | 6 (46.2) |
| Total | 1029 (100) | 424 | 603 | 66 | 274 | 112 | 150 | 257 | 162 |

was 0–6 years (median age 2.04 years). All retinoblastoma cases were aged under 10 years, with 90.4% aged 0–4 years. Twenty-three (76.7%) of retinoblastoma diagnoses were confirmed by cytology/histology, while 23.3% were clinical, often owing to referral only after enucleation. Laterality and family history were not recorded in POND.

### *Soft tissue sarcomas*

There were only 14 cases of embryonal rhabdomyosarcoma (1.4%). The median age at diagnoses was 8.41 years. The male-to-female ratio was 3.7:1. Only three rhabdomyosarcoma patients had a confirmed cytological or histological diagnosis.

KS was recorded in 11 (1.1%) cases, with 10 being males and 1 female. The median age at diagnosis was 7.28 years. Nine patients (81.8%) were HIV-positive, and two HIV-negative (18.2%). Half (50%) of the KS diagnoses were confirmed with cytology/histology, whereas the remainder were clinical diagnoses.

### *Malignant bone tumors*

Osteosarcoma was diagnosed in 8 (0.8%) patients, with a male-to-female ratio of 1:3. The age range was 6.44–14.15 years, median 10.21, mean 9.81 (SD: 2.70). In only three patients the diagnosis was by radiology and/or cytology.

### *Leukemia*

ALL was the most common recorded leukemia in 14 (1.4%) cases, with a male-to-female ratio of 6:1 and an age range of 4.3–14.51 years, with a median age at diagnosis of 8.41 years. Half of the patients with ALL were aged 5–9 years, with the other half aged 10–15 years. There were three (0.3%) cases of other unspecified leukemias.

### *Patterns of malignant tumors over time*

BL cases increased from 40 in 2004 to peak at 93 in 2009, after which the cases decreased to 47 in 2015, with a median annual number of 66 cases [IQR 49.5–77.5] (Fig. 2). Overall, there were more BL cases [414 (52.5% of all BL)] in the first period from 2004 to 2009 than in the second period from 2010 to 2015 [375 (47.5% of all BL)]. Wilms' tumor was registered only from 2007. Fifty-nine (78.7%) of the total 75 Wilms' tumors were recorded from 2010 to 2015. Only one retinoblastoma was recorded prior

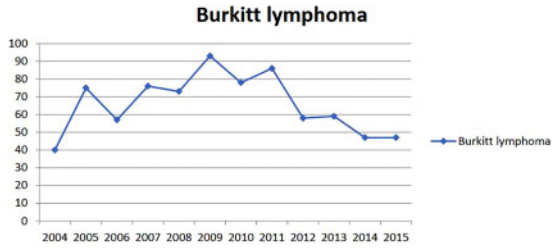


**Fig. 2.** Variation of BL cases by year.

to 2010, whereas 56 (98.2%) were recorded in the period 2010–15. Seven (87.5%) of the osteosarcomas, 14 (100%) of the rhabdomyosarcomas and 9 (81.8%) of the KSs were recorded after 2009 (Fig. 3; Table 2). Only one leukemia diagnosis was recorded prior to 2010, compared with 13 ALL diagnoses and 3 other leukemia diagnoses after 2010 (Fig. 4). The proportion of diagnoses confirmed by histology/cytology increased to 379 (88%) during the period 2010–15, compared with 313 (71.8%) for the period 2004–09 ($p<0.001$) .

## DISCUSSION

The average annual number of cases reported at the Chantal Biya Foundation Hospital in Yaounde, the capital of Cameroon, between 2005 and 2007 was 117.78 [9]. This study described 1029 cases of childhood cancer registered at two hospitals in Northwest Cameroon over a 12-year period, with an average of 85.75 cases per year, which was lower than those reported for Yaounde [11]. A lower (103) annual incidence was also reported at the Komfo Anokye Teaching Hospital, Ghana [12]. In Ibadan, Nigeria, an average of 31 cases per year was registered from 1991 to 2010 [13], whereas 23.67 per year were registered at Gondar in Ethiopia between 2010 and 2013 [14].

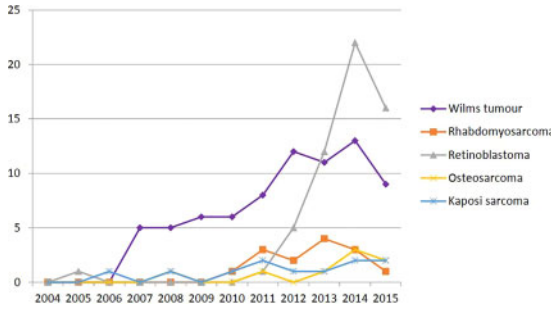


**Fig. 3.** Variation of Wilms' tumor, rhabdomyosarcoma, retinoblastoma, osteosarcoma, and KS cases by year.

Stefan *et al.* [1] purported that BL was the most common cancer in children in West Africa. In Yaounde, the capital of Cameroon, BL accounted for 52% of all childhood cancers [9], similar to Kumasi, Ghana, with about 40.8% of cases, while this comprised only 11.8% in Ibadan, Nigeria [13]. The higher proportion of BL in our study (76.7%) would seem to reflect the twinning childhood cancer program in Cameroon, which was first established as a treatment program for BL. Reports from Nigeria [13] and Ghana [15] documented a decrease in BL, while we first noticed an initial increase in BL from 2004, peaking with 93 cases in 2009, followed by a decrease to 47 in 2015. Babatunde *et al.* attributed the decline in Nigeria and Ghana to the establishment of more facilities for the management of childhood cancers, which was not the case in Northwest Cameroon. Offor *et al.* (15) attributed the decline in BL to better malaria control according to the postulation of Mutalima *et al.* [16] that BL incidence drops when malaria incidence drops.

Stefan *et al.* [1] described nephroblastoma as the most common solid tumor in Africa, with rates exceeding 10% in several countries. Nephroblastoma was also the second most common in Gondar, Ethiopia, with 18.3% of all cases [14]. In Ibadan, Nigeria, renal tumors were 6.6% of all cases [13], whereas in Yaounde this was reported as a rare malignancy constituting 0.73% of all cases [9]. Nephroblastoma was the second most common diagnosis in our study, accounting for 7.3% of all cases. An official multicenter protocol for the treatment of Wilms' tumors commenced in 2007, with the two hospitals in this study (https://paediatriconc.wixsite.com/wilmsafricaproject) participating since 2014, which may explain the increase between 2010 and 2015 [12]. Treatment protocols for retinoblastoma and KS were implemented in 2011, explaining the increase for number of cases with either retinoblastoma or KS after 2010.

Retinoblastomas constituted 5.5% of cases, <21% in Nigeria [13] with the age range below 6 years, as was predominantly the case in Nigeria. The other

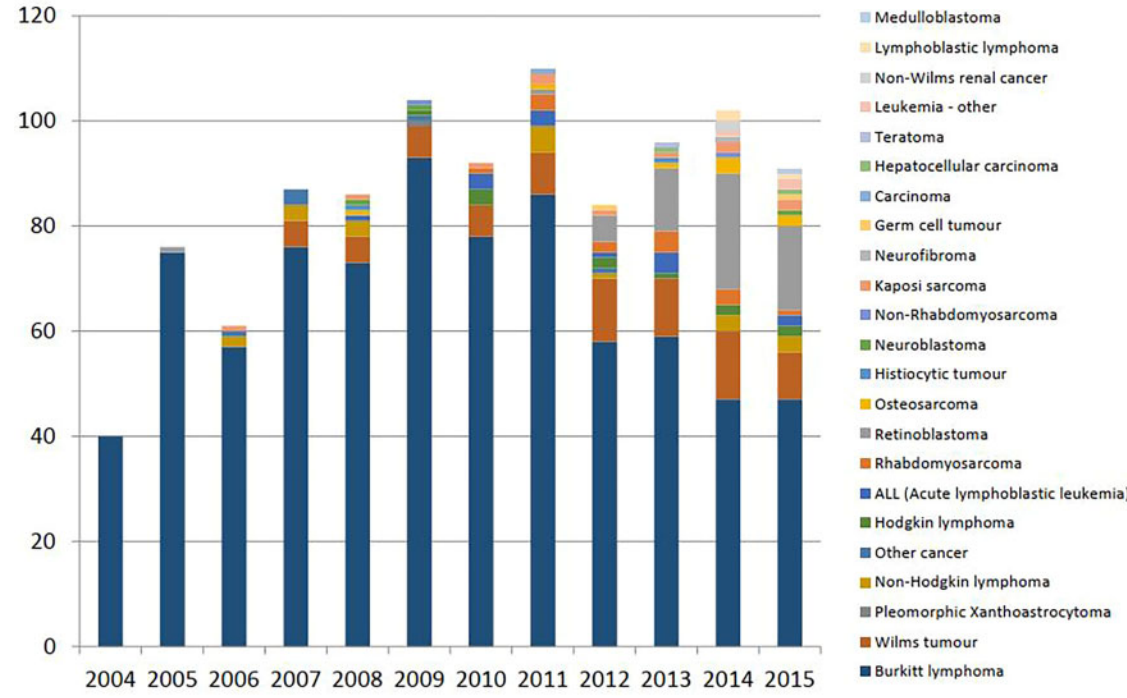


**Fig. 4.** Distribution of cases by all diagnoses over years.

less common other tumors included Hodgkin's lymphoma, rhabdomyosarcoma, neuroblastoma and osteosarcoma. Kaposi sarcoma was reported as the most common cancer in children in Southern Africa, with high incidence attributed to the HIV pandemic [1]. In this study, we had an incidence of 1.1% for KS with 18% of them HIV negative. In Jos, Nigeria, sarcomas were reported to make up 39% of the recorded cases [17].

Only a few leukemias were registered in this study (1.7%), as these patients traditionally were referred to the Chantal Biya Hospital in Yaounde, Cameroon for treatment, owing to the availability of resources such as blood products, which was lacking at Banso and Mbingo Hospitals [18]. The relative frequency was much higher (10.2%) in Ibadan and Gondar (18.1%) [13, 14] and it was the second most common malignancy in Kumasi, Ghana (10%) [12]. Rodriguez-Galindo *et al.* [19] argued that in malaria endemic areas, it is possible that children with leukemia may be misdiagnosed for an infectious disease and may die without cancer being suspected or confirmed as the real diagnosis. This is a major concern in a country such as Cameroon, which records a high incidence of malaria [20]. With limited knowledge on cancers among the general population and first-line health care providers and limited diagnostic facilities, leukemia patients exhibiting signs and symptoms similar to those of malaria could be misdiagnosed.

Most (79.9%) of the diagnoses were confirmed by cytology and 20.1% were based on clinical findings only, including imaging. The absence of central nervous system tumors in this registry can be explained by the unavailability of computerized tomography scans. This is unlike the reports from Ibadan and Yaounde where all the patients included were confirmed by cytology/histology [9, 13]. In Gondar, Ethiopia, only 33% of cases had cytology confirmation [14]. Dependence on clinical findings supported by imaging and laboratory is not uncommon in the diagnosis of cancer in developing countries. Chasimpha *et al.* [21] in their report on the PBCR in Blantyre, Malawi, noted that less than half of the cases registered were confirmed by histology or cytology. Difficult access to pathology services

constitutes a major hindrance to pediatric oncology care in Africa and other developing countries [2, 19]. Even where available, these services are usually only resourced to conduct basic histopathology [22]. Proceeding with treatment based on clinical diagnosis only is recommended when there is no quick access to pathology for patients with suspected BL [23] given the fast growing nature of the disease [24]. Moreover, according to current recommendations, histological confirmation is not essential for initiation of treatment for Nephroblastoma [25]. However, it is not uncommon in the African setting for some renal tumors to be initially diagnosed as nephroblastoma but eventually found to be another cancer, a situation which is unlikely in the developed world [26].

The establishment of twinning partnerships between HICs and LMICs is a practical approach to strengthen pediatric oncology programs in LMICs. Twinning begins with determining priorities to be addressed, which leads to the identification of potential partners and a gradual process of building the partnerships [19]. Twinning partnerships provide a platform for capacity building and improved diagnoses and are usually more beneficial when they also include a strong research component [19, 27]. Hospital-based registries are one of the first research projects to be established to provide initial data, which later can be used to establish a population-based registry.

### Limitations

Certain patients may not have been registered, as they were not treated at the local hospitals. Additionally, the International Classification of Diseases for Oncology Coding [28] was not used in the data entry, allowing for non-specific entries such as unspecified carcinoma, non-Hodgkin's lymphoma, non-Wilms' renal tumor or non-rhabdomyosarcoma. Finally, the registry did not collect data on the topography of the tumors, making it impossible for this report to describe the location and laterality of the cancers registered.

## CONCLUSION

This study describes the childhood cancers registered at two hospitals in Northwest Cameroon between 2004 and 2015. Although population-based registries are the best tool in planning health services, this report can assist with local childhood cancer treatment program development and ensure pediatric access to cancer health care with curative intent. The report demonstrates how pediatric oncology registration can be implemented, improved and sustained in an LMIC setting. Such registries may serve as an important source of data for population-based registries, as Rodriguez-Galindo *et al.* [19] indicated that hospital-based tumor registry is the first source of reliable information on childhood cancer. This is a potential first step in the direction of a possible population-based cancer registry. As a future direction for pediatric cancer registration in Cameroon, hospital-based registries should be created in all pediatric oncology centers, with support from the National Committee for the Fight against Cancer. This will generate national level statistics on all children diagnosed with cancer in the country which is essential for health sector planning in non-communicable disease control.

## ACKNOWLEDGMENTS

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# CHAPTER 4

## The outcome and cost of a capacity-building training programme on the early recognition and referral of childhood cancer for health care workers in Northwest Cameroon

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Late diagnosis is one of the causes of low survival rates of childhood cancer in low- and middle-income countries. As the general population and primary health care workers have a low childhood cancer awareness, late diagnosis is common.

The aim of this study was to evaluate the outcome and cost of a capacity-building programme to improve the knowledge of childhood cancer among health care workers in the Northwest region of Cameroon. Training workshops were conducted in six health districts of Northwest Cameroon between June and September 2016 with a group of paediatric oncology nurses and nurse practitioners. Participants (n = 113) were taught to recognise the warning signs of childhood cancer and to utilise effective referral pathways for a suspected childhood cancer patient to specialist care. The overall knowledge score increased from 50.88% in the pretest to 84.79% in the posttest while 99% of participants felt competent to identify children with early signs of cancer.

This is the first report regarding a nurse-led capacity-building project for childhood cancer awareness in Africa to our knowledge. The Sanofi Espoir Foundation's My Child Matters award for nurses sponsored the research. To sustain the knowledge gained by the participants and prompt referrals, we recommend that refresher training courses be organised regularly.

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RESEARCH ARTICLE

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# The outcome and cost of a capacity-building training programme on the early recognition and referral of childhood cancer for healthcare workers in North-West Cameroon

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## Abstract

**Aim:** Early cancer diagnosis is necessary to improve survival rates. The aim of this study was to assess the outcome and cost of the childhood cancer training programme amongst healthcare workers.

**Design:** This was a prospective pre–post study design, using questionnaires for pre- and post-training testing. The warning signs of childhood cancer were used as the main teaching content to improve recognition and early diagnosis.

**Methods:** Pre-training and post-training knowledge, as well as attitude questionnaires, was administered at the beginning and at the end of each training workshop. Paired samples *t* test and chi-square were used to compare the change in knowledge and differences between groups.

**Results:** The overall percentage knowledge score increased from 51%–85% ($p < .001$). The doctors had a better knowledge score than the nurses in the pre-test (70% versus 50%, $p = .008$), but there was no significant difference in the post-test scores. The cost of training was €25.06 per healthcare worker.

**Conclusion:** We recommend similar training programmes in public health to improve early diagnosis of childhood cancer.

KEYWORDS

Cameroon, capacity building, childhood cancer, early diagnosis, my child matters

## 1 | BACKGROUND

There are vast disparities in childhood cancer survival rates between developed countries and low- and middle-income countries (LMIC). Great progress has been made over the past half-century in the care of children with cancer, with 80% of children with cancer cured in high-income countries (HIC). However, the survival rates in developing countries still range between 20%–70% (Chantada, Lam, & Howard, 2019). This makes the plight of children with cancer a global concern, as 80% of children diagnosed annually with cancer live in LMIC (Israëls et al., 2013).

To improve childhood cancer survival in LMIC, paediatric oncology experts have suggested actions that include the promotion of early diagnosis; capacity-building training programmes, effective

childhood cancer care programmes; a reduction in treatment-related deaths; and a reduction in treatment abandonment (Friedrich et al., 2015; Mostert et al., 2011). Twinning partnerships between HIC and LMIC have led to a significant improvement in local childhood cancer management capacity, drug availability and the development of locally adapted protocols [5–8].

The Stellenbosch University-Cameroon Baptist Convention Health Services (CBCHS) twinning programme has operated a childhood cancer treatment programme since 2003, with two treatment centres in the north-west region. Both centres provide free treatment and support for the feeding and transportation of all children younger than 15 diagnosed with cancer. Hesseling et al. reported that up to 84% of these patients presented at the hospital with advanced-stage disease and only 16% with limited disease. The event-free survival was 100% for stage I, 85% for stage II, 60% for stage III and 27% for stage IV disease (Hesseling et al., 2012). Early diagnosis with more limited disease therefore implies a better chance to be cured with the currently available facilities and expertise (Miller et al., 2019).

Delays in the health system have been shown to be a major contributor to delays in the diagnosis of childhood cancer [11–13]. A previous survey of 50 childhood cancer patients at Mbingo Baptist Hospital in Cameroon showed that 70% of them presented to the treatment centre more than three weeks after the onset of disease, with the delay being shorter for patients referred by health professionals than for self-referred patients (Kouya, 2012). Brown et al. reported that the delay in diagnosis was longer when childhood cancer patients in Nigeria visited several health facilities (Brown, Adeleye, & Ibeh, 2015).

With a low physician to population ratio in Cameroon of 0.08 per 1,000 of the population (Central Intelligence Agency, 2018), most of the health care in rural settings is left in the hands of nurses and community healthcare workers (National Institute of Statistics, 2012). Traditional medicine is also a relatively popular choice for health care in Cameroon and therefore recognized by law and integrated into the healthcare system (Asonganyi, 2013). Fifty-five per cent of children with Burkitt lymphoma in North-West Cameroon primarily visit traditional healers as the first choice for care [18]. The traditional healers may make incorrect diagnoses and apply various forms of treatment that are ineffective and often painful and/or harmful to children (Afungchwi, Hesseling, & Ladas, 2017). This situation highlights the critical importance of empowering rural nurses and community healthcare workers to be frontline actors to educate communities, as well as

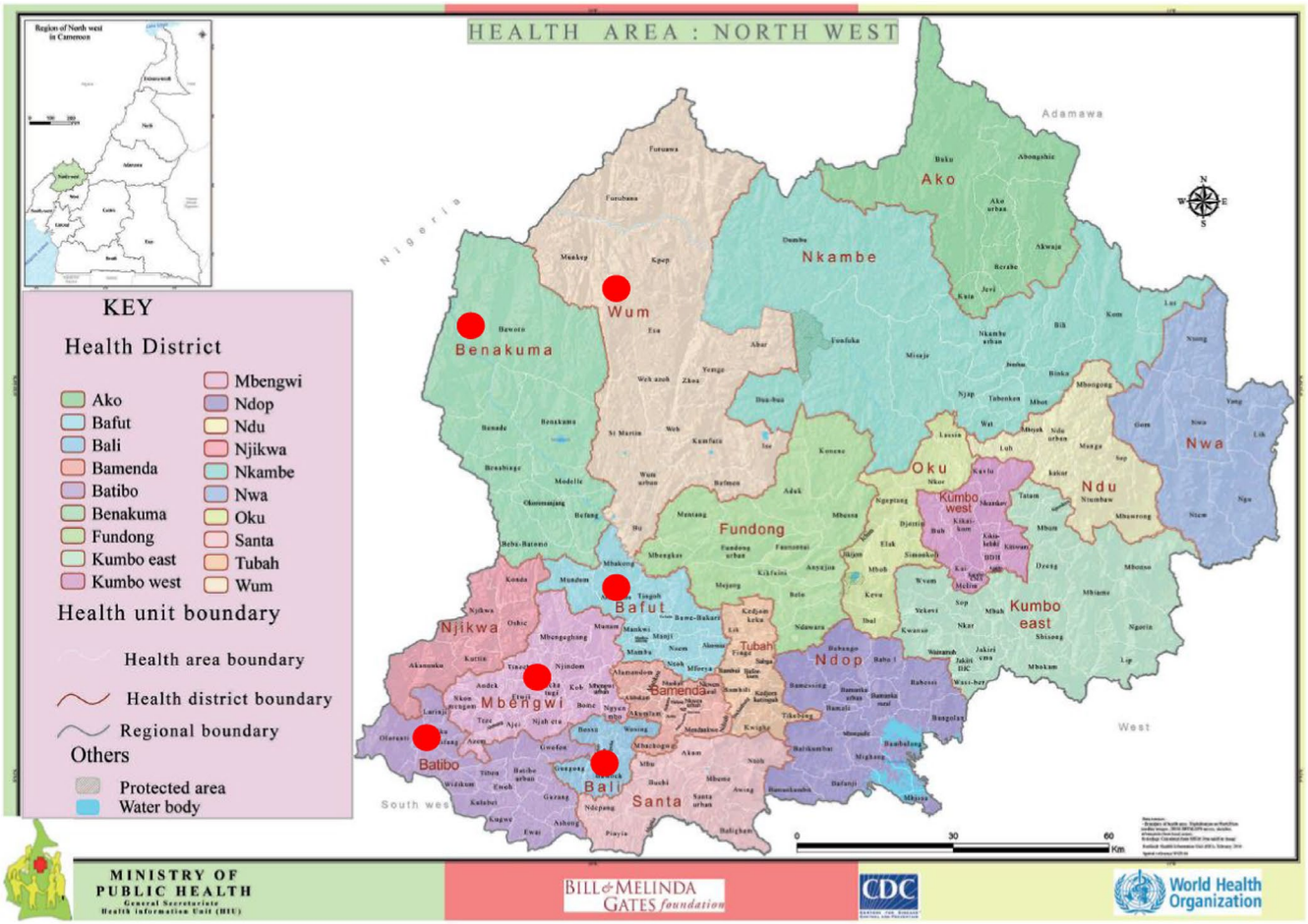


**FIGURE 1** Map of North-West Cameroon, showing health districts indicated by red dots (Bafut, Mbengwi, Batibo, Benakuma, Wum, Bali). Source: Ministry of Public Health, Cameroon. https://www.dhis-minsante-cm.org/portal/

to identify children with cancer for early referral and treatment (Mbah Afungchwi & Challinor, 2016).

An important tool is to train healthcare workers, especially nurses and community healthcare workers, to recognize the early warning signs and symptoms of childhood cancer. It is also important to improve the linkage between community healthcare workers and cancer referral centres and to improve transport support for children with cancer (Buckle et al., 2013). A training programme in rural South Africa has led to an increase in referrals and average annual diagnoses, although not necessarily decreasing the delay in diagnosis (Poyiadjis, Wainwright, Naidu, Mackinnon, & Poole, 2011). The effect on patient outcome has not been measured. Similarly, educating healthcare professionals in Botswana has led to improvement in healthcare workers' knowledge of childhood cancers, with concomitant improved referral rates (Slone, Ishigami, & Mehta, 2016a).

This study aimed to assess the outcome and cost of a SANOFI-sponsored training programme with the title, "My Child Matters," regarding knowledge of childhood cancer amongst healthcare workers in the north-west region of Cameroon.

## 2 | METHODS

This was a prospective pre–post study design. The Sanofi Espoir "My Child Matters" programme (Sanofi Espoir Foundation, 2020) supported the establishment of a network of 133 healthcare providers (including 20 traditional healers) trained to potentially identify childhood cancer cases in six health districts of North-West Cameroon in 2016. Head nurses and medical doctors of all the leading health centres and three prominent traditional healers from each health district were invited to participate in the training workshops at their various district health services' headquarters. The selection of participating centres was based on the recommendation of the district medical officers and district supervisors. The healthcare facilities included healthcare centres headed by nurses, sub-divisional medical centres headed by physicians and a district hospital headed by physicians. Participants included head nurses of all lead health centres, medical officers of all sub-divisional medical centres and district hospitals were invited to participate in the training, three prominent traditional healers from each health district and the district supervisory teams. Of this group of participants, 18 were selected as "ambassadors" and equipped with mobile phones and mobile money accounts to communicate with childhood cancer centres and to refer patients promptly for diagnosis and treatment.

The training programmes were held between June and September 2016 and covered six health districts, namely Mbengwi, Bafut, Batibo, Bali, Wum and Benakuma, in North-West Cameroon, with a total surface area of 6,601 $km^2$ and a total population of 439,956 (Northwest regional delegation of public health, 2015) (Figure 1). The workshops lasted 4 hr and consisted of PowerPoint presentations with case studies and pictures, followed by group discussions on effective referrals. The topics covered included an explanation of what cancer is, the common childhood cancers and their presentations and a discussion on how to effectively refer a child with cancer to a treatment centre. Participants were provided with brochures and flyers on the warning signs of childhood cancer that contained the Saint Siluan warning signs of cancer in children, developed by the South African Children's Cancer Study Group (Poyiadjis et al., 2011), with pictures of example cases. The facilitators of the training workshops were paediatric oncology nurses and nurse practitioners from two childhood cancer centres in the north-west region. The project design and workshop content development were overseen by the oncologist at Mbingo Baptist Hospital and the paediatric oncologist from Stellenbosch University.

A pre-training knowledge and attitude questionnaire (Appendix 1) was administered to the attending healthcare professionals at the beginning of each training workshop and again at the end of the training workshop in the same group (Appendix 2), to assess initial knowledge and post-training knowledge. The questionnaire included questions on the education and experience of the healthcare worker; the types of childhood cancers; signs of childhood cancer; and childhood cancer treatment sites in Cameroon. It also included attitude-related questions: whether they had ever referred a child with cancer and whether or not they educated their communities about childhood cancer. The Saint Siluan warning signs for childhood cancer was used to grade the correctness of their knowledge of childhood cancer warning signs (Poyiadjis et al., 2011). Participation in the pre- and post-test was optional and on provision of informed consent. The knowledge of risk factors of cancer was graded based on published literature on cancer aetiology, while knowledge on treatment sites and types of childhood cancers were graded based on expert knowledge. The cost of the entire capacity-building training programme was recorded on a spreadsheet.

### 2.1 | Statistical analysis

Descriptive statistics were used to present the characteristics of the study participants. The five questions of the questionnaire which assessed knowledge had a moderate internal consistency, with a Cronbach's alpha coefficient of 0.6. The IBM Statistical Package for the Social Sciences (SPSS) version 25 was used to analyse the data. The paired samples *t* test was used to compare the change in knowledge scores before and after the training. A chi-squared test was used to compare the difference in scores between physicians and nurses. The level of statistical significance was set at p values less than 0.05. Atlas.ti version 8 was used to code and group free-text responses into themes. The cost was analysed for various aspects of the project, and the total cost per participant trained was estimated.

### 2.2 | Ethics

Ethics clearance was obtained from the Cameroon Baptist Convention Health Services Institutional Review Board (IRB2018-42) and the Health Research Ethics Committee of Stellenbosch

University (project ID 8,041, HREC reference number S18/08/163). Responding to the questionnaire was completely voluntary, following the reading of the participant information sheet and consent to participate.

## 3 | RESULTS

### 3.1 | Characteristics of participants

A total of 113 healthcare professionals and 20 traditional healers were trained across the six districts. Traditional healers were left out of the pre- and post-training tests because most of them were not literate and could not complete the paper-based questionnaires. Twenty eligible respondents (17.7%) did not participate. Ninety-three of the participants (82.3%), all healthcare workers, completed both the pre-training and post-training test. Most were from primary healthcare centres (78.5%), followed by district hospitals (17.2%) and sub-divisional medical centres (4.3%). Most were State Registered Nurses (three years' training; 40%), followed by nursing assistants (ten months' training; 20%), brevete nurses (two years' training; 15.6%), bachelor's degree nurses (four years' training; 10%), nurse aides (7.4%) and physicians (6.7%). Most participants had either between five and 10 years' (35.5%) or more than 10 years' (34.4%) working experience in health care, while 17.2% had worked between two and five years and 12.9% for less than two years. Ninety-six of the participants (85%) consulted children in their day-to-day practice. Nine thousand brochures were distributed amongst the trainees, as were printed handouts of all the modules taught.

Eighteen per cent of the respondents in the pre-training test did not have any knowledge of childhood cancers. Those who had some knowledge of childhood cancers reported having acquired this knowledge during their training at their nursing or medical school (61%), from medical or nursing textbooks and journals (23.4%), from the Internet (22.3%), or from another physician or nurse (16%). A few (15.1%) had been giving health talks regarding childhood cancers in their communities (Table 1).

### 3.2 | Change in knowledge

The first part of the knowledge test included information of cancer-causing physical agents such as radiation and sunlight; chemical agents such as tobacco smoke and pesticides; viruses and bacteria; canned foods and grilled goods; and genetic factors. The mean recognition score for these risk factors increased significantly, from 3.19 in the pre-test to 4.21 in the post-test ($p < .001$). Participants were asked to list four types of childhood cancers, and the mean score of correct answers for this question increased significantly, from 1.38 in the pre-test to 2.94 in the post-test ($p < .001$). In the pre-test, 10 correct responses for cancer type (exact cancer names were not required) and their frequencies were identified: blood cancer ($N = 51$, 54.8%), bone cancer ($N = 24$, 25.8%), brain cancer ($N = 16$, 17.2%), Burkitt lymphoma ($N = 11$, 11.8%), eye cancer ($N = 9$, 9.7%), Kaposi sarcoma ($N = 3$, 3.2%), lymphoma ($N = 10$, 10.8%), nephroblastoma ($N = 3$, 3.2%) and neuroblastoma ($N = 1$, 1.1%). In the post-test, the specific types of cancers were identified, with their frequencies as follows: retinoblastoma ($N = 49$, 52.7%), Burkitt lymphoma ($N = 48$, 51.6%), nephroblastoma/Wilms' tumour ($N = 35$, 37.6%), osteosarcoma ($N = 33$, 35.5%), leukaemia ($N = 31$, 33.3%), Kaposi sarcoma ($N = 21$, 22.6%), lymphoma ($N = 20$, 21.5%), neuroblastoma ($N = 2$, 2.2%), Hodgkin's lymphoma ($N = 1$, 1.1%) and non-Hodgkin's lymphoma ($N = 1$, 1.1%). Far fewer responded with the broad categories, such as blood cancer ($N = 4$, 4.3%), bone cancer ($N = 11$, 11.8%), eye cancer ($N = 10$, 10.8%) and brain cancer ($N = 1$, 1.1%),

The third section tested knowledge of the warning signs of childhood cancer (Table 2). The mean score for this question changed from 1.87 in the pre-test to 3.60 in the post-test on a point scale of 4 ($p < .001$). Finally, participants were asked to list dedicated paediatric oncology units in Cameroon. The mean score for this question increased from 1.37–2.91 on a scale of 3 ($p = .087$). Four correct sites were identified in the pre-test, with the following frequencies: Mbingo Baptist Hospital ($N = 49$, 52.6%), Banso Baptist Hospital ($N = 41$, 44.1%), Chantal Biya Foundation Mother and Child Centre in Yaounde ($N = 14$) and Baptist Hospital Mutengene ($N = 7$, 7.5%). In the post-test, the same four sites were listed in different frequencies, as follows: Mbingo Baptist Hospital ($N = 84$, 90.3%), Banso Baptist Hospital ($N = 78$, 83.9%), Chantal Biya Foundation Mother and Child Centre in Yaounde ($N = 55$, 59.1%) and Baptist Hospital Mutengene ($N = 52$, 55.9%). When asked if they thought it was possible to cure a child with cancer in Cameroon, 86% said yes in the pre-test and 98% agreed in the post-test ($p = .019$).

When knowledge scores were compared between doctors and nurses in the pre-test, there were no significant differences in the mean scores for knowledge regarding factors predisposing to cancer ($p = .799$), types of childhood cancers (0.137) or dedicated paediatric oncology units in Cameroon ($p = .086$). However, the doctors scored higher than the nurses regarding knowledge of the warning signs of childhood cancer [2.50 ($SD$ 1.643) versus 1.31 ($SD$: 0.891), $p = .137$] and in the overall knowledge score [69.61 ($SD = 29.159$) versus 49.79 ($SD = 16.218$), $p = .008$]. In the post-test, there was no significant difference in scores for types of childhood cancers ($p = .438$), signs of childhood cancers ($p = .688$), dedicated paediatric oncology units in Cameroon ($p = .517$) and overall knowledge score ($p = .845$). However, the nurses scored significantly higher (4.30, $SD = 0.915$) in identifying the risk factors for cancer than the doctors (3.50, $SD$ 1.225), $p = .047$.

At the end of the training, 99% of the participants confirmed that they would be able to effectively refer childhood cancer patients to treatment centres. All (100%) participants thought that the training would benefit their community and their clinical practice, that they would teach their colleagues about childhood cancers and would be giving health talks on childhood cancer to their community members.

The length and form of higher education in terms of healthcare training were associated with improved childhood cancer knowledge, as there was a significant correlation between the participants'

**TABLE 1** Characteristics of participants

| Participant characteristic | Frequency (%) |
|---|---|
| Type of facility where participant works ($n$ = 93) | |
| Health centre | 73 (78.5) |
| Sub-divisional medical centre | 4 (4.3) |
| District hospital | 16 (17.2) |
| Level of training of participant ($n$ = 90) | |
| Nurse aide | 7 (7.4) |
| Nursing assistant | 18 (20.0) |
| Brevete nurse | 14 (15.6) |
| State Registered Nurse | 36 (40.0) |
| BSc nurse | 9 (10.0) |
| Physician | 6 (6.7) |
| Participant's years of experience in health care ($n$ = 93) | |
| 0–2 years | 12 (12.9) |
| 2–5 years | 16 (17.2) |
| 5–10 years | 33 (35.5) |
| More than 10 years | 32 (34.4) |
| Source of childhood cancer knowledge | |
| Nursing or medical school | 58 (61) |
| Another physician/nurse | 15 (16) |
| Internet | 21 (22.3) |
| Medical or nursing textbooks/journals | 22 (23.4) |
| No knowledge | 17 (18.1) |
| Participants who consult children ($n$ = 90) | 86 (95.6) |
| Participants who have been giving health talks on childhood cancers in their communities prior to training | 14 (15.1) |

form of training in health care and their mean score for knowledge about childhood cancer types, signs of childhood cancer and the availability of treatment all together ($p$ = .005). However, these scores did not show a significant correlation with years of experience in health care ($p$ = .692).

### 3.3 | Costs

As training programmes need financial support, the total costs were also documented. The total cost for the project was €4,476.32. The cost of training was €3,834.124, of which €518.32 was used to provide mobile phones and mobile money accounts for ambassadors to communicate with paediatric oncology unit teams and transport suspected cases, with an average of €25.06 per healthcare worker attending. The major part (48%) of the training cost was for the transportation of participants and catering, followed by 21% for the transportation of facilitators, 12% for printing brochures and leaflets, 9% for training materials, and 5% for lodging and catering for facilitators (Figure 2).

The participants provided several suggestions for improving the early diagnosis of childhood cancers in the region. The most common suggestions were awareness creation in communities ($N$ = 19), quick referral of suspected cases to treatment centres ($N$ = 18), training more healthcare providers ($N$ = 12) and refresher training courses on the early diagnosis of childhood cancers ($N$ = 10). Some participants suggested proper physical examination of children at consultation ($N$ = 5), the designation of more focal persons for referrals ($N$ = 4), the provision of more leaflets on warning signs to healthcare centres and communities ($N$ = 3), the inclusion of childhood cancer as a disease of surveillance ($N$ = 3) and improving collaboration with traditional healers ($N$ = 3). A few suggested campaigns to actively search for children with signs of cancer in communities ($N$ = 2), screening for lumps at Infant Welfare Clinics ($N$ = 2), counter-referral of referred patients after diagnosis and treatment ($N$ = 2) and advocacy with community leaders and politicians ($N$ = 2).

## 4 | DISCUSSION

Capacity building is defined as any activity or modification aimed at or resulting in an improved outcome within a health system (Baillie, Bjarnholt, Gruber, & Hughes, 2009). Capacity building is used as a means to promote surveillance for diseases, notably communicable diseases in Africa, and has been shown to be effective in the surveillance of disease outbreaks (Durrheim, Harris, Speare, & Billinghurst, 2001). In Cameroon, capacity building within the Expanded Program on Immunization is used to strengthen the surveillance of diseases with epidemic potential, including poliomyelitis, yellow fever, measles and neonatal tetanus.

Cameroon has a three-tier health system, the most basic part of which is the peripheral level, consisting of health centres, sub-divisional medical centres and district hospitals (http://www.statistics-cameroon.org/downloads/pets/2/Rapport_principal_Sante_anglais.pdf). It was the district level that was targeted for this capacity-building project. The health professionals at this level have few specialized care services and therefore are usually abreast of most communicable diseases that require prompt management and are included in their minimum package of activity. Only 6.7% of our participants were physicians. This is not unexpected, given a doctor-to-population ratio of 0.08 per 1,000 (Central Intelligence Agency, 2018) compared with a nurse-to-population ratio of 0.8 per thousand (Global Health Workforce Alliance, 2020lliance, 2020) and the fact that, as reported in 2013 (World Bank, 2013), 40% of the country's doctors practice in the central region, where the capital city Yaounde is located. Most health professionals who attended the training were nurses, similar to the case in Botswana, although the ratio of nurse to physician in that setting was much smaller (1.6:1) than in this report (14:1) (Slone et al., 2016b). This highlights the importance of including nurses in capacity-building training programmes in Africa to promote the early identification and prompt referral of childhood cancer patients. Noteworthy is the fact that

**TABLE 2** Change in knowledge

| Knowledge | Pre-test | Post-test | *p* value | *t* | *df* |
|---|---|---|---|---|---|
| Recognition of factors that predispose to cancer | *n* (%) | *n* (%) | | | |
| Physical agents like radiation and sunlight | 68 (72.3) | 89 (94.7) | <.001 | 4.635 | 93 |
| Chemical agents like tobacco smoke and pesticide | 81 (86.2) | 93 (98.9) | .001 | 3.380 | 93 |
| Viruses and bacteria | 48 (51.1) | 51 (54.3) | .534 | 0.624 | 93 |
| Canned food/grilled foods | 40 (42.6) | 81 (86.2) | <.001 | 8.137 | 93 |
| Genetic factors | 63 (67) | 82 (87.2) | <.001 | 4.318 | 93 |
| Mean score of knowledge about cancer risk factors (max. 5) | 3.19 | 4.21 | <.001 | 8.071 | 93 |
| Mean score of knowledge about types of childhood cancers (max. 4) | 1.38 | 2.94 | <.001 | 10.557 | 93 |
| Mean score of knowledge about signs of childhood cancers (max. 4) | 1.87 | 3.60 | <.001 | 12.629 | 93 |
| Mean score of knowledge about childhood cancer treatment centres in Cameroon (max. 3) | 1.37 | 2.91 | .087 | 1.730 | 93 |
| Percentage overall score on knowledge items | 50.88 | 84.79 | <.001 | 17.747 | 93 |

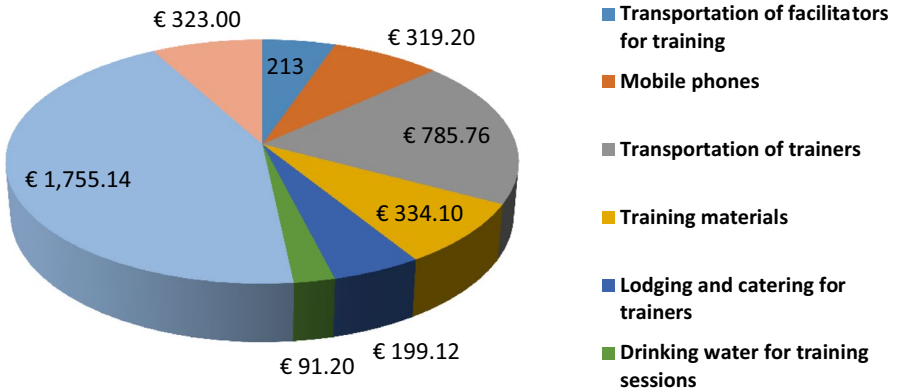


**FIGURE 2** Cost distribution

95.6% of the healthcare workers consulted children, irrespective of their level of healthcare training.

The Saint Siluan signs have also been used in South Africa (Poyiadjis et al., 2011) and in Botswana (Slone et al., 2016a) for educating healthcare providers on childhood cancer. Providing nurses with educational material has been shown to be effective in enhancing knowledge acquired from special training (David & Banerjee, 2010). In a group of medical students in South Africa, similar signs and symptoms were identified, with the most common ones being easy bruising, fatigue, unexplained bleeding, unexplained fever, weight loss and loss of appetite. Signs in the eye, like a white spot in the eye and a bulging eyeball, were also identified, which was not the case amongst our participants in the pre-test (Geel et al., 2017).

Training programmes regarding the warning signs of childhood cancer are effective tools to increase awareness and referral of patients to healthcare centres in LMICs. Following similar training on early warning signs in South Africa, the number of patients diagnosed in the region increased for both solid and haematologic malignancies (Poyiadjis et al., 2011). In Honduras, a nationwide retinoblastoma campaign was successful in reducing diagnostic delays (Leander et al., 2007).

The Botswana training programme reported an average cost of $11.20 per participant (Slone et al., 2016a), while the cost for this project in Cameroon was €25.06 ($ 27.64) per healthcare provider. The biggest burden of the cost was transportation, lodging and catering for trainees and trainers. Distances between health centres in the districts are long, and only 7% of the country's roads were paved in 2016 (Central Intelligence Agency, 2018). Although each training workshop was done in about four hours, it required a whole day for the trainees and an overnight stay for the trainers. This mirrors the difficulties experienced by patients who need to travel to hospitals out of their home districts and stay for several months to receive treatment.

The contribution of community participation is essential for disease surveillance (Ndiaye, Quick, Sanda, & Niandou, 2003). In Cameroon, the use of trained community-directed distributors (CDDs) in onchocerciasis control has proven to be reliable and cost-efficient (Tanya et al., 2012). If the trained health professionals transfer childhood cancer knowledge to community members, it is expected that the delay from onset of disease to diagnosis will also significantly reduce late diagnosis, with the potential to improve cure rates.

### 4.1 | Limitations

It is difficult for the clinical team to conduct frequent outreach training while maintaining the quality of clinical care at the centres due to limited human resource capacity (Slone et al., 2016a). The trainers in this project were all nurses and nurse practitioners, with no paediatric oncologist physically available to train in the districts. Secondly, the training programme was intensive, with teaching of childhood cancer signs, types and referrals within four hours with the potential risk that the knowledge would not be retained, necessitating regular refresher courses. Given that the traditional healers could play a significant role in early diagnosis of childhood cancer, the approach of this study with self-administered questionnaires failed to assess the outcome of the training amongst traditional healers who participated in them. Future similar initiatives should consider an in-person assessment component to capture the outcome for traditional healers. Finally, the study only measures immediate outcome of the project and does not re-evaluate trainees to see how much of the acquired knowledge is retained over time.

## 5 | CONCLUSION

Delays in diagnosis can be either due to patient delay or healthcare system delay. In Nicaragua (De Angelis et al., 2012) and South Africa (Stefan & Siemonsma, 2011), healthcare system delay was shown to be a major problem, hence the need to implement educational initiatives to improve childhood cancer knowledge amongst first-line healthcare providers (Rodriguez-Galindo, Friedrich, Morrissey, & Frazier, 2013). Our capacity-building project significantly improved childhood cancer knowledge amongst healthcare workers in the six districts covered. These health professionals are most often managing children with infectious diseases and malnutrition (WHO, 2015). Teaching them about childhood cancer makes them realize the reality of cancer in children in Cameroon and increases the likelihood of early diagnosis of childhood cancer and potential improved cure rates. It thus increases their suspicion index for childhood malignancies and gives them clear knowledge of how to facilitate access to prompt diagnosis and life-saving treatment for these children. Joko-Fru et al. (Joko-Fru et al., 2018) assert that survival in the case of common and curable cancers in Africa is poor and could be improved by increased support for activities around cancer detection, treatment and registration.

Our recommendation is for complete integration of training programmes into the public health system, with incorporation into the district health service activities involving dialogue structures in this system. To do this effectively, it will be necessary to train trainers at the district level to serve as focal persons for childhood cancer. These trainers could then be empowered to conduct routine refresher training with healthcare providers in their various districts. A clear monitoring and evaluation framework for childhood cancer suspicion and referral should be developed together with the district medical officers, which fits well within the current monitoring and evaluation procedures in the region. Cancer registries should also be developed and used to track trends and delays in childhood cancer diagnosis in the region.

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## CONFLICT INTERESTS

There is no conflict of interest.

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## APPENDIX 1

### Pre-training questionnaire for capacity-building training project

**Improving referral rates for early diagnosis of childhood cancers in north-west Cameroon by use of trained ambassadors and mobile money transfer**

### Pre-training test

Please provide a code number (code name) at the bottom of the page.

1. What type of facility do you work in?
   a. Health centre
   b. Subdivisional medical centre
   c. District hospital
   d. Regional hospital
2. What is your level of training in health care
   a. Nurse Aide
   b. Nursing assistant
   c. Brevete Nurse
   d. State registered nurse
   e. BNS nurse
   f. Physician
3. How long have you been working in health care?
   a. 0–2 years
   b. 2–5 years
   c. 5–10 years
   d. More than 10 years
4. Do you ever consult children?
   a. Yes
   b. No
5. What are some common causes of cancer (Tick all correct answers)
   a. Physical agents like radiation and sunlight
   b. Chemicals like tobacco smoke and herbicides
   c. Canned food/grilled foods
   d. Some viruses, bacteria and parasites
   e. Genetic factors
6. List four cancers that occur in Children _____
   _____
   _____
7. State four signs that are common in childhood cancers _____
   _____
   _____
   _____
8. List three centres in Cameroon where childhood cancer is managed._____
   _____
   _____
9. Can childhood cancers be cured in Cameroon?
   a. Yes
   b. No
10. Where did you get your knowledge on childhood cancers?(Please tick all that apply)
    a. From Nursing/medical school
    b. From another nurse/ physician
    c. From the media
    d. From the Internet
    e. From text books/journals
    f. I have no knowledge about childhood cancers
11. Do you ever give health talks about cancers in children in your community?
    a. Yes
    b. No
12. Would you like to have more knowledge about childhood cancer?
    a. Yes
    b. No

## APPENDIX 2

### Post-training questionnaire for capacity-building project

**Improving referral rates for early diagnosis of childhood cancers in north-west Cameroon by use of trained ambassadors and mobile money transfer.**

### Post-training test

Please use the same code number (code name) from your pre-training test.

1. What are some common causes of cancer (tick all correct answers)
2. Physical agents like radiation and sunlight
3. Chemicals like tobacco smoke and herbicides
4. Canned food/grilled foods
5. Some viruses, bacteria and parasites
6. Genetic factors
7. List four cancers that occur in Children

_____
_____
_____

8. State four signs that are common in childhood cancers

_____
_____
_____

9. List three centres in Cameroon where childhood cancer is managed.

_____
_____
_____

10. Can childhood cancers be cured in Cameroon?
    a. Yes

b. No

11. Did this training provide you with knowledge that could benefit your community and your practice?
    a. Yes
    b. No
12. Will you be giving health talks about childhood cancers in your community in future?
    a. Yes
    b. No
13. Can you effectively refer childhood cancer patient through local ambassadors?
    a. Yes
    b. No
14. Will you be teaching colleagues how to identify children with cancer in future?
    a. Yes
    b. No

Please write down any suggestions you have for improving early diagnosis of childhood cancer

# CHAPTER 5

## Destitution, treatment adherence and survival of children with Burkitt lymphoma in a twinning programme in Northwest Cameroon

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As part of the twinning programme for paediatric oncology between Stellenbosch University and the Cameroon Baptist Convention Health Services (CBCHS), medical treatment was provided free of charge and assistance was provided for transportation, accommodation and nutritional support of patients and families. Nutritional support included millet, rice, eggs, groundnuts and a cash grant for cooking, appropriate for the local context.

In this study, a questionnaire was used to determine how socioeconomic factors affected treatment adherence and follow-up for children diagnosed with Burkitt lymphoma. A destitution score was assigned to participants on a linear scale of 1–10 based on income, family size and living conditions, with 1 being completely destitute and 10 being the least destitute. Nonadherence was defined as missing an appointment by more than one week. Outcome information was obtained by telephone follow-up or home visits.

Only 8% of 497 children (0–15 years) were not adherent to treatment while 25% were nonadherent with follow-up visits. Most (66.5%) parents/guardians were subsistence farmers with very limited financial support from friends, family or charities. Destitution level had no significant effect on treatment adherence, but survival rate was significantly lower for children in single-mother households. Good treatment adherence was probably due to the adequate financial and social support provided by the twinning programme.

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RESEARCH ARTICLE

# Destitution, treatment adherence and survival of children with Burkitt lymphoma in a twinning programme in Northwest Cameroon

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## Abstract

**Background:** Burkitt lymphoma (BL) is a curable childhood cancer. Treatment adherence is crucial for a good outcome, but is potentially problematic in low- and middle-income countries owing to parental financial constraints.

**Aims:** To investigate the association of destitution with treatment adherence and its effect on the survival of patients with BL.

**Methods:** Patients received free medical treatment from a twinning programme at two Cameroon Baptist hospitals. A destitution assessment questionnaire, based on socioeconomic status, was completed at diagnosis. Medical records were reviewed for treatment adherence and survival. Chi-squared and Fisher's exact tests were used to compare groups. Kaplan-Meier plots were used to calculate overall survival, and log-rank chi-squared tests when comparing survival rates between patient subgroups. Significance was measured at $P < .05$.

**Results:** The 225 children with BL had a mean age of 8.2 years (median 8.0) and the overall survival was 52%. The mean family destitution score was 56% on a linear scale. Few (8%) patients delayed treatment appointments. A quarter (25%) experienced more than a 1-week follow-up delay and 9.8% absconded within 1 year. The destitution score was not significantly associated with delay of treatment, but with delay in follow-up ($P < .001$). Guardian relationship (single mother) and patient's age were significantly associated with overall survival ($P = .025$).

**Conclusions:** Though linked to poor follow-up, destitution was not significantly associated with absconding patients, poor outcome or poor adherence to treatment, probably due to comprehensive financial support from the international twinning programme. However, additional support for single mothers should be considered.

KEYWORDS
adherence, Burkitt lymphoma, destitution, socioeconomic status, survival, twinning programme

## 1 | INTRODUCTION

Burkitt lymphoma (BL) is a curable childhood cancer if treated with combination chemotherapy. In high-income countries, the recorded 5-year survival rate is 92% for children under 18 years,[1] while the 1-year survival rate in sub-Saharan Africa varies between 25% and 52% owing to limited drug availability and supportive care, and cost of treatment.[2] BL accounts for 30-50% of all childhood cancers in equatorial Africa, and mostly affects children between the ages of 2 and 15 years.[3,4]

Cameroon, situated in Central Africa, has a total population of approximately 25.6 million inhabitants, of which 42% are aged below

Abbreviations: ASIR, age-standardised incidence rate; BL, Burkitt lymphoma; CBCHS, Cameroon Baptist Convention Health Services; HIV, human immunodeficiency virus; IQR, interquartile range; IRB, Institutional Review Board; NGO, non-governmental organisation; USD, US dollar.

15 years and 30% live below the poverty line.[5] Cameroon has a three-tier health system structure with central and regional hospitals serving as referral centres for the district hospitals, sub-divisional medical centres and integrated health centres. Cameroon's per capita expenditure on health was reported in 2016 as US dollar (USD) 63.3, with 5.1% of total GDP spent on healthcare.[6]

The age-standardised incidence rate (ASIR) of lymphomas in children aged below 15 years in sub-Saharan Africa is estimated at 9.8 per million per person years.[7] The Yaounde cancer registry in Cameroon reported an ASIR of 46.8,[8] and an incidence rate of 25.8 per million in children below 15 years has been reported in the northwest region of Cameroon.[9] Treatment adherence is crucial for successful treatment outcome and survival, which has been shown to be affected by socioeconomic family circumstances.[10]

Stellenbosch University and Cameroon Baptist Convention Health Services (CBCHS) initiated a BL treatment programme in 2003 in three hospitals in semi-urban areas in the northwest and southwest regions of the country. Free medical treatment, as well as rice and groundnut rations, cash for parents to prepare meals and partly subsidised transport were provided. The 1-year event-free survival rate of 61% in 129 children treated between 2008 and 2011[11] illustrated the beneficial effect of twinning partnerships in childhood cancer care.[12,13] This study was, however, the first report of survival specific to childhood BL in Cameroon and local comparisons could not be made. The study investigated the association between destitution level (as a reflection of socioeconomic circumstances) and overall outcome, treatment adherence, abandonment and regular follow-up data in a twinning programme with equal support for all patients.

## 2 | METHODS

This study was part of the BL clinical trial conducted at two Baptist hospitals of Northwest Cameroon and used a prospective questionnaire-based investigation of socioeconomic factors affecting families of children diagnosed with BL. All guardians of children aged ≤15 years who were admitted for treatment of BL to Banso Baptist Hospital or Mbingo Baptist Hospital between January 2008 and December 2014 were included. Having provided informed consent, the guardians completed the questionnaire with the assistance of a trained research nurse, if available at the time of admission, between 2008 and 2014. This questionnaire had previously been developed and used for assessing destitution levels of orphans of patients with human immunodeficiency virus (HIV) and their caregivers in the CBCHS HIV care and prevention programme. Permission was obtained for its use in the present study for children with cancer. Although HIV and BL are different diseases, there are shared socioeconomic issues such as low community awareness, stigma and repeated need for hospital visits, which determine accessibility to care.

Demographic data (age and sex of patient, guardian or parent occupation, marital status and relationship to the patient), including socioeconomic factors (family size, living conditions, material and financial resources), were collected. BL was staged with the St Jude staging system (stages I and II defined as limited stage; stages III and IV defined as advanced stage). A destitution score was assigned to each family (score 0-10), which was based on family size, availability of insurance, support from friends and family, difficulties providing food, renting or owning accommodation for family and monthly income. Items were scored and linearly transformed to a 0-100% scale (100% score reflected maximum destitution and 0% no destitution) (Appendix 1). All patients received the same support, which included full coverage for medication and other treatment-related costs; daily rations of raw rice, one egg, 200 g of dried groundnuts and 40 g of powdered milk and USD 20 toward transportation costs. Survival was confirmed through home visits or telephonically. Individual patients' medical records were reviewed for treatment adherence and survival. Non-adherence was defined as a delay of 1 week or longer for chemotherapy or follow-ups, excluding delay due to chemotherapy-related toxicity or death. All cost indicators were converted from Cameroon franc to USD, using 2014 exchange rates.[14]

Analyses were done with IBM statistics version 25. Continuous variables were described using means, standard deviation and ranges, as well as medians and interquartile ranges (IQR), and categorical variables using frequency distributions. Chi-squared test ($\chi^2$) *P*-value was presented to compare groups, and Fisher's exact *P*-value was presented for a cell size less than five. Kaplan–Meier plots were used to calculate overall survival, and log-rank chi-squared ($\chi^2$) tests with *P*-value were presented when comparing survival rates for different subgroups of patients. Participants were categorised according to monthly income, with the first group having USD 0-47, the second group with USD 48-93, the third group with USD 94-185, and the fourth with more than USD 185. For the purpose of survival analyses, destitution score (0-100%) and age (0-16) were categorised in four groups based on percentiles (1 to cases up to the 25th percentile, 2 to cases between the 25th and 50th percentile, 3 to cases between the 50th and 75th percentile, and 4 to cases above the 75th percentile). Significance was measured at $P < .05$.

Ethics approval for this study was obtained from CBCHS Institutional Review Board (IRB2008-4; IRB2011-7) and the Health Research Ethics Committee of Stellenbosch University (HREC reference no. S18/08/163). All guardians provided signed informed consent for their and their child's participation in the study.

## 3 | RESULTS

BL was diagnosed in 497 children (0-15), and 225 guardians (45.3%) completed the questionnaires. There was no record of participation refusal.

The mean age of the children with BL, of whom 132 (59.5%) were boys, was 8.2 years (range 2-15 years standard deviation [SD] 2.6; median 8.0 years, IQR 6.0-10.0). Most had advanced disease (stages III and IV: n = 199, 88.4%). Most parents were married (n = 199, 88.4%), with the father as the principal guardian (n = 188, 83.6%) (Table 1).

Regarding socioeconomic factors (Table 2), most guardians were subsistence farmers (n = 150, 66.5%) or self-employed (n = 75, 33.5%),

**TABLE 1** Demographic and clinical information of the children and their guardians

| Demographic and clinical characteristics | | n (%) |
|---|---|---|
| Child age | Mean, SD (range) | 8.2, 2.6 (2.0-15.0) |
| | Median (IQR) | 8.0 (6.0-10.0) |
| Child sex | Male | 132 (59.5) |
| | Female | 90 (40.5) |
| Disease stage | Stage I | 9 (4.1) |
| | Stage II | 13 (5.9) |
| | Stage III | 180 (81.4) |
| | Stage IV | 19 (8.6) |
| Guardian | Father | 188 (83.6) |
| | Mother | 24 (10.7) |
| | Other | 13 (5.8) |
| Marital status | Single | 3 (1.3) |
| | Married | 199 (88.4) |
| | Widowed | 17 (7.6) |
| | Divorced | 6 (2.7) |

Abbreviation: IQR, interquartile range; SD, standard deviation.

**TABLE 2** Socio-economic factors of the included households

| Socio-economic factors | | n (%) |
|---|---|---|
| Number of children in household: mean, SD (min.-max.) | | 7.3, 6.0 (1.0-36.0) |
| | Median, IQR | 5.0 (4.0-9.0) |
| Number of spouses: mean (min.-max.) | | 1.4, 1.0 (0.0-5.0) |
| | Median, IQR | 1.0 (1.0-2.0) |
| Occupation | Farmer | 150 (66.5) |
| | Trader | 21 (9.2) |
| | Other | 54 (24.3) |
| Guardian receives a salary | | 21 (9.4) |
| Income | USD 0-47 | 141 (62.7) |
| | USD 48-93 | 53 (23.6) |
| | USD 94-185 | 22 (9.8) |
| | USD >185 | 9 (4.0) |
| Renting home | | 29 (12.9) |
| Does household: | | |
| | Use pipe-borne water | 86 (38.6) |
| | Use electricity | 77 (34.4) |
| | Use kerosene for lighting | 167 (77.7) |
| | Have land for building | 179 (79.9) |
| | Have land for cultivation | 206 (92.4) |
| | Keep animals | 135 (60.5) |
| Family receives: | | |
| | Financial gifts | 9 (4.1) |
| | Income from rent | 3 (1.4) |
| | Insurance, family or friendly society assistance | 48 (21.4) |
| Household experienced difficulties providing food | | 35 (15.6) |
| Destitution score: mean, SD (min.-max.) | | 56.0, 10.6 (20.0-80.0) |
| | Median (IQR) | 60.0 (50.0-60.0) |

Abbreviations: IQR, interquartile range; SD, standard deviation; USD, US dollar (2014).

while only 9% (n = 21) were employed with a monthly salary. Most households had an income under USD 47 (n = 141, 63%), but had access to land for building (n = 179, 80%) and cultivation (n = 206, 92%). Few households received financial support by way of gifts (n = 9, 4%) or rental income (n = 3, 1%). A fifth (n = 48, 21%) received material support (food and clothing) from family or charities. Only two parents indicated that they had healthcare coverage (0.9%). A minority (16%) reported food insecurity (Table 2). The mean destitution score was 56% (SD 10.6, range 20-80%; median 60%, IQR 50-60%), indicating poverty but not severe destitution.

Few patients were non-adherent during active treatment (n = 18, 8% for treatment delay), while 56 children had more than a 1-week follow-up delay (25%). The destitution score was not significantly associated with treatment delay (Fisher's exact *P*-value = .068), but was significantly associated with follow-up delay (Pearson $\chi^2$ *P*-value < .001). There was no association between treatment delay or follow-up delay and the relationship of the principal guardian (Fisher's exact *P*-value = 1.000 and Pearson $\chi^2$ *P*-value = .313, respectively). Also, household income was not associated with treatment delay or follow-up delay (Fisher's exact *P* = 1.000 and Fisher's exact *P* = .113, respectively).

The median follow-up time for overall survival was 14 months (mean 29.6 months, range 0-113 months and IQR 6-54 months). Overall survival was 51.6% (n = 116); 41.8% died (n = 94) and 15 absconded (6.7%) (Figure 1). One-year survival was 51.1% (n = 115) and 39.1% died (n = 88), with 22 absconders (9.8%). Two-year survival was 41.8% (n = 94) and 41.3% died (n = 93), with 38 absconders (16.9%). Overall survival increased for children whose primary guardian was their father or another guardian, compared to when the primary guardian was the mother (chi-square = 5.040, *P* = .025) (Figure 2). Overall survival differed significantly between age groups (percentile groups – 1: 2-6 years, 2: 7 years, 3: 8-9 years, 4: 10-15 years) (Figure 3) (chi-square = 8.851, *P* = .031). The youngest and oldest groups had better survival rates than the two groups in between. There was no difference in survival between percentile groups with destitution scores (chi-square = 0.699, *P* = .873) (Figure 4). Two-year survival showed no significant differences between groups for sex or age of the child, treatment delay, follow-up delay, guardian relationship, destitution score or household income.

## 4 | DISCUSSION

Overall survival was 52% for this study population, with a male:female ratio of 1.5:1, similar to that in other reports.[4,11] The mean age of

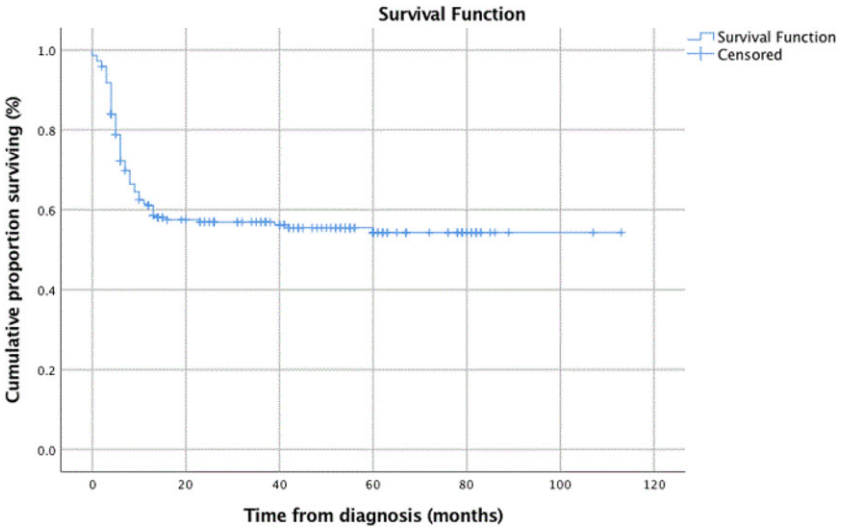



**FIGURE 1** Overall survival including absconding patients (median follow-up 14.0 months, mean 29.6 months)

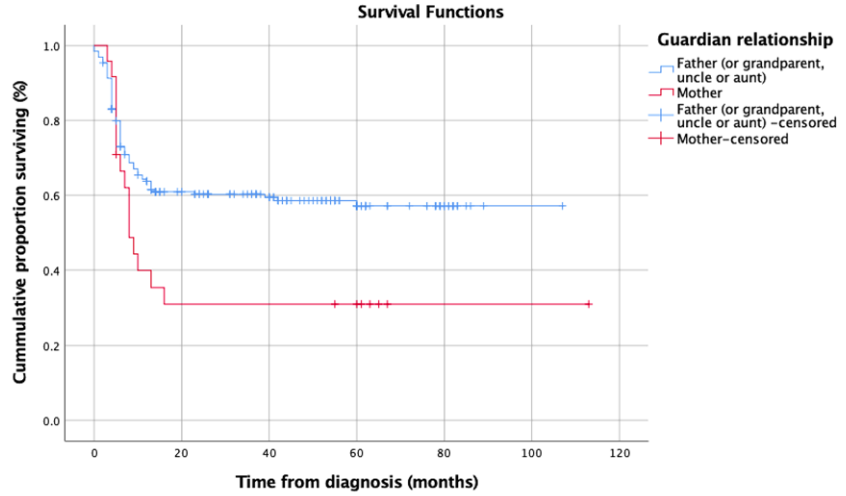



**FIGURE 2** Overall survival for guardian relationship including absconding patients

Log Rank Mantel-Cox Chi-Square = 5.040, p=0.025

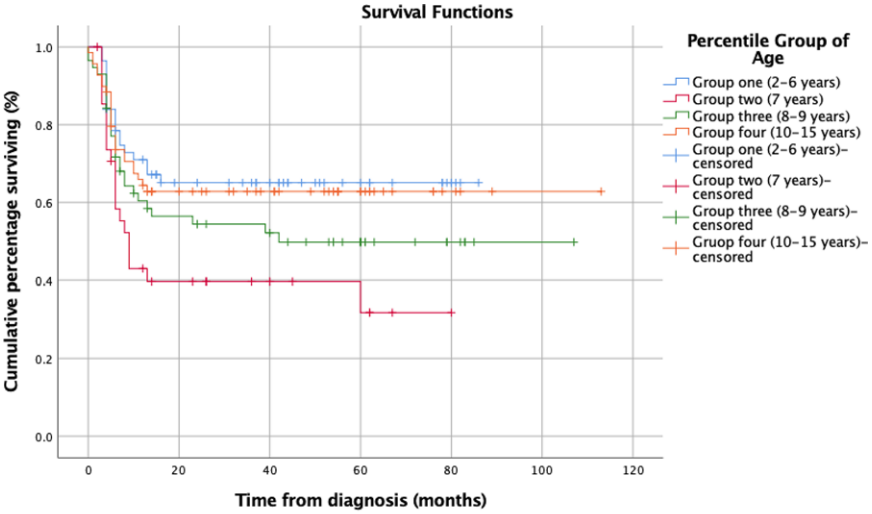
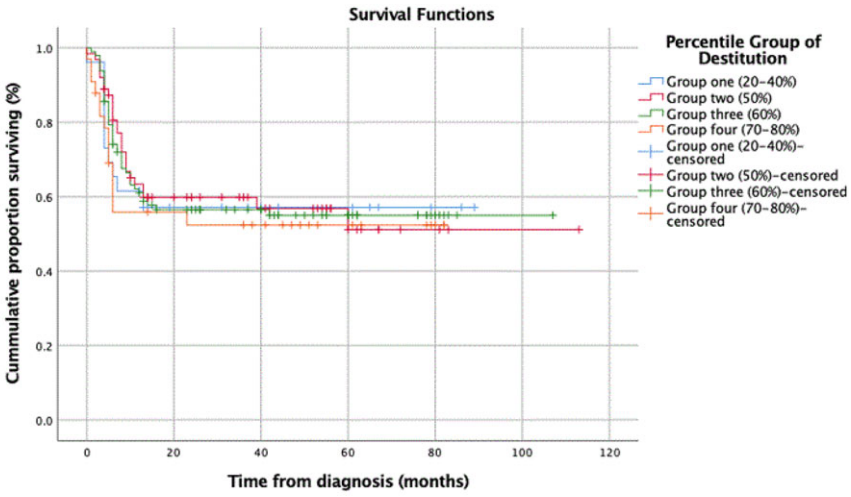



**FIGURE 3** Overall survival for age (percentile groups) including absconding patients

Log Rank Mantel-Cox Chi-Square = 8.851, p=0.031




Log Rank Mantel-Cox Chi-Square = 0.699, p=0.873

**FIGURE 4** Overall survival for destitution percentile groups including absconding patients

8.2 years was slightly older than that in some reports,[15,16] but consistent with previous studies in Northwest Cameroon.[17] The Psychosocial Issues Working Group of the International Paediatric Oncology Society suggested that refusal, non-compliance and abandonment were major issues influencing overall survival in low- and middle-income countries.[18] Abandonment rates of up to 72% were reported in western Kenya for all childhood cancers, while it was 32% for patients with BL in Nigeria[13,19–22] – differing from this study, where 92% adhered to treatment and 75% returned for regular follow-ups. These comparatively favourable percentages were probably due to the significant financial support provided to the families by way of free medical treatment and assistance with food and transport fees.

For most patients, the principal guardian was the father, though he had rarely been the caregiver when the child was hospitalised. This reflected the culture of Anglophone Cameroon, where men were family heads and breadwinners, while women bore the responsibility of child care.[23] A lower survival rate was found among children of single mothers, possibly related to lower community support levels available to single mothers. Ntoimo and Odimegwu[24] reported higher malnutrition and under-five mortality rates in single-mother households in Cameroon and suggested that the amount and quality of support that single mothers received from family members depended on cultural perceptions of single parenthood.

Families cultivated crops and bred animals for their own consumption and for selling on the local market, which probably explained the reported lack of food insecurity. Most patients lived in rural villages where land was mostly inherited and inexpensive to purchase. Village chiefs readily allocated land and authorised its purchase. Subsistence farming was the main economic activity of parents of children with BL in Nigeria[20] and Kenya.[22] Houses in rural Northwest Cameroon were predominantly constructed with sun-dried mud bricks and aluminium sheet roofing. Electricity was available to 55% of households in Cameroon[13] and to 34.4% of the guardians in the study. In the absence of electricity, firewood and bush lamps with kerosene were used. Pipe-borne water was available to 38.6% of the rural population, being lower than the 52.7% who were estimated to have access to improved water supply in 2015.[13] Access to electricity and tap water was far more limited for families of patients with childhood cancer in Kenya.[22] It is not clear from this study how the living amenities of families might have contributed to their adherence to chemotherapy and follow-ups, as this factor was not included in estimating destitution scores.

A positive correlation has been described between income and health status.[25] Factors such as education, work environment, housing and living environment, health and social care services and water and sanitation are known to affect health outcomes proportionately.[26] Only 21% of the households in this study received financial support from insurance or family – less than that in a Kenyan study, where 41% of patients with childhood cancer received financial support from families.[27] In this study, guardians were interviewed on admission and their response regarding family support was not specific to periods of illness. The need for support from sources other than families was met by introducing twinning partners, such as World Child Cancer, UK, the Beryl Thyer Memorial Africa Trust, UK, and others. Ribeiro and Pui[28] recommended a more sustainable model that relied on local charitable institutions.

In Cameroon, 95% of household expenditure on healthcare is in the form of out-of-pocket payments, since health insurance is underdeveloped and there is no national health insurance scheme.[29] Only 0.9% of children in this study had health insurance coverage and most of the existing schemes had strict limitations on the amount and types of treatment covered. Given that most families in this study had low monthly incomes, few could have managed without the free treatment offered by the twinning partners. In Kenya, the risk of treatment abandonment was higher, while event-free survival was lower for children from families not enrolled in the National Health Insurance Fund compared to children from enrolled families.[30] Financial difficulty was the greatest contributing factor to treatment abandonment in western Kenya and south-eastern Nigeria.[20,22] Especially travel between hospital and home for chemotherapy and follow-up appointments would not have been possible without financial support. On the farm, families had

crops and animals at their disposal for food, but during the hospitalisation period, they had to buy ready-cooked food or buy foodstuffs to cook for their child and themselves in the hospital kitchen. They would not have coped without the food rations and cash provided by the programme.

Adherence to chemotherapy appointments was 91.1%, but adherence to compulsory follow-up visits at 6 and 12 months was only 75%. This was a significantly high level of compliance when compared to abandonment rates reported among all patients with childhood cancer (54%) in Kenya,[30] patients with Wilms' tumour (31%) in Kenya,[31] patients with retinoblastoma (34.8%) in Ghana[32] and patients in northwestern Ethiopia where 64.8% were discharged either because of refusal or non-availability of treatment.[33] Low socioeconomic status, as seen in this study, and use of traditional medicine (55%), as reported elsewhere,[34] were similar in this study's setting as in other developing countries.[21,22] One aspect of the BL programme of this study that is not reported in the programmes cited above[30–33] is the provision of free treatment, and support for transportation and feeding costs.

The 9.8% abandonment rate within 1 year of treatment is much lower than that in other sub-Saharan countries, for instance 54% in western Kenya for all childhood cancers, and 32% in patients with BL in Nigeria.[13,19–22,30] The findings of this study compare better with that recorded in a twinning programme in Recife, Brazil (0.5%),[12] in which the benefits of a twinning programme for the treatment of children with cancer in a developing country are demonstrated.

For this study, dedicated beds, free drugs, free hospitalisation, nutritional support and public transport (limited to USD 20) were provided, and an investment was made in staff capacity development. Research grants and various non-governmental organisations (NGOs) assisted in establishing essential infrastructure and ran clinical trials. The cost of public transportation, however, often exceeded the funds available. Several authors have pointed out financial difficulties as the main reason for treatment abandonment in paediatric oncology.[13,20,22,35,36] The study findings support the statement that twinning programmes, which support both capacity building and resource mobilization, will save the lives of children with cancer in developing countries.[28] The findings present a case where the application of suggestions from previous studies and expert opinions was successful in reducing rates of treatment abandonment for BL in a sub-Saharan setting. The significant lower survival rate among children of single mothers exposed a so-far-overlooked social aspect affecting care for children with BL and calls for in-depth studies to establish the reasons for this difference and how the support provided by twinning programmes could be modified to be more equitable for single mothers.

Income level did not affect adherence to chemotherapy schedules, but affected adherence to post-chemotherapy appointments. It is worth noting that the support for transportation cost to families in the programme was capped at USD 20. This amount, usually exhausted during the follow-up phase, might have affected adherence. However, there might be other reasons that were not captured by this study. The role of proper counselling in promoting adherence at this stage should be emphasised, as long-term follow-up is essential to determine possible long-term side effects of chemotherapy.[13,36] There is a need to focus on counselling techniques for the clinical staff.[37] The lack of a significant effect of the destitution score on non-adherence to treatment and 1-year survival confirms that impoverished patients can achieve a good outcome with proper, material support. However, this raises a question about the presence of other factors affecting survival rates.

Other factors affecting survival rates included late diagnosis,[38] and common use of unsafe traditional and complementary treatment.[34,39] The predominance of late stage III (81%) and IV (9%) disease in this cohort was similar to that in earlier reports in this region.[11] It was apparent that patients were more likely to survive when the principal guardian was the father and other members of the family than when it was the mother alone. This suggests a weaker social network available to single mothers, as Mostert et al suggested, which is usually an overlooked contributor to treatment abandonment.[30] Most patients had advanced-disease at diagnosis, irrespective of their destitution level, indicating a general low level of cancer awareness in the general population. Therefore, it is inherent in local childhood cancer programmes to focus on community education initiatives that include training of healthcare professionals and traditional healers to improve early diagnosis.

## 5 | LIMITATIONS

The destitution score of all families could not be assessed because a research nurse was not available to do this on admittance of patients to hospital. There was no record of any parent refusing to participate in the study. It could not be established whether those not included in the study were the same as those included, and this potential bias could have affected the results of the study. However, all interviews were conducted before the beginning of treatment and therefore participation would not have been affected by the ability to adhere to treatment.

This study, being quantitative in its approach, was unable to provide explanations for some of the findings. Since community support systems available to patients and guardians were not explored, no clarity was obtained about the poor survival of children of single mothers. Other aspects that might contribute to adherence, other than the support provided by the programme, will require an in-depth qualitative investigation.

## 6 | CONCLUSION

Most patients with BL in Northwest Cameroon were poor and could not afford drugs and other treatment costs. The 1-year survival rate of 58.2% and good compliance with treatment by mainly destitute patients were achieved with the comprehensive support of various NGOs in an international twinning programme.

The crucial finding was that the children of single mothers had a significantly worse outcome, regardless of twinning programme support – a finding that needs further exploration. Furthermore, the findings emphasised the urgent need for advocacy to governments of poor countries to provide essential cancer drugs, treatment facilities

and training opportunities. The continued contributions by NGOs and international academic institutions are essential to enable the diagnosis and treatment of children with cancer in sub-Saharan Africa.

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## CONFLICT OF INTEREST

The authors have no conflict of interest.

## AUTHOR CONTRIBUTIONS

Glenn M. Afungchwi participated in the study design, finalised data collection, completed data analysis and drafted the manuscript. Peter Hesseling contributed to study design and data analysis, and critically reviewed and revised the manuscript for intellectual content. Sabine L. van Elsland carried out final statistical analysis and participated in the drafting of the manuscript. Francine Kouya contributed to data collection and manuscript writing. Mariana Kruger conceptualised the study design, contributed to data collection, supervised data analysis and critically reviewed and revised the manuscript for important intellectual content.

## DISCLAIMER

The views expressed in this article are those of the authors and are not an official position of any affiliated institution or funder.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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# CHAPTER 6

## Use of traditional and complementary medicine among children with cancer at three hospitals in Cameroon

As little was known about the types and determinants of traditional and complementary medicine (T&CM) use in paediatric oncology in Africa, a study was conducted to determine the prevalence and types of T&CM used by paediatric oncology patients in Cameroon and to explore the determinants of T&CM use, the associated costs, the perceived benefits and harm, and disclosure of T&CM use to the medical team.

A prospective, cross-sectional survey was first conducted among carers of children with Burkitt lymphoma aged below 15 years at the Cameroon Baptist Convention hospitals between 2003 and 2014. A limitation of the study was that the health care workers involved in the treatment of these children interviewed the parents/caregivers, which might have led to underreporting the use of T&CM. A follow-up study was therefore conducted involving newly diagnosed children below 15 years of age with a cancer diagnosis between November 2017 and February 2019, and interviews were conducted by staff who were not part of the research team to minimise potential underreporting.

The survey of Burkitt lymphoma patients (Chapter 6a) found that 55% had consulted a traditional healer, with 76.1% of them having consulted a traditional healer before visiting any conventional health care facility. The diagnoses suggested by traditional healers for Burkitt lymphoma included witchcraft, poison, liver problem, abscess, hernia, side pain and toothache. The traditional healers mostly applied massage, cuts, incantations and herbal mixtures for treatment, charging between US$0,4 and US$200 or payment by barter for their services. The choice to use T&CM was based on belief systems, recommendation from relatives or accessibility.

T&CM was available to 90% of respondents in the follow-up study (Chapter 6b), including 80 parents or guardians in the survey. Nearly a quarter (24%) thought that T&CM was effective for cancer treatment. The rate of use of T&CM was 67.5% before diagnosis and 26.3% after diagnosis. The most common T&CM strategies used were herbs or other plant-based medicines or teas taken by mouth, prayer for healing purposes and skin cutting. The reported side effects of T&CM use included pain and worsening of cancer symptoms. T&CM

was mostly paid for in cash (36.3%) or was free of charge (20%). Nearly half (44%) of the respondents reported that they would not disclose the use of T&CM to their doctor.

In conclusion, we found that paediatric oncology patients had used T&CM before and during treatment. These treatments might have effects on cancer symptoms, finances and treatment adherence.

# CHAPTER 6a

## The role of traditional healers in the diagnosis and management of Burkitt lymphoma in Cameroon: Understanding the challenges and moving forward

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RESEARCH ARTICLE Open Access

# The role of traditional healers in the diagnosis and management of Burkitt lymphoma in Cameroon: understanding the challenges and moving forward

Glenn M. Afungchwi[1*], Peter B. Hesseling[2] and Elena J. Ladas[3]

## Abstract

**Background:** Burkittlymphoma(BL) is the most common childhood cancer in Cameroon with a reported incidence of 3 per 100,000 children under 15 years in the Northwest region. Treatment at three Baptist mission hospitals has a recorded cure rate of over 50%. Traditional medicine(TM) is recognized by the national health system, but its scope is undefined and entraps children with BL. The aim of this study was to investigate the attitudes and practices of parents and traditional healers (TH) towards TM in children with BL in order to develop recommendations for an integrative approach and improved access to life-saving treatment for children with BL.

**Methods:** This is a descriptive case series of children diagnosed with BL treated at Banso, Mbingo, and Mutengene Baptist Hospitals between 2003 and 2014. A questionnaire was used to obtain the following information: demographic information, religion, the rate of use of TM, reasons why guardians chose to use TM, the diagnoses made by the TH, treatment offered, and the type of payment requested, based on the accounts of patient caregivers. Data was analyzed using Center for Disease Control Epi Info 7.

**Results:** Three hundred eighty-seven questionnaires were completed by parents/guardians. 55% had consulted a TH, of whom 76.1% consulted the TH as first choice. Common diagnoses provided by TH included liver problem, abscess, witchcraft, poison, hernia, side pain, mushroom in the belly and toothache. Methods of management included massage, cuts, concoctions, and incantations. The fee for these services included chickens, farm tools, and cash ranging from 200FCFA (0.4USD) to 100,000FCFA(200USD). The choice of TM was based on accessibility, failed clinic/hospital attendance, recommendation of relatives, and belief in TM.

**Conclusions:** TH are involved in BL management in Cameroon. TH are ignorant about BL, resulting in non-referral, and thus delay in diagnosis and treatment. Collaboration with TH could reduce late diagnosis and improve cure rates of BL and other childhood cancers.

**Keywords:** Burkitt lymphoma, Traditional medicine, Supportive care, Traditional healer, Cameroon

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## Background

Childhood cancer constitutes a major public health problem in Cameroon [1]. Incidence rates in Africa are not readily available due to the limited availability of cancer registries [2]; however, several global studies performed in low- and middle-income countries (LMICs) have documented a rise in its incidence over the past decade. This is attributed to several factors, but is partly due to improved education and training of medical personnel in the identification of childhood cancer. Burkitt lymphoma(BL) is the most common childhood cancer in Cameroon, with a reported incidence rate of 3 per 100,000 children below age 15 years in the Northwest region [3]. BL classically presents with a facial and or abdominal swelling. Previously, there was only one national paediatric cancer treatment centre in Yaounde; however, since 2003, paediatric cancer treatment services have been established at three Baptist mission hospitals in rural Northwest and Southwest Cameroon. Diagnosis of BL remains a challenge in Cameroon with the scarcity oncologist and pathology services. Diagnosis in the northwest region is accomplished by cytology of fine needle aspirations, Bone marrow aspirations, and cerebrospinal fluid, as well as on the basis of abdominal ultrasound [4]. An event-free survival rate of 60% has been reported for BL at these rural centres [4], with a long-term survival of over 50% [5].

Studies have demonstrated that up to 90% of children with cancer use some form of traditional medicine (TM); with the use of TM significantly higher in LMICs compared to high-income countries [6, 7]. Surveys have also found that the use of TM has been associated with delays in access to conventional treatment as well as abandonment of therapy. These challenges have been even more pronounced in Africa where indigenous practices are deeply embedded in the culture and way of life. In Cameroon, TM as a practice has evolved naturally over many generations. It is an attractive source of health care, which consumes an estimated 7% of household health care expenditure [8]. Given the significant advances in the treatment of childhood cancer, increased attention is warranted to ensure that children are offered effective treatments for cancer while simultaneously recognizing the role of TM.

The World Health Organization (WHO) in the Alma Ata Primary Health Care Declaration recognized the importance of TM in providing primary health care [9]. This recognition has been moderated with the provision of specific guidelines for assessment of safe practices applicable to traditional medicine practice [10]. The practice of traditional medicine is officially recognized in Cameroon, with an office of traditional medicine at the ministry of public health and its incorporation in all levels of the health care system [11]. Civil administrators are expected to allow the practice of traditional medicine in their health localities. In 1993 a national association was formed for the promotion of traditional medicine, offering registration and licensing to traditional healers (THs) who show certain levels of competence [12].

The practice of traditional medicine in Cameroon remains largely undefined and includes children with (undiagnosed) cancer, including BL. There is limited data from Africa as a whole on TM and pediatric oncology despite being home to a large percentage of children with cancer simultaneously being a region with a deep and complex history of TM. The objective of this study was to investigate the current diagnostic and management methods used by THs for children with BL.

## Methods

This is a descriptive case series of children diagnosed with BL treated at Banso, Mbingo, and Mutengene Baptist Hospitals between 2003 and 2014. The inclusion criterion was children between the ages of 0and 15 years with a confirmed cytological diagnosis or clinical diagnosis of BL, experiencing a response to induction treatment, and without any contrary cytology report [4, 5]. A questionnaire was used to obtain the following information: demographic information, religion, the rate of use of TM, reasons why guardians chose to use TM, the diagnoses made by the TH, treatment offered, and the type of payment requested, based on the accounts of patient caregivers. Diagnosis of BL was confirmed from participants' medical charts.

The primary respondents were the parents and other caregivers who brought the children to the hospital for treatment. The questionnaire wasapplied after counselling of parents about their child's disease, treatment, expected course, cost and need for follow up. Participation was entirely optional, with no effects on the treatment and other supportive care offered. The study was approved by the institutional review board and informed consent was obtained.

The questionnaire was read and explained to respondents by a research assistant nurse at each centre. These nurses were all involved in the care of the child. Despite a literacy rate of 75% for persons above 15 years in Cameroon [13], most of the patients enrolled in the centres were from rural settings and predominantly from farming families with a relatively lower level of literacy.

### Statistical analysis

Demographic characteristics were summarized as median, range, mean, standard deviation for continuous variables, and as counts and percentages for nominal variables. Statistics were generated using Center for Disease Control Epi Info™.

## Results

The 387 questionnaires completed represent 42% of all patients treated, with 222 (57.4%) males, 164 (42.4%) females, and one not recorded (0.2%). The median age was 8 (range1-17 years), with a mean of 7.9 years(SD +/− 2.4). Respondents were primarily Christian ($N$ = 251;68.9%) followed by Muslims ($N$ = 116; 30%), and not specified ($N$ = 20;5%). Two hundreds and thirteen (55%) respondents had consulted a TH before admission, 162 of whom (76.1%) had consulted the TH as their first choice before attending a health centre or hospital and the remaining 51 (23.9%) after prior consultation at a local conventional health centre or hospital. The rate of use of TM was 54.6% amongst Christians and 53.4% amongst Muslims.

Participants reported several reasons for seeking out a TH for their child (Table 1). For the majority of participants, ineffective hospital treatment or family beliefs were the primary reasons for seeking treatment with TH. Advice from the community was influential in choosing TH as well as beliefs in the theories of TH such as witchcraft. Importantly, we found that participants sought out TH for symptoms that are usually not well-controlled in conventional health care facilities in Cameroon such as pain management.

TH provided a wide-variety of causes of the child's illness (Table 2). Witchcraft was the most frequent explanation given for the disease, followed by disease of the spleen or liver and abscess or boil. The disease

**Table 1** Reasons for consulting traditional healers

| REASON | FREQUENCY | PERCENTAGE FREQUENCY |
|---|---|---|
| Previous visits to a clinic/hospital did not help | 51[a] | 24% |
| Family belief and preference for Traditional Medicine (TM) | 51 | 24% |
| Advice from neighbours or family | 31 | 15% |
| Thought it was witch craft | 19 | 9% |
| Had no money | 13 | 6% |
| Unknown to respondent | 9 | 4% |
| Thought it was a strange(bad) disease that only a traditional healer (TH) can treat | 7 | 3% |
| Was the nearest source of pain relief for the child | 7 | 3% |
| Knows that a TH is good at treating side pain | 5 | 2% |
| Knowledge that 'boh' is usually treated by a TH | 3 | 1% |
| Knows that a TH is good at treating boil/abscess | 2 | 1% |
| Knows a TH is good at spleen problems | 2 | 1% |
| Thought liver problems cannot be treated in the hospital | 1 | <1% |
| The TH saw child and offered to help | 1 | <1% |
| The TH is renowned for fracture treatment | 1 | <1% |

[a]surgery in two cases

**Table 2** The various explanations for Burkitt's lymphoma by traditional healers

| EXPLANATION | FREQUENCY | PERCENTAGE FREQUENCY |
|---|---|---|
| Witch craft | 35 | 16% |
| Spleen diseases(enlargement) | 35 | 16% |
| No explanation | 27 | 13% |
| Abscess/ Boil | 13 | 6% |
| Side pain | 10 | 5% |
| Belly bite | 9 | 4% |
| Liver disease | 8 | 4% |
| Informant does not know | 8 | 4% |
| Hernia | 6 | 3% |
| Toothache/ dental problem | 6 | 3% |
| Poison | 6 | 3% |
| Bladder stone | 5 | 2% |
| Abdominal disease | 4 | 2% |
| Leg problem (paralysis) | 4 | 2% |
| Growth/cancer | 4 | 2% |
| 'Boh'(Mushroom) | 3 | 1% |
| Worms | 3 | 1% |
| Sinusitis | 3 | 1% |
| Frog in the abdomen | 2 | 1% |
| Faecal mass | 2 | 1% |
| Malaria | 2 | 1% |
| Kwashiokor | 2 | 1% |
| Mumps | 2 | 1% |
| Strong sick | 1 | 0.5% |
| Goitre | 1 | 0.5% |
| Rheumatism | 1 | 0.5% |
| Yellow fever | 1 | 0.5% |
| Overeating | 1 | 0.5% |
| Lung disease | 1 | 0.5% |
| Growth pains | 1 | 0.5% |
| Child abuse | 1 | 0.5% |
| Double umbilicus | 1 | 0.5% |
| Child's shadow not in body | 1 | 0.5% |
| Dirt in the belly | 1 | 0.5% |
| Injury after fall | 1 | 0.5% |
| Palpitations | 1 | 0.5% |
| Moving object in the body | 1 | 0.5% |

was described as cancer in a few cases. In some the patients were managed with no explanation given for the disease. A variety of interventions were used to treat the illness. The methods included skin cuts, burns or drills, with local application of herbal pastes on cut wounds, and the ingestion of solid and liquid concoctions (Fig. 1 and Fig. 2).

Finally, our survey evaluated the form of payment for the TM treatment (Table 3). The majority of participants (54%) paid money in exchange for the services provided by a TM healer while others exchanged items for treatment in the barter system. In some cases, there was no charge for the TH's services or payment was deferred awaiting recovery.

## Discussion

To the authors' knowledge, this is the first report on the use of TM among children with cancer in Cameroon. We found that the majority (55%) of guardians/parents consulted a TH for their child's disease, which is within previously reported rates of 15% to 95% [14–16]. Our results confirm the description of TM by the WHO as a common, but underestimated, treatment method [9]. We also found that respondents consulted a TH because they did not have money, or because it was the nearest source of help. Similar findings have been reported in other studies in Cameroon [12] and elsewhere in Africa [15]. This supports the WHO's description of TM as the most available and affordable treatment option in sub-Saharan Africa [17]. Importantly, our results underscore the need for educational initiatives aimed at the conventional and TM community.

Delays in the diagnosis and initiation of treatment of childhood cancer is a significant factor impacting survival among children located in LMICs. Hesseling et al. reported 84% of children with BL in Cameroon had St. Jude's Stage III or IV disease at time of diagnosis [4]. Consultation with THs may be a factor in delayed diagnosis of BL. Our survey found that 76% of users of TM sought treatment with a TH before attending a conventional health centre or hospital, which is a figure in line with other reports in Sub-Saharan Africa [17]. In Ngaoundere, the Adamawa region of Cameroon, TH is the most available form of health care for patients outside urban settings due to the paucity of health centres and hospitals [12]. Our survey found that the remaining participants (24%) who visited a TH did so after consulting a local health centre or hospital, illustrating a significant need for more knowledge on BL amongst the health care professionals in these health care units.

The reasons reported for choosing TM reflects a high level of belief in TM as part of the overall culture of the population, given the variety of ethnic groups whom each have a unique natural medicinal heritage [18]. The authors could not find any outcome reports for children with BL treated by TM, on the contrary there is report of 60% event free survival for children with BL treated in three childhood cancer treatment centers in the Northwest and Southwest regions of Cameroon [4]. Health practitioners sometimes fail to suspect BLbecause of insufficient knowledge about the disease. A survey in three of the seven divisions of Northwest Cameroon revealed that 51% of rural nurses do not know about BL. They make incorrect diagnoses, provide the wrong treatment, and fail to refer patients to cancer treatment centers. Therefore, there is

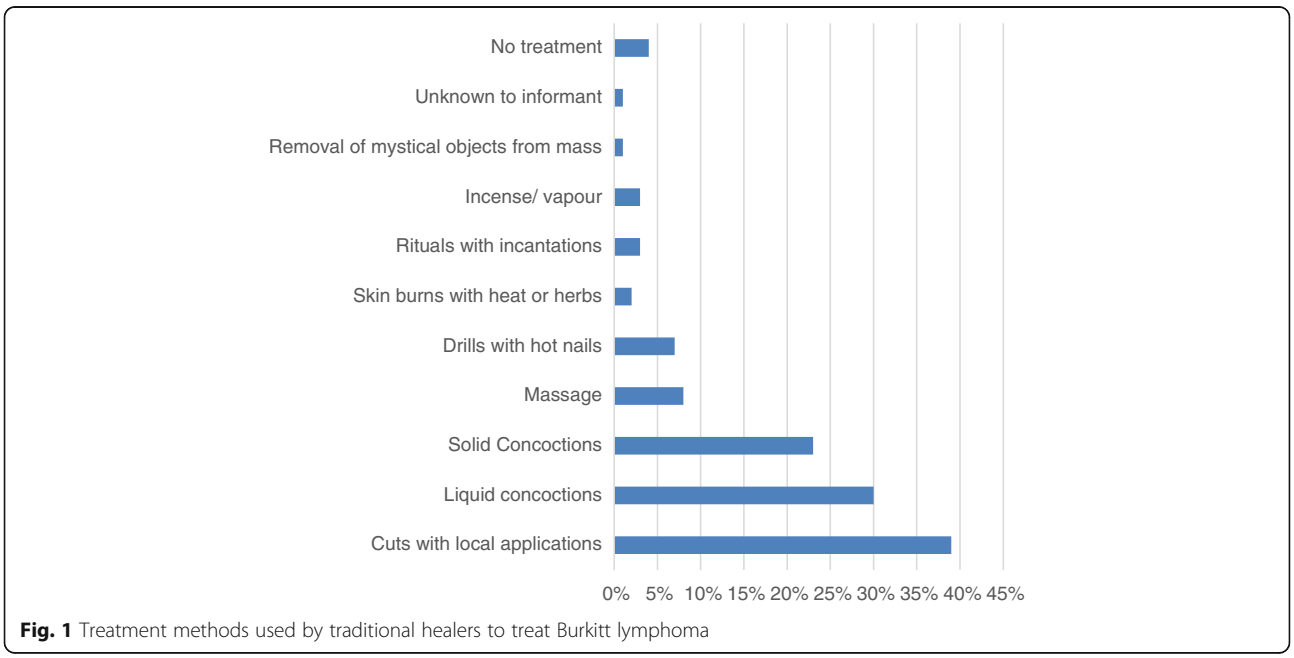


**Fig. 1** Treatment methods used by traditional healers to treat Burkitt lymphoma

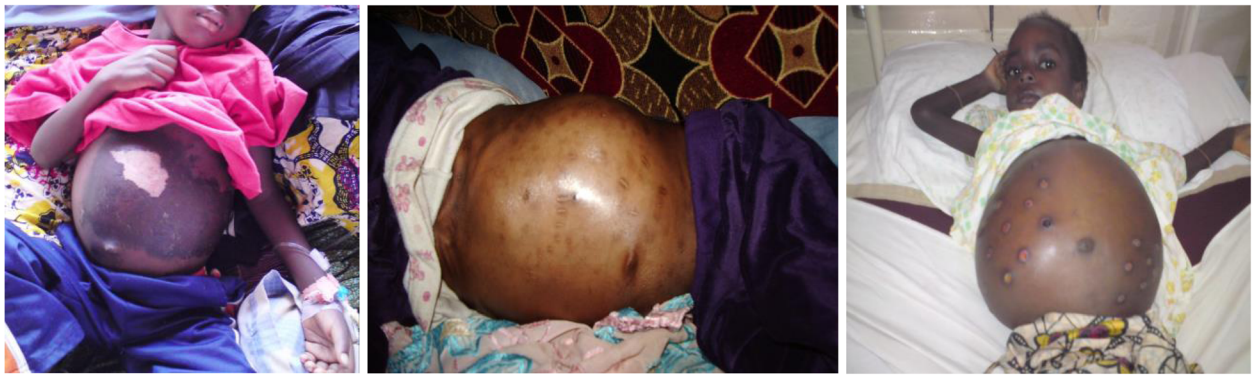

**Fig. 2** *Treatment methods used by traditional healers to treat Burkitt lymphoma. Left to Right*: Skin burn with corrosive herbs; skin cuts over region of tumour; drills into tumour through the skin by use of heated nails

an urgent need for trained health care personnel to provide sensitization to health workers at the community level about the diagnosis and available treatment of BL patients. Such sensitization efforts have been made in the Northwest region of Cameroon, and ongoing efforts are being made to provide this knowledge to practicing nurses, and nurses in training. The inclusion of childhood cancers in the training curricula for nurses nationwide will further help address this problem.

Nearly 10% of participants reported that witch craft was the cause of disease and 8% believed that witchcraft was the cause of the cancer [15]. This finding supports previous investigations that beliefs in TM theories are strongly linked to use of TM [19]. We found that diagnoses made by TH are based on superstition, attribution to commonly known diseases with even distant similarities in physical appearance, or suspicion of a mystical affliction. This denotes a lack of knowledge about BL amongst TH in the region, which can be assumed a general situation for all childhood cancers given that BL is the most common childhood cancer reported in the country [1]. Collectively, this finding suggests that childhood cancer awareness is limited amongst health care providers in Cameroon, including TH and underscores the need to educate TH on childhood cancer presentations and the availability of curative care. Such a training for TH was done on a large scale by the South African Childhood Cancer Parents Organization (CHOC) [20]. Additionally, widespread Childhood Cancer awareness campaigns by the Cameroon Baptist Convention Childhood cancer program are underway. The goal of these programs isto educate communities on the early signs of childhood cancer, by use of group lectures and the distribution of brochures and flyers.

**Table 3** Payment Methods for the Services of Traditional Healers

| Method of payment | Number | Frequency |
|---|---|---|
| Money (USD 0.4 – USD 200) | 114 | 54% |
| Barter system[a] | 84 | 40% |
| No charge | 50 | 24% |
| Unknown to informant | 5 | 2% |
| Payment deferred till recovery | 2 | 1% |
| Any token | 1 | 0.5% |

[a]The Barter system included the provision of fowls, palm oil, salt, palm wine, cutlass, and cooking pots in exchange for treatment

We found that treatment modalities were not too different in other developing countries [6, 14–16], but cuts and drills are unique to Cameroon [6]. TM in Cameroon is a practice that is learned by inheritance, apprenticeship, or as a gift from the 'spirits'. The diagnostics and treatments of TH are guided by the way they learn their trade. The most common methods are those that harness the rich biodiversity of the local forests, grasslands, and maritime geographies [21]. The plurality of methods used in traditional medicine constitutes a major setback to its credibility, and facilitates the proliferation of charlatans [12]. The need to sensitize TH about BL is clear, given the fact that they form a legal part of the Cameroon health care system, and offer care to about 80% of the population at various points in time [12]. These TH need to be included in the surveillance for pediatric cancers, and be educated on algorithms for referral of suspected cases.

Our study is limited by the cross-sectional design and as such is subject to its limitations. The survey was administered by staff nurses who had other patient care duties resulting in inconsistent availability for administering the survey as well as limited time to collect all demographics of interest. A developing regional initiative is addressing this in a comprehensive manner. There is also the possibility of biased response since these nurses were members of the patient care teams. Due to limited staffing, we were unable to examine survival

differences between patients who used TM and those who did not use TM. However, this is an important point for future investigation. Additionally, this study does not investigate the association between socioeconomic status and the use of TM. However, it is observed that the lack of money is the fourth most common reason why patients of children with BL seek medical care from TH.

## Conclusion

In conclusion, THs constitute an important part of the health care system in Cameroon. Despite the non-standardized nature of their diagnostic and interventional practices and charges, they arguably have a genuine concern for the health of the populations they serve. This study convincingly shows a significant knowledge deficit among THabout the presentation of BL. This is only one ramification of the overall low level of awareness on pediatric cancers in the general population [22]. We believe that respectful collaboration, and education of TH on the early warning signs of cancer, and the availability of good curative and palliative care, will increase the number of children with BL who are suspected in he communities and referred to specialized centers to be diagnosed and adequately treated. Such collaboration with THs has created a tremendous difference in care for patients with HIV/AIDS in Africa [23], and must continue to be explored to improve survival rates for children with cancer.

#### Abbreviations

AIDS: Acquired immunodeficiency syndrome; BL: Burkitt lymphoma; CDC: Center for disease control; CHOC: Childhood cancer parents' organization; FCFA: Franc communauté financière africaine; HIV: Human immunodeficiency virus; LMIC: Low-middle-income countries; TH: Traditional healer; TM: Traditional medicine; USD: United States dollars; WHO: World Health Organization

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#### Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

#### Authors' contributions

GA and PH conceptualized and implemented the study; GA, EJL, and PH reviewed data analysis; All authors read and approved final manuscript.

#### Competing interests

The authors declare that they have no competing interests.

#### Consent for publication

Consent for publication has been obtained. Signed informed consent has been obtained from parents for the publication of pictures.

#### Ethics approval and consent to participate

The study was approved by the Cameroon Baptist Convention Institutional Review Board. Signed informed consent to participate was obtained from parents for participation in the study.

## Publisher's note



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# CHAPTER 6b

## Survey of the use of traditional and complementary medicine among children with cancer at three hospitals in Cameroon

*This chapter is publication ready and will be submitted to Pediatric Blood and Cancer for publication. (Impact factor: 2.355) https://onlinelibrary.wiley.com/journal/15455017*

As a previous study indicated that traditional and complementary medicine (T&CM) use was common for families with children diagnosed with Burkitt lymphoma (Chapter 6a), a follow-up study was conducted to determine the prevalence and types of T&CM used by paediatric oncology patients in Cameroon, using interviewers not part of the care team. Secondary aims explored the determinants of T&CM use, the associated costs, the perceived benefits and harm, and disclosure of T&CM use to the medical team.

A prospective, cross-sectional survey was conducted among parents and carers of children below 15 years of age who had a cancer diagnosis and received cancer treatment at three Cameroon Baptist Convention mission hospitals between November 2017 and February 2019. The interviewers were not part of the treating team of health care workers to minimise underreporting.

This study proved that there was significant availability (90%) and use (67.5%) of T&CM, while 24% of respondents thought that T&CM would be effective for cancer treatment. Common T&CM remedies included herbs or other plant-based medicines, or teas taken by mouth, prayer for healing purposes and skin cutting. T&CM was mostly paid for in cash (36.3%) or provided free of charge (20%). Of importance was the fact that nearly half (44%) of the respondents did not want to disclose the use of T&CM to their doctor. Cultural beliefs in the healing ability of traditional healers and cost were deciding factors for using T&CM.

In conclusion, we found that paediatric oncology patients used T&CM before and during treatment, but that parents and carers were unlikely to disclose this use to the health care team treating the child.

# Survey of the use of traditional and complementary medicine among children with cancer at three hospitals in Cameroon

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Key words: Traditional and complementary medicine, childhood cancer, Cameroon, determinants of use.

## INTRODUCTION

Low- and middle-income countries (LMICs) experience a general lack of diagnostic and treatment resources with variable access to childhood cancer treatment, with subsequent poor survival (1). These issues are complicated by delays in seeking medical treatment as well as treatment refusal and/or abandonment of cancer therapy (2–5). These obstacles may be particularly notable in geographical areas with diverse and rich traditional medical systems such as exist in Africa. Identifying preventable causes of treatment delay, refusal and abandonment is therefore important in reducing the overall rate of childhood mortality in LMICs.

International and national surveys have found that the use of traditional and complementary medicine (T&CM) was highly prevalent among children with paediatric malignancies (3,6,7). Dioro et al. demonstrated that T&CM use ranged from 6% to 100%, with median rate of use more prevalent in LMICs (66.7% ± 19%) than in high-income countries (HICs) (47.2% ±

20%, p = 0.02) (6). Families described using these agents for a variety of reasons including treating the side effects of cancer therapy, improving wellbeing and curing the cancer, with the latter being most common in LMICs at a rate of 53%. There were single African from Kenya, Cameroon, and Morocco (8–10).

T&CM is an integral part of the cultures and belief systems of many populations for the management of a variety of illnesses. The World Health Organization (WHO) has recognised the importance of working with T&CM practitioners and the need to document the reasons, indications, forms and species of T&CM therapies used in developing countries as outlined in the WHO T&CM Strategy (11). In the African context, providing integrated care with T&CM practitioners has demonstrated success in the treatment of HIV/AIDS (12). The reports mentioned above identified practices such as visiting local healers, scarification and ingestion or application of honey, plants or other concoctions of unknown content (8–10). As with many other LMICs, the reasons for the use of T&CM in Cameroon have been influenced by cultural beliefs, availability of and access to conventional medical care, and socioeconomic status (13).

Given the limited published data, the role of T&CM among children with cancer in Africa is generally poorly understood. It is unclear how many children with cancer in Africa are not diagnosed and whether these children are using T&CM in lieu of conventional medicine. It is also unknown whether children diagnosed with cancer in Africa are using T&CM in conjunction with conventional therapy. The primary objective of this study was to determine the prevalence and types of T&CM used in Cameroon, using interviewers not part of the childhood cancer management plan to minimise underreporting. Secondarily, we explored the determinants of T&CM use, the associated costs, the perceived benefits and harm, and disclosure of T&CM use to the medical team.

## METHODS

This was a prospective, cross-sectional survey. All children below 15 years of age who had a cancer diagnosis and received cancer treatment at Banso Baptist Hospital, Mbingo Baptist Hospital or Baptist Hospital Mutengene in Cameroon between November 2017 and February 2019 were eligible for participation in the study.

Patients diagnosed, were consecutively approached for survey participation by an interviewer who was not part of the health care team. He/she was able to obtain informed consent and

conduct the survey, which was done in a face-to-face interview. Enrolment was halted in February 2019 due to civil conflict within the country, potentially impacting study findings due to limited accessibility to travel.

The survey was adapted from a validated survey of T&CM use in LMICs previously used in Central and South America (14). The initial survey was reviewed, and adaptations were suggested by eight reviewers, including four members of the research team and four additional paediatric oncology care providers in Cameroon, to ensure that the questions and potential answers were valid in the local context. The survey gathered demographic information regarding both the child with cancer and his/her family. Included were questions about the child's clinical presentation with cancer, services consulted prior to arrival at the oncology centre and access to community services. A number of questions concerned T&CM practices used prior to and during treatment, associated costs, disclosure to the oncology team as well as the families' beliefs about T&CM therapies. All survey data was entered in the REDCap database.

Statistical Considerations

The prevalence of T&CM use, as well as the reasons for T&CM use and the types of T&CM used were summarised along with demographics and presented descriptively. Pearson's chi-square and Fisher's exact test were used to investigate whether the use of T&CM was influenced by beliefs, signs and symptoms or demographics. Associations between T&CM methods used, costs and side effects experienced were also investigated by Pearson's chi-square and Fisher's exact test.

Ethics approval was obtained from the Cameroon Baptist Convention Institutional Review Board (IRB2017-14), the Stellenbosch University Health Research Ethics Committee (S18/08/163 [PhD]), the Columbia University Institutional Review Board (IRB-AAAR5963) and the Hamilton Integrated Research Ethics Board (HiREB Project #: 3680).

## RESULTS

### Participants

There were 80 participants who completed the survey while three declined. The majority were mothers (n = 46; 57.5%), followed by fathers (n = 13; 16.3%), grandmothers (n = 8;

10%), other caregivers (n = 12; 15%) and one child. The median time from diagnosis to interview was 3.5 weeks (IQR 1.23–10.3). Demographic details about the patients and their families are summarized in Table 1. The children with cancer were mostly male (n = 48; 60.0%), with a median age of 8.1 years (IQR 4.1–11.1). The majority had been diagnosed with Burkitt lymphoma (n = 42; 52.5%) and were receiving treatment with curative intent at the time of interview (n = 65; 82.3%). Most patients and their parents were attending or had attended school, but half of parents reported completion of primary education (mothers 58.0%, fathers 52.8%). The majority of children belonged to Christian denominations (n = 68; 88.3%), and eight (10.4%) were Muslim. There were occasions where religion differed between parents and/or parents and children, most notably with two parents (one mother and one father) reporting being adherent to African traditional religion and five parents (one mother and four fathers) reporting being nondenominational. Access to household amenities varied widely across the surveyed families, with most (n = 71; 88.8%) reporting access to a cellular/mobile phone and few (n = 8; 10.0%) having access to a motor vehicle.

Access to Medical Care

Forty-five (57.0%) families reported living five hours or further from a hospital at diagnosis, and 50 (63.3%) reported moving to be closer to the treatment facility. All participants (n = 80; 100%) had health care providers in their communities. The majority had access to a doctor or a nurse (n = 76; 95%) as well as a traditional healer (n = 72; 90%). All respondents (n = 80; 100%) had a health care facility in their community available to their family. The most common facilities included public hospitals (n = 63; 78.8%) and health centres/clinics (n = 63; 78.8%) while 67.5% (n = 54) had access to a traditional healer's home/clinic (n = 54; 67.5%).

**Table 1: Demographics and access to care**

| Characteristic, N = 80 | Total n (%) | No TCM n (%) | TCM n (%) | p-value |
|---|---|---|---|---|
| Age, mean, sd (range) | 8.0, 4.6 | 7.6, 4.8 (0.8- | 8.1, 4.5 (0.6- | - |
| Median (IQR) | 8.3 (4.1- | 7.4 (4.1- | 8.5 (4.1- | - |
| 0-? years | | | | |
| ?-18 years | | | | |
| Gender | | | | |
| Male | 48 (60.0) | 18 (69.2) | 30 (55.6) | - |
| Female | 32 (40.0) | 8 (30.8) | 24 (44.4) | 0.242 |
| Ethnicity | | | | |
| Other | 1 (1.3) | 1 (3.8) | 0 (0.0) | - |
| Africa | 79 (98.8) | 25 (96.2) | 54 (100) | 0.323^ |
| Diagnosis | | | | |
| Burkitt lymphoma | 42 (52.5) | 12 (46.2) | 30 (55.6) | - |
| Non-Hodgkin lymphoma | 7 (8.8) | 1 (3.8) | 6 (11.1) | 0.658^ |
| Nephroblastoma (Wilms tumor) | 13 (16.3) | 7 (26.9) | 6 (11.1) | 0.109^ |
| Bone and soft tissue sarcoma | 9 (11.3) | 3 (11.5) | 6 (11.1) | 1.000^ |
| Other | 9 (11.3) | 3 (11.5) | 6 (11.1) | 1.000^ |
| Therapy stage | | | | |
| Primary treatment | 65 (82.3) | 20 (76.9) | 45 (84.9) | - |
| Relapse treatment | 7 (8.9) | 3 (11.5) | 4 (7.5) | 0.673^ |
| Palliative or metronomic treatment | 7 (8.9) | 3 (11.5) | 4 (7.5) | 0.673^ |
| Patient attended school prior to diagnosis | | | | |
| No | 23 (29.9) | 7 (28.0) | 16 (30.8) | - |
| Yes | 54 (70.1) | 18 (72.0) | 36 (69.2) | 0.804 |
| Highest Level of school completed by | | | | |
| No education | 11 (13.8) | 2 (7.7) | 9 (16.7) | - |
| Primary | 40 (50.0) | 15 (57.7) | 25 (46.3) | 0.297^ |
| Secondary | 12 (15.0) | 4 (14.4) | 8 (14.8) | 0.640^ |
| Post-secondary | 17 (21.3) | 5 (19.2) | 12 (22.2) | 0.668^ |
| Highest level of school completed by | | | | |
| No education | 4 (5.3) | 1 (4.2) | 3 (5.8) | - |
| Primary | 38 (50.0) | 15 (62.5) | 23 (44.2) | 1.000^ |
| Secondary | 16 (21.1) | 3 (12.5) | 13 (25.0) | 1.000^ |
| Post-secondary | 18 (23.7) | 5 (20.8) | 13 (25.0) | 1.000^ |
| Religion of child | | | | |
| Catholic | 16 (20.8) | 7 (28.0) | 9 (17.3) | - |
| Protestant | 40 (51.9) | 14 (56.0) | 26 (50.0) | 0.541 |
| Pentecostal | 12 (15.6) | 3 (12.0) | 9 (17.3) | 0.434^ |
| Muslim | 8 (10.4) | 1 (4.0) | 7 (13.5) | 0.189^ |
| Other | 1 (1.3) | 0 (0.0) | 1 (1.9) | 1.000^ |
| Attend religious services regularly | | | | |
| No | 8 (10.1) | 0 (0.0) | 8 (15.1) | - |
| Yes | 71 (89.9) | 26 (100) | 45 (84.9) | 0.048^* |

| | | | | |
|---|---|---|---|---|
| Number of people in the household; Median (IQR)<br>0-6 people<br>7-19 people | 6.4, 2.8 (2-6.0 (4.0-8.0) | 6.4, 2.2 (3.0-6.0 (5.0-8.0) | 5.5, 2.9 (2.0-6.0 (4.0-8.0) | -<br>- |
| Composite wealth index | | | | |
| Quintile 1 | 13 (16.3) | 3 (11.5) | 10 (18.5) | - |
| Quintile 2 | 15 (18.8) | 6 (23.1) | 9 (16.7) | 0.435^ |
| Quintile 3 | 36 (45.0) | 11 (42.3) | 25 (46.3) | 0.731^ |
| Quintile 4 | 10 (12.5) | 3 (11.5) | 7 (13.0) | 1.000^ |
| Quintile 5 | 6 (7.5) | 3 (11.5) | 3 (5.6) | 0.320^ |
| Travel time to treatment facility from | | | | |
| <2 hours | 9 (11.4) | 1 (4.0) | 8 (14.8) | - |
| 2-5 hours | 25 (31.6) | 6 (24.0) | 19 (35.2) | 0.644^ |
| 5-10 hours | 23 (29.1) | 11 (44.0) | 12 (22.2) | 0.103^ |
| 10 hours to 1 day | 17 (21.5) | 7 (28.0) | 10 (18.5) | 0.190^ |
| >1 day | 5 (6.3) | 0 (0.0) | 5 (9.3) | 1.000^ |
| Moved closer to the treatment facility | | | | |
| No | 29 (36.7) | 7 (26.9) | 22 (41.5) | - |
| Yes | 50 (63.3) | 19 (73.1) | 31 (58.5) | 0.206 |

**Health care beliefs and choices**

Children presented with either a swelling or a lump (n = 63; 78.8%) and pain (n = 43; 53.8%) while other symptoms included blood in the urine, constipation, loss of appetite and difficulty in walking. Most parents believed that their child's symptoms were related to an infection (n = 25; 31.3%) or trauma or injury (n = 18; 22.5%) prior to cancer diagnosis, although 12 families (15%) believed that the symptoms were due to witchcraft. When their children developed these symptoms, the majority of participants first sought care at a hospital (public: n = 26; 32.5%, private: n = 17; 21.3%) or a health centre/clinic (n = 22; 27.5%) while 19 (23.8%) sought care from a traditional healer. The reasons for their choices were based on trust in that type of health care (n = 47; 58.8%) and/or health care provider (n = 45; 57.5%). The health care provider suggested treatment in 53 (67.9%) cases, and the treatment only worked in 5 (9.4%) of these cases. Thirteen (16.5%) participants were referred to the cancer treatment centre by the first health care provider whom they consulted. The majority of families (n = 49; 61.2%) reported that religion rarely or never influenced the medical choices that they made for their children (Table 2). Few participants understood what cancer is and the treatments required for its cure (n=24; 31.2%).

**Table 2: Health care beliefs and choices prior to cancer diagnosis**

| | |
|---|---|
| Symptoms experienced prior to diagnosis (multiple answers possible) | |
| Fever | 24 (30.0) |
| Weight loss | 42 (52.5) |
| Pain | 43 (53.8) |
| Swelling or limp | 63 (78.8) |
| Bleeding | 15 (18.8) |
| Diarrhoea | 8 (10.0) |
| Constipation | 21 (26.3) |
| Other | 20 (25.0) |
| Thought symptoms were due to (multiple answers possible) | |
| Trauma or injury | 18 (22.5) |
| Infection | 25 (31.3) |
| Stomach worms | 11 (13.8) |
| Witchcraft | 12 (15.0) |
| Initial care for first symptoms (multiple answers possible) | |
| Doctor / nurse at public hospital | 26 (32.5) |
| Doctor / nurse at private hospital | 17 (21.3) |
| Doctor / nurse at health centre clinic | 22 (27.5) |
| Birth attendant / community health worker at primary healthcare post | 3 (3.8) |
| Traditional healer at home / clinic | 19 (23.8) |
| Other healthcare provider | 13 (16.3) |
| Reason for initial care choice (multiple answers possible) | |
| Cost | 9 (11.3) |
| Distance from home | 20 (25.0) |
| Trust in type of medicine | 47 (58.8) |
| Trust in type of healthcare provider | 46 (57.5) |
| Other | 16 (20.0) |
| Do not know | 2 (2.5) |
| Religion influences medical choices caregiver makes for child, N (%) | |
| Always | 13 (16.3) |
| Often | 6 (7.5) |
| Sometimes | 12 (15) |
| Rarely | 10 (12.5) |
| Never | 39 (48.8) |

Prior to the cancer diagnosis, 72 (91.1%) participants had generally consulted health care workers when their child was not well. They most commonly consulted a public hospital (doctor/nurse) (n = 46; 57.5%), health centre/clinic (doctor/nurse) (n = 44; 55%) or private hospital (doctor/nurse) (n = 33; 41.3%), and only 18 (8.8%) generally consulted a traditional healer's home/clinic when unwell.

Beliefs regarding the benefits of T&CM varied widely. The minority (n = 10; 19.6%) of families thought that T&CM always or often had fewer side effects than Western medicine while one caregiver reported that T&CM was always or often effective for cancer treatment and four (9%) thought that T&CM always or often offered relief of symptoms. The majority of families (n = 25; 54%) thought that T&CM was less effective than Western medicine. The cost of treatment was rarely or never a factor for the majority of families when considering either T&CM (n = 47; 70.0%) or Western medicine (n = 59; 75.6%). The cost of transportation was a major deciding factor when considering where to seek care for 12 (15.8%) respondents. Nineteen families (24.7%) stated that they would talk to their doctor about T&CM therapies if they were using or interested in information on traditional medicine while only 14 (18.1%) respondents indicated that they would speak to a member of their health care team (Table 3).

**Table 3: Beliefs about T&CM**

| Belief | Always | Often | Sometimes | Rarely | Never |
|---|---|---|---|---|---|
| Traditional medicine has fewer side effects than Western medicine (n = 51). | 4 (7.8) | 6 (11.8) | 13 (25.5) | 15 (29.4) | 13 (25.5) |
| Traditional medicine is effective for cancer treatment (n = 43). | 1 (2.3) | 0 (0) | 6 (14.0) | 2(4.7) | 34 (79.1) |
| Traditional medicine offers relief of symptoms (n = 44). | 2 (4.5) | 2 (4.5) | 7 (15.9) | 5 (11.4) | 28 (63.6) |
| Traditional medicine is less effective than Western medicine (n = 46). | 12 (26.1) | 13 (28.3) | 9 (19.6) | 5 (10.9) | 7 (15.2) |
| Traditional medicine will relieve the side effects of | 3 (7.1) | 1 (2.4) | 3 (7.1) | 11 (26.2) | 24 (57.1) |

| | | | | | |
|---|---|---|---|---|---|
| Western medicine (n = 42). | | | | | |
| The cost of treatment is a deciding factor when considering a visit to a traditional healer (n = 67). | 4 (6.0) | 6 (9.0) | 10 (14.9) | 15 (22.4) | 32 (47.8) |
| The cost of treatment is a deciding factor when considering a visit to a Western medicine clinic, hospital or health care post (n = 78). | 7 (9) | 5 (6.4) | 7 (9.0) | 22 (28.2) | 37 (47.4) |
| The cost of transportation is a deciding factor when considering where to seek care (n = 76). | 8 (10.5) | 4 (5.3) | 16 (21.1) | 17 (22.4) | 31(40.8) |
| If parents/guardians were using or interested in information on traditional medicine, they would talk to their doctor about T&CM therapies (n = 77). | 15 (19.5) | 4 (5.2) | 14 (18.2) | 10 (13.0) | 34 (44.2) |
| If parents/guardians were using or interested in information on traditional medicine, they would talk to someone other than their doctor in their medical team (e.g. nurse, dietitian or psychologist) about T&CM therapies (n = 77). | 6 (7.8) | 8 (10.4) | 22 (28.6) | 7 (9.1) | 34 (44.2) |

**T&CM Use**

The majority (n = 54; 67.5%) of participants had used at least one form of T&CM before diagnosis and 21 (26.3%) after diagnosis. All patients who had used T&CM after diagnosis had also used it before diagnosis. When prayer for healing purposes was excluded, 50

(62.5%) had used T&CM before and 12 (15%) after initiating cancer therapy. Of those using T&CM, 12 (22.2%) used only one type of T&CM, most used 2–4 types (n = 39; 72.2%) and only a few used 5 or more types (n = 3; 5.5%).

Table 4 describes the most common treatments used prior to cancer diagnosis included a visit to a traditional healer (n = 35; 43.8%), use of herbs or other plant-based medicines or teas taken by mouth (n = 29; 36.3%), prayer for healing purposes (n = 24; 30%) and skin cutting with application of pastes/herbs to the wound (n = 13; 16%). Three (5.6%) of those who used T&CM believed that it was effective while 42 (94.4%) believed that it was not. Children experienced side effects with the use of these treatments, including worsening of symptoms (n = 29; 36.3%), pain (n = 22; 27.5%), signs of infection (n = 6; 7.5%) and other effects (n = 11; 13.8%) such as difficulty breathing or convulsions. Respondents were not able to match the side effects with the various therapies.

Following diagnosis, the common T&CM therapies included prayer for healing purposes (n = 15; 18.8%) and herbs or other plant-based medicines or teas taken by mouth (n = 7; 8.8%). The mean number T&CM strategies applied per user was two. Side effects experienced from these therapies included pain (n = 6; 7.5%), signs of infection (n = 3; 3.8%) and worsening of the original symptoms (n = 3; 3.8%). Two (2.5%) patients had delayed their scheduled conventional cancer treatment to initiate T&CM treatments first. The reasons outlined for using T&CM after diagnosis were the belief that hospital medicine alone could not cure cancer (n = 3; 3.8%) and that faith in God was the ultimate healer (n = 15; 18.8%).

The payment for T&CM varied among participants. It was free for 16 (20%) while others used cash (n = 29; 36.3%), credit (n = 1; 1.3%), barter/exchange of labour or items (n = 3; 3.8%) or other unspecified types of payment (n = 10; 12.5%). The median amount of cash payments was 34 560 (US$57,6) [IQR 4 000 (US$6,67) to 15 000 (US$25] (https://www1.oanda.com/currency/converter/), and the items commonly exchanged in barter payments were palm wine, chickens and palm oil.

**Table 4: T&CM strategies used prior to and after cancer diagnosis**

| T&CM method used, n (%) | Before diagnosis | After diagnosis |
|---|---|---|
| Visiting a traditional healer | 35 (43.8) | 3 (3.8) |
| Herbs or other plant-based medicines or teas taken by mouth | 29 (36.3) | 7 (8.8) |
| Application of pastes, herbs, creams, poultices, leaves or other treatments to the skin | 11 (13.8) | 1 (1.3) |
| Skin cutting | 11 (13.8) | 1 (1.3) |
| Skin cutting with application of pastes/herbs to the wound | 13 (16.3) | 1 (1.3) |
| Water treatments, sweat baths or medicine baths | 5 (6.3) | 1 (1.3) |
| Inhalation of medicines, incense, aromatherapy or other treatments | 2 (2.5) | 0 (0) |
| Touch therapies or manual healing such as massage or hands-on healing | 5 (6.3) | 1 (1.3) |
| Prayer for healing purposes | 24 (30.0) | 15 (18.8) |
| Healing ceremonies | 2 (2.5) | 1 (1.3) |
| Any other home remedies or non-Western medicines or practices | 9 (11.3) | 3 (3.8) |
| Total number of patients who used at least one form of T&CM including prayer for healing purposes | 54 (67.5) | 21 (26.3) |
| Total number of patients who used at least one form of T&CM excluding prayer for healing purposes | 50 (62.5) | 12 (15.0) |

## CORRELATIONS OF TRADITIONAL AND COMPLEMENTARY MEDICINE USE

Demographic characteristics and health beliefs were shown to be associated with the use of T&CM prior to and after diagnosis. As shown in Table 5, before diagnosis, use of T&CM correlated with availability of a T&CM practitioner in the community ($p = 0.056$) and previous utilisation of T&CM when the child was sick ($p = 0.006$). It also correlated with cost when choosing a source of health care ($p = 0.024$). After diagnosis, use of T&CM correlated with availability of a traditional healer in the community ($p = 0.038$) and the belief that T&CM had fewer side effects than hospital medicine ($p = 0.004$). Cost concerns were

also seen to correlate with use of T&CM after diagnosis, including when cost of treatment was a deciding factor for using T&CM ($p = 0.008$) for visiting a hospital ($p = 0.020$) or when cost of transport was a deciding factor in choosing a source of health care ($p = 0.004$). The use of T&CM after diagnosis correlated with the belief that the symptoms of the child were related to infection ($p < 0.001$), stomach worms ($p = 0.006$), witchcraft ($p = 0.011$), use of T&CM before diagnosis ($p < 0.001$), the child being in school ($p = 0.034$) and Pentecostal religion ($p = 0.025$).

**Table 5: Correlations between T&CM use and demographics and beliefs**

| **Before diagnosis** | **No T&CM used n (%)** | **T&CM used n (%)** | **P-value** |
|---|---|---|---|
| Generally consult T&CM practitioner. | 1 (3.8) | 17 (31.5) | 0.006 |
| Symptoms before diagnosis – diarrhoea. | 0 (0) | 8 (14.8) | 0.039 |
| First sought care – public hospital. | 13 (50) | 13 (24.1) | 0.020 |
| First sought care – traditional healer. | 0 (0) | 19 (35.2) | 0.001 |
| Health care practitioner suggested treatments. | 12 (50) | 41 (75.9) | 0.024 |
| Cost is deciding factor in using T&CM. | 4 (26.7) | 31 (59.6) | 0.024 |
| **After diagnosis** | **No T&CM used N (%)** | **T&CM used N (%)** | **P-value** |
| Traditional healer is available. | 36 (61) | 18 (85.7) | 0.038 |
| Parents/guardians know what cancer is. | 13 (22.4) | 11 (57.9) | 0.004 |
| Before diagnosis parents/guardians thought symptoms were related to infection. | 11 (18.6) | 14 (66.7) | < 0.001 |
| Before diagnosis parents/guardians thought symptoms were related to stomach worms. | 4 (6.8) | 7 (33.3) | 0.006 (Fisher's exact) |

| | | | |
|---|---|---|---|
| Before diagnosis parents/guardians thought symptoms were related to witchcraft. | 5 (8.5) | 7 (33.3) | 0.011 (Fisher's exact) |
| First sought care – traditional healer. | 9 (15.3) | 10 (47.6) | 0.006 (Fisher's exact) |
| T&CM was tried before diagnosis. | 33 (55.9) | 21 (100) | < 0.001 |
| Paid for treatment in cash. | 15 (25.4) | 14 (66.7) | 0.001 |
| Patient has entered school. | 37 (63.8) | 17 (89.5) | 0.034 |
| Household has a computer. | 12 (20.3) | 0 (0) | 0.030 (Fisher's exact) |
| Child is Pentecostal. | 5 (8.5) | 7 (33.3) | 0.011 (Fisher's exact) |
| Mother is Pentecostal. | 8 (13.6) | 8 (38.1) | 0.025 (Fisher's exact) |
| Guardian is Pentecostal. | 1 (1.7) | 5 (23.8) | 0.04 (Fisher's exact) |
| T&CM has fewer side effects than hospital medicine. | 18 (60.0) | 20 (95.2) | 0.004 |
| Cost is deciding factor in using T&CM. | 19 (41.3) | 16 (76.2) | 0.008 |
| Cost is deciding factor in visiting hospital. | 26 (44.8) | 15 (75) | 0.020 |
| Cost of transport is deciding factor. | 27 (49.1) | 18 (85.7) | 0.004 |

Pain as a side effect was significantly associated with visiting a traditional healer ($p = 0.000$), herbs or other plant-based medicines or teas taken by mouth ($p = 0.034$), application of pastes, herbs, creams, poultices, leaves or other treatments to the skin ($p = 0.041$), skin cutting ($p = 0.001$) and prayer for healing purposes ($p = 0.004$) (Table 6). Worsening of symptoms was associated with visiting a traditional healer ($p = 0.001$), herbs or other plant-based medicines or teas taken by mouth ($p = 0.002$), skin cutting ($p = 0.010$), water treatments, sweat baths or medicine baths ($p = 0.005$) and prayer for healing purposes ($p = 0.028$).

**Table 6: Correlations between T&CM methods and side effects experienced**

| T&CM method | Side effect present n (%) | Side effect absent n (%) | Fisher's exact |
|---|---|---|---|
| **Pain** | | | |
| Visiting a traditional healer | 17 (48) | 18 (51.4) | 0.000 |
| Herbs or other plant-based medicines or teas taken by mouth | 12 (41.4) | 17 (58.6) | 0.034 |
| Application of pastes, herbs, creams, poultices, leaves or other treatments to the skin | 6 (54.5) | 5 (45.5) | 0.041 |
| Skin cutting | 8 (72.7) | 3 (27.3) | 0.001 |
| Skin cutting with application of pastes/herbs to the wound | 8 (61.5) | 5 (38.5) | 0.005 |
| Prayer for healing purpose | 12 (50.0) | 12 (50.0) | 0.004 |
| **Worsening of symptoms** | | | |
| Visiting a traditional healer | 20 (57.1) | 15 (42.9) | 0.001 |
| Herbs or other plant-based medicines or teas taken by mouth | 17 (58.6) | 12 (23.5) | 0.002 |
| Skin cutting | 8 (72.7) | 3 (27.3) | 0.010 |
| Skin cutting with application of pastes/herbs to the wound | 9 (69.2) | 4 (30.8) | 0.009 |
| Water treatments, sweat baths or medicine baths | 5 (100) | 0 (0) | 0.005 |
| Prayer for healing purpose | 13 (54.2) | 11 (45.8) | 0.028 |

Payment methods also varied with the type of T&CM used, as outlined in Table 7. Prayer for healing purposes was associated with no charge for treatment ($p = 0.014$), and payment by barter was associated with herbs or other plant-based medicines or teas taken by mouth ($p = 0.044$). Cash payment was associated with visiting a traditional healer ($p = 0.000$), herbs or other plant-based medicines or teas taken by mouth ($p = 0.000$) and skin cutting ($p = 0.000$).

**Table 7: Correlations between T&CM methods and types of payment**

| T&CM method | Payment method applied n (%) | Payment method did not apply n (%) | Fisher's exact |
|---|---|---|---|
| **No payment (free of charge)** | | | |
| Prayer for healing purpose | 9 (37.5) | 15 (62.5) | 0.014 |
| **Barter** | | | |
| Herbs or other plant-based medicines or teas taken by mouth | 3 (10.3) | 26 (89.7) | 0.044 |
| **Cash** | | | |
| Visiting a traditional healer | 23 (65.7) | 12 (34.3) | 0.000 |
| Herbs or other plant-based medicines or teas taken by mouth | 20 (69.0) | 9 (31.0) | 0.000 |
| Skin cutting | 8 (72.7) | 3 (27.3) | 0.010 |
| Skin cutting with application of pastes/herbs to the wound | 9 (69.2) | 4 (30.8) | 0.009 |

## DISCUSSION

This study provided unique perspectives on the prevalence of and motivations for T&CM use among children with cancer in a culturally pluralistic society such as Cameroon (13,15). Identifying these features as well as the types of T&CM used and the side effects noted was critically important at a time when the WHO was promoting an agenda for safe integration of T&CM and conventional medicine (11).

According to this survey, 67.5% of families used at least one form of T&CM. This was consistent with the average rate of 66.7% reported in LMICs (6). Similar rates of use were reported for other low-income settings including 65.2% in Jordan (16) and 60% in Turkey, and higher rates were reported in Guatemala (90%) and Kenya (95%) (9,16,17). The rate was higher than the 55.7% previously reported for Burkitt lymphoma patients in Cameroon (9). This survey used interviewers who were not part of the treatment team, as in the previous report, to improve disclosure, as suggested by Ladas et al. (14).

Previous work in LMICs identified a median rate of 53% use of T&CM with intent to cure while several reports indicated the use of T&CM for supportive care and symptom management (6,18). In Mexico, 32% of respondents used T&CM for cure while 53% used it to relieve the effects of conventional treatment (19). In Kenya, 23% of health care providers believed that patients were using T&CM for cure while 21% believed that it was used for supportive care (20). In many settings, this was associated with high rating of effectiveness, such as in Mexico (79%), Guatemala (72%), Argentina (66%) and Uruguay (75%) (18,19,21). Most studies in paediatric oncology populations have reported effectiveness of more than 50% (6). This study indicated that T&CM was never effective for cancer cure (79.1%) or symptom management (63.6%). In fact, among those who had used T&CM prior to diagnosis, only 5.6% of T&CM users experienced it as effective.

The most common T&CM strategy employed was visiting a traditional healer, as described by 43.8% of respondents. Childhood cancer patients and their families sought care from traditional healers in all income settings, including in Kenya, Canada, Malaysia and Israel, indicating the importance of the health system globally as reported by the WHO (8,11,22–24). There was a high use of herbs or other plant-based medicine therapies (n = 29; 36.3%) in this study, similar to what is commonly reported in other LMICs such as Guatemala and Jordan (6,14,16). Prayer for healing purposes was less frequently used according to this survey (n = 24; 30%) compared to the 45% use reported in Guatemala (18).

Skin cutting raised safety concerns as reported in this study and emphasised the call for regulations to ensure safety in T&CM use in Cameroon (11,13,18). Although skin cutting may appear to be a practice localised to Cameroon, with rapid globalisation and migration, T&CM practices originating in some parts of the world might increasingly be seen in other parts of the world with different medico-legal implications (25). Very few previous studies have investigated the side effects of T&CM while in Lebanon, participants indicated no side effects at all (6,26).

For families from LMICs, health care costs might be catastrophic. While a previous survey in Guatemala reported that 53% of T&CM used was free, T&CM was only provided for free to 20% of the families in this study (14). For those who paid in cash (36.3%), the median cost was US$57,6, which was lower than the US$141 reported in Jordan in 2010 (16). Fokunang et al. noted that while T&CM was free or obtained by means of barter trade in Cameroon, payment was increasingly monetary in urban settings (13).

Disclosure was low among T&CM users with reported means of 21% in LMICs, 32% in upper-middle-income countries and 45% in HICs (6). This was remarkably similar to the

44% of participants in this study who stated that they would never reveal to their doctor or other members of the medical care team if they were using T&CM. The low levels of disclosure of T&CM use was typically because clinicians did not ask or because patients did not think that such information would be useful to the medical care team (27). Fear of a judgmental attitude from the health care team was reported (8,20). Improved knowledge of T&CM use by clinicians and promotion of open communication with parents by health care providers would encourage disclosure, which might contribute to safer integration of these therapies (6,20,21,27).

Use of T&CM was associated with treatment abandonment or refusal in previous reports (2,4,5). Only two (2.5%) patients in this study had delayed treatment due to use of T&CM. An unknown factor was the number of patients who might have died due to cancer progression while using T&CM therapies exclusively (21). Paediatric oncology professionals in Cameroon should actively seek ways to ensure disclosure about T&CM use amongst patients and families.

While this study had many strengths, it also had a few limitations. First, patient sampling was by convenience as it relied on the availability of social workers to interview families in the paediatric oncology unit, and important perspectives might have been missed. There was also the possibility of information bias from the parents. To mitigate this, the survey was administered by social workers who were not part of the day-to-day care team of the patients. Finally, using a structured questionnaire for the survey did not provide space for subjective expression of beliefs. More in-depth information might be obtained by means of qualitative studies.

## CONCLUSION

This study found the use of T&CM common prior to diagnosis. It is important to note that nearly half of the families reported that they would never disclose T&CM use to their treating health care team. The most common T&CM strategy employed was seeking care from a traditional healer, although many families also utilised herbs or other plant-based medicines taken by mouth or applied to the skin and prayers for healing purposes, similar to strategies used in other parts of the world. The exception to this was the use of skin cutting, with the only previous report of this practice in Cameroon. Health care providers should have knowledge regarding the cultural perceptions of disease and behaviours towards T&CM therapies in order to establish a relationship of full disclosure that ensures safe and culturally sensitive care to patients.

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# CHAPTER 7

## Two decades of childhood cancer care in Cameroon: 2000 – 2020

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Childhood cancer is not a priority for health authorities in Cameroon. Treatment for children with cancer started in the year 2000 with one treatment site. By 2020, there were five dedicated treatment sites with two hub centres and three satellite centres, receiving an average of 250 new patients annually. The aim of this study was to evaluate the progress made with paediatric oncology care in Cameroon from 2000 to 2020 through a literature review.

All published articles related to childhood cancer in Cameroon and webpages, published conference abstracts and other relevant documents were reviewed and included 40 relevant articles. Main themes were: awareness, diagnosis, registration, epidemiology, treatment, outcome, advocacy, partnerships, traditional and complementary medicine, supportive care, palliative care and capacity building.

Significant progress was seen with capacity building and collaboration between paediatric oncology professionals in the country as well as with international paediatric oncology institutions and research groups. Strong advocacy led to inclusion of paediatric oncology specific priority actions in the national strategic plan for the fight against cancer.

Enhanced and sustained commitment of government, non-governmental organizations, charities, childhood cancer specialists, patient and parent groups, is necessary to meet the objective of the WHO-SIOP global initiative for childhood cancer with a target survival of 60% for common and curable childhood cancers by 2030.

# Title: Two decades of childhood cancer care in Cameroon: 2000 – 2020

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**Abbreviations Key:**

| Abbreviation | Full term |
|---|---|
| ABV | Adriamycin (doxorubicin), Bleomycin, Vincristine |
| AIDS | Acquired Immune Deficiency Syndrome |
| Bl | Burkitt lymphoma |
| BBH | Banso Baptist Hospital |
| BHM | Baptist Hospital Mutengene |
| CANCaRe | Collaborative African Network of clincal Care and Research for Childhood Cancer |
| CBCHS | Cameroon Baptist Convention Health Services |
| CPM | Cyclophosphamide |
| CPOG | Cameroon Pediatric Oncology Group |
| FAPOG | Francophone Africa Pediatric Oncology Group |
| GICC | Global Initiative for Childhood Cancer |
| HAART | Highly Active Antiretroviral Therapy |
| HIV | Human Immunodeficiency Virus |
| MBH | Mbingo Baptist Hospital |
| MDT | Multidisciplinary team |
| NGO | Non-Governmental Organization |
| RSA | Republic of South Africa |
| SIOP | International Society of Pediatric Oncology |
| T&CM | Traditional and Complementary Medicine |
| USD | United States Dollar |
| WHO | World Health Organization |

## ABSTRACT

### BACKGROUND

Before the year 2000, there was no dedicated childhood cancer service in Cameroon. The aim of this study was to investigate the progress made with pediatric oncology care in Cameroon from 2000 to 2020.

### METHOD

A literature search was conducted for published articles on childhood cancer in Cameroon and relevant documents and conference abstracts were reviewed. The articles were analyzed under the themes: awareness, diagnosis, epidemiology, treatment, outcome, advocacy, partnerships, traditional and complementary medicine, palliative care and capacity building.

### RESULTS

Low awareness on childhood cancer was addressed with education activities targeting the general population and health care professionals. Cancer diagnosis was achieved with cytology, histology and simple imaging. Management for common and curable cancers was implemented with use of modified treatment regimens for low- and middle- income settings. Nutritional support was shown to mitigate the effects of malnutrition on treatment toxicity and support was provided for transportation and accommodation. There was good collaboration between the pediatric oncology professionals nationally and twinning with international partners. Capacity building activities led to the availability of three pediatric oncologists and pediatric oncology trained nurses. Advocacy nationally led to the support of the Ministry of Health with pediatric oncology specific priority actions in the latest national cancer control plan.

### CONCLUSION

Childhood cancer should receive the necessary attention of health care policy makers in Cameroon. With continued commitment of government, non-governmental organizations, charities, childhood cancer specialists, patient and parent groups, there should be an improved future for children with cancer in Cameroon.


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## BACKGROUND

Cameroon is a Central African country with a population of about 27 million, 42% of which are younger than 15 years and 30% of which live on less than US$1.95 per day [1]. The under-five-mortality (UFM) rate is 73 per 1000 live births [2]. There is no universal health coverage. The annual per capita expenditure on health is about US$58, of which 74% is out-of-pocket expenditure [1]. While infectious diseases, especially HIV/AIDS, malaria and tuberculosis, still constitute major causes of illness and death in Cameroon, the incidence of non-communicable disease such as cardiovascular diseases, diabetes and cancer has increased [3].

Childhood cancer is not yet a healthcare priority in Cameroon. Based on the data from the Yaoundé Cancer Registry, an incidence rate of 25/1 000 000 children younger than 14 years was reported [4]. Up until the beginning of the 21st century, no treatment programs for childhood cancers had been introduced in Cameroon. In 2000, the first childhood cancer treatment center was established in the nation's capital, Yaoundé [5]. The Stellenbosch University pediatric oncology team in South Africa established a twinning program with the Cameroon Baptist Convention Health Services (CBCHS) and the Beryl Thyer Memorial Africa Trust with the aim of providing curative treatment for Burkitt lymphoma, the most common childhood cancer in Northwest Cameroon in 2003 [6]. The aim of this study was to investigate the progress of pediatric oncology care in Cameroon from 2000 to 2020.

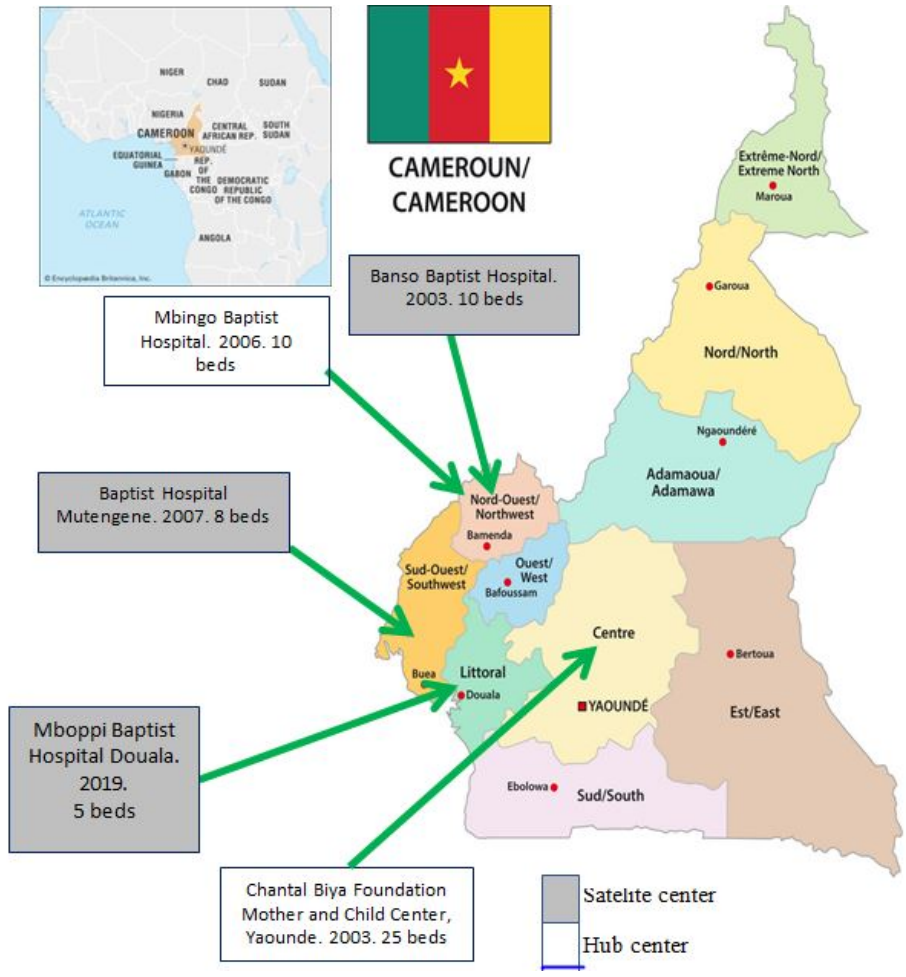
## METHODOLOGY

Two dedicated childhood cancer programs provide pediatric oncology services in Cameroon. At the Chantal Biya Foundation Mother and Child Hospital in Yaoundé is a 25-bed unit under the direction of a single pediatric hematologist/oncologist. The unit receives on average 130 patients annually [7]. At the time of the study, the care team consisted of pediatricians and general practitioners, two of whom had received pediatric oncology training, and nurses. Pathology services and blood product support was available from the Center Pasteur in Yaoundé, which is adjacent to the hospital [5].

The second program is the childhood cancer program of the CBCHS. The program was initiated at Banso Baptist Hospital (BBH) and later extended to Mbingo Baptist Hospital (MBH) in 2006, Baptist Hospital Mutengene (BHM) in the Southwest in 2007, and Mboppi

Baptist Hospital Douala (MBHD) in the Littoral region in 2019. The entire effort subsequently has been coordinated as a single program. MBH serves as the hub, with the other three hospitals as satellite centers under its direction. This pediatric oncology twinning program admits on average 120 new patients annually. Care is directed by a pediatric oncology-trained physician, who resides at the hub center, MBH, and surgeons. Care across the centers is provided by physicians, pediatricians, general practitioners, nursing practitioners, and nurses with induction training in pediatric oncology. Multidisciplinary team (MDT) meetings across all centers are held weekly and MDT meetings with consultants from Stellenbosch University and Leeds Children's Hospital once a month. The MDT at the hub, MBH, includes a pediatric surgeon, ophthalmologist, radiologist and pathologist (Fig. 1).

**Figure 1: Map of Cameroon showing location of dedicated pediatric oncology units**




The literature search for published articles on childhood cancer in Cameroon focused on Pubmed, Medline and Google Scholar. The search terms were 'child', 'cancer', 'pediatric',

'oncology', 'epidemiology', 'treatment', 'outcome', 'incidence', 'Burkitt lymphoma', 'retinoblastoma', 'nephroblastoma' and 'Cameroon'. The search extended also to relevant documents, webpages and conference abstracts by pediatric oncology professionals in Cameroon. The articles were analyzed under these themes: awareness, diagnosis, registration and epidemiology, management and outcomes, supportive care, palliative care, advocacy and partnerships, traditional and complementary medicine and capacity building. The selected themes were selected to correspond with themes used by previous authors who have presented situational analyses on childhood cancer care [8, 9].

The Johns Hopkins Nursing Evidence-Based Practice Research Evidence Appraisal ranking was used to rate the strength and quality of evidence for the various studies [10]. Level I was attributed for strength of evidence if randomized controlled trial or meta-analyses thereof, Level II for quasi-experimental studies, Level III non-experimental, qualitative, or meta-synthesis studies; Level IV expert opinion and Level V literature reviews [10].

Six of the selected publications were not research. The majority (n = 31) of the reports were quantitative studies, with additional two qualitative studies, and one literature review.

The quality of the studies was rated as follows:

A. High: consistent results, sufficient sample size, adequate control, and definitive conclusions; consistent recommendations based on extensive literature review that includes thoughtful reference to scientific evidence or

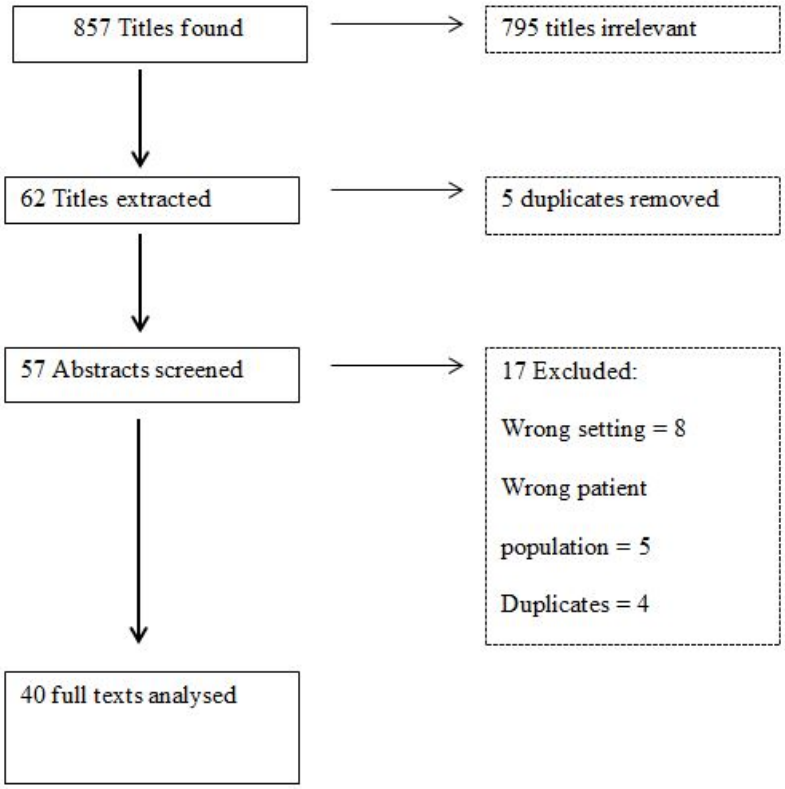
B. Good, reasonably consistent results, sufficient sample size, some control, and fairly definitive conclusions; reasonably consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence or

C. Low/Major flaw: little evidence with inconsistent results, insufficient sample size, conclusions cannot be drawn [10].

## RESULTS

Among the 857 articles found containing the search terms, 57 abstracts were selected for screening. After screening 11 articles were removed because of wrong patient population (5), wrong setting (8) or duplication (4). Eventually, 40 articles were analyzed (Fig. 2).

**Figure 2: Selection of articles for review**




The majority of the research articles were level III strength of evidence (24/40), eight were level II and one level V. Regarding quality of evidence, most (18) of the studies were rated as good quality (B), twelve as poor quality (C), and three of high quality (A).

Two of the reports addressed awareness [7, 11], ten addressed diagnosis, registration and epidemiology [5, 12–20], eighteen addressed management and outcomes [7, 14, 16, 21–35], four addressed supportive care [36–39], five addressed palliative care [40–44], four addressed advocacy and partnerships [35, 37, 45, 46], and one addressed traditional and complementary medicine [39] (Supplement 1).

## CHILDHOOD CANCER AWARENESS IN CAMEROON

The general level of childhood cancer awareness in Cameroon is low, among the general population as well as healthcare professionals, as demonstrated by a study conducted in the Northwest Region. Healthcare professionals know little about childhood cancer types and symptoms; nor do they know where childhood cancer treatment services are located [11]. Low awareness results in late diagnoses, as illustrated by the fact that most patients diagnosed at the various treatment centers across the country are diagnosed with advanced

disease (stages III and IV/metastatic disease) [7, 30, 47]. A median delay of eight months from onset of disease to consultation at the pediatric oncology center was reported in Yaoundé, with patients seeking healthcare at a median of three other healthcare providers, including traditional healers, before arriving at the pediatric oncology unit [7].

In order to improve awareness of childhood cancer in Northwest Cameroon, community education activities have been undertaken by means of community radio stations and the distribution of leaflets. An educational program targeting primary healthcare workers and traditional healers has significantly improved their knowledge about childhood cancer and their ability to refer suspected cases for management. Collaboration with traditional healers has been useful also to improve their knowledge and to establish referral pathways for children with cancer [11, 48].

## DIAGNOSIS, REGISTRATION AND EPIDEMIOLOGY

Diagnosing childhood cancers is a major challenge because of a paucity of competent health professionals to recognize and examine the disease. This is compounded by the near absence of pathology experts. In the Northwest Region, for example, only two pathologists are serving a population of 1 913 278 [17]. Cancer is diagnosed by means of fine-needle aspiration, biopsy and cytology of body fluids [16, 30, 47]. Imaging is useful, but without advanced imaging facilities, ultrasound has been reported to be essential for accurately staging patients with lymphoma [19]. Evidence from Yaoundé show that peripheral blood smear and bone marrow microscopy are effective in identifying hematological malignancies. These techniques confirm the diagnosis of leukemia while ruling out other conditions with similar symptoms, such as malaria and sickle cell anemia [13]. In addition to the technical challenges, another major challenge to childhood cancer diagnosis in Cameroon is the lack of capacity to detect early warning signs and thus to refer patients to pediatric oncology units [7, 11].

Cancer registration has improved significantly in Cameroon between 2000 and 2020. Statistics from the Yaoundé Cancer Registry for 2004 to 2006 have been included in the third volume of the International Incidence of Childhood Cancer published by the International Agency for Research on Cancer [49]. The estimated incidence for all cancers is 25 per million children younger than 15 years [4]. The common childhood cancers in Yaoundé are lymphomas, soft-tissue sarcomas, leukemias, retinoblastomas and renal tumors. Burkitt

lymphoma (Bl) is the most common of the lymphomas [5, 14].

The CBCHS childhood cancer program initiated an electronic hospital-based pediatric cancer registry in 2008 at their hospitals at Banso, Mutengene and Mboppi. The first formal analysis of 1029 registered cases has shown that the most frequent diagnoses are lymphomas, followed by Wilms tumor, retinoblastoma, rhabdomyosarcoma and Kaposi sarcoma [17].

Burkitt lymphoma is the most common childhood cancer in the country [5, 14, 20, 47] with an incidence rate of 3,7/100 000 reported in the Northwest Region, clustering in the hot plain districts of Nwa and Ndop [15, 20, 47]. The odds of developing Burkitt lymphoma is reported to be 3,7 times higher for non-sickle-trait carriers in the region [50]. The proportion of Burkitt lymphoma diagnoses in the Northwest decreased from 2004 to 2015 because the numbers for other cancer types, such as retinoblastoma and nephroblastoma, have increased. This probably is the result of increased access to specialized medical and pathology services [17, 18, 20]. Some publications about the epidemiology of retinoblastoma and Hodgkin lymphoma did appear, but very few cases have been reported [12, 24, 27].

## MANAGEMENT AND OUTCOMES OF COMMON CHILDHOOD CANCERS

Childhood cancer in Cameroon is managed by means of curative treatment for common and curable cancers as well as palliative care. The protocols that have been adopted are modified treatment regimens with reduced toxicity to adapt to the resources for supportive care that are available locally [51, 51]. Outcomes vary by disease and are usually under pressure of difficult access to essential cancer medicines, late diagnosis and lack of registries [7, 21]. Results regarding survival are fragmentary, but do indicate improved survival, especially for Burkitt lymphoma and nephroblastoma [14, 16, 23, 26, 28, 52]. Proper follow-up is essential for measuring outcomes, and the CBCHS centers keep both paper-based and electronic records at dedicated childhood cancer registry offices at MBH, BBH and BHM. Additional follow-up has been done by means of outreaches and by using mobile phones to establish specific outcomes [26, 29].

### *Burkitt lymphoma*

Hesseling et al. introduced a modified treatment protocol for Burkitt lymphoma in Northwest Cameroon in 2003 and reported an event-free survival of 61% for Burkitt lymphoma at the

above- mentioned three Baptist Hospitals, two of which were in the Northwest Region [22, 30]. This was the first report on Burkitt lymphoma survival specific to Cameroon. A salvage treatment was developed for relapsed patients, which has achieved a 36% survival rate [26]. The Francophone Africa Pediatric Oncology Group (FAPOG) included patients from Yaoundé and had reported that the overall Bl survival rate is 60% [35]. Patient destitution level had been reported to affect adherence to Burkitt lymphoma treatment in the region. Decreased survival rates were seen especially among children of single mothers, which highlighted the necessity for individualized psychosocial support to patients and families [39].

A follow-up study of 87 Burkitt lymphoma patients who presented with paraplegia reports that 33% have been alive at a median follow-up of 40 months, with 24% having residual problems with mobility, bladder control or bowel control [26]. This demonstrates that patients require long-term follow-up for residual problems to be identified and rehabilitation to be offered. An HIV prevalence rate of 1,5% has been reported in this population, and HIV status does not affect survival if the patients are treated with both antiretroviral therapy (ART) and chemotherapy. ART and therapy based on cyclophosphamide (CPM) have produced a long-term survival rate of 37,5%, with 91% of the patients being in the advanced stage of the disease [23].

*Nephroblastoma*

In Yaoundé, a five-year overall cancer survival rate of 70% has been reported [16]. A recent FAPOG publication shows an overall survival rate of 72% for seven Francophone African sites, including Yaoundé. However, this report only included standard risk patients and excluded patients who died before or after surgery and those who abandoned treatment [32]. The first report on survival of nephroblastoma in Mbingo Baptist Hospital, in Northwest Cameroon, shows a rate of 44% with a median follow-up of 84 months (7 years) for 35 patients treated by means of both chemotherapy and surgery [34].

The CBCHS pediatric oncology units collaborated in the Collaborative Wilms Tumor Africa Project, which included five African countries and reported a two-year event-free survival of 49.9%. There were fewer abandonments and deaths during treatment compared to a baseline assessment before the collaborative project [31, 53].

*Other cancers*

Other common and curable cancers in Cameroon include retinoblastoma, Hodgkin disease and Kaposi sarcoma. A 12-month patient survival rate of 59,2% is reported for retinoblastoma, with survival influenced mostly by stage of disease [52]. Among a cohort of 12 patients with Kaposi sarcoma at the CBCHS pediatric oncology units, 10 have survived after 40 months, showing that a good medium-term outcome can be obtained for children with Kaposi sarcoma by means of four cycles of ABV (doxorubicin, bleomycin and vincristine) and highly active ART (HAART) [28]. A five-year patient survival rate of 82% has been reported for a cohort of 26 patients with Hodgkin disease [27].

**SUPPORTIVE CARE**

In light of limited access to essential medicines and blood products, supportive care generally is provided following specified guidelines for low- and middle-income countries, with emphasis on tumor lysis syndrome prevention, febrile neutropenia management, infection control and nutritional support [51]. In Yaoundé, half of the patients are malnourished on admission [36]. The nutritional support program in the Northwest includes daily portions of rice, groundnuts, eggs, milk and a cash grant to parents to provide balanced diets for the children. Consequently, morbidity and deaths during treatment have decreased [38].

Given the few centers available, most children with cancer need to travel long distances from their homes to seek treatment. In the Northwest Region, the monthly income of more than 80% of families of Bl patients was below US$100, which made follow-up visits difficult, as they cannot afford the travelling costs [39]. With assistance from non-governmental organizations, the CBCHS childhood cancer program provides transport cost support and set up a parents' home to host the family members of patients who come from distant localities, thus facilitating completion of treatment and follow-up visits [39].

One aspect of dire need is psychosocial support. At the Mbingo Baptist Hospital, the MDT includes a play lead/teacher to improve the children's quality of life during hospitalization or in the parents' home while awaiting chemotherapy. A survey of adolescents who survived childhood cancer at younger ages has found that many of them do not have a clear understanding of their diagnoses and struggle with residual challenges related to the physical and emotional effects of cancer. A psychosocial support project was launched in five pediatric oncology units in Cameroon that included staff training in psychosocial care,

resilience building and an annual action plan for a psychosocial support improvement (Kouya et al., 2020. Unpublished).

## PALLIATIVE CARE

The concept of palliative care used to be relatively unknown in Cameroon, despite the urgent need of patients with advanced disease [42], until a dedicated children's palliative care component was added to the CBCHS childhood cancer program in the Northwest Region in 2013. This service employs a trained pediatric palliative care nurse to provide palliative care to all patients at the hospital, and at home for patients with terminal disease, involving the families and community support systems [43]. This model of palliative care is recommended as the way forward in overcoming financial and cultural challenges to meet patients' palliative care needs [42]. An evaluation of this program two years later has shown improved quality of life for participating patients [40]. The need for bereavement care in particular is acute, as losing a child to cancer usually destabilizes the lives of extended families [41].

## PARTNERSHIPS AND ADVOCACY

The CBCHS childhood cancer program is the fruit of twinning between a local healthcare organization (CBCHS hospitals), a South African university as a South-South partnership (Stellenbosch University), a United Kingdom hospital (Leeds Children's Hospital) and two non-governmental organizations based in the United Kingdom (the Beryl Thyer Memorial Africa Trust UK and World Child Cancer UK). This has brought together funding bodies, pediatric oncology experts, healthcare providers, patients, parents and survivors to work together in identifying healthcare needs of children with cancer and to implement interventions to ensure survival of children diagnosed with cancer. Technical oversight for this collaboration has been provided by pediatric oncologists from Stellenbosch University since 2003 and from Leeds Children's Hospital since 2016, while the CBCHS has provided management and monitoring.

Cameroon pediatric oncology units have participated in two major regional research groups. The center in Yaoundé is a member of the FAPOG group that conducts clinical research projects on Bl and nephroblastoma. World Child Cancer UK also supports this center. The CBCHS centers (MBH, BHM, BBH) are members of the Collaborative African Network for Cancer Care and Research, which conducts clinical research in nephroblastoma and supportive care improvement [46].

Local advocacy groups have been created for pediatric oncology. The Northwest Childhood Cancer Parents' Organization in Cameroon was founded in 2010 as a patient-parent stakeholder group that assists with sensitization, advocacy, fundraising and program evaluation. In May 2018, all healthcare professionals and civil associations involved in the care of children with cancer united to form the Cameroon Pediatric Oncology Group (CPOG) with the aim of improving access to diagnosis and treatment for all children with cancer in Cameroon. This group has harnessed the local expertise to provide capacity building for nursing care, palliative care, childhood cancer awareness creation and referrals. The initiative also has led to an advocacy group for childhood cancer established nationally with formal collaboration status with the National Committee for the Fight Against Cancer and the Ministry of Health. In July 2020, the National Strategic Plan for the Prevention and Control of Cancer 2020–2024 was launched, which includes specific priority actions for childhood cancer [54].

## TRADITIONAL AND COMPLEMENTARY MEDICINE

Disease in the cultural context in Cameroon can be explained in many different ways. Thus, it is addressed by a multitude of traditional therapies [44]. More than half of patients with Burkitt lymphoma in Northwest Cameroon have consulted a traditional healer, and many different diagnoses have been obtained and managed in various ineffective and sometimes harmful ways [48]. In a recent survey regarding the use of traditional and complementary medicine (T&CM) among children with cancer in Northwest Cameroon the rate of consultation has been 67%. Many survey participants present with significant side effects, including infections and worsening of cancer symptoms. Even after diagnosis, a few patients have been found to delay hospital treatment to pursue some T&CM treatment [55]. For optimal results in such a context, it is recommended that educational and research relationships be established between T&CM practitioners and childhood cancer medical experts in a spirit of mutual respect, with a view to finding the best ways to support patients [56].

## CAPACITY BUILDING

Staff capacity for childhood cancer care in Cameroon has improved significantly over the past two decades. From initially having one pediatric oncologist at the center in Yaoundé in 2000, the country had an additional three qualified pediatric oncologists by 2010 [54]. When

the CBCHS treatment program began in the Northwest Region, adult physicians, nurse practitioners and nurses managed the treatment with daily links to pediatric oncologists in South Africa. Since then, staffs have been trained on site in Cameroon by expert pediatric oncologists from the twinning partners, notably Stellenbosch University and later Leeds Children's Hospital. Three nurses have been trained in pediatric oncology nursing abroad, and one nurse has been trained in children's palliative care. One physician has been trained in pediatric oncology, while another has undertaken pathology training. Research capacity has been built, too, with two nurses and one physician obtaining master's degrees based on pediatric oncology research in public health. One nurse (first author) undertook research towards a PhD study with childhood cancer advocacy as research focus [11, 17, 39, 47, 57].

Capacity building has occurred within the framework of regional and international research groups, too, notably through FAPOG, the Collaborative African Network of Clinical Care and Research for Childhood Cancer (CANCaRe), and the International Society of Pediatric Oncology (SIOP) with local staff benefitting from physician fellowships, nurses' training and continued education and mentorship [46, 58].

## DISCUSSION

This review has provided a synopsis of the setting up of pediatric oncology services in Cameroon, their development, current challenges and recommendations for future improvement. The landscape of pediatric oncology in Cameroon is not dissimilar to the situation in other African countries and lessons can be learned from some other settings in the efforts to achieve the goal of 60% survival for all children with cancer in Cameroon.

The problem of low community awareness has been described in other parts of Africa [59, 60]. Similar attempts have been implemented with education of health care professionals and communities and were equally successful in improving knowledge of childhood cancers. Social media presents a powerful tool to dispel myths regarding cancer in children and to assist in conducting education regarding early diagnosis teaching for health care professionals and the general society [61].

Diagnosis has been improved through the use of fine-needle aspirations especially with ultrasound guidance as reported in Cameroon. Advanced imaging has been seen to improve

childhood cancer diagnosis in Africa with increased use of computerised tomography and magnetic resonance imaging [62]. Improving diagnostic capacity in terms of staff training and advance imaging equipment should be considered priority for improving overall survival rates in the country.

Similar to this report, improved pathology and diagnostics have led to improvement in the accuracy of the epidemiological picture of cancer in other parts of Africa [63, 64]. Collection of clinical data and cancer registration should be an essential tool in the application of adapted treatment regimens to assist withsuccessful childhood cancer program development [65–67]. While hospital-based registries assisted with facility-based planning and assessment, the true national picture on service delivery and survival rates would be challenging to obtain without the creation of a national pediatric oncology registry.

This report demonstrated a good level of patient follow up in pediatric oncology services in Cameroon, which was not always the case in most LMICs [68]. The 61% survival rate for Burkitt lymphoma was similar to a report from South Africa [69]. Adding anthracycline to the treatment can potentially improve survival rates as demonstrated in Malawi [70]. For nephroblastoma, the 68% to 70% current survival rates reported weree higher than 41% reported from Kenya (64) and 56% from Rwanda [71, 72]. The participation of Cameroon pediatric oncology units in international collaborative research on nephroblastoma could be regarded as a good example and potential reason for improved survival rate [46, 53, 73, 74].

Similar to this report, similar problems with treatment toxicity, malnutrition and non-adherence were reported elsewhere in Africa [60, 75–77]. The problem of pain, however, was not explored in Cameroon but was reported to be an important concern in pediatric oncology [78]. While the twinning project seen in Cameroon provided nutrition support and transportation assistance, there was a need for access to essential antibiotics to combat blood stream infections [79], consistent access to opioid pain medication and application of distraction techniques to control pain and improve patient comfort during treatment [80].

This report demonstrated a good example of home-based care filling in the gap of inadequate palliative care in pediatric oncology in Africa [42, 81, 82]. However, this initiative was very limited in geographical scope at the moment and required expansion to include other centers and other parts of the country. The inclusion of palliative care in the recent national cancer control plan for Cameroon 2020 – 2024 was due to advocacy on the part of the oncology

professionals and provided an opportunity for political commitment to improve access to palliative care [54, 83].

The use of T&CM in pediatric oncology was reported previously [84–86]. Cameroon as a cultural pluralistic society with a variety of ecosystems demonstrated diverse T&CM practices. It was important to obtain a good understanding of the beliefs and attitudes of patients regarding these practices throuhg open conversation with families to encourage disclosure, which was considered a good way to improve patient safety [87]. The reality of T&CM could not be ignored and more integrative approaches should be implemeted to ensure patient's safety in the context of co-existing medical systems [88].

This review of literature documented the progress made with pediatric oncology care in Cameroon over two decades and enabled the identification of areas requiring improvement. The resultes described were from published peer-reviewed literature. This was a feasible and inexpensive model to evaluate pediatric oncology progress, which could be applied in other LMICs. One weakness of this report was that it did not include conference presentations and student theses about childhood cancer-related topics. Additionally, this report identified gaps in pediatric oncology services in comparison with other settings in Africa and globally. However, the extent of the problems identified and the amount of resources required to address them should be further investigated.

## CONCLUSION

Childhood cancer should receive the necessary attention of health care policy makers 360 in Cameroon to ensure improved survival according to the current goal of the Global 361 Childhood Cancer Initiative (GICC) of the World Health Organization and the 362 International society of Pediatric Oncology (WHO-SIOP) [58, 59]. Much progress was made in the past two decades, with the establishment of treatment centers, capacity building for healthcare, and advocacy for access to care. The key to these successes definitely is the strong national and international collaborations between the various centers and international childhood cancer experts, which has gained the support of the National Ministry of Health in Cameroon.

A significant milestone was achieved with the inclusion of pediatric-oncology-specific priority actions in the National Strategic Plan for Prevention and Control of Cancer [64]. With the continued commitment of government, non-governmental organizations, charities,

childhood cancer specialists, and patient and parent groups, the future for children with cancer in Cameroon is looking brighter in the context of the WHO-SIOP global initiative for childhood cancer, which has set a target survival rate of 60% for common and curable childhood cancers by 2030 [89, 90].

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There is no conflict of interest.

**Author contributions:**

Afungchwi GM1,2, Kruger M2, Kouya F1, Tih P1, McCormick P3, Pondy-Ongotsoyi AH4,5, Hesseling PB2

Glenn Mbah Afungchwi participated in the study design, literature review, and drafted the manuscript.

Mariana Kruger conceptualized and contributed to study design, literature search and review, critically reviewed and revised the manuscript for intellectual content.

Francine Kouya contributed to literature search and manuscript writing.

Pius Tih contributed to literature search and critically reviewed and revised the manuscript for intellectual content.

Peter McCormick contributed to literature search and critically reviewed and revised the manuscript for intellectual content.Pondy-Ongotsoyi Angele-Hermine contributed to literature search critically reviewed and revised the manuscript for intellectual content.

Peter Hesseling conceptualised the study design, contributed to literature search and review, supervised data analysis, critically reviewed and revised the manuscript for important intellectual content

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Supplement 1 : Summary of articles reported

| Authors | Year | Title | Study type | Strength of evidence | Quality of evidence | Main findings |
|---|---|---|---|---|---|---|
| Enow-Orock et al. | 2012 | A pediatric oncology group pilot study on childhood cancers at the Chantal Biya Foundation Yaounde, Cameroon: Report of 350 cases | Quantitative | III | B | The most common diagnosis was Burkitt lymphoma followed by other non-Hodgkin's lymphomas and Hodgkin's lymphoma |
| van Heerden et al | 2020 | Pediatric Oncology Clinical Trials and Collaborative Research in Africa: Current Landscape and Future Perspectives | Not research | N/A | N/A | African children have limited access to clinical trials for cancer. The common impediments include limited treatment facilities, limited funding, limited research capacity and inconsisitend and weak ethics regulations. |
| Tamannai et al. | 2015 | An evaluation of a palliative care outreach programme for children with Burkitt lymphoma in rural Cameroon | Qualitative | III | B | Home-based palliative care by a trained paediatric palliative care nurse improved quality of life for children with terminal disease. |
| Eden et al. | 2019 | Are essential medicines available, reliable and affordable in low-middle income countries? | Quantitative | III | A | Availablility of key drugs was inconsistent and drug cost for families was often the cause of treatment abandonment. |
| Hesseling et al. | 2010 | Burkitt Lymphoma: Residual Abdominal Tumor Volume After Induction Therapy Correlates With Outcome | Quantitative | III | C | Children with residual volume greater than 35ml on day 29 (two weeks after end of induction phase) were more likely to relapse |
| Hesseling et al. | 2018 | Burkitt's lymphoma: The prevalence of HIV/AIDS and the outcome of treatment | Quantitative | III | B | Prevalence of HIV was 1.5% amongst childen with Burkitt lymphoma. The patients had a long-term survival of 37.5% with low cost high-frequency cyclophosphamide-based therapy |
| Bella et al | 2010 | Childhood ocular tumors: Epidemiological and histopathological aspects at the Yaoundé gynaeco obstetric and | Quantitative | III | C | Occular tumours were amongst children consulting at the Yaounde gyneco-obstetric and paediatric hospital between 2003 and 2009. 75% of ocular tumours were retinoblastoma |

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| | | pediatric hospital | | | | |
| Epee et al. | 2014 | Clinical features and prognosis of retinoblastoma at the University Teaching Hospital of Yaounde Cameroon | Quantitative | III | C | Leukokoria and exophthalmia were the common signs noticed by parents. Only two patients were alive at 1 year follow up. |
| Israels et al. | 2013 | Clinical trials to improve childhood cancer care and survival in sub-Saharan Africa | Not research | N/A | N/A | Clinical trials improve staff capacity and outcome and imprves financial acces to treatment for patients. Collaboration and reliance on local expertise is necessary for their success. |
| Ongotsoyi et al | 2019 | Contribution of Bone Marrow Examination in the Diagnosis of Pediatric Pathologies at the Mother and Child Center of Chantal Biya Foundation | Quantitative | III | C | Bone marrow analysis was useful in diagnosing hematologic malignancies and identifying non-malignant diseases with hematological manifestations. |
| Traore et al. | 2011 | Cyclophosphamide monotherapy in children with Burkitt lymphoma: A study from the French-African Pediatric Oncology Group (GFAOP): Cyclophosphamide in African Burkitt Lymphoma | Quantitative | II | B | Overall survival for Burkitt lymphoma was 50.5% and ws affected by disease stage. Cyclophosphamide treatment is effective for stage I and II disease, but other strategies adapted to resource limited settings are required for stage III and IV disease |
| Hesseling et al. | 2015 | Endemic Burkitt Lymphoma: Long-term Outcome in 87 Patients Who Presented With Paraplegia in Cameroon | Quantitative | III | B | Survival rate at end of treatment was 36% for patients with paraplegia. 29(33%) were alive at a media follow up of 40 months with 7 (24%) having residual walking, bladder control, or bowel control problems. There was no correlation between duration of paraplegia before diagnosis and outcome. |
| Ketchen | 2018 | Epidemiology and Treatment Outcome of Lymphomas in Children: A Study From a Developing Area in Cameroon | Quantitative | III | B | Lymphomas were 36% of all childhood malignancie. Five year overall survival was 74% for Hodgkin lymphoma and 51% for non Hodgkin lymphoma and was significantly affected by disease stage. |
| Lewis et al | 2012 | Epidemiology of Burkitt's lymphoma in Northwest Province, Cameroon, 2003–2010 | Quantitative | III | C | Average incidence rate of 4.54 per 100 000 children below 15 years. Highest incidence was seen in the low lying plains of Ndop district. |

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| Ongotsoyi et al | 2019 | Epidemiology, Clinical Features and Management of Wilms Tumour at the Mother and Child Center-CBF, Yaounde | Quantitative | III | B | Abdominal distension was the most common sign. One third had disseminated disease to the lungs or liver. 77% completed treatment with a 5 year overall survival of 70% |
| Ongotsoyi et al | 2018 | Evaluation de l'État Nutritionnel chez les Enfants Atteints de Cancers Hospitalisés au Centre Mère et Enfant de Yaoundé | Quantitative | III | B | Prevalence of stunting in patients below 5 years was 15.6%. Malnutrition rate was 62.12% in children above 5 years by mid upper arm circumference measurement. |
| Pondy et al | 2018 | Evaluation of the Response to Chemotherapy in the Treatment of Hodgkin's Disease at the Mother and Child Center of the Chantal Biya's Foundation in Yaounde, Cameroon | Quantitative | III | B | Hodgkin disease was 1.96% of all childhood cancer cases. The most common presenting sign was peripheral adenopathy. The overall 5 year survival was 82%; being 100% for patients ranked favourable at initiation and 78% for those ranked unfavourable. |
| Hesseling et al. | 2017 | Kaposi's sarcoma: Good outcome with doxorubicin, bleomycin and vincristine sulphate (ABV) chemotherapy and highly active antiretroviral therapy | Quantitative | III | C | All patients were treated with ABV and the ten HIV patients were on HAART. After a median follow up of 40.5 months, 10 of these patients were alive, including 8 with HIV. |
| Makak and Otsamba | 2020 | Oncopediatrics death: Does cancer endanger the family in Cameroonian context? | Qualitative | III | A | The high financial and emotional burden of childhood cancer treatment on the family tends to deplete resources of extended families in the Cameroonian setting and results in nuclear families having to sought for themselves and feeling abandoned in event of death of the child, contrary to the culture of solidarity amongst extended families. Understanding the cultural and psychosocial determinants of family cohesions can enable better provision of bereavement support to families of children with cancer. |
| Hesseling et al. | 2008 | Rescue chemotherapy for patients with resistant or relapsed endemic Burkitt's lymphoma | Quantitative | II | C | 36% survival was obtained for patients with relapse of Buritt lymphoma with a simple 15-day schedule of cyclophosphamide and vincristine plus intrathecal methotrexate |

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| Ongotsoyi et al | 2019 | Route of Children with Cancer to the Hematology-Oncology Unit of the Mother and Child Center of the Chantal Biya Foundation | Quantitative | III | C | Majority of patients were from at least 250Km away from the POU. The mean delay from onset to presentation waas 8.3 weeks with majority of patients presenting with Stage III or IV disease. The median number of facilities visited before the POU was 3, mostly conventional health care facilities. Other sources of health care attempted included traditional healers, faith healers and roadside drug vendors. |
| Ongotsoyi et al | 2019 | Soins palliatifs pédiatriques au Cameroun : comment répondre à la discontinuité des soins ? | Not research | N/A | N/A | Home-based palliative care is a necessity for children with cancer in Cameroon with the current high rates of late diagnosis, abandonment of treatment and consequent low survival rates. |
| Hesseling et al. | 2012 | The Cameroon 2008 Burkitt Lymphoma Protocol: Improved Event-Free Survival with Treatment Adapted to Disease Stage and the Response to Induction Therapy | Quantitative | II | B | One year event-free survival of 61% was achieved with low dose, high frequency cyclophosphamide-based therapy with addition of intravenous methotrexate and vincristine for patients with residual tumour of 30mL or more after induction. |
| Paintsil et al. | 2015 | The Collaborative Wilms Tumour Africa Project; Baseline evaluation of Wilms tumour treatment and outcome in eight institutes in sub-Saharan Africa | Quantitative | III | B | Survival rate at end of treatment was 39% across all 8 centres in 5 countries. Survival rate for 3 centres in Cameroon was 53%. |
| Afungchwi et al. | 2020 | The Evolution of a Hospital-Based Cancer Registry in Northwest Cameroon from 2004 to 2015 | Quantitative | III | B | The most common malignancies were Burkitt lymphoma, nephroblastoma and retinoblastoma. Proportion of Burkitt lymphoma reduced and other diagnoses increased as staff capacity and access to pathology improved. |
| Wright et al. | 2009 | The incidence, clustering and characteristics of Burkitt lymphoma in the Northwest province of Cameroon | Quantitative | III | C | Incidence rate of Burkitt lymphoma was 5.9 per 100,000 children below 15 years. Clustering was sen in Ndop district which has a high rate of malaria. |
| Afungchwi et al. | 2020 | The outcome and cost of a capacity-building training programme on the early recognition and referral of childhood cancer for healthcare | Quantitative | II | B | The percentage knowledge score for identifying childhood cancer signs and referring patients increased from 51% to 85%. The cost of training was 25 Euros per health care professional trained |

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| | | workers in North-West Cameroon | | | | |
| Afungchwi et al. | 2017 | The role of traditional healers in the diagnosis and management of Burkitt lymphoma in Cameroon: understanding the challenges and moving forward | Quantitative | III | B | 55% of them consulted TH before diagnosis with 76.1% of them doing so as first choice of health care. Choice of TM was mostly by lbelief or advice from friends and family, sometimes because of futile attempts at conventional health centres. Cancer was only suspected in 2% of the cases who consulted Traditional healers. The treatment methods applied were potentially harmful in most cases. |
| Marjerrisso n et al | 2012 | The use of ultrasound in endemic Burkitt lymphoma in Cameroon: Use of Ultrasound in eBL | Quantitative | III | C | Use of ultrasound was more effective in detecting abdominal tumours than clinical assessment and resulted in significantly higer rate of abdominal involvement than previously reported |
| Hesseling et al. | 2008 | Treating burkitt's lymphoma in Malawi, Cameroon, and Ghana. | Not research | N/A | N/A | A special report showing succesful establishment of effective, well tolerated and affordable treatment for Burkitt lymphoma in resource-limited settings |
| Yao et al | 2019 | Treatment of Wilms Tumor in Sub-Saharan Africa: Results of the Second French African Pediatric Oncology Group Study | Quantitative | II | B | Overall three year survival rate was 72% for localized disease when high risk patients and patients who abandoned treatment were excluded |
| Hesseling et al. | 2019 | Wilms tumour: Long-term survival of patients treated at Mbingo Baptist Hospital in Cameroon between 2007 and 2012 | Quantitative | II | C | Overall survival of 44% after 84 months follow up was acjhieved with a modified SIOP protocol. Survival was better for stage I and II than for stage III and IV. |
| Chitsike et al | 2020 | Working Together to Build a Better Future for Children With Cancer in Africa | Not research | N/A | N/A | Three centres in Cameroon are part of the Collaborative African network of care and research for childhood cancer (CANCaRe Africa), an initiative which promotes regional collaboration to improve treatment for nephroblastoma, improve supportive care and reduce abandonement for children with cancer in sub-Saharan Africa. |
| Borah and Kouya | 2018 | Epidemiology of pediatric cancer in the Northwest Region of Cameroon | Quantitative | III | C | Incidence rate for all cancers in Northwest Cameroon was 5.9 per 100000 children 0-14 years. The most common diagnoses were Burkitt lymphoma, retinoblastoma and nephroblastoma |

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| Bouda et al | 2019 | Advanced Burkitt Lymphoma in Sub-Saharan Africa Pediatric Units: Results of the Third Prospective Multicenter Study of the Groupe Franco-Africain d'Oncologie Pédiatrique | Quantitative | II | A | one year overall survival was 60% with use of the Groupe Franco Africain Lymphome B 2009 (GFALMB 2009) protocol which includes high dose intravenous methotrexate, doxorubicin, cytarabine and vepesine for patients with poor response . Survival was lower in stages III and IV. Abandomenet was an improtant cause of treatment failure. |
| Trehan and Ladas | 2020 | A multi-platform approach to promote clinical and research activities in nutrition and pediatric oncology | Not research | N/A | N/A | Three POUs in Cameroon are part of the International Initiative for paediatrics and nutrition, with active clinical research on nutrition and capacity building for nutritionists. |
| Hesseling et al. | 2018 | Burkitt lymphoma – Nutritional support during induction treatment: Effect on anthropometric parameters and morbidity of treatment | Quantitative | II | B | Nutritional support to children with Burkitt lymphoma with food gants led to improvement of TSF and MUAC measurements and was associated with less morbidity and fewer deaths during induction phase of treatment. |
| Afungchwi et al. | 2019 | Destitution, treatment adherence and survival of children with Burkitt lymphoma in a twinning programme in Northwest Cameroon | Quantitative | III | B | Family destitution level did not affect adherence to treatment in a twinning program that provided support for transportation. More support is required for single mothers. |
| Wharin et al | 2019 | An Attempt to Deliver Home-Based Palliative Care to Children with Cancer in Sub-Saharan African Villages-Our Cameroon Experience | Not research | N/A | N/A | Home-based palliative care for children with cancer was successfully implemented in rural Cameroon. Good counselling skills are required to meet the challenges of poorly understood prognosis and tendency to attempt traditional medicine. Periodic unavailability of morphine is an important issue. |
| Belika et al. | 2017 | Cameroonian context of pediatric palliative care: Ethnanalysis of child diseases | Literature review | V | B | Patients' and families choices of care and treatment options at end of life is determined by cultural interpretation and implications of disease and symptoms |

# CHAPTER 8

## Conclusions and future directions

As poor childhood cancer survival was documented due to late diagnosis and treatment abandonment in LMICs such as Cameroon, the overall goal of this dissertation was to improve early diagnosis and referral of children with cancer in Cameroon.

In this dissertation, the experience with the twinning paediatric oncology programme of Stellenbosch University and the CBCHS, established in the Northwest region, was used to demonstrate the epidemiology of childhood cancer and to document the success of both the provided support programmes and the implementation of a capacity-building nurse-led training programme. In the Year of the Nurse and Midwife 2020, the dissertation demonstrated the success of nurse-driven programmes for education as well as clinical care and research (1). Empowering nurses with specialist training and mentoring was essential for the development of health care services (2,3).

The first study described in this dissertation documented the significant progress made in Africa between 2014 and 2018 with regard to successful management of childhood cancers (Chapter 2). Overall survival improved especially for common childhood cancers such as Burkitt lymphoma, nephroblastoma and retinoblastoma (4–8). Adapted treatment regimens were implemented appropriate for local contexts, supportive care services improved, better nutritional support was implemented and management of infections improved (9–11). The reports presented in this review provide examples of factors that can assist in successful early diagnosis, referral and management of childhood cancers in low- and middle-income countries (LMICs).

The twinning programme in Northwest Cameroon was proven to be very effective as documented in this dissertation with regard to the establishment of a hospital-based childhood cancer tumour registry (12). Although population-based registries should be used in planning health services, the analysis of a hospital-based registry could assist with local childhood cancer treatment programme development. The research therefore investigated the incidence of childhood cancer in Northwest Cameroon (Chapter 3), which assisted with planning health care services and resource allocation and provided a first step in the potential development of a national population-based tumour registry. This report also provided information which will

inform prioritization of education needs and resources for improving early diagnosis, referral and management.

An interventional health care worker capacity-building training project was thereafter successfully conducted to improve childhood cancer diagnosis in Northwest Cameroon. The focus was the improvement of health care workers' knowledge regarding the warning signs of childhood cancer to ensure early referral to an appropriate treatment facility (Chapter 4). This was the first report of a nurse-led capacity-building programme for childhood cancer regarding early diagnosis in Africa, a model that could be replicated easily in other LMICs (13).

The socioeconomic circumstances of families with a child with cancer were also investigated through determination of destitution level and association with treatment adherence as well as survival of a child with cancer in Cameroon as poor socioeconomic circumstances might impact negatively on survival (Chapter 5). Fortunately, there was no negative correlation with treatment adherence or survival, but it should be noted that through the existing twinning programme, there was adequate support regarding treatment costs, transport funding and nutritional support. One aspect highlighted in the study was that single-mother households were significantly associated with poorer survival (14). This study further proved the need for support strategies in twinning programmes in LMICs to ensure improved treatment adherence and survival, especially additional support for single-parent households. Improved treatment adherence can reduce the health problems caused by cancer and its treatment, and improve survival for children with cancer.

As the use of T&CM might impact negatively on the management of childhood cancers in Cameroon, the use was studied first in families with children with Burkitt lymphoma (Chapter 6a) and thereafter with parents of children newly diagnosed with cancer (Chapter 6b). As documented elsewhere in the world, there was significant use of T&CM and a reluctance to share the use thereof with the health care team managing the child's cancer (15–19). These studies provided an insight into the beliefs and practices of families of children with cancer and their families regarding the use of T&CM and how that affects early diagnosis and referrals to conventional treatment. The reports documented the need for open conversations regarding the use of T&CM in the therapeutic relationship between paediatric oncology professionals and families in a nonjudgmental manner with the goal of ensuring the patient's safety. A need also exists for collaboration between health care professionals and

traditional healers with two-way learning for early diagnosis and appropriate, evidence-based management of patients.

The progress of cancer treatment achieved in Cameroon between 2000 and 2020 was summarised in Chapter 7 after review of available publications. Significant progress was documented with capacity building and collaboration among paediatric oncology professionals in the country as well as with international paediatric oncology institutions and research groups. These efforts contributed to progressive diagnosis, referral and management of children with cancer in the country. Strong advocacy should lead to inclusion of paediatric oncology-specific priority actions in the national strategic plan for the fight against cancer (20).

Despite the aforementioned progress, paediatric oncology in Africa remains fraught with issues of low community awareness, suboptimal access to essential medicines, poverty with the absence of universal health coverage and popularity of T&CM. Enhanced and sustained commitment of governments, NGOs, charities, childhood cancer specialists, and patient and parent groups should exist to meet the objective of the WHO-SIOP global initiative for childhood cancer with a target survival of 60% for common and curable childhood cancers by 2030 (21,22).

**FUTURE DIRECTIONS**

As a future direction for paediatric cancer registration in Cameroon, hospital-based registries should be created in all paediatric oncology centres with the support from the National Committee for the Fight against Cancer in Cameroon (20). This will generate national-level statistics on all children diagnosed with cancer in the country, which is essential for health sector planning in noncommunicable disease control.

As a means to improve early diagnosis of childhood cancer across the country, our recommendation is for complete integration of training programmes into the public health system, with incorporation into the district health service activities involving the dialogue structures in this system. To do this effectively, it will be necessary to educate trainers at the district level to serve as focal persons for childhood cancer. These trainers may then be empowered to conduct routine refresher training with health care providers in their various districts. A clear monitoring and evaluation framework for childhood cancer suspicion and referral that will fit well into the current monitoring and evaluation procedures in the region

should be developed together with the district medical officers.

For the best results to be obtained with psychosocial support, there is a need for individual family assessment of socioeconomic status and development of evidence-based models for patient support that are customised according to individual needs. The vulnerability of children of single mothers is an area that requires careful inquiry.

With the popularity of T&CM, health care providers need knowledge of the cultural perceptions of disease and behaviours towards T&CM therapies in order to establish a relationship of full disclosure that ensures safe and culturally sensitive care to patients. Such knowledge can be provided through workshops on effective communication with input from clinical psychologists and anthropologists.

The continued contributions by NGOs and international academic institutions are essential to enable children with cancer in Cameroon to obtain an accurate diagnosis and to receive adequate and complete treatment. There is a need for advocacy with government to provide essential cancer drugs, treatment facilities and training opportunities, especially as it is a child's right to be cured of any potentially life-threatening but curable condition.

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# THE NATURE AND SCOPE OF CONTRIBUTIONS

Glenn Mbah Afungchwi conceptualised chapters 1, 2, 4, 6, 7 and 8 and assisted with conceptualisation of chapters 3 and 5. He developed the study protocols and obtained ethics approval for all the studies. He recruited most of the patients for the prospective and retrospective studies and performed all data analyses. He wrote all the published and unpublished chapters.

Mariana Kruger conceptualised chapters 2, 4 and 5 while she assisted with conceptualisation of the other chapters. She critically reviewed the study protocol, reviewed all manuscripts for publication and supervised the dissertation. She critically reviewed and revised all chapters for intellectual content.

Peter Hesseling conceptualised chapters 2, 5 and 7 while he assisted with conceptualisation of the other chapters. He critically reviewed the study protocol, reviewed all manuscripts for publication and co-supervised the dissertation. He critically reviewed and revised all chapters for intellectual content.

Kouya Francine contributed to data collection for chapters 3 and 5 and review of the manuscripts for chapters 3, 4, 5 and 7.

Stacey Marjerrisson assisted with conceptualising Chapter 6b and adapting the data collection form and critically reviewed and revised the chapter for intellectual content.

Elena Ladas assisted with adapting the data collection form for Chapter 6b and contributed to reviewing chapters 6a and 6b.

Paul Wharin and Richard Bardin contributed to data collection and reviewing the manuscript for Chapter 3.

Enow Sam Agbor contributed to data collection and reviewing the manuscript for Chapter 5.

Pius Tih, Peter McCormick and Angele Pondy-Ongotsoyi contributed to searching literature and documents and reviewing the manuscript for Chapter 7.

Sabine van Elsland assisted with data analysis and reviewed the manuscripts for chapters 5 and 6b.

All co-authors agreed that the papers would form part of Glenn Mbah Afungchwi's PhD dissertation.

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- The Sanofi Espoir Foundation's My Child Matters award for nurses

# LIST OF ABBREVIATIONS

| | |
|---|---|
| 6-MP | 6-Mercaptopurine |
| ABV | adriamycin (doxorubicin), bleomycin, vincristine |
| AIDS | acquired immunodeficiency syndrome |
| ALL | acute lymphoblastic leukaemia |
| ASIR | age-specific incidence rate |
| BBH | Banso Baptist Hospital |
| BHM | Baptist Hospital Mutengene |
| Bl | Burkitt lymphoma |
| CANCaRe | Collaborative African Network of Clinical Care and Research for Childhood Cancer |
| CBC | Cameroon Baptist Convention |
| CBCHS | Cameroon Baptist Convention Health Services |
| CHL | classic Hodgkin lymphoma |
| CHOICE | Choosing Interventions that are Cost-Effective |
| CNS | central nervous system |
| CPM | cyclophosphamide |
| CPOG | Cameroon Paediatric Oncology Group |
| CT | computerised tomography |
| DALY | disability-adjusted life years |
| EPI | Expanded Programme on Immunization |
| FAPOG | Francophone Africa Pediatric Oncology Group |
| FNA | fine-needle aspiration |
| GDP | gross domestic product |
| GICC | Global Initiative for Childhood Cancer |
| GLOBOCAN | Global Cancer Incidence, Mortality and Prevalence |
| HAART | highly active antiretroviral therapy |
| HICs | high-income countries |
| HIV | human immunodeficiency virus |
| IQR | interquartile range |
| IRB | Institutional Review Board |
| KS | Kaposi sarcoma |

| | |
|---|---|
| LMICs | low- and middle-income countries |
| MBH | Mbingo Baptist Hospital |
| MDT | multidisciplinary team |
| MIBG | meta-iodobenzylguanide |
| MRI | magnetic resonance imaging |
| MUAC | mid-upper-arm circumference |
| NGOs | nongovernmental organisations |
| NHIF | National Health Insurance Fund |
| NHL | non-Hodgkin lymphoma |
| PICU | Paediatric Intensive Care Unit |
| POND | Paediatric Oncology Networked Database |
| POU | paediatric oncology unit |
| RSA | Republic of South Africa |
| SD | standard deviation |
| SIOP | International Society of Paediatric Oncology |
| SSA | sub-Saharan Africa |
| T&CM | traditional and complementary medicine |
| TM | traditional medicine |
| TSF | triceps skinfold |
| UK | United Kingdom |
| US$ | United States dollar |
| WHO | World Health Organization |
| WT | Wilms tumour |

# APPENDIX

## BOOK CHAPTER

Challinor JM, Day SW, **Afungchwi GM**, Alqudimat MR. Pediatric Oncology Nursing Research in Low-and Middle-Income Countries. In Pediatric Oncology Nursing 2020 (pp. 275-342). Springer, Cham.

Abstract:

Cancer and other non-communicable diseases are a growing public health issue now that infectious disease control (e.g., HIV/AIDS, malaria, and tuberculosis) has made great strides across low- and middle-income countries (L&MIC). The large majority (85%) of children and adolescents with cancer reside in L&MIC where children represent up to 50% of a country's population, and resources are severely limited for the comprehensive cancer care these patients require. Nursing care of these patients and families must be based on research performed in country to account for challenges in access to care and limited resources and opportunities for nursing specialization. Examples of these challenges include cancer stigma, poverty, traditional medicine practices, cultural norms and decision-making hierarchies, limited education opportunities, lack of universal healthcare, and poor transportation infrastructure to access tertiary care. This chapter summarizes the 137 articles in five languages from 2008 to 2018 that communicate nursing research findings pertaining to pediatric oncology issues from L&MIC across all six World Health Organization (WHO) regions. Despite little or no funding, nurses in academic and clinical settings are actively exploring care priorities in their settings, most often (but not limited to) addressing parent coping, nurse and nursing care issues including symptom management (pain and fatigue, especially), and children's quality of life. The nursing research evidence presented here will begin to inform personalized and precision health in L&MIC to ensure that care is culturally acceptable and considers the environment, nursing practice, nursing science, family, lifestyle behaviors, and response to disease and treatment of this large patient population.

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REVIEW

# Interventions to improve early detection of childhood cancer in low- and middle-income countries: A systematic review

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Weeda Zabih and Anilkrishna B. Thota are co-first authors; Sumit Gupta, and Avram E. Denburg are co-senior authors.

## Abstract

**Background:** Childhood cancer outcomes in low- and middle-income countries (LMICs) lag behind those in high-income countries (HICs), in part due to late presentation and diagnosis. Though several interventions targeting early detection of childhood cancer have been implemented in LMICs, little is known about their efficacy.

**Methods:** We conducted a systematic review to identify studies describing such interventions. We searched multiple databases from inception to December 4, 2019. Studies were included if they reported on LMIC interventions focused on: (a) training of health care providers on early recognition of childhood cancer, or (ii) public awareness campaigns. We used preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines to conduct our review. The risk of bias in nonrandomized studies of interventions (ROBINS-I) checklist was used to assess quality of studies.

**Results:** Twelve studies met inclusion criteria (n = 5 full text, n = 7 abstract only). Five studies focused on retinoblastoma only, while the others focused on all types of childhood cancer. The majority studied multiple interventions of which early detection was one component, but reported overall outcomes. All identified studies used pre-post evaluative designs to measure efficacy. Five studies reported statistically significant results postintervention: decrease in extraocular spread of retinoblastoma, decrease in rates of refusal/abandonment of treatment, increase in number of new referrals, increase in knowledge, and an absolute increase in median 5-year survival. Other studies reported improvements without tests of statistical significance. Two studies reported no difference in survival postintervention. The ROBINS-I checklist indicated that all studies were at serious risk of bias.

**Conclusion:** Though current evidence suggests that LMIC interventions targeting early detection of childhood cancer through health professional training and/or public awareness campaigns may be effective, this evidence is limited and of poor quality. Robust trials or quasi-experimental designs with long-term follow up are needed to identify the most effective interventions. Such studies will facilitate and inform the widespread uptake of early detection interventions across LMIC settings.

KEYWORDS
cancer, childhood, early detection, LMIC

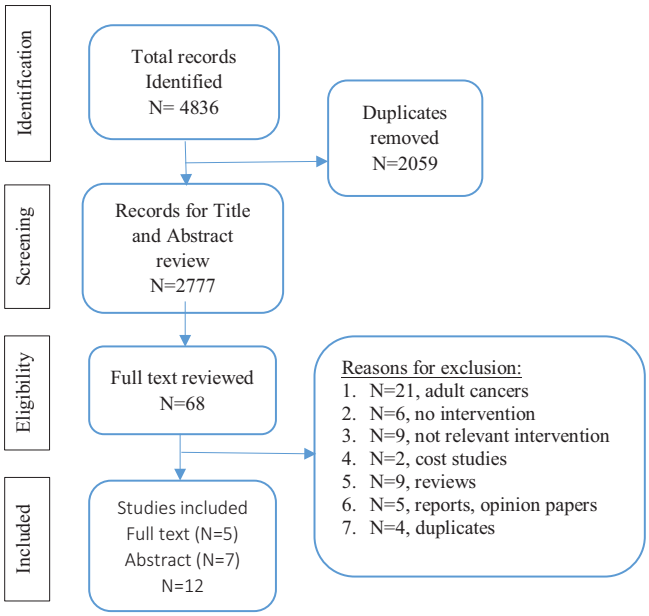


**FIGURE 1** Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram illustrating study selection process

## 1 | BACKGROUND

Childhood cancer is largely curable, with a survival rate of over 80% in high-income countries (HICs).[1–4] However, survival in low- and middle-income countries (LMICs) lags behind, with survival rates in some settings as low as under 10%.[5,6] More than 80% of children who die from cancer worldwide do so in LMICs.[6] Emerging evidence suggests that this survival gap can be diminished through both targeted childhood cancer program development and broader health system strengthening.[7–9] Moreover, current evidence indicates that childhood cancer treatment in LMIC settings is cost-effective.[10–12]

Improved childhood cancer outcomes in LMICs will require overcoming multiple barriers that presently compromise care delivery and impact survival.[7–9,13] As modifiable risk factors for childhood cancer are unknown, efforts to increase timely diagnosis and access to effective treatment are crucial. A lack of both professional and public awareness of the early warning signs and symptoms (EWSS) of childhood cancer is a fundamental barrier in many LMICs.[5,14–18] An increased awareness of EWSS would contribute to more timely recognition of childhood cancers, referral for specialized care, diagnosis, and treatment initiation. This in turn holds the possibility of less advanced stage disease and lower disease- and treatment-related mortality.[5,6,14–18]

Though several interventions targeting early detection have been implemented in LMICs, little is known about their efficacy. We therefore conducted a systematic review of the literature to identify interventions implemented in LMIC to improve early detection of childhood cancer. We specifically aimed to map the scope, quality, and efficacy of interventions focusing on the training of health care providers and public awareness campaigns.

**Abbreviations:** EWSS, early warning signs and symptoms; HIC, high-income country; LMIC, low- and middle-income country; ROBINS-I, risk of bias in nonrandomized studies of interventions

## 2 | METHODS

### 2.1 | Data sources and search strategy

This review followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[19] We searched Ovid MEDLINE, Embase, EBM Reviews, Cochrane Central Register of Controlled Trials, Web of Science, Applied Social Science Index and Abstract (ASSIA), Sociological Abstracts, ABI Inform, and Scopus from database inception to December 4, 2019. Search terms were developed in consultation with a literature search expert at the Sickkids Hospital; keywords included "cancer," "early detection of cancer," "education," "health providers," "awareness," "campaign," and "intervention." To maximize capture, lists of specific childhood cancers and LMICs were also included. A sample search strategy can be found in Appendix 1.

### 2.2 | Screening and study selection

Studies were included if they met the following inclusion criteria: (a) described an intervention aiming to improve early detection of childhood cancer (defined as cancer diagnosed between 0 and 18 years of age); (b) conducted in LMIC setting; (c) intervention targeted either health care professionals (eg, training) or general public (eg, awareness campaigns); and (d) eligible study design, including randomized control trials, cohort studies, case-control studies, pre-post comparisons, or other observational study designs. Conference abstracts were also included. We excluded case series, review articles, book excerpts, commentaries, editorials, opinion papers, as well as studies written in languages other than English.

Two authors (Anilkrishna B. Thota, Weeda Zabih) independently examined titles and abstracts to identify all possibly eligible studies. Discrepancies were discussed and a third author (Sumit Gupta or Avram E. Denburg) was involved in cases where consensus could not be reached. Possibly eligible studies were obtained for full-text review and again screened independently by two reviewers (Anilkrishna B. Thota, Weeda Zabih) to determine final eligibility.

### 2.3 | Data abstraction and quality assessment

A data extraction form was developed and piloted. Using this tool, two authors (Anilkrishna B. Thota, Weeda Zabih) independently extracted relevant data from each study, including year of publication, sample size, design, characteristics of the interventions, target population, duration of intervention, and key reported outcomes.

We used the risk of bias in nonrandomized studies of interventions (ROBINS-I) checklist to assess the methodological quality of the

included studies.[20] Similarly, two authors (Weeda Zabih, Avram E. Denburg/Sumit Gupta) independently assessed each article and discussed final results. The ROBINS-I tool is structured into seven mandatory preintervention, intervention, and postintervention domains through which bias may be introduced into a study. Options for each domain-level judgment are: (a) low risk of bias; (b) moderate risk of bias/some concerns; (c) serious risk of bias; (d) critical risk of bias; and (e) no information. Domain-level judgments provide the basis for an overall risk-of-bias judgment.

### 2.4 | Synthesis

We generated summary tables to describe study characteristics, interventions, and reported outcomes. Given the heterogeneity of study populations, interventions, and evaluation outcomes, quantitative synthesis or meta-analyses were not possible. We instead used a narrative synthesis approach to summarize our findings.[21]

## 3 | RESULTS

### 3.1 | Search results

Our search yielded a total of 4836 articles from all databases. After removing duplicates, the remaining 2777 titles and abstracts were screened (Figure 1). Sixty-eight studies were identified for full-text review. Ultimately, 12 studies met our inclusion criteria, including five full articles and seven abstracts. We attempted to contact abstract authors to enquire whether their results had been subsequently published in full-text format, but in doing so did not identify additional studies that met inclusion criteria.

### 3.2 | Study characteristics

All 12 studies were published between 2004 and 2018. Ten studies (83%) were conducted in a single LMIC,[14,16,17,22–28] while two (17%) were conducted across multiple LMICs.[15,18] All 12 studies used a pre-post design to evaluate the effectiveness of their interventions, comparing postintervention data to baseline data collected retrospectively. No study included a control group. Five studies (42%)[14,16,18,22,23] focused on retinoblastoma only, while the remaining seven (58%)[15,17,24–28] focused on all childhood cancer types. Six studies (50%)[14,22,24–26,28] evaluated interventions that targeted health care professionals, while four studies(33%)[15,17,18,23] reported on training of health care professionals and public awareness campaigns. Two studies (17%)[16,27] focused on public awareness campaigns only. Sample size was not consistently reported across all included studies. Only seven studies (58%)[14,15,17,24–26,28] provided the number of health care professionals trained, ranging from 55 to 14 553. Table 1 shows additional study characteristics.

### 3.3 | Interventions focusing on training of health care professionals

Table 2 provides details of the EWSS interventions studied. Ten studies (83%)[14,15,17,18,22–26,28] reported on the training of health care professionals on recognizing the EWSS of childhood cancer. Studies were extremely heterogeneous in terms of intervention scope and duration, and reported outcomes. Interventions ranged from a 1-day workshop on a single topic in one LMIC to multiple large-scale interventions (including training of health care professionals) implemented in multiple LMICs over several years. The latter included public-private partnerships,[15,25] twinning programs,[18] and the establishment of center of excellence through local and international collaborations.[22]

Several studies described EWSS interventions in conjunction with other initiatives, including the establishment of satellite clinics and referral centers/systems, developing treatment protocols, building local professional networks, online conferences, e-consultations, continuing education, and clinical research infrastructure support. Of 10 studies (83%)[14,15,17,18,22–26,28] targeting health care professionals, four studies (40%)[15,17,18,23] had a public awareness campaign component. In all studies that implemented multiple interventions, outcomes were reported collectively without attribution to a specific intervention component.

Studies varied extensively in terms of training material, target population, and mode of delivery. Four studies (40%)[14,18,22,23] focused on early detection of retinoblastoma. These studies targeted ophthalmologists, pathologists, oncologists, nurses, and primary providers. The content of training material for studies that focused on all childhood cancer types[15,17,24–26,28] also varied and included broader subject areas (eg, fundamentals of oncology care that included material on EWSS),[15] and more specific topics solely related to EWSS (eg, Saint Siluan warning signs of cancer in children,[17] early identification/sign and symptoms of cancer in children[24–26,28]). These studies[15,17,24–26,28] targeted mainly pediatricians, primary health care providers, nurses, and community health care workers. Modes of delivery included in-person training, distribution of printed material, and e-learning/online training.

For all 10 studies (83%) that reported on training of health care providers, reported outcomes were also heterogeneous. Sources of data used to measure outcomes included: standardized questionnaires pre-post workshop,[14] hospital-based clinical registries and NGO databases,[15] patient charts,[17,18,22,23,28] and interviews with nurses and patients' families.[28] Several studies (30%)[24–26] did not provide information on data sources. Statistically significantly improved outcomes reported were as follows: increase in knowledge,[14] increase in number of new cases referred,[17] decrease in occurrence of extraocular disease in retinoblastoma,[18] decrease in rates of refusal/abandonment of treatment,[18] and 5-year median (5.1%) increase in survival.[15] The latter was associated with a broad range of interventions of which EWSS training constituted only a small part. Other outcomes that were reported as proportions without performing tests of statistical significance included: earlier referral,[15,24] fewer extraocular

**TABLE 1** Characteristics of included studies

| | Author (year) | Study title | Region/country | Study design | Target population (sample if applicable) | | Cancer Type |
|---|---|---|---|---|---|---|---|
| 1 | Hill et al (2015)[14] | Cancer genetics education in a low- to middle-income country: evaluation of an interactive workshop for clinicians in Kenya | Kenya | Pre-post | Health professionals (n = 55) | - | Retinoblastoma |
| 2 | Howard et al (2018)[15] | The My Child Matters programme: effect of public-private partnerships on paediatric cancer care in low-income and middle-income countries | Multiple LMIC | Pre-post | Health professionals (n = 1298) | Public | All childhood cancer types |
| 3 | Leander et al (2007)[16] | Impact of an education program on late diagnosis of retinoblastoma in Honduras | Honduras | Pre-post | - | Public | Retinoblastoma |
| 4 | Poyiadjis et al (2011)[17] | The Saint Siluan warning signs of cancer in children: impact of education in rural South Africa | South Africa | Pre-post | Health professionals (n = 610) | Public | All childhood cancer types |
| 5 | Wilimas et al (2009)[18] | Development of retinoblastoma programs in Central America | Central America (El Salvador, Guatemala, and Honduras) | Pre-post | Health professionals | Public | Retinoblastoma |
| 6 | Alcasabas et al (2014)[22] *Abstract only* | Impact of implementing a retinoblastoma program in a public tertiary hospital in a resource limited setting | Philippines | Pre-post | Health professionals | . | Retinoblastoma |
| 7 | Epelman et al (2004)[23] *Abstract only* | National campaign for early diagnosis of retinoblastoma in Brazil | Brazil | Pre-post | Health professionals | Public | Retinoblastoma |
| 8 | Fiori et al (2018)[24] *Abstract only* | Public health actions on the improvement of the early diagnosis of the young childhood cancer in the west of Parana-Brazil | Brazil | Pre-post | Health professionals (n = 2203) | – | All childhood cancer types |
| 9 | Gomes et al (2009)[25] *Abstract only* | United through the cure: a public policy encouraging early diagnoses of childhood cancers in Rio de Janeiro | Brazil | Pre-post | Health professionals (n = 124) | – | All childhood cancer types |
| 10 | Ntacyabukura et al (2018)[26] *Abstract only* | Childhood cancer early detection training program for primary healthcare providers | Rwanda | Pre-post | Health professionals (n = 90) | . | All childhood cancer types |
| 11 | Purwanto (2018)[27] *Abstract only* | The role of Teman Kanker application in supporting childhood cancer control in Indonesia | Indonesia | Pre-post | – | Public | All childhood cancer types |
| 12 | Souza et al (2013)[28] *Abstract only* | Impact assessment of the early diagnosis program: does building capacity of primary health care workers have an impact on referrals for suspected pediatric cancer? | Brazil | Pre-post | Health professionals (n = 14 553) | – | All childhood cancer types |

retinoblastomas,[15] decrease in lost to follow up (13% vs 2%),[18] increase in referral rate,[22,25,26,28] drop in extraocular presentation by 19%,[22] >30% increase in number of patients seen per year,[22] increased early stage disease,[24] shorter lag time (duration between suspected disease and diagnosis),[25,28] and increased accuracy of diagnosis.[26] A small number of studies reported no difference postintervention outcomes: Wilimas et al reported no difference in survival among patients with retinoblastoma in Guatemala, Honduras, and El Salvador,[18] while Poyiadjis et al reported no difference in detection of early stage disease among children diagnosed with cancer in South Africa after an awareness campaign.[17]

### 3.4 | Public awareness campaigns on childhood cancer

Six studies (50%)[15–18,23,27] reported on public awareness campaigns on childhood cancer. Of these, three (50%)[16,18,23] focused on early detection of retinoblastoma, while the remaining three (50%)[15,17,27] focused on all childhood cancer types. No data were provided on the demographics or number of target individuals reached. Studies aimed to reach individuals within the catchment area of one or more health care facilities. Brochures, flyers, social media, television, radio, newspapers, and mobile apps were used to deliver the main messages. Four studies

**TABLE 2** Characteristics of interventions and measures of efficacy

| | Author (year) | Description of interventions | Target population | Duration | Key outcomes reported |
|---|---|---|---|---|---|
| 1 | Hill et al (2015)[14] | Workshop/training genetic testing and counseling on retinoblastoma (project attached to a conference) | Ophthalmologists, pathologists, oncologists, ophthalmic clinical officers, nurses | 1 day | • Significant increase in knowledge post intervention ($P < .01$) |
| 2 | Howard et al (2018)[15] | 1-Year training program for health care professionals (large-scale public private partnership program focused on diagnosis and treatment of childhood cancer) | Nurses, physicians, primary health care providers | 10 years | • Improved survival rate from 2006 baseline to 2016-2017 in 10 index countries.<br>• Median 5-year survival increase of 5·1% (1.5-17.5%).<br>• Improved knowledge<br>• Earlier referral<br>• Fewer extraocular retinoblastomas |
| | | Awareness on childhood cancer | Public | | |
| 3 | Leander et al (2007)[16] | Public awareness campaign (linked to a national vaccination campaign) on retinoblastoma | Less literate population (public) | 3 years | • Significant decrease in extraocular spread ($P = .002$) from baseline (July 1995-June 2003) to postintervention (June 2003-Jan 2005) - 73% vs 35%. |
| 4 | Poyiadjis et al (2011)[17] | Education on Saint Siluan early warning signs (awareness campaign) | Primary health care providers | 6 months | • Statistically significant increase in the # of new patients referred in the 6 years following the campaign ($P = .001$),<br>• No difference in detection of early stage disease.<br>• *(1990-2001 = baseline 12 yrs, six years later post intervention 2001-2007)* |
| | | Awareness on Saint Siluan early warning signs (awareness campaign) | Public | | |
| 5 | Wilimas et al (2009)[18] | Education on early diagnosis and treatment of retinoblastoma (twinning program) | Pediatric oncologists, ophthalmologists, primary providers | Several years | • Significant decrease (from 73% to 35%) in the occurrence of extraocular disease in Honduras.<br>• Increased referrals.<br>• No change in survival<br>• Significant decrease in rates of refusal/abandonment of treatment from 2004-2008 compared to baseline (2000-2003) (21% vs. 11%, P = 0.014)<br>• Decrease in lost to follow up 22(13%) vs 3(2%). |
| | | Awareness on early warning signs of retinoblastoma | Public | | |
| 6 | Alcasabas et al (2014)[22] *Abstract only* | Education on early warning signs (center of excellence through local and international collaborations) of retinoblastoma | Health care providers from health centers and hospitals | Several years | • Compared to baseline estimates (2005-2010), the mean annual referrals increased from 7 to 14, and extra-ocular presentation dropped by 19% in 2011-2014.<br>• >30% Increase in number of patients seen/yr compared to baseline<br>• Increase in stage 1 patients in last 2 yrs postintervention. |

(Continues)

**TABLE 2** (Continued)

| | Author (year) | Description of interventions | Target population | Duration | Key outcomes reported |
|---|---|---|---|---|---|
| 7 | Epelman et al (2004)[23] *Abstract only* | National awareness campaign/education on early detection of retinoblastoma | Primary care providers, ophthalmologists, pediatricians | Several months | • Increased # of new cases (> 100) diagnosed during the campaign |
| | | National awareness campaign on early detection of retinoblastoma | Public | | |
| 8 | Fiori et al (2018)[24] *Abstract only* | Training program on early identification of childhood cancer | Doctors, nurses, technician/nursing assistants, community health agents, upper, medium level professionals | 10 years | • Increased early stage disease.<br>• Increased referrals<br>• *Intervention 2008-2017* |
| 9 | Gomes et al (2009)[25] *Abstract only* | Training on early detection/diagnosis (large scale public private partnership) of childhood cancer | Pediatricians | 1 year | • Shorter time between suspected disease and diagnosis.<br>• *Intervention 2007-2008* |
| 10 | Ntacyabukura et al (2018)[26] *Abstract only* | Education/training program on early warning signs and symptoms of childhood cancer | Primary health care providers, nurses, community health workers | 3 months | • Increased knowledge (accuracy of diagnosis)<br>• Increased # of referrals |
| 11 | Purwanto (2018)[27] *Abstract only* | Education/awareness on early detection of childhood cancer using a mobile application (Teman Kanker) (Friend of Cancer) | Patients, survivors, parents, medical practitioners, volunteers, citizens, and other social communities | 6 months | • 1300 Users 6 months postlaunch (increased awareness) |
| 12 | Souza et al (2013)[28] *Abstract only* | Education program on early warning and diagnosis of childhood cancer | Primary health care providers | Several months | • 23% Rise in the number of children referred<br>• The median lag time fell after the program by 61% in the regions which received the intervention (from 13 to 5 weeks) (lag time: time between symptoms and diagnosis) |

**TABLE 3** Risk of bias in nonrandomized studies of interventions (ROBINS-I)

| | Preintervention | | At intervention | Postintervention | | | | |
|---|---|---|---|---|---|---|---|---|
| Study | Bias due to confounding | Bias in selection of participants into the study | Bias in classification of interventions | Bias due to deviation from intended intervention | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result | Overall risk of bias |
| Hill et al (2015)[14] | S | M | M | M | S | M | M | S |
| Howard et al (2018)[15] | S | M | M | S | M | M | S | S |
| Leander et al (2007)[16] | S | M | S | M | S | M | S | S |
| Wilimas et al (2009)[18] | S | M | S | M | M | S | S | S |
| Poyiadjis et al (2011)[17] | S | M | M | M | M | S | M | S |

Abbreviations: L, low risk of bias; M, moderate risk of bias; N, no information; S, serious risk of bias.

(67%)[15,17,18,23] also reported on training of health care providers. Outcomes for studies that involved multiple interventions[15,17,18,23] in addition to public awareness have been described above. Only two studies (33%)[16,27] focused solely on awareness campaigns. Of these Leander et al[16] focused on early detection of retinoblastoma in Honduras, linking their intervention to a vaccination campaign and thus reaching the general population through 1334 government health clinics. They reported a significant decrease in extraocular spread

of retinoblastoma postintervention (43/59 [73%] vs 8/23 [35%]; $P = .002$). Purwanto[27] described their use of a mobile app (Teman Kanker or Friend of Cancer) to increase the awareness of EWSS in Indonesia. They reported 1300 users 6 months postlaunch. Although the study only reported uptake of the intervention, use of the mobile app was presumed to have increased public, patient, and parent awareness of EWSS and to have connected them to health care providers.

### 3.5 | Critical appraisal of included studies

In order to assess the quality of evidence incorporated in this review, we used the ROBINS-I checklist. Preintervention, intervention, and postintervention domains were assessed in each study based on signal questions and detailed instructions in ROBINS-I guidance manual (Table 3). Only five studies with full text availability were assessed; studies available in abstract form only were not. All studies assessed had at least one domain identified to be at serious risk of bias, which translated into an overall serious risk of bias for that particular study. Some examples of bias in selected studies included lack of data on baseline characteristics of participants, nonrandom sampling methods (convenience samples), missing data, lack of a reliable tool to measure outcomes, and selective reporting of outcomes.

## 4 | DISCUSSION

This review is the first to report on interventions to improve early detection of childhood cancer in LMIC settings, with a focus on training health care providers and increasing public awareness. The identified interventions showed some evidence of efficacy, though this evidence was limited in scope and quality. All studies assessable for quality were deemed at serious risk of bias. Despite interventions reporting effectiveness in key clinical outcomes and an increase in knowledge/awareness,[14–18] the quality of the current evidence is low.

Some interventions have been successfully implemented in LMIC settings to improve the early detection of adult cancers, including those of the breast, prostate, cervical, or colon. Though the relevant signs and symptoms differ, successful interventions targeting adults with cancer in LMICs can potentially be tailored to LMIC pediatric populations. Use of social media (Facebook, Twitter),[29,30] awareness through social events,[31] policy advocacy campaigns reaching out to organized groups within the community,[32] national social marketing compaigns,[33] and the use of technology such as tablet-based interactive education[34] have all been shown to be both feasible and effective in LMIC settings in increasing uptake of breast, colon, and prostate cancer screening. Using a cluster randomized controlled trial design, Pace et al reported on the efficacy of a training program for health workers in Rwanda targeting the early diagnosis of breast cancer. Compared to the control group, health centers receiving the intervention experienced a statistically significant increase in breast cancer referrals (1484 visits [increase of 7.9 visits/month] vs 308 visits; $P = .007$) and an increase in incidence of early stage disease (3.3/100 000 vs 0.7/100 000 person-years; $P = .048$) in intervention areas.[35] Other studies have also demonstrated the efficacy of training community health workers in the early detection and referral of breast and cervical cancer.[35–41] Whether such interventions in the adult cancer space can translate effectively to improvments in the early detection of childhood cancers in LMICs is a subject for future research.

Several of the above examples from the adult cancer literature represent methodologically rigorous studies yielding high-quality evidence. In contrast, among the pediatric studies, we identified multiple methodological limitations, including small samples, convenience sampling, lack of randomization, absence of a comparison group, no data on baseline characteristics, and lack of valid tools to measure outcomes consistently. In addition, the long-term impact of the interventions could not be determined by any of the included studies, which most often used only two data points in a pre-post design. Given these limitations, the reported impact of interventions, while encouraging, is likely of insufficient validity to convince most policymakers to prioritize scale-up. The current evidence also does not enable determination of which interventions are the most effective and whether these interventions can be replicated in other LMIC settings.

The main objective of EWSS interventions in childhood cancer is to improve survival and reduce morbidity through shortened diagnostic intervals and consequent changes in stage distribution. However, pediatric cancers vary extensively in terms of disease biology and clinical behavior, both of which impact symptom onset and progression, diagnostic intervals, and cancer outcomes. The assumption that shortening diagnostic intervals will result in improved survival is thus dependent on cancer type and jurisdiction.[42,43] Furthermore, training of health care providers and awareness of the public are only bounded aspects of efforts to improve early diagnosis, and may not provide the desired results if not coupled with other interventions aimed at broader health system strengthening. To address these uncertainties, there is a critical need for robust multipronged trials using experimental or quasi-experimental study designs. The high-quality evidence generated by such studies will enable experts to direct efforts and resources toward initiatives that can provide effective and efficient results. Robust evaluations of efficacy in specific health system contexts will provide a strong rationale for policymakers to support the incorporation of such interventions into national health policy frameworks and regional health program priorities.

Our findings should be interpreted within the context of the study's limitations. First, only studies published in English were included. Second, seven of the included studies were only available in abstract form. Even after efforts were made to contact authors of these abstracts, only limited data were available. Quality and bias assessments were thus not possible for these studies. Third, due to the heterogeneity of outcomes reported, quantitative analysis in the form of a meta-analysis was not possible. Finally, and more broadly, recent modeling has suggested that interventions targeting only one cause of inferior LMIC childhood cancer outcomes will have limited impact on improving such outcomes.[7] Interventions to improve early detection,

while critical, should therefore be considered in the context of other efforts targeting access to and the quality of care.

## 5 | CONCLUSION

The current evidence on the impact of interventions targeting the recognition of EWSS of childhood cancer in LMIC settings suggests promising results but is substantially limited in scope and quality. There is a need for robust trials to guide advocates and policymakers in determining which interventions are most effective in specific LMIC contexts.

### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPLEMENT ARTICLE

# Nutritional traditional and complementary medicine strategies in pediatric cancer: A narrative review

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## Abstract

Traditional and complementary medicine (T&CM) strategies are commonly used by pediatric cancer patients. Nutritional approaches to T&CM include bioactive compounds, supplements, and herbs as well as dietary approaches. Pediatric cancer patients and their families commonly request and use nutritional T&CM strategies. We review the potential risks and benefits of nutritional T&CM use in pediatric cancer care and provide an overview of some commonly used and requested supplements, including probiotics, antioxidants, cannabinoids, vitamins, turmeric, mistletoe, *Carica papaya*, and others. We also discuss the role of specific diets such as the ketogenic diet, caloric restriction diets, whole-food diets, and immune modulating diets. There is a growing body of evidence to support the use of some T&CM agents for the supportive care of children with cancer. However, further study is needed into these agents and approaches. Open communication with families about T&CM use is critical.

**KEYWORDS**
nutrition, pediatric oncology, supportive care, traditional and complementary medicine

## 1 | INTRODUCTION

Traditional and complementary medicine (T&CM) strategies include medicines and practices to support health that are outside of the conventional medicine paradigm. As defined by the National Center for Complementary and Integrative Health (NCCIH), T&CM practices can include biologically based therapies such as herbs and supplements, mind-body interventions, such as yoga or tai chi, and alternative medical systems such as Traditional Chinese Medicine.[1] Both self-directed and practitioner-led T&CM are commonly used by children with cancer and their families worldwide.[2] Despite a lack of empiric evidence for their effectiveness in curing malignancy, many families are utilizing T&CM strategies with curative intent.[3] Many families and patients also use T&CM strategies to address supportive care-related issues including chemotherapy-induced nausea and vomiting, anxiety, and risk of infection.[4] Yet, < 50% of families disclose using T&CM agents to their child's oncology team, and some families even abandon conventional cancer care to pursue T&CM therapies in isolation.[2,5-7] As such, it is imperative that pediatric oncology health providers have open discussions with their patients and families about T&CM agents, and have an understanding of the potential risks and benefits of T&CM use in cancer care to facilitate open and inclusive discussion. Open and inclusive discussion has the potential to allow for safe integration of T&CM strategies into conventional care, and for increased knowledge sharing between patients and providers. This narrative review will focus on commonly used nutritional T&CM strategies, their potential risks and benefits, and provide an overview of current evidence. A summary of definitions is provided in Table 1.

Abbreviation: ALL, acute lymphoblastic leukemia; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CBD, cannabidiol; COG, Children's Oncology Group; FDA, Food and Drug Administration; HSCT, hematopoietic stem cell transplantation; MTX, methotrexate; NCCIH, National Center for Complementary and Integrative Health; T&CM, traditional and complementary medicine; THC, tetrahydrocannabinol.

## 2 | POTENTIAL RISKS AND BENEFITS OF T&CM

There are unique risks associated with the use of T&CM therapies. One of the largest risks is as a result of the less stringent regulation

  

**TABLE 1** Definitions of nutrition-related traditional and complementary medicine (T&CM) strategies

| Term | Definition |
|---|---|
| Functional food (or bioactive food) | Whole foods with potential health benefits beyond basic nutrition, often promoting health and reducing the risk of disease.[106] |
| Bioactive compound | A substance typically found in functional foods, such as probiotics, fiber, or minerals, thought to be responsible for changes in health status.[107] |
| Supplement | A nonfood substance or combination of substances, including vitamins, minerals, herbs, plant-based products, or other bioactive compounds taken with the intent of improving health.[108] |
| Nutraceuticals | Foods that include both functional foods and foods that have been supplemented with additional bioactive compounds for the purposes of improving health.[109] |
| Immunonutrition | Use of specific nutritional supplements or foods to modulate the immune system.[104] |

of T&CM agents as compared with prescription drugs. In many countries, dietary T&CM products are classified as dietary supplements and thus they are exempt from drug regulations through agencies such as the Food and Drug Administration (FDA) in the United States or Health Canada in Canada.[8] There is wide variability in the quality of available products, and products may be mislabeled[9] or contaminated with heavy metals, microbial organisms, or other pharmaceutical agents.[10,11] Although the FDA and Health Canada are working to provide additional oversight, patients should be aware that T&CM products are regulated differently from medications.

In patients with cancer undergoing chemotherapy, there are concerns about the potential for interactions with the use of dietary supplements, which may increase toxicity or decrease the effectiveness of chemotherapy.[12-14] The efficacy of methotrexate (MTX) is known to be directly affected by folic acid; however, dietary studies in pediatric acute lymphoblastic leukemia (ALL) suggest that intake of folate through diet and fortification does not have an adverse effect on MTX activity, unless the doses of folate given are very high.[15] Most interactions between bioactive compounds and chemotherapies in children have not been specifically investigated, and thus patients and families should be cautioned about this risk. Oncologists and oncology pharmacists can often provide some insight where there are known interactions by cross-referencing the chemotherapy agents in a child's treatment plan with the T&CM agents a family is hoping to use.[16]

A less overt risk of the use of T&CM strategies is their cost.[17] Having a child diagnosed with cancer and undergoing treatment comes with a significant financial burden for families, even when controlled for insurance status.[18] Many dietary supplements are costly, and often not covered by insurance. Costs of T&CM may vary significantly based on product used, amount, services engaged, and on location. In families who are already facing a significant financial burden, the additional cost of therapies of uncertain or unproven benefit may represent a significant risk.[8,17]

Nutritional status is of essential importance to children with cancer. Children who are malnourished have inferior tolerance of side effects, increased risk of infection, lower quality of life, and decreased survival.[19,20] Many children are already malnourished at presentation with cancer, both in high-income and low- and middle-income countries.[21] If dietary T&CM strategies are used to the exclusion of a more balanced diet, it may put the child at risk for further malnourishment. Although the use of exclusionary diets is unusual, providers should be aware of their associated risks.

Although there are potential risks associated with T&CM strategies, they are being widely used across the globe.[2] Many T&CM strategies have important cultural significance, particularly among indigenous peoples for whom traditional medicine is central to their approach to health and wellness.[22] Incorporation of these strategies into conventional pediatric oncology treatment may provide more holistic care to these families. For many oncologists, the uncertainty and risks associated with T&CM lead to a reluctance to engage in conversations about T&CM with families, providing instead only dissuasion toward all T&CM practices. Based on the clinical experience of the authors, having open and honest discussions about the risks and benefits of individual practices is optimal, and can lead to minimizing abandonment of conventional cancer therapy to pursue T&CM exclusively. There are no identified cases whereby exclusive use of T&CM has been curative for a child with cancer.[23,24] It is therefore imperative that oncologists work to harmonize T&CM with conventional care where families desire.

## 3 | NATURAL HEALTH PRODUCTS

There are many nutritional compounds that have been suggested to have anticancer benefits.[25,26] Providing a comprehensive guide of every agent in use is outside of the scope of this review. We provide an overview of agents that are commonly sought based on the clinical experience of the authors. See Table 1 for definitions of the some of the most commonly used terms throughout this review.

In a recent systematic review of T&CM agents used for curative intent, there were no high-quality studies in pediatric oncology demonstrating the effectiveness of T&CM agents in achieving pediatric cancer cures.[3] A similar systematic review of T&CM agents used for supportive care in pediatric oncology summarized evidence for the use of bioactive compounds for supportive care indications.[4]

### 3.1 | Prebiotics and probiotics

Prebiotics are compounds that induce the growth or activity of beneficial intestinal microflora.[27] A single prospective randomized controlled trial of a prebiotic enriched formula was conducted in children undergoing chemotherapy. The formula was well tolerated, and patients who received the formula had a modest increase in levels of beneficial bacteria in the intestine.[28] The potential clinical benefit of prebiotics in children with cancer remains unclear and further study is required.[27]

Probiotics are live microorganisms consumed to supplement or restore beneficial bacteria that help maintain that natural

intestinal microflora.[27] Preclinical models suggest that probiotics may ameliorate the risk of infection associated with graft-versus-host disease[29,30] and play an important role in healthy weight management in children.[31] Recent studies have investigated the safety and efficacy of probiotics in the pediatric oncology population. A placebo-controlled study conducted in Japan demonstrated reduced frequency and duration of febrile episodes in children treated with *Bifidobacterium breve*; there was no increased risk of invasive infection associated with administration of probiotics in this study.[32] A recent pilot study demonstrated the safety and feasibility of using *Lactobacillus plantarum* in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT) with severe neutropenia.[33] Of note, probiotic agents obtained for this study were certified free of bacterial and fungal contamination. Risk of infection associated with probiotic consumption may be related to strain or contamination of products.[10,34] A Children's Oncology Group (COG) randomized controlled trial of the effectiveness of *Lactobacillus plantarum* in preventing graft-versus-host disease in children undergoing HSCT is currently undergoing enrollment (NCT03057054). The clinical benefit, appropriate strain, dose, and optimal administration of probiotics remain to be determined.

## 3.2 | Antioxidants

Antioxidants prevent oxidation, theoretically protecting the body against oxygen-free radicals and cell damage.[35] In the setting of cancer therapy, radiation and some chemotherapies are associated with the creation of oxygen-free radicals, which can contribute to both their anticancer and toxic side effects.[35] Antioxidants are found naturally in foods and can include vitamins C and E (discussed below), some minerals, such as selenium, and flavonoids found in fruit, wine, and soy.[36,37] However, supplementation with antioxidant supplements in the setting of cancer has demonstrated mixed results; some studies show that antioxidants can antagonize the cytotoxic effects of chemotherapy and particularly radiotherapy, reducing their effectiveness,[38,39] whereas others demonstrate that chemotherapy is less effective in the setting of oxidative stress,[40] and that appropriate levels of antioxidants are associated with fewer therapy delays and less chemotherapy toxicity.[41,42] The impact of antioxidant therapy may also depend on the timing of the administration. Given these data, high-dose antioxidant supplementation that exceeds the upper limits as defined by the dietary reference intakes should be discouraged.[39]

## 3.3 | Cannabinoids

There has been extraordinary public interest in the use of cannabis and cannabinoids for the treatment of pediatric cancer and cancer-related side effects. Cannabinoids include tetrahydrocannabinol (THC), which is the primary psychoactive compound in cannabis, and cannabidiol (CBD). Recently, particular attention has been paid to CBD oil as a cancer "cure." Clinically available cannabinoids include nabilone and dronabinol.[43]

Despite the public enthusiasm for the efficacy of cannabinoids in treating cancer, evidence is lacking. Preclinical studies have shown some potential antitumor properties of cannabis and cannabinoids.[44] There are only limited clinical adult studies and no interventional studies at all in children demonstrating efficacy.[43] A prospective observational cohort study of medical marijuana in pediatric brain tumor patients is currently investigating this issue (NCT03052738). However, medical marijuana use has been implicated in serious clinical effects in children with cancer, such as hypotension.[45] Further study is required before these agents can be recommended. For an overview of issues related to cannabis and cannabinoid use in pediatric oncology, see the review by Ananth and colleagues.[43]

Cannabinoids have demonstrated efficacy in the treatment of chemotherapy-induced nausea and vomiting in adults and in appetite stimulation in adults.[46,47] Although synthetic cannabinoids such as nabilone and dronabinol are used for these indications in pediatric patients, their safety and efficacy have not been demonstrated in pediatric trials. Furthermore, the long-term impacts of these agents have not yet been studied. The American Academy of Pediatrics and Canadian Pediatric Society have issued position statements against the use of recreational cannabis and cannabinoid by youth because of concerns about brain development. Parents should be cautioned that the purity of other cannabinoids cannot be guaranteed and should not be used as a substitute for nabilone or dronabinol.

## 3.4 | Vitamins and supplements

Interest in the use of vitamins for the treatment of cancer has been long standing. In the 1970s, vitamin C was identified as a possible treatment for cancer and was investigated by prominent scientists, including the Nobel Prize winner Linus Pauling.[48] Since then, vitamin C has been investigated in multiple trials for a cancer treatment, without conclusive benefit being demonstrated.[49,50] Vitamin C supplementation has not been specifically studied in pediatric cancers.

Vitamin D is purported to have anti-inflammatory and immunomodulatory effects and has thus garnered great interest as a potentially preventative or curative agent for cancers, based on epidemiologic studies that have shown a relationship between vitamin D deficiency and cancer risk.[51,52] Vitamin D has an essential role in bone growth and health, particularly in the long term.[53] Vitamin D deficiency has been shown to be associated with oral mucositis during high-dose MTX treatment for children with ALL.[54] Low serum levels of vitamin D have also been associated with an inferior survival in European children with leukemia.[55] In North America, the vast majority of pediatric patients with ALL have been shown to have a deficit in vitamin D levels at diagnosis and throughout therapy.[56,57] Recently, a study of Hodgkin lymphoma that included adolescents demonstrated that vitamin D deficiency was associated with impaired progression-free survival and impaired overall survival.[58] Given this constellation of findings, it is important to ensure children with cancer have sufficient vitamin D intake. The contribution of high-dose vitamin D supplementation is not yet known.

Several agents have been investigated for their effects on mucositis prevention. Glutamine, an amino acid, has been the most widely studied agent with studies showing conflicting results.[59-62] Vitamin supplementation for the prevention and treatment of mucositis has also been studied. A randomized trial comparing topical to systemic vitamin E showed a significant improvement in the treatment of mucositis in patients who received topical but not systemic vitamin E.[63] A subsequent randomized controlled trial of topical application of vitamin E or Pycnogenol (Maritime Pine) versus glycerin placebo showed benefit of both vitamin E and Pygnogenol in the treatment of grades 1-3 mucositis.[64] However, vitamin E has been shown to be ineffective in the prevention of mucositis.[65] Vitamin A was also evaluated for the prevention of mucositis and was found ineffective.[66] Traumeel S is a homeopathic remedy purported to have anti-inflammatory properties. It was evaluated in a COG phase 3 randomized placebo-controlled trial as a prevention and treatment for mucositis in patients undergoing HSCT, without demonstrated benefit.[67] Another trial demonstrated topical application of honey was helpful in mucositis in children with ALL.[68] At this juncture, there is no strong evidence for any supplementation that is of clear benefit in the setting of mucositis; however, topical vitamin E or honey may be helpful for some children.

Chemotherapy-induced febrile neutropenia is a common side effect associated with pediatric cancer treatment. In a population of South African children with cancer at risk of vitamin A deficiency, those with low levels of vitamin A (< 20 $\mu$g/dL) at diagnosis were shown to have a higher incidence of episodes of febrile neutropenia.[69] Although limited, these data may support appropriate vitamin A supplementation in children who are deficient. Further study of the prevalence of vitamin A deficiency and the safety of vitamin A supplementation is required. An open-label, matched pair study of fermented wheat germ extract conducted in 22 pediatric oncology patients showed fewer episodes of febrile neutropenia in children treated with the fermented wheat germ extract.[70] Further study is required of this agent to evaluate its potential efficacy and safety. A recent meta-analysis of studies of the use of topical honey for mucositis demonstrated benefit.[71] In a randomized cross-over study from Egypt, raw, unprocessed clover honey was given to children with standard risk ALL in maintenance therapy.[72] Honey twice weekly was shown to significantly decrease the number of admissions to the hospital for febrile neutropenia and the duration of those hospital admissions. Although these children did not experience adverse events, raw honey can contain spores of clostridium botulinum, which may confer a significant risk to immunocompromised children with cancer and infants less than one year of age; caution should be used.

There has been interest in the use of T&CM strategies for the prevention and treatment of MTX-induced hepatotoxicity. Omega 3 fatty acids, typically found in fish and some seeds, reduced liver enzymes and increased antioxidants in children with ALL undergoing maintenance therapy.[73] A multicenter pilot study of milk thistle demonstrated a decrease in aspartate aminotransferase (AST) and total bilirubin levels,[74] whereas another study showed that black seed oil decreased liver enzymes, alkaline phosphatase (ALP), and prothrombin time.[75] The risks and benefits of using any of these agents would require consideration of the other medications in use, and the clinical situation of any child experiencing MTX-induced hepatotoxicity. Levocarnitine is a "vitamin-like" compound synthesized from lysine and plays an important role in the oxidation of fatty acids.[76] Levocarnitine has been studied as a potential treatment for asparaginase-induced hepatotoxicity, with case series demonstrating benefit.[77,78] Further study into the safety and efficacy of this agent is needed before its use can be recommended.

Glutamic acid, a nonessential amino acid found in protein-rich foods, has been investigated in two studies of neurotoxicity. Although a pilot study showed improvements in paresthesias, constipation, and reflexes,[79] a larger multicenter consortium study did not find any benefit.[80] Glutamine has also been investigated as a potential intervention for vincristine-induced neuropathy. A recent pilot randomized controlled trial of glutamine for vincristine-induced neuropathy showed a clinically and statistically significant reduction in sensory neuropathy and an improvement in quality of life in children receiving glutamine.[81]

The endogenously produced sleep hormone melatonin is a commonly used supplement for sleep,[82] with a growing interest in examining its antioxidant properties and its potential use as an appetite stimulant. There is evidence of benefit for use of melatonin for sleep in healthy children but no direct evidence in children with cancer.[83,84] In a double-blind placebo-controlled trial of melatonin as an appetite stimulant in adults with advanced cancer, there was no benefit of melatonin over placebo.[85] There is a phase I trial being conducted for dose findings for melatonin for use as an appetite stimulant in children.[86] A variety of studies have examined the use of melatonin as an adjuvant to chemotherapy and radiation in adult patients with cancer, with a possible benefit of melatonin.[87] At present, there are no randomized controlled trials examining melatonin as a curative agent for pediatric cancers. Despite this lack of direct data, melatonin has recently been recommended by Children with Cancer (UK) as a standard of care to improve cure for all children with pediatric cancer in the United Kingdom; several pediatric oncologists have expressed concern.[88] At this juncture, there are inadequate data to recommend the use of melatonin as an antioxidant, as an appetite stimulant or for curative intent. Melatonin for sleep may be considered.

Selenium, an essential dietary trace mineral, has been examined in two different randomized, double-blinded cross-over trials among children with leukemia, lymphoma, and solid tumors. The first study demonstrated some improvements in fatigue and nausea by patient or proxy report, as well as renal and kidney function among those supplemented with selenium, whereas the second demonstrated improved neutrophil counts.[89,90] A well-rounded diet should provide adequate selenium intake.

### 3.5 | Plant-based bioactive compounds and nutraceuticals

Turmeric is a rhizome plant, whose root is used as a spice in dishes from across the globe. Its most investigated active agent, curcumin, is purported to have immunomodulatory, anti-inflammatory,

chemopreventative, chemosensitizing, and radiosensitizing effects.[91] Curcumin has been evaluated in adult patients with pancreatic cancer, with some antitumor activity being demonstrated.[92] There are no published clinical studies of curcumin in pediatric cancer patients. Bioavailability of curcumin in humans appears to be poor[93]; however, strategies to improve the bioavailability of curcumin are being investigated.[94] Topical turmeric has been studied in adults as an intervention for chemotherapy- and radiotherapy-induced mucositis with potential benefit demonstrated.[95,96] No studies in children have been conducted to date. As curcumin is known to interfere with the P450 enzyme, it may impact on the metabolism of cyclophosphamide and doxorubicin, among other agents.[97] The risk of interaction is likely low because of the low gut absorption of curcumin. Although routine use of turmeric in food is likely safe, caution should be used when considering supplementation.

Mistletoe is a plant that grows on other trees and has been used in tea form for centuries to treat a variety of conditions. There are currently several oral, intravenous, and homeopathic formulations available, although safety and efficacy profiles differ between formulation and provenance.[98,99] Among adults with cancer, there have been several studies investigating intravenous or subcutaneous European mistletoe use for both supportive care and curative intent.[100,101] Two case reports of mistletoe therapy among children with lymphoid papulosis and cutaneous lymphoma have demonstrated resolution of the malignant cutaneous lesions with mistletoe monotherapy.[102,103] As all patients in the reported clinical studies appear to have been adults, studies are necessary to determine the potential efficacy of mistletoe in children.

*Carica papaya* is a tropical plant whose fruits, leaves, and seeds have been widely used by indigenous peoples for supportive management of several diseases. In one preclinical study, *Carica papaya* leaf extract was shown to significantly inhibit proliferation of tumor cell lines.[104] These results have not yet been recapitulated in the clinical setting. The use of *Carica papaya* leaf extract for thrombocytopenia is gaining popularity in settings where platelet transfusion is not readily available. *Carica papaya* leaf extracts has been studied in the management of Dengue hemorrhagic fever where its use has been associated with increased platelet counts and shorter duration of hospitalization both for adult patients[105-107] and pediatric patients.[108]

## 4 | DIETS

Dietary strategies to manage illness have gained enormous popularity in the pediatric cancer population and in society at large.[26] The importance of nutrition in pediatric patients with cancer has been demonstrated in several well-designed clinical studies. Dietary strategies may help promote health; however, overly restrictive diets may deprive children of essential nutrients and may contradict accepted clinical practice guidelines for pediatric cancer care.[20,109,110] Engaging a dietician in the management of these patients is critical to ensure optimal nutritional status throughout the course of therapy.

### 4.1 | Ketogenic diet

The ketogenic diet is a high-fat, low-protein, and very low carbohydrate diet that has recently garnered significant public interest. Patients with intractable epilepsy have been successfully treated with the ketogenic diet.[111] The rationale for the use of the ketogenic diet in oncology patients is based on the Warburg observation that cancer cells rely on glucose for metabolism.[112] However, evidence of benefit from the ketogenic diet in cancer is lacking.[113] There are no high-quality studies of the use of the ketogenic diet in pediatric cancer patients. Case series have demonstrated their use in pediatric patients with gliomas, with conclusions on the effectiveness unclear.[114] A phase II trial of the ketogenic diet in patients with relapsed and refractory brain tumor patients is currently under way (NCT03328858).

### 4.2 | Caloric restriction diets

Similar to the ketogenic diet, other strategies attempt to "starve" tumor cells of glucose by decreasing overall caloric intake.[115] This is a particularly worrisome strategy as starvation diets may deprive pediatric patients of essential micronutrients, cause weight loss and muscle wasting, and lead to impaired tolerability of chemotherapy.[110] The utility of these diets has not been demonstrated in pediatric patients. Any benefit that may be derived by these types of diets must be weighed against the risks of malnutrition discussed above.

### 4.3 | Whole-food diets

Other dietary strategies attempt to use whole foods to prevent or treat cancers. For example, the macrobiotic diet endorses a predominantly vegetarian, whole-food diet. The evidence for the efficacy of this diet is lacking.[116] However, encouraging a diet high in vegetables and whole grains is congruent with recommendations for a healthy diet provided by the American Institute for Cancer Research (www.aicr.org) and American Cancer Society (www.acs.org). Parents and patients should be counseled to ensure that any diet also adheres to recommended guidelines for pediatric nutrition and to recommendations specific to pediatric patients with cancer.

### 4.4 | Immune boosting and modulating diets

Another popular dietary strategy is the use of diets and supplements to "boost" the immune system, both to fight infections and to optimize the body's own immune system against fighting cancer.[117,118] Many websites and popular news articles in recent years have emphasized the role of particular foods in boosting the immune system (for example: https://time.com/5313656/best-foods-for-immune-system/). The largest academic body of work in this realm has been among adults requiring gastric surgeries, whereby enteral or parenteral nutrition is supplemented with immunonutrients such as arginine, glutamine polyunsaturated fatty acids, or others to optimize healing.[119] Studies in the adult setting have demonstrated fewer infectious complications after cancer surgeries when patients were provided with enteral immunonutrition as compared with standard enteral or parenteral

nutrition.[120-122] However, immune modulating diets have not been studied in a rigorous manner in the pediatric cancer population, and further research is required.

## 5 | CONCLUSION

Many nutritional T&CM strategies exist and are used by pediatric patients with cancer and their families. Although these strategies are popular, rigorous studies of their safety and efficacy are often not available. Children with cancer should be encouraged to eat well-rounded diets that include fresh fruits and vegetables, whole grains, and proteins, to meet their dietary needs.[123] Given that no specific micronutrient has been found to offer specific benefit over others, it is likely that a well-rounded diet will provide adequate and safe amounts of the beneficial compounds found in food.

In many cases, such as with cannabinoids, public enthusiasm for integrative health strategies has outpaced current research. As such, further investigation of these agents, including clinical trials in children, is urgently required. Agents for study should be prioritized based on consultation with stakeholders, including families of children with cancer. Substances that are being used by families but that may also be associated with significant risk should be studied in a rigorous manner. For example, targeted studies of CBD oil and other cannabinoids that are being widely used by families but may cause significant adverse events are necessary. Agents that may be of benefit for supportive care or for curative purposes should also be prioritized. A global approach that includes Traditional Knowledge Holders may help identify priorities for research. For example, a recent article identified six different extracts from leaves demonstrating antitumor effects.[124] Research consortia, such as the COG, have the resources and expertise to continue to lead ongoing investigations of incorporating T&CM strategies into cancer care.

Nutritional status remains of crucial importance for all children, but particularly for children with cancer. Some nutritional T&CM strategies can be safely incorporated into pediatric cancer therapy, with careful research and collaborative discussion between providers and families.

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### CONFLICTS OF INTEREST

The authors have no conflicts to disclose.

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LETTER TO THE EDITOR

# Comment on: An ethical imperative: Safety and specialization as nursing priorities of WHO global initiative for childhood cancer

## Advocating for the baseline nursing standards

To the Editor:

As we celebrate 2020 as the Year of the Nurse and the Midwife and recognize the Global Initiative for Childhood Cancer, members of the International Society of Pediatric Oncology (SIOP) Baseline Nursing Standards Taskforce would like to highlight advocacy efforts promoting the baseline nursing standards.[1,2] Your published article, *An ethical imperative: safety and specialization as nursing priorities of WHO Global Initiative for Childhood Cancer* (Pergert and colleagues) reveals the importance of ongoing efforts to support implementation of the baseline nursing standards.[3] Given that the majority of hospitals are not meeting the standards in low- and middle-income countries, as well as some high-income countries,[4,5] advocacy initiatives are required to raise awareness of the need to meet these standards. During the COVID-19 pandemic, health facilities are facing new challenges in meeting the standards. To achieve the WHO global initiative's goal to save one million children's lives by 2030, it is important to continue efforts to address baseline nursing standards.

Pediatric oncology as a subspecialty requires a nursing workforce with specialized education and clinical skills to achieve optimal patient outcomes. Knowledge itself is not enough if nurses lack the resources and support to practice or implement appropriate nursing care in their work settings. The six baseline nursing standards focus on key elements essential to delivering quality and safe care (Table 1). Collectively, they serve as a framework and foundation for positive pediatric oncology nursing practice environments internationally.

Advocacy efforts to disseminate the baseline standards are well established. To date, 14 organizations have endorsed the standards. Members of the SIOP Pediatric Oncology in Developing Countries (PODC) Nursing Working Group hosted a "Leadership and Advocacy Workshop: Disseminating the Baseline Nursing Standards" prior to the SIOP conference in October 2017. Twenty-two pediatric hematology/oncology nurse leaders and four stakeholder-group representatives (parents, physicians, advocates) from 14 countries met, and established goals and strategic priorities for advocacy of the standards. As a result, the Baseline Nursing Standards Advocacy Toolkit was developed and can be found on the SIOP nursing website https://siop-online.org/baseline-nursing-standards-advocacy-toolkit. The toolkit contains practical advocacy resources, including a PowerPoint presentation, an endorsement letter template, publications, podcasts, a social media campaign, and examples of elevator speeches for each standard. Furthermore, the standards have been featured in international presentations, such as a keynote presentation (S. Day) in SIOP Lyon, an award session, and nursing abstract presentations at SIOP congresses and continental meetings.

**TABLE 1** Baseline standards for pediatric oncology nursing

- **Staffing based on patient acuity**
  - Nurse patient ratio 1:5
  - Nurse to patient ratio 1:2 in critical care and BMT units
  - Nurse retention/nonrotating
- **Formalized orientation**
  - Minimum 2 weeks of formal orientation
  - 3-4 weeks of supervised clinical experience
  - Verification of competency
- **Continuing education**
  - Minimum 10 h/year
- **Multidisciplinary teamwork**
  - Acknowledgment of nurses as core member of the pediatric oncology team
- **Resources for safe care**
  - Safe care for staff, patients, and family
  - PPE for handling chemotherapy
  - Protection against hazards and infections
- **Evidence-driven practice**
  - Nursing policies and procedures to guide the delivery of quality nursing care

To reach the WHO target of doubling the global childhood cancer survival rate to 60%, achievement of baseline nursing standards for pediatric oncology must be prioritized and appropriately resourced by hospital administrators, governments, and other stakeholders. Amid a global pandemic where nursing resources are stretched, creative ways to support and advocate for implementation of the standards is needed. In recognition of the recent publication by the Nurse Specialists of the Global Initiative for Childhood Cancer noting the baseline standards, now is the time to act and improve childhood and adolescent cancer outcomes through raising the standard of pediatric oncology nursing practice around the world.

A special thank you to Rachel Hollis for her commitment and ongoing advocacy efforts focused on the baseline nursing standards.

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# Working Together to Build a Better Future for Children With Cancer in Africa

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There has been substantial improvement in survival of children with cancer in high-income countries. However, great challenges remain in low- and middle-income countries, where > 80% of children with cancer live.[1] Survival in many countries in Africa, for example, is estimated to be < 20%.[2] The WHO recently launched the Global Initiative for Childhood Cancer (GICC), which aims to increase survival of children with cancers worldwide to > 60% by 2030 by promoting access to high-quality cancer care for all children and with an initial focus on common and curable cancer types.[3]

As a group of pediatricians caring for children with cancer in Africa, we recognized the need to focus on 3 activities—quality service provision, local data, and locally relevant clinical research—to allow us to improve outcomes together. We realized that service provision would not improve if we continued to rely on fragmented protocol development and outcome assessment at separate units. We required local data to develop locally relevant, collaborative studies to find sustainable solutions to local challenges that will result in substantial and sustained long-term gains. On the basis of these 3 pillars of quality service, local data, and locally relevant research, we are committed to coordinate research to establish and promote best practices within our network.

Oncology units in well-resourced settings have benefitted greatly from multicenter collaborations in all aspect of cancer care delivery, resulting in improved outcomes for children with cancer. Multicenter collaborations can and should be global in their design and value.[4] Accurate local data on numbers of patients on treatment, accuracy of diagnosis, causes of treatment failure, and the efficacy of specific interventions are required to inform the strategies for improved care and outcomes. Our aim is to increase the survival of children with common and curable cancers in Africa to exceed 60%, in line with the WHO GICC.

With the same goal in mind, the Collaborative Wilms Tumor Africa project was formed in 2014 and has been implementing a consensus-adapted treatment guideline in 8 centers in sub-Saharan Africa as a multicenter clinical trial.[5] This guideline was developed by the Committee for Pediatric Oncology in Developing Countries (PODC) of the International Society of Paediatric Oncology (SIOP).[6,7] Currently participating centers are in Blantyre (Malawi); Eldoret (Kenya); Accra and Kumasi (Ghana); Mbingo, Banso, and Mutengene (Cameroon); and Harare (Zimbabwe). Funding was received from SIOP and World Child Cancer and distributed to all participating centers to cover treatment, travel, and other associated costs for patients.

In the first 4 years of the trial (2014-2018), 201 patients were included. After implementation, compared with the baseline evaluation, survival without evidence of disease at the end of treatment increased (69% *v* 52%, respectively; $P = .002$), abandonment of treatment declined (12% *v* 23%, respectively; $P = .009$), and fewer patients died during treatment (13% *v* 21%, respectively; $P = .06$).[8] Two-year event-free survival was 49.9% ± 3.8% in this patient cohort when abandonment of treatment was considered an event.[9] The Collaborative Wilms Tumor Africa Project Phase II is planned to start in the second half of 2020 and aims to improve survival further. There are minor revisions to the comprehensive adapted treatment guideline based on lessons learned in Phase I.[10]

After establishing, implementing, and evaluating initial treatment guidelines, we analyzed clinical data and recognized that the major barrier to using more intensive treatment regimens was the lack of optimal supportive care.[9] In 2019, Supportive Care for Children With Cancer in Africa (SUCCOUR) was initiated, with a goal to improve supportive care and reduce treatment-related mortality further. Building on the regional network of the Collaborative Wilms Tumor Africa Project and the lessons learned, SUCCOUR aims to promote improvements in supportive care for every child in Africa to be able to be cured from cancer.

We are currently conducting a baseline evaluation of current practices and outcomes in the following important areas of supportive care: malnutrition, febrile neutropenia, abandonment, and treatment-related mortality. This baseline evaluation will be fundamental to understanding the current situation and will

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facilitate the development and prioritization of supportive care interventions. It will provide a benchmark for future evaluation of the impact of implemented interventions.

Abandonment, or incomplete treatment, is known to be an important problem in our centers, and our goal will be to reduce it to zero. Hence, the third project, Toward Zero Percent Abandonment, was started in Blantyre, Malawi, in 2019. It aims to eliminate incomplete treatment. Abandonment of treatment is a known common and preventable cause of treatment failure in low-income countries.[11] The baseline evaluation of this project in Malawi documented that 49 (19%) of 264 patients diagnosed in 2018 and 2019 with common and curable cancers had abandoned treatment.[12] Interventions in Malawi to prevent abandonment include full coverage of treatment, accommodation and transport costs, a tracking system to remind patients of appointments, and more systematic and improved counseling of parents of the need to complete treatment. We intend to introduce this project in all participating centers over the next 1-3 years.

The Collaborative Wilms Tumor Africa Project, SUCCOUR, and Toward Zero Percent Abandonment form the current core of the Collaborative African Network of Clinical Care and Research for Childhood Cancer (CANCaRe Africa). We see the network as a platform on which to build these collaborative studies with the intention that other studies can and will be added to create change. The vision of CANCaRe Africa is that children with common and curable cancers in sub-Saharan Africa will achieve survival rates $>$ 60%-70%, in line with the GICC. The mission is to achieve this by reducing treatment-related deaths to $<$ 10%; reducing abandonment of treatment to $<$ 10%; and developing, implementing, and evaluating locally appropriate treatment guidelines.

CANCaRe Africa has collaborated and aligned with other national and international initiatives. We are sharing our best practices with the WHO GICC, allowing our platform, experience, and knowledge to serve the broader community. Collaborative research and innovation are essential to achieving the targets established by the WHO initiative, and we are actively supporting these WHO workstreams. Collaborative research and innovation are essential to achieving the targets established by the WHO GICC; we are actively supporting WHO workstreams related to establishing treatment standards, to incorporating supportive care programs as part of universal health coverage, and to defining core indicators used in monitoring programs and research. SIOP, including SIOP Africa and SIOP PODC, is the global scientific pediatric oncology umbrella organization.[13] We collaborate within the SIOP community to learn from other groups, develop our guidelines, and implement and evaluate them according to robust scientific standards. We also work closely with our national governments, allowing for sustainable uptake of our programs in the public sector. Current funding for the activities of this regional network comes from SIOP, World Child Cancer, and the Sanofi Espoir Foundation, who share our vision. We hope to expand these partnerships and include others to have sustainable and hopefully increased funding to deliver on our aims and objectives.

Over the past few years, we have learned many lessons.[14] We do work according to a shared vision, mission, and principles by designing feasible interventions, achieving incremental steps, and ensuring long-term sustained impact. We give priority to interventions with the highest expected impact on child survival, cognizant of the current profound inequalities. Our philosophy is that local leaders are in the best position to assess feasibility of interventions and set priorities. Transparency, trust, and a shared purpose are essential. We work through national institutional review boards, ensure the validity of our results, and routinely report successes and challenges internally and externally. Friendship, good communication, and comradery are facilitators in achieving our vision and at the core of our success.

We have established an active regional network for childhood cancer that can be a platform for further initiatives to improve care and survival, including but not limited to the WHO GICC. This is only the beginning of our work. Together, we are finding sustainable solutions to shared local challenges for children with cancer in our community and around the world.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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GLOBAL ONCOLOGY: RESEARCH ARTICLE

# Improvement of overall survival in the Collaborative Wilms Tumour Africa Project

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## Abstract

**Introduction:** The Collaborative Wilms Tumour (WT) Africa Project implemented an adapted WT treatment guideline in six centres in sub-Saharan Africa. The primary objectives were to describe abandonment of treatment, death during treatment, event-free survival (EFS) and relapse following implementation. An exploratory objective was to compare outcomes with the baseline evaluation, a historical cohort preceding implementation.

**Methods:** The Collaborative WT Africa Project is a multi-centre prospective clinical trial that began in 2014. Funding was distributed to all participating centres and used to cover treatment, travel and other associated costs for patients. Patient characteristics, tumour characteristics and events were described.

**Results:** In total, 201 WT patients were included. Two-year EFS was 49.9 ± 3.8% when abandonment of treatment was considered an event. Relapse of disease occurred in 21% (42 of 201) of all included patients and in 26% (42 of 161) of those who had a nephrectomy. Programme implementation was associated with significantly higher survival without evidence of disease at the end of treatment (52% vs 68.5%, $P = .002$), significantly reduced abandonment of treatment (23% vs 12%, $P = .009$) and fewer deaths during treatment (21% vs 13%, $P = .06$).

**Conclusion:** This collaborative implementation of an adapted WT treatment guideline, using relatively simple and low-cost interventions, was feasible. Two-year EFS was almost 50%. In addition, a significant decrease in treatment abandonment and an increase in survival at the end of treatment were observed compared to a pre-implementation cohort. Future work should focus on decreasing deaths during treatment and will include enhancing supportive care.

KEYWORDS
abandonment, paediatric oncology, SIOP PODC, supportive care, survival, Wilms tumour

## 1 | INTRODUCTION

Wilms tumour (WT) is a childhood kidney tumour. It is one of the common and curable cancer types targeted by the Global Initiative for Childhood Cancer, launched by the World Health Organization (WHO), with a goal to improve outcomes globally.[1,2] Multi-centre clinical trials in high-income countries using a combination of chemotherapy, surgery and radiotherapy have resulted in remarkable improvement in overall survival rates to above 85%.[3] However, outcomes are substantially worse in low-income countries. Estimated survival in most African countries is much lower, with a documented 5-year overall survival of 42% in Malawi and 11% survival with short follow up in

Abbreviations: EFS, event-free survival; PODC, pediatric oncology in developing countries; SIOP, International Society of Pediatric Oncology; SUCCOUR, Supportive Care for Children with Cancer in Africa; WHO, World Health Organization; WT, Wilms tumour.

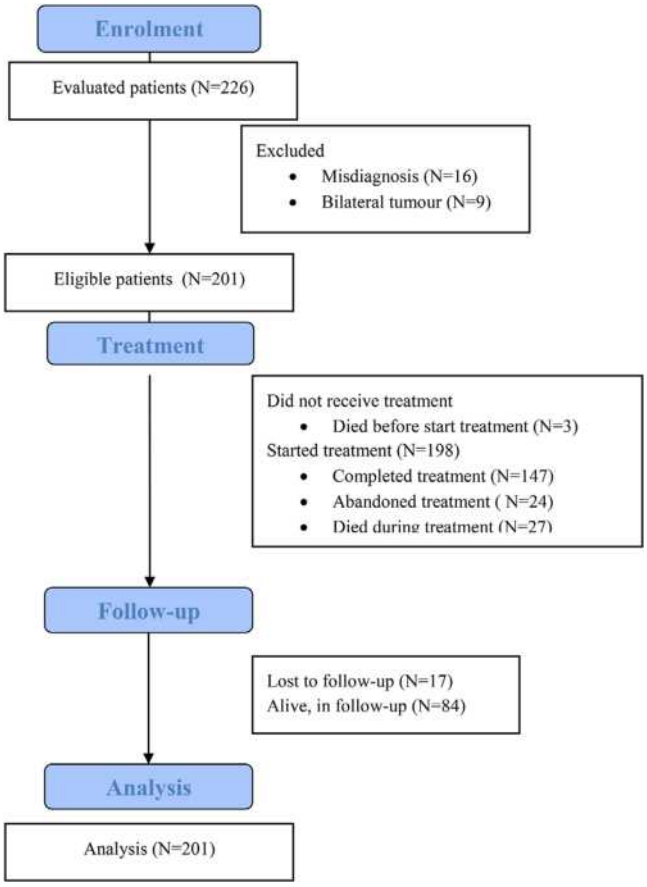


**FIGURE 1** Flow diagram of patient identification, allocation to treatment and receipt of treatment (2014-2018)

**TABLE 1** Patient and tumour characteristics at diagnosis (n = 201)

| Patient characteristics | Values |
|---|---|
| Median age in years (range) | 3.6 (0.3-13.4) |
| Female sex, n (%) | 118 (59%) |
| Duration of symptoms > 2 months, n (%) | 103 (51%) |
| History of weight loss, n (%) | 159 (79%) |
| Tumour characteristics | |
| Tumour side | |
| Tumour left side | 108 (54%) |
| Tumour right side | 93 (46%) |
| Localised or metastatic | |
| Localised | 139 (69%) |
| Metastatic | 62 (31%) |
| Site metastases[a] | |
| Lung | 48 |
| Liver | 13 |
| Lung and liver | 1 |
| Other | 3[b] |
| Missing | 0 |
| Median tumour size in cm (range) | |
| By tape measure (n = 152) | 17 (2-40) |
| By imaging (n = 133) | 14 (2-29) |

[a]Patients may have multiple sites of metastasis.
[b]Brain metastasis, peritoneum, not specified.

Sudan.[4,5] These poorer outcomes have been attributed to many factors including late presentation with advanced disease, inability to afford therapy, nonavailability of drugs and difficult access to essential services including adequate supportive care.

The Collaborative WT Africa Project started in 2014. The aim was to share data and local experiences using the consensus treatment guideline of the International Society of Pediatric Oncology pediatric oncology in developing countries (SIOP PODC) as the standard of care.[6,7]

Primary objective was to describe abandonment of treatment, death during treatment, event-free survival (EFS) and relapse following implementation of the Collaborative WT Africa Project. Exploratory objective was to compare outcomes between the adapted WT cohort and a historical cohort preceding implementation.

## 2 | METHODS

This prospective multi-centre clinical trial included implementation of the treatment guideline, adapted to local circumstances, and uniform patient registration and evaluation of outcome in all participating centres. Funding was distributed to all participating centres and used to partially cover treatment, travel and other associated costs for patients.

Patient enrolment began in January 2014, after local Institutional Research Board (IRB) approval was obtained at each centre. Patients were included prospectively from January 2014 in six centres in Malawi (Blantyre), Cameroon (Mbingo, Banso, Mutengene) and Ghana (Accra and Kumasi). All these centres had curative intent treatments for WT available.[6] Only the centres in Ghana (Accra and Kumasi) had access to radiotherapy for their patients. This protocol was registered (NCT01991652). Patient inclusion for this report was completed in January 2018, after a 4-year period.

All patients with a clinical and ultrasound diagnosis of a unilateral WT were included. Those with histological findings incompatible with WT were excluded as were those with bilateral WT. A detailed description of the adapted WT treatment guideline is reported elsewhere.[6,8] All patients had plain chest radiography and ultrasound of the abdomen to document tumour size and the presence of metastases. Pre-operative chemotherapy consisted of a 4-week two-drug or 6-week three-drug regimen depending on the presence of local or metastatic disease, respectively, with optional treatment prolongation in the case of large tumours. Patients weighing less than 12 kg or with severe acute malnutrition had a one-third dose reduction of all chemotherapy. Post-operative chemotherapy was stratified by pathological stage and risk classification of the tumour, if available, or by surgical stage.[6] Postoperative chemotherapy was according to the SIOP PODC guidelines for centres in Malawi and Cameroon. In Ghana, where radiotherapy was available, postoperative chemotherapy was

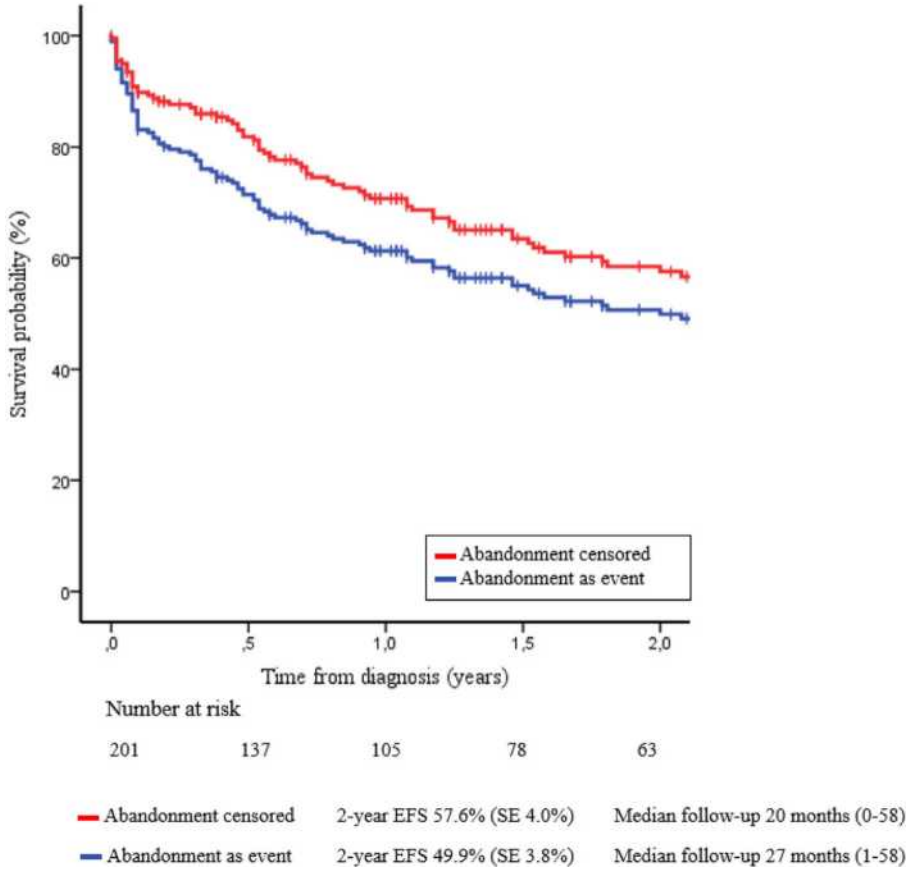


**FIGURE 2** Event-free survival of patients with abandonment of treatment considered an event (in blue) and abandonment of treatment censored (in red)

longer and treatment included radiotherapy for patients with high-risk disease.

Patient details (age and sex), duration of history and observed weight loss were documented. Tumour size was determined both clinically by means of a tape measure and by imaging (ultrasound or computerised tomography scan).

Outcome at the end of treatment was categorised as (a) alive without evidence of disease, (b) treatment abandonment, (c) death during treatment, (d) persistent disease (unresectable disease, relapse of disease, or persistent disease after the completion of the full treatment), or (e) death from other cause. Survival time was calculated from diagnosis to the last moment of contact, either by clinic visit or active follow up (phone or in person).

In order to conduct exploratory comparative analysis, we retrospectively collected data on treatment outcomes for those who would have met eligibility criteria for this multi-centre study but presented in the 2 years prior to programme implementation. Only treatment outcome could be abstracted and not demographic details or other outcomes due to resource constraints. These outcomes have been reported previously.[8,9] Statistical analysis was performed using SPSS 22.0. Survival was calculated using a Kaplan-Meier curve. A Pearson chi-square test, test of independence, was used to compare the end-of-treatment outcome between the two cohorts. A $P$-value < .05 was considered statistically significant.

## 3 | RESULTS

From January 2014 to January 2018, 201 patients were enrolled prospectively as follows: 75 from Blantyre (Malawi), 69 from Accra (Ghana), 37 from Mbingo, Banso and Mutengene (Cameroon) and 20 from Kumasi (Ghana). Figure 1 shows the flow diagram of patient identification, enrolment and completion of treatment.

Table 1 shows the patient and tumour characteristics of enrolled participants. Tumours of 38% (50/133) of patients had a maximum diameter greater than 15 cm on imaging. Metastases were detected at diagnosis in 31% (62/201) of patients.

Two-year EFS (Figure 2) was 49.9% with a median follow up of 27 months (range 1-58 months) with abandonment of treatment considered an event.

Table 2 shows the outcome of patients at the end of treatment in the prospective multi-centre study.

Of the 201 patients, 24 (12%) abandoned treatment, 27 (13%) died during treatment and 47 (23%) had a disease-related cause of treatment failure either before or after the end of planned treatment. Two patients died of another cause. Of the 201 patients, 42 (21%) had a relapse of disease after a median follow up of 27 months (range 1-57 months). Of these 42 relapses, six occurred during postoperative chemotherapy and 36 after the end of planned treatment. The relapse rate was 12% (11/89) in Ghanaian centres with access to radiotherapy

**TABLE 2** End-of-treatment outcome comparison between the 2014-2018 cohort and the 2011-2012 cohort (baseline evaluation)

| End-of-treatment outcome | 2011-2012 n = 122 | 2014-2017 n = 201 | *P*-value[a] |
|---|---|---|---|
| Alive, no evidence of disease | 63 (52%) | 138 (68.5%) | .002 |
| Abandonment of treatment | 28 (23%) | 24 (12%) | .009 |
| Death during treatment | 26 (21%) | 27 (13%) | .064 |
| Disease-related event[a] | 5 (4%) | 11 (5%) | .81 |
| Death other cause | 0 | 1 (0.5%) | N.S. |
| Total | 122 (100%) | 201 (100%) | |

[a]Death before start of therapy, persistent disease, relapse.

and 28% (31/112) in centres without radiotherapy and a shorter postoperative chemotherapy (in Cameroon and Malawi; $P = .008$).

Of the 201 patients, 161 had a nephrectomy. In this group of patients who had a nephrectomy, 42 of 161 (26.1%) had a relapse. If we exclude the one patient who was <6 months old, then 42 of 160 (26.2%) had a relapse of disease.

Table 2 also compares the outcomes at the end of treatment between the pre-implementation and the post-implementation cohort. Programme implementation was associated with significantly higher survival without evidence of disease at the end of treatment (52% vs 68.5%, $P = .002$), reduced abandonment of treatment (23% vs 12%, $P = .009$) and less death during treatment (21% vs 13%, $P = .06$).

## 4 | DISCUSSION

This paper reports on one of the few multi-centre clinical trials for childhood cancer in Africa. It demonstrates the benefits of a regional collaborative network. This network identifies shared local challenges and develops and implements sustainable interventions, giving priority to those with the highest expected impact on survival. Implementation and evaluation of an adapted treatment guideline was feasible.

Compared to the baseline evaluation of the pre-implementation cohort, the programme was associated with significantly higher survival without evidence of disease at the end of treatment, reduced abandonment of treatment and reduced death during treatment.

Although we achieved 2-year EFS of 49.9 ± 3.8%, this is still much lower than survival in high-income countries.

Reliable childhood cancer survival data are rare in sub-Saharan Africa. Follow up of patients to establish these data is extremely challenging, given the other priorities of parents than to come for review with a healthy child, limited resources, bad roads and lack of addresses for clinic staff to be able to follow up. Consequently, the follow up of the pre-implementation cohort is limited. Analysis of end-of-treatment outcome, without longer-term follow up, is useful though and gives relevant information as it will determine the number of patients who died during treatment and abandoned treatment.

The frequency distribution of causes of treatment failure in low-income countries differs from those in high-income settings.[10] These causes include abandonment of treatment, death during treatment and disease-related causes such as unresectable disease or relapse of disease. Each of these causes requires specific interventions to improve results as described below.[11]

Abandonment of treatment was reduced from 23 to 12%. Our objective is to decrease it further. It is often the most common cause of treatment failure in low-income countries and shown to be largely preventable with financial support for medical treatment and associated costs, adequate counselling and other appropriate interventions.[12] In our opinion, the funding support to partially cover treatment, travel and other associated costs for patients played an essential role in the reduction of abandonment of treatment in our programme.

Similarly, the number of patients who died during treatment decreased from 21 to 13%. It was not possible to distinguish between treatment-related mortality or progressive disease in these patients. Death during treatment is assumed to be related to acute malnutrition, late presentation with severe disease and limited supportive care, especially nursing capacity. Interventions to reduce deaths during treatment could include either decreasing intensity of treatment or to improve supportive care. Decreasing intensity of treatment in general is not an attractive option since it will increase the number of children with disease-related deaths. In response to this clear need, the Collaborative WT Africa Project group started SUCCOUR, a project to improve supportive care for children with cancer in Africa.[13] The vision of SUCCOUR is that all children with cancer in Africa will have the best supportive care to be cured from cancer. The project includes a nursing component, with funding for a 'SUCCOUR' nurse on the ward, who does clinical service and serves as a 'role model' for the key role of nurses in supportive care and monthly educational web meetings on supportive care. A baseline assessment of current practice and outcomes in four important areas of supportive care has been done to help decide which interventions need to get priority and to be able to evaluate impact.

Finally, 26% of our patients above age 6 months who had a nephrectomy had a relapse of disease compared to 13% in a similar cohort in the most recent SIOP renal tumour study group (RTSG) study.[14] Late presentation and the absence of radiotherapy likely contributed to the high relapse rate in our study. This is supported by the finding that the relapse rate was higher (28%) in centres without radiotherapy and shorter postoperative chemotherapy than in centres with radiotherapy and longer postoperative chemotherapy (12%).

## 5 | CONCLUSIONS

This collaborative implementation of an adapted WT treatment guideline, using relatively simple and low-cost interventions, was feasible. Two-year EFS was almost 50%. In addition, a significant decrease in treatment abandonment and increase in survival at the end of treatment were observed compared to a pre-implementation cohort. Future work will focus on decreasing deaths during treatment and will include enhancing supportive care. The aim is to decrease both

abandonment of treatment and death during treatment to below 10%, and to increase survival of children with this common and curable tumour in sub-Saharan Africa to over 60%, in line with the Global Initiative for Childhood Cancer, launched by the WHO.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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# Highlights from the 13th African Continental Meeting of the International Society of Paediatric Oncology (SIOP), 6–9 March 2019, Cairo, Egypt

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Conference Report

## Abstract

The 13th African continental meeting of the international society of paediatric oncology, held on 6–9 March 2019 in Cairo, was organised in collaboration with the Children Cancer Hospital (57357) in Egypt and the global parents' organisation (Childhood Cancer International) and supported by a large international faculty. With 629 delegates from 37 countries (24 African), this was the largest forum of healthcare professionals focused on children and young people with cancer in Africa to showcase advances and discuss further improvements. Three targeted workshops, on nursing care, pharmacy and nutrition, attracted large numbers and catalysed new collaborative initiatives in supportive care studies, extended roles for pharmacists in quality control and care delivery and addressed malnutrition concurrently with cancer treatment. The Collaborative Wilms Tumour Africa Project, open in seven sub-Saharan countries, and the trials in Burkitt's lymphoma reported encouraging outcomes with further initiatives in supportive care (the supportive care for children with cancer in Africa project). While acknowledging deficits in radiotherapy provision, available in only 23 of 52 African countries, centres with facilities reported their technical advances that benefit patients. Of great importance for children with brain tumours, who are underdiagnosed in Africa, was the first announcement

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of African paediatric neuro-oncology society, whose 63 current members aim to tackle the shortage of neurosurgeons through training fellowships, workshops and a dedicated conference. The congress provided the opportunity to discuss how African countries will work with the WHO global initiative aiming to improve childhood cancer survival to 60% in all countries by 2030. This conference report is dedicated to the three Kenyan delegates who died tragically on the Ethiopian Airlines flight ET302 on their way home, full of new ideas and pride in what they had achieved so far. All those who heard their presentations are determined to continue their excellent work to improve cancer care for children in Africa.

**Keywords:** *childhood cancer, clinical pharmacy, nutritional assessment, paediatric cancer nursing, paediatric neurosurgery*

## Introduction

Successful treatment of childhood cancers in Africa is of increasing importance due to the high proportion of children and adolescents in the African population and the continuous decrease in death rates from other causes [1]. This 13th biannual continental meeting of the international society of paediatric oncology (SIOP), in conjunction with African representatives from parents' organisations [Childhood Cancer International (CCI)] and the Children's Cancer Hospital (57357) in Egypt (CCHE), Cairo, aimed to showcase progress in this field across multiple disciplines and received 340 abstracts from more than 33 countries, many describing very positive progress through collaborative prospective clinical research [2].

Delegates were welcomed to the congress by Prof Elhamy Rifky A.Khalek (President of the Conference and the host of the event), Prof Laila Hesssissen, President of SIOP Africa and the members of the Local Organising Committee. Prof Rifky welcomed the participants and gave a brief summary of the congress and the schedule. The congress was attended by a total of 629 delegates from 37 countries (24 African), including 156 paediatric oncologists, 53 paediatricians, 32 radiotherapists, 27 surgeons, 92 nurses, 59 pharmacists, 14 diagnostic services (including nine pathologists), 102 nutritionists and 38 parents. Scholarships were available for 156 medical and nursing delegates, for which support from Sanofi Espoir Foundation, CCI, CCHE (57357), Egyptian National Cancer Institute, Ministry of Public Health, Pfizer Pharmaceuticals, New Bridge and Abbott Nutrition is acknowledged.

Professor Sherif Aboul Naga (CCHE, Cairo, Egypt) described in the opening ceremony how the CCHE 57357 (CCHE, widely known as Hospital 57357) was created, inspired by the model of the St. Jude Research Hospital in Memphis. The people of Egypt and friends from all over the world and most particularly in the Arab World generously contributed, and it was built completely by donations. The hospital's mission is to provide the best comprehensive family-centred quality care and a chance for cure to all children with cancer seeking its services, free of charge and without discrimination. It opened in 2007 with 179 beds and, by 2018, had grown to 320 beds and has over 15,000 patients under active treatment. It has all the 'state-of-the art' clinical facilities (including two linear accelerators with plans for proton beam therapy) and comprehensive support services, in-house schooling and child life and play. Since its inception, the CCHE leadership realised that carrying out research in medical and non-medical areas was a prerequisite to progress in achieving cures and a better future for children with cancer. Hence, the adoption of an advanced health informatics system, which enabled it to be a paperless hospital, with the complete digitalisation of operational aspects and acquisition of a strong database. They made a significant and transformational investment in clinical pharmacy staff and processes. He emphasised the importance of investing in people, with all staff given time for and expected to contribute to research and education. Leadership training and embedding key performance indicators at all levels, with regular targeted feedback to departments and teams, have enabled the organisation to make remarkable progress in improving survival rates to an estimated 73% average overall survival rate for those treated today.

One of the biggest barriers for delegates who wished to attend was obtaining a visa in a timely fashion. Of the 33 participants affected, some of whose work had been selected for prize consideration, only 22 were able to obtain a visa on time to attend. Visas were only issued after personal interventions by the local organising committee, adding considerably to the administrative burden of organising a clinical conference in Africa. This issue needs to be considered by both future delegates and conference organisers, to ensure timely sharing of learning to benefit children with cancer and the healthcare professionals who care for them.

The programme covered almost all aspects of childhood cancer care, from improving diagnosis to delivering successful treatment adapted to the available resources. The importance of working collaboratively and involving parents to define needs was emphasised to demonstrate that, even in the most resource-challenged settings, progress in survival rates and quality of care can be achieved through targeted interventions (Figure 1). Three dedicated workshops in the key areas of nursing, pharmacy and nutrition, described in detail in the following section, were very well attended and focused on the specific challenges faced by African children with cancer and the paediatric services who care for them. The congress highlighted the impressive progress made through prospective clinical trials and studies and how this research effort has reaped wider benefits for paediatric care and built durable collaborative research networks. Further information is available from [2, 3].

## Nursing workshop

The nursing programme at SIOP Africa Cairo 2019 comprised two full days of workshop, keynote lectures, free-paper sessions and discussions of collaboration, attended by nurses from seven countries. A workshop on nursing research was delivered by Dr Faith Gibson, laureate of the SIOP Nurse lifetime achievement award 2018. Dr Gibson taught the nursing group how to identify useful research topics, various types of quantitative and qualitative research methodologies suitable for answering multiple research questions and research steps from planning to the dissemination of findings. Nurses expressed several areas of research priorities, a list of which was collated for further exploration within the group.



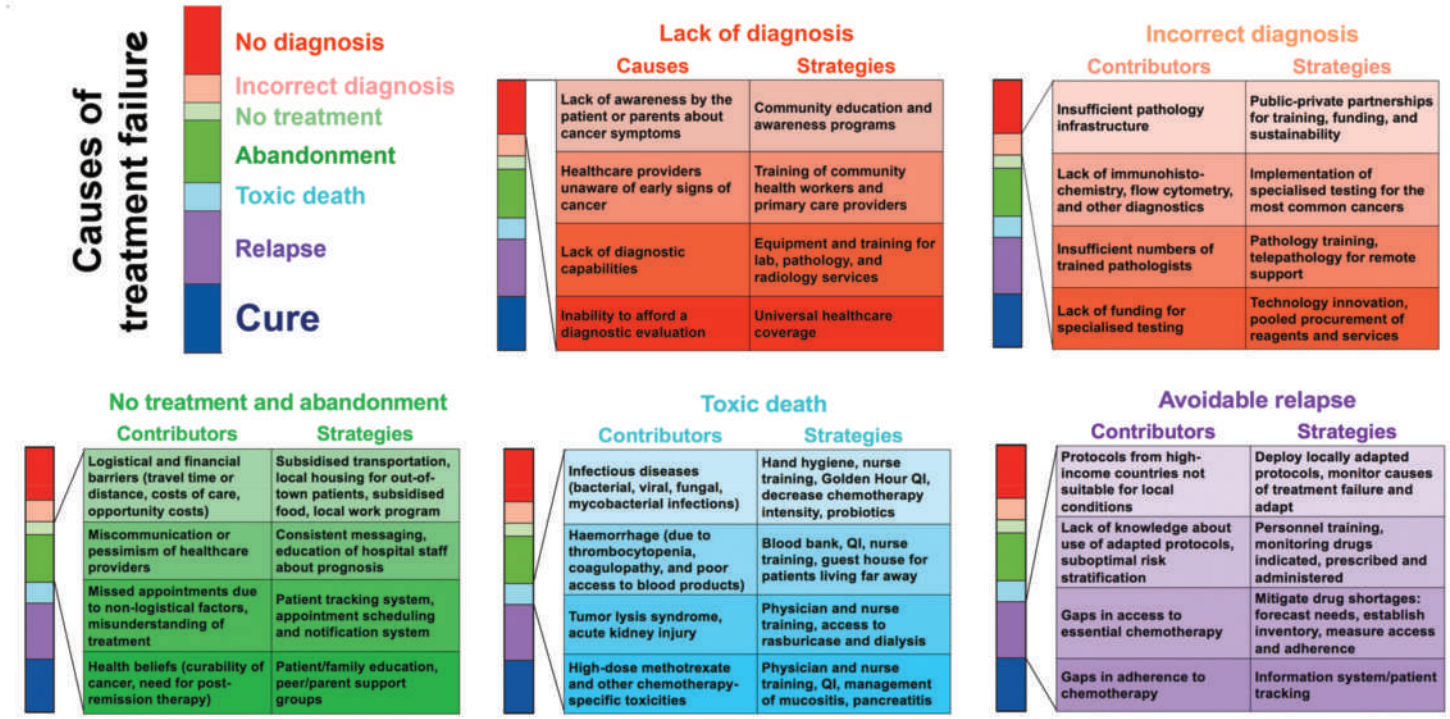


**Figure 1. Cause-specific interventions to reduce treatment failure for children with cancer in low- and middle-income countries. (Used with the permission of Scott C Howard, MD, MSc.)**

Three keynote lectures were delivered. Prof Nagwa Elkhateb from Egypt emphasised the importance of pain assessment using culturally and age-appropriate tools, followed by the meticulous pharmacological or non-pharmacological intervention. Sr Rachel Hollis (Leeds Hospitals NHS Trust, UK) gave a keynote lecture on the SIOP Paediatric Oncology in Developing Countries (PODC) nursing baseline standards for low- and middle-income countries (LMICs) and advocacy. These six standards for quality nursing care include staffing based on patient acuity; formal orientation programmes; continuous education; recognition of nurses as integral members of the multidisciplinary teams; resources for safe care; and research for evidence-based nursing practise [4]. A recent survey showed that the disparities in the attainment of the baseline standards with LMICs were largely disadvantaged [5]. An advocacy toolkit for these standards is available on the SIOP website [6]. Prof Zeinab Lotfy (Modern University for Technology and Information, Cairo, Egypt) of Egypt talked about the essence of communication skills in nursing education, highlighting the need for the consideration of local cultural realities in important aspects of nursing care such as breaking bad news and educating children and families on their treatment.

There were 11 free papers, three of which were recognised for their quality and relevance. Joan Nakabiri (Uganda Cancer Institute, Kampala, Uganda) from Uganda presented on how a continuous nurse's education programme has increased the knowledge and confidence of paediatric oncology nurses at the Uganda Cancer Institute. Hany Eskander from CCHE was recognised for an assessment of intensive care nurses' knowledge and practises regarding utilisation of infection control standards which showed a positive correlation between knowledge and practise of infection control [7]. He recommended continuous education on the latest evidence-based infection control practises. Finally, Vera Njamnshi (Cameroon Baptist Convention Health Services, Cameroon) from Cameroon was recognised for presenting on the contribution of the nurses' role in planning, patient follow-up, informed consent and data collection for assessing the fertility of long-term female Burkitt lymphoma survivors.

Collaboration was one of the central themes of the nursing programme. In order to facilitate communication and sharing of knowledge and initiative in-between conferences, the nurses decided to create SIOP Africa nursing WhatsApp and Facebook groups. An evaluation form completed by most participants showed that they were satisfied with its various components. A few suggestions for future meetings were: to include more content related to palliative care and psychosocial support, to arrange sitting in a U-shape for better interaction and to allocate more time for group work.



## Clinical pharmacy workshop

For the first time in Africa, a one-day workshop was held to bring together all those working in clinical pharmacy services and those prescribing chemotherapy for children with cancer. Sessions were interactive with networking resulting in several future cooperative projects—in particular, those that empowered pharmacists in Africa to enhance their role to improve safety and efficacy of treatment for children with cancer and to use resources more efficiently. Dr SA Naga, the founder of clinical pharmacy in Egypt, opened with the history of the clinical pharmacy concept, the recognition of its value and examples of practical implementation in Egypt. Klaus Meier (HKK (Heidekreis-Klinikum GmbH Krankenhaus), Soltau, Germany), current President of the European Society of Oncology Pharmacy (ESOP), presented the ESOP's plan to develop oncology pharmacy practise over a period towards 2025, including the launch of a certification programme for Oncology Pharmacists comprising 100 hours of training including webinars and face-to-face international and national educational activities. He discussed how the current ESOP programme includes oral chemotherapy, QUAPOS (oncology pharmacy practise standards), the contamination project, safe handling and clean working, the essential requirement for oncology practise, the EUSOP certification programme and, finally, the ECOP conference in Malta. Both speakers urged oncology pharmacists in Africa to unite and work together to implement the best evidence-based pharmacy practise.

The surgical session was well attended by different generations of different sub-specialties including paediatric surgeons, paediatric oncologists and paediatric radiotherapists from different institutes from all over Egypt as well as different African countries. The session was also enriched by fruitful discussions following each presentation. One of the main recommendations during these discussions was to encourage multicentric studies and surveys suggested by physicians and researchers interested in cancer children with all of its different specialties in Egypt. It was proposed that a future conference should ensure greater attendance by international paediatric oncology surgical faculty from the International Society of Paediatric Surgical Oncology (IPSO).

## Nutrition workshop

Malnutrition is widespread among children living in Africa with approximately 46% of children diagnosed with cancer also being diagnosed with malnutrition [8]. Managing malnutrition can be challenging for paediatric cancer units (PCUs) with limited resources [9]; however, the clinical implications of not remediating malnutrition leads to reduced survival and increased treatment-related toxicities [10]. On the final day of the conference, a nutrition workshop was convened, which included dieticians, nurses, physicians, parent groups and nongovernmental organisations (NGOs). Dr Elena Ladas (Columbia University, USA) and Dr Ronald Barr (McMaster University, Canada) opened the workshop with presentations on the impact of nutritional status on survival and outcome and the importance of performing sequential nutritional assessments throughout treatment. An important highlight was the ease and use of mid-upper circumference (MUAC) to determine nutritional status. Regional data on nutritional status, and barriers to care, were provided by clinicians in Ethiopia (Dr Daniel Hailu), South Africa (Judy Schoeman), Malawi (Dr Trijn Israels) and Egypt (Dr Sahar Khairy). Striking figures on the rates of malnutrition among children with cancer were presented; for example, in Malawi, incidence reaches 95% when MUAC or triceps skinfold thickness is utilised for nutritional assessment.

Limited access to nutritional products has been reported among PCU in Africa [9]. Ms Bella Beryl Jamona (Hope for Cancer Kids, Kenya) discussed the challenges clinicians face in providing optimal care to Kenyan children. Prof Mariana Kruger (Tyerberg Children's Hospital, Stellenbosch, South Africa) (South Africa) and Dr Lillian Gesami-Steytler (Windhoek, Namibia) presented on limited access to enteral products and challenges faced when implementing ready-to-use therapeutic formulas. A persistent barrier was the poor availability of these products in PCUs and the lack of trained personnel able to manage children with cancer when they also have severe acute malnutrition. Several case studies illustrated varied approaches to the delivery of nutritional care in a limited resource setting by Dr Samer Mohamed (CCHE, Egypt), Dr Jane Kaijage (Tumaini la Maisha, Tanzania) and Dr George (College of Medicine, Blantyre, Malawi). For example, clinicians in Tanzania use home-made smoothies as supplements during cancer care, whereas Malawi relied upon supplements provided by the acute malnourished ward. Education of staff has been reported as a barrier to nutritional intervention [9]. The International Initiative for Paediatrics and Nutrition (IIPAN) has established an intensive programme in Africa to begin to close this gap in clinical care. Happiness Ndifon, a nutritionist from Cameroon Baptist Convention Health Services, Cameroon, presented how she had implemented a nutrition programme in Cameroon after attending a 2-week intensive training course at an IIPAN training site (South Africa).

Finally, the oncology team from 57357 Children's Hospital in Egypt presented on the centre's research. Topics included the role of nutritional therapy and sensitisation to radiotherapy (Dr Ahmed El-Saka), high aflatoxins in Egyptian food (Dr Afaf Amin) and the important role of breastfeeding as part of immunomodulatory therapy (Gihan Fouad).

In conclusion, the workshop established that there is a need for collaborative, prospective studies on nutritional status in PCU in Africa and, by including MUAC, standardised assessment can be achieved. Education of staff members and synergy among nutritional groups within hospitals, particularly with existing malnutrition clinics, is a pressing need for PCU in Africa. Moreover, PCU need financial and product support to be able to increase nutritional interventions. The request for similar workshops to improve nutritional care in their PCU in future years was received, with the first workshop planned in Kenya and subsequent plans for the next SIOP Africa congress to be held in Kampala, Uganda, in 2021.

## Progress in optimising management of the most curable childhood solid tumours

### *Burkitt's lymphoma*

Catherine Patte (Institut Gustav Roussy, France) reported the latest results of the international intergroup randomised trial, the 'Inter-B-NHL Ritux 2010 trial,' run in eight European countries, Australia, Canada, Hong Kong and the USA. This showed that the addition of rituximab to a standard backbone of intensive chemotherapy (the Lymphomes Malins B (LMB) regimen) improved event-free survival (EFS) from 84% to 92% for advanced stage B-cell lymphoma and B-cell acute leukaemia, and it is now used as a standard in high-income countries (HICs) [11]. Although the longer term immune status of these patients is still under evaluation, a few long-lasting profound B

immunodeficiencies have been observed. Hence, rituximab is not currently recommended in addition to chemotherapy in patients with low (stages I and II) or intermediate (stage III with low lactate dehydrogenase level) stages who have an EFS > 97% with no expected late sequelae related to chemotherapy. In particular, the benefit of rituximab in sub-Saharan countries, where most children are malnourished and more susceptible to infections, must be evaluated before recommending its use. C Patte also reported results of GFAOP studies showing that LMB-based chemotherapy is feasible in sub-Saharan countries and that initial dose intensity is crucial. H Abdel Rahman (National Cancer Institute, Cairo University and CCHE, Egypt) showed in a prospective study of fluorodeoxyglucose positron emission tomography (FDG-PET) for assessment of residual masses in mature B cell non-Hodgkin lymphoma that it is not specific enough and recommends the continued need for histological confirmation to avoid unnecessary treatment escalation. Dr Jenny Geel (University of Witswatersrand, Johannesburg) described efforts to improve overall survival for childhood cancer in South Africa, a country with 16.5 million children aged <15 years. They are taking a disease-by-disease approach to implement a unified national diagnostic and treatment protocol, aiming to improve survival rates, decrease toxicity, and understand and control the costs. The first tumour chosen is Hodgkin's lymphoma. E Moussa (National Cancer Institute, Cairo University and CCHE, Egypt) developed the controversies in the treatment of Hodgkin Lymphoma. Posters reported on North African single centre result in NHL and high-dose (HD), focussing on unusual sites and causes of treatment failures (toxic deaths and malnutrition). One poster on Burkitt highlighted the benefit of a second pre-phase before starting the induction chemotherapy. Another one confirmed the value of PET after two courses of chemotherapy as a predictor of outcome in HD. Prof Peter Hesseling (Stellenbosch University, South Africa) presented results indicating a risk of decreased fertility in girls receiving important doses of cyclophosphamide for the treatment of Burkitt lymphoma.



## *Wilms tumour*

In the session on renal tumours, Prof Kathy Pritchard-Jones (University College London, UK) gave an update on optimisation of clinical risk stratification for the treatment of Wilms tumour (WT) in the SIOP Renal Tumours Study Group new 'UMBRELLA' protocol following further analyses of the previous randomised trial that had recommended omission of doxorubicin from postoperative chemotherapy for all stage II/III intermediate-risk histology WTs [12]. Pending the outcome of ongoing molecular biomarker research, focused on the somatic gain of chromosome 1q, she showed evidence for excess relapse in tumours with volume greater than 500 mL after pre-operative chemotherapy, when the histological subtype was mixed or regressive subtype. It is now recommended that these tumours continue to be treated with doxorubicin included in postoperative chemotherapy [13]. Modest doses of doxorubicin are also now recommended for children with micrometastases visible only on computed tomography (CT). However, it is still acceptable to do staging using a chest X-ray, which is widely available in LMICs.

The collaborative WT Africa Project, presented by Dr Francine Kouya (Cameroon Baptist Convention Health Services, Cameroon) has implemented an adapted WT treatment guideline in sub-Saharan Africa, based on SIOP Renal Tumours Study Group (RTSG) protocols, as a multicentre prospective clinical trial. Seven centres in Malawi, Cameroon, Ghana and Zimbabwe are participating (Figure 2). The collaborative project's primary aims are to improve survival to more than 50% by reducing abandonment of treatment and death during treatment to below 10%. A retrospective, baseline evaluation of end of treatment outcome was done for a 2-year period prior to the introduction of the guideline. Compared to the baseline evaluation, abandonment of treatment decreased from 23% to 13% ($p$ = 0.03) and death during treatment decreased from 21% to 13% (N.S.). End-of-treatment survival without evidence of the disease increased in the first 2 years of the project from 52% to 68% ($p$ = 0.01) [14].

This collaboration, using relatively simple and low-cost interventions has strengthened the local healthcare teams' knowledge and use of sustainable tools to decrease abandonment of treatment and reduce toxic deaths. The increase in survival without evidence of disease at the end of treatment is expected to translate into improved long-term survival. The group is currently analysing the data of the first 4 years of the project and preparing to start phase II of the project in January 2020. This is expected to include some modifications to postoperative chemotherapy and a uniform relapse strategy. The group is also developing supportive care for children with cancer in Africa (SUCCOUR), a project to improve supportive care for children in sub-Saharan Africa. Centres in Africa wishing to join these projects are most welcome.


**Figure 2. The Collaborative Wilms Tumour Africa Project brings together healthcare providers, hospitals, academic institutions, professional societies, and non-governmental organisations to improve cancer care and outcomes in several countries of Africa.**



## *Supportive care for children with cancer in Africa*

Improved supportive care has the potential to benefit children with all types of cancer and those in general paediatric care. SUCCOUR is a comprehensive, inclusive project led by doctors and nurses to promote improvements in supportive care. It builds on the lessons learnt from the Collaborative WT Africa Network with step-by-step development and implementation of simple, effective and cost-effective supportive care interventions, giving priority to those with the highest expected impact on child survival [15, 16] (Figure 1). Each site first conducts a baseline evaluation of current practises and outcomes in several areas of supportive care such as febrile neutropenia, nutrition, abandonment and the use of traditional medicine. Gaps in care and best practises will be identified and addressed through educational workshops, advocacy, developing local appropriate supportive care guidelines, rigorous outcome evaluation and development of specific interventions based on the collected local evidence. It will reference the well-developed framework for cause-specific interventions to reduce treatment failure for children with cancer in LMICs (Figure 1).

## *Prevention and management of toxicity associated with high-dose methotrexate*

High-dose methotrexate (HDMTX), defined as a dose higher than 500 mg/m$^2$, is used to treat a range of adult and childhood cancers. Although HDMTX is safely administered to most patients, it can cause significant toxicity, including acute kidney injury (AKI). AKI constitutes an oncologic emergency in patients receiving HDMTX but can be successfully prevented and managed even in LMICs. Monitoring of serum creatinine, urine output and serum methotrexate concentration is used to assess renal clearance, with concurrent hydration, urinary alkalinisation and leucovorin rescue, to prevent and mitigate toxicity. Maintenance of alkaline urine pH is especially important because it prevents methotrexate crystallisation in the urine and greatly reduces the rate of methotrexate entry into urothelial cells, thus protecting the kidney by two distinct mechanisms. Where measurement of methotrexate levels is not available or not available within a clinically useful timeframe, successful

management of patients requiring HDMTX therapy depends on using somewhat lower doses (2–3 g/m$^2$ instead of 5–8 g/m$^2$), meticulous measurement of urine output and mucosal erythema, prevention of vomiting, assuring no loss of IV access during the infusion and frequent measurement of creatinine to allow rapid response to any increase. A recent study from Chandigarh, India, used methotrexate 5 g/m$^2$ for children with acute lymphoblastic leukaemia (ALL) in a setting where they could not measure methotrexate levels. Using extra hydration, close monitoring and frequent checks of urine pH and creatinine, they delivered 100 courses of HDMTX without worrisome toxicities [16, 17].

## Importance of asparaginase in treating acute lymphoblastic leukaemia

ALL affects 120,000 people each year worldwide, including children and adults. It can be permanently cured more than 80% of the time with treatment regimens that combine glucocorticoids, anthracyclines, vincristine, mercaptopurine and asparaginase [18]. Scott Howard (University of Tennessee, Memphis, USA) discussed approaches to the most effective use of asparaginase, which rely on minimising the likelihood of initial allergic reactions and having access to at least a second formulation of the drug for those who do react. Native *Escherichia coli* asparaginase (Elspar, Leunase, Kidrolase and others) is on the WHO list of essential medications, while other formulations, currently PEGylated-*E. coli* asparaginase (Oncaspar), and Erwinia asparaginase (Erwinaze), as second-line asparaginase for patients who develop hypersensitivity to *E. coli* asparaginases, are not.

In recent times, there have been problems felt around the world regarding the availability and affordability of asparaginase and question marks have been raised about the quality of some suppliers [1]. In HICs, PEG-*E. coli* asparaginase is used as frontline therapy because it is long-acting and has low rates of hypersensitivity (10%–15%) and silent neutralising antibody formation (1%) than native *E. coli* asparaginase. Most LMICs use the much cheaper native *E. coli* asparaginase, to which allergic reactions (20%–42% of patients with ALL) and neutralising antibody formation (in another 30%–40%) are much common. This means that two-thirds of patients do not attain the required asparaginase depletion unless they have access to a second asparaginase product, usually Erwinia asparaginase. Unfortunately, the supply of Erwinia asparaginase has been limited to HIC, and recent shortages have affected patients even in HIC. When no second product is available, the inability to complete asparaginase treatment increases the risk of relapse. Therefore, minimisation of allergic reactions to the initial form of asparaginase improves outcomes and reduces costs.

The recently published UKALL 2003 trial used PEG-*E. coli* asparaginase in a schedule that included several days of glucocorticoids prior to each dose of PEG-*E. coli* asparaginase in the low-risk and intermediate-risk patients, who had a 1% rate of allergic reaction and excellent event-free survival [19]. Patients on the high-risk arm received several doses of PEG-*E. coli* asparaginase without preceding glucocorticoids and had a reaction rate of 6%, such that, in the whole study, the reaction rate was 2% [19]. This has led to an immediate change in practise, and modification of existing protocols to include glucocorticoids a couple of days before each PEG-*E. coli* asparaginase dose, in the hope of reducing allergic reactions to 1%, thus allowing patients to complete all asparaginase and reducing the need for second-line asparaginase (e.g. Erwinia). Prof Howard discussed five strategies to the choice of first-, second- and third-line asparaginase, and concluded that the most clinically effective and cost-effective strategy is upfront use of PEG-*E. coli* asparaginase with second-line *Erwinia* asparaginase, when available, in the 10%–15% of patients who develop hypersensitivity. The average patient who receives PEG-asparaginase 1000–2500 U/m$^2$ has adequate asparaginase activity for 14–24 days, a duration that would require repeated dosing of native *E. coli* asparaginase 2–3 times per week during this interval, or a total of 6–9 doses, to achieve comparable asparaginase activity [20].

### *Information systems*

All strategies to reduce treatment failure for children with cancer depend on a robust information system to facilitate continuous, relentless quality improvement. The advanced health informatics system of CCHE, hospital 57357, is not affordable in most African settings. Alternative systems adapted to the practical challenges faced in Africa were presented. Prof Scott Howard described Resonance Oncology (www.ResonanceOncology.org), an academically led, cloud-based, cancer information system, available at no cost to centres in LMICs. Baseline risk assessment for abandonment can be stored in the oncology adapted resonance patient centre (RPC) abandonment module and the risk score calculated there. RPC can also contain all the patient's clinical information, chemotherapy roadmap and appointments, and serves as a unified source of information about the patient's care and outcomes. The system supports multiple languages, and the abil-

ity to produce analytics and visualisations in real time allows sites to quickly and frequently assess the causes of treatment failure by region, country, cancer centre, year of diagnosis or cancer type [21]. When cancer registry data, abandonment risk factors, treatment appointment adherence and outcomes (causes of treatment failure) are collected in real time for all patients, deployment of interventions can be based on local needs and priorities (Figure 1). A prize-winning oral presentation by Jeremie Hassan (Tumaini la Maisha, Tanzania) 'Increasing Safety and Consistency of Chemotherapy Treatment in Resource-Limited Countries via Excel-Based Prescription Automation' described the work in Microsoft Excel to create printable chemotherapy prescription smart sheets for common childhood cancer. Eight protocols have been fully automated until now. There were highly interactive discussions with the audience who found it as a very good method to reduce treatment errors that could lead to a greatly improved treatment safely and efficiency.

The surgical session was well attended by different generations of paediatric surgeons and other medical specialities and emphasised the importance of formal multidisciplinary discussion with oncologists and radiotherapists to optimise individual patient care. A major recommendation was to promote the importance of involvement in multicentric studies and surveys. It was proposed that a future conference should be organised with a larger faculty from IPSO, the SIOP surgeons.

## Treatment of brain tumours in childhood

The neuro-oncology session provided the opportunity to address the challenges associated with the development of paediatric neuro-oncology programmes in countries with limited resources. A number of factors affect these efforts, such as lack of awareness of paediatric brain tumours, late diagnoses, limited imaging facilities, absence of paediatric neurosurgical training, lack of expertise in neuropathology, difficulties to access radiation services and absence of multidisciplinary approach. Several solutions have been investigated, and, so far, the most successful experiences are with the development of twinning programmes between institutions in high-income and low-income countries. The use of teleconferences allows face-to-face interactions, and regular reviews and discussions of challenging cases have a major impact on clinical practise.



In this context, Dr Giorgio Perilongo (University of Padova, Italy) discussed the management of paediatric low-grade gliomas, reminding the audience that this condition has been listed in the six diseases targeted by the WHO Global Initiative for Childhood Cancer. Major advances in the understanding of the molecular biology of this condition have happened during the last decade, leading to the development of new strategies targeting the RAS/MAP-Kinase pathway. However, these progresses are unlikely to benefit African patients in the near future, and the management of African patients should take into account a number of factors, including distance from the hospital, side effects of chemotherapy and risk of abandonment. In this context, radiation may have still an important role, in particular, when conformal radiation is available. The management of medulloblastoma is far more complex, as it requires a timely and multidisciplinary approach. Dr Kieran (Boston Children's Hospital, USA) reviewed the recent progress in the management of this condition and addressed the main factors of success which include access to a paediatric neurosurgery facility, timely referral to the radiation oncology unit, and adjuvant chemotherapy and follow-up provided by an experienced neuro-oncology team. Dr Bouffet provided an overview of paediatric cancers associated with mismatch repair deficiency (MMRD), an often under-recognised condition closely associated with parental consanguinity. MMRD is not exceptional in Africa where consanguinity is common. Children with MMRD develop malignant brain tumours, lymphoma and colon cancers. There is emerging evidence that some MMRD-related solid tumours can be successfully treated with immune checkpoint inhibitors, and the management of cancers associated with this condition may require a specific approach. Dr Zaghloul reported on the ongoing trial of radiotherapy for patients with diffuse intrinsic pontine glioma (DIPG), which suggests that hypofractionated radiation is given over 13 or 15 sessions at a dose of 3 Gy per session (39 or 45 Gy). Both are equivalent (non-inferior) to standard fractionation (54 Gy in 30 fractions). This experience has certainly important implications, in particular, when access to radiation facilities is limited.

## Radiotherapy

In the Radiation Oncology session chaired by Jeannette Parkes (University of Cape Town, South Africa) and Mohamed Zaghloul (National Cancer Institute, Cairo University and CCHE, Egypt) eight important topics were discussed exploring the problems, limitation and future

of radiation oncology in Africa. Parkes (South Africa) presented the important issue of the interdependence of radiotherapy and neuroimaging, with the need for services to keep abreast of advances in imaging to improve the quality and accuracy of radiotherapy. Zaghloul (Egypt) presented the situation of radiation oncology in Egypt and on the continent of Africa. The causes of the deficiencies in radiotherapy service availability were widely discussed together with the suggested ideas to improve its level [22]. Egypt, as an example, could showcase the importance of collaboration between governmental institutions, universities, NGOs, international bodies and societies like IAEA, ASTRO, ASCO, ESTRO, PROS (Paediatric Radiation Oncology Society) to improve both the quantity and quantity of radiotherapy to serve African patients [23]. Dorra Aissoui (Habib Bourguiba University Hospital, Tunisia) presented a profile of the positive changes for paediatric radiation oncology that had occurred in her centre during 2010–16. The improvements achieved are expected to reflect upon survival and quality of life for the children treated.

Several presenters from Egypt described clinical and technical advances in treating patients at their centres. Soha Ahmed (Aswan University and CCHE, Egypt) presented the experience at CCHE to salvage children with recurrent ependymoma after re-excision of the recurrence (or without surgery) through reirradiation. She summarised the international as well as CCHE experience and concluded that it is not only feasible but also beneficial in terms of overall survival and progression-free survival. Engy Salah (CCHE) presented the experience of re-irradiation in DIPG patients in their first progression. Comparison of 27 re-irradiated patients with a retrospective matched cohort of 27 patients receiving best supportive care demonstrated safety and suggested efficacy. Further presentations described a new technique, deep inspiratory breath hold (DIBH) in mediastinal Hodgkin's Lymphoma in adolescents. Haytham Shaheen (CCHE) presented a full description of the technique, its scientific background and advantage using the novel surface scan (Catalyst) together with cone beam CT. Shaheen convinced the audience of the simplicity, accuracy and efficiency of the system. Hany Ammar (CCHE) compared the different radiotherapy techniques during treatment with DIBH. The DIBH offer much superior dosimetric distribution than free breathing.

Volumetric modulated arc therapy was shown to be more accurate and to provide improved tumour coverage with reduced dose to surrounding normal structures, while requiring reasonable monitor units and time on the machine compared to intensity-modulated radiotherapy and conformal radiotherapy. Finally, Caroline Elmaraghy (CCHE, Egypt) presented the CCHE experience in treating focal brainstem glioma. In a retrospective study, 72 patients were treated either by careful watching, chemotherapy or radiotherapy according to certain criteria depending on symptoms, site, size and progression of the tumour. Although those who received radiotherapy had slightly better overall survival and progression-free survival, the differences were not statistically significant. The interaction between the audience and the speakers were high with exchanging ideas and experiences.

Professor El Beltagy, professor of neurosurgery, Cairo University and Head of Neurosurgery, CCHE, Egypt presented the rationale for and the official launch of the African paediatric neuro-oncology society (APNOS). Many problems are encountered in the diagnosis and treatment of childhood brain tumours in Africa due to lack of resources and scarcity of appropriately trained neurosurgeons and other physicians. There is a deficiency in paediatric neurosurgeons in Africa with a median number of neurosurgeons per 100,000 population of 0.01. Not only is there a severe shortage of trained neurosurgeons, but also equipment, funding and teaching programmes. These signify poorly developed health systems and uneven distribution of neurosurgical and radiotherapy facilities in many countries and across the continent. The consequences are the high mortality and morbidity rates seen today from conditions requiring neurosurgical interventions, with a delay in diagnosis and complicated clinical presentations.

After successful activities over the past 3 years, including workshops for neurosurgery and training programmes for African doctors, the decision was taken to initiate the APNOS and announce its creation during the SIOP Africa 2019 conference. APNOS is an initiative to strengthen collaboration between African countries to improve diagnosis and management of paediatric brain tumours between experts in neuro-oncology and neurosurgeons from many African countries. APNOS has 63 members and board members from different African countries (Egypt, Morocco, Algeria, Tunisia, Libya, Sudan, Nigeria, Zimbabwe and Kenya). APNOS aims to be a leading model of collaboration towards a childhood brain cancer-free Africa, through establishing, facilitating and supporting the paediatric neuro-oncology services across Africa through continuous training, education and capacity building to help alleviate the suffering of African children with brain tumours. The first APNOS congress is planned for the first half of 2020, to be held in Cairo, Egypt, as the first of a series of planned semi-annual neurosurgery workshops in Egypt, Morocco and Sudan, covering different topics including hydrocephalus, endoscopic surgery and tumour surgeries. APNOS is also supervising the neurosurgical fellowship programme (CCHE-57357; starting 2019). In the field of radiation oncology, APNOS collaborated with the Paediatric Radiation Oncology Society (PROS) to help the implementation of the first practical radiotherapy course in

2016 (CCHE-57357), and continues to collaborate on the medical biophysics training programme and preparation for the paediatric medical biophysics 57357 fellowship together with the radiation oncology fellowship programme (CCHE-57357; starting 2019). There is also an ongoing Paediatric Oncology fellowship programme for neuro-oncology training (currently ongoing at CCHE-57357). It is a 30-month fellowship programme in collaboration with the Dana Farber Cancer Institute, including a 6-month paediatric neuro-oncology subspecialty training. Through this programme, there are two African graduates so far from Ethiopia and Kenya.

## Report of the joint session with parents

CCI Africa was established a year ago in Johannesburg, under the supervision of Ruth Hoffman, the CCI global president. The SIOP Africa congress was the first meeting held in partnership with CCI Africa, with an integrated 'parent track.' The programme was led by Ruth Hoffman and the board of CCI Africa, which has seven members from South Africa, Zimbabwe, Uganda, Kenya, Nigeria, Ghana and Egypt, with Carl Queiros as elected President of the CCI African Regional Committee. There were presentations from representatives of parent groups from South Africa, Zimbabwe, Nigeria, Kenya and the Alexandria group of childhood cancer care (AGCCC) in Egypt. Three members of AGCCC presented on the Egyptian experience of founding the first support group for children with cancer and their families in Alexandria city, describing how they mobilised all the potential powers of the community as well as NGOs to establish the Hospitality House Caring for Cancer Children. There was a very fruitful discussion and dialogue between two survivors: one from Kenya (Mr Sydney) and one from Cairo, Egypt (Mr Mahmoud). Overall, this first joint session between CCI Africa and healthcare professionals involved in SIOP Africa was very fruitful and pointed the way for other regions to achieve better care and support for cancer children and their families in the African setting.



## Conclusion

This SIOP Africa congress highlighted many positive actions in improving care and survival rates for children with cancer in Africa. It provided an important forum for policy discussions with WHO in relation to their global mapping initiative of childhood cancer services, that commenced with African countries. All but six African countries responded, but some stated they have no specific services for cancer in children and young people. WHO's 2015 ambition was to reduce deaths from four non-communicable diseases by 25%. Cancer was not mentioned specifically, although it was included in the overall target. Now the WHO 2018 Global Initiative for Childhood Cancer has a specific target to improve childhood cancer survival rates in all countries to at least 60% by 2030. This target is tractable by the knowledge we have now.

The conference showcased many twinning initiatives that will contribute to sustainable improvements, such as the Francophone GFAOP that has helped to establish 20 childhood cancer units in 16 countries, offers a 1-year diploma course from the University of Paris Sud and has trained 240 doctors and nurses who have treated >8,000 children. The business meeting of SIOP Africa highlighted that governments need to listen to the issues and the potential solutions provided—only 18 African countries have cancer plans identified through the survey and only six mentioned the specific needs of children with cancer. Furthermore, the importance of partnership working with parents' organisations cannot be ignored—while CCI Africa is now a visible improvement partner, there are large parts of Africa without parents' organisation registered with CCI. The SIOP Africa 2019 conference has provided model solutions that now need to be adopted at scale. We hope that our governments are listening!

As our closing remarks, we would like to dedicate this conference report to three wonderful healthcare professionals and human beings, who lost their lives on their way home from the conference, full of new ideas and pride in what they had achieved so far. We hope that all those who read this report will be inspired by their work and will continue their excellent work to improve cancer care for children in Africa. https://siop-online.org/a-tribute-to-jayne-bella-grace/

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## Conflicts of interest

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COMMENTARY

# An ethical imperative: Safety and specialization as nursing priorities of WHO Global Initiative for Childhood Cancer

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Cancer is a leading cause of global childhood mortality from noncommunicable diseases, affecting approximately 300 000 children/adolescents (0-19 years old) annually.[1] Of these children/adolescents, approximately 89% live in low- and middle-income countries (LMIC) with an average 30% estimated survival rate, less than half the rate in high-income countries (HIC).[2] This inequality galvanized the launch of the World Health Organization (WHO) Global Initiative for Childhood Cancer in September 2018 to improve survival rates to 60% by 2030.[3] WHO has designated 2020 as the Year of the Nurse and Midwife and highlights that nurses, together with midwives, constitute the largest group of health workers[4]; therefore, strengthening nursing is critical to meeting this target.

Although WHO initiatives for nursing have generally prioritized primary care,[5] the Global Initiative for Childhood Cancer is aiming for highly specialized care in LMIC. To achieve the 2030 target, implementation and scale-up require recognizing the needs and capacities of health professionals, including nurses. Nurses in LMIC are frequently exposed to occupational hazards due to work environments that lack the required resources for safe care, such as personal protective equipment (PPE) for handling chemotherapy.[6,7] The absence of specialized education, coupled with frequent rotation of trained staff, leaves nurses ill-equipped to safely deliver care for children/adolescents with cancer.[8] The Nurse Specialists of the Global Initiative for Childhood Cancer join public calls for all nurses (particularly those in resource-limited settings), to be provided with protection when managing hazardous drugs as well as oncology specialization training to ensure optimal nursing care.[9–11]

It is an ethical imperative that nurses are strengthened and equipped with knowledge and skills required to care for this vulnerable population and provided a safe environment for doing so. Baseline standards for the provision of safe and effective nursing care in LMIC have been published by the Paediatric Oncology

Abbreviations: HIC, high-income countries; LMIC, low- and middle-income countries; PODC, Paediatric Oncology Developing Countries; PPE, personal protective equipment; SIOP, International Society of Paediatric Oncology; WHO, World Health Organization.

**TABLE 1** International Society of Paediatric Oncology (SIOP) Pediatric Oncology in Developing Countries (PODC) baseline nursing standards for paediatric oncology in low- and middle-income countries[12]

| Baseline nursing standards | Description of what is needed |
|---|---|
| 1. Inpatient staffing plans | Nurse-to-patient ratios at different care levels:<br>• Oncology inpatient: 1 nurse to ≤ 5 patients<br>• Bone marrow transplant: 1 nurse to ≤ 2 patients<br>• Intensive care unit: 1 nurse to ≤ 2 patients<br>Dedicated staff (nonrotating)<br>Acuity-based staffing plans |
| 2. Formalized orientation program | ≥ 2 weeks theory/clinical skills training<br>Learning objectives<br>Knowledge/skills validation<br>≥ 3 to 4 weeks clinical preceptorship |
| 3. Continuing education | ≥ 10 hours/year/nurse |
| 4. Multidisciplinary teamwork | Nurses included in patient rounds and diagnosis/treatment plan discussions with patients and families |
| 5. Resources for safe care | Hand hygiene supplies<br>Chemotherapy PPE<br>Chemotherapy prepared by pharmacist<br>• If chemo prepared by nurse, biosafety cabinet, and medical screening available |
| 6. Evidence-based nursing policies | Inpatient and outpatient pediatric oncology nursing policies |

Developing Countries (PODC) Nursing Working Group of the International Society for Paediatric Oncology (SIOP).[12] The standards provide a framework for promoting a positive practice environment for care delivery (Table 1) and have received widespread endorsement (https://siop-online.org/baseline-nursing-standards/).

## 1 | SAFE WORKING ENVIRONMENT

Chemotherapy is a standard treatment required to cure most childhood cancers. Nurses, pharmacists, and physicians who prepare chemotherapy,[13,14] as well as hospital support personnel (e.g., cleaners and waste management staff) and families who are exposed to chemotherapy and hazardous waste, face immediate and long-term health risks, including cancer, miscarriages, and infertility.[15,16] Adverse effects from hazardous drug exposure are entirely preventable with proper use of PPE for chemotherapy administration and biosafety cabinets for preparation, especially in settings without closed system transfer devices for chemotherapy administration as mandated in many HIC.[17,18]

Cost and supply chain challenges can be major barriers to reliable availability of essential devices and technology in LMIC.[19] Nonetheless, the cost of securing PPE for safe handling of chemotherapy and hazardous drugs and materials is minimal in comparison with other costs of scaling up cancer treatment.[20] It is not ethically defendable to invest in contemporary pediatric cancer treatment while failing to protect nurses and other health professionals from avoidable health risks in their work environments as recommended in numerous international guidelines.[11,18] Given that PPE has been secured for infectious disease management (e.g., Ebola[21]) and other public health threats,[22,23] obtaining these resources to deliver chemotherapy safely is surely achievable.

There has been a persistent failure in LMIC to ensure access to PPE for safe preparation, administration, and disposal of chemotherapy for nurses,[8] pharmacists, and physicians.[14,24] This includes chemotherapy-tested gloves, masks, protective eyewear and disposable impermeable gowns,[11] and at minimum, a level 2B biosafety cabinet with appropriate ventilation.[25] There is also a lack of appropriate training for health professionals in safe handling practices,[26,27] although there are increasing efforts to address this.[28,29]

## 2 | SPECIALIZED PEDIATRIC ONCOLOGY NURSES

Investing in health workforce specialized education and training is supported by WHO Education Guidelines.[30] Given the complexity of pediatric cancer diagnoses, treatment, and care, nurses require specialized education and clinical training to deliver safe, quality care and reduce risk for patient harm.[10,31] Specialized nursing education in all settings where children/adolescents with cancer are cared for, including operating rooms and intensive care units, improves quality and outcomes while strengthening broader health services.[32]

Many train-the-trainer programs in pediatric oncology nursing have been conducted since the 1990s. However, few of these programs have established sustained specialized nursing education in either an in-country school of nursing or a hospital clinical setting, although successful programs have been established in Pakistan, Egypt,[10] Jordan,[33] Lebanon,[34] and Latin America.[35] Ultimately, successful specialized nursing education programs (from diagnosis through survivorship or palliative care) are those with local ownership and integration in officially recognized nursing education systems.

In too many countries, nurses are rotated between departments or for mandatory public health service,[32,36] hindering achievement of increasing competence and expertise.[12] Pediatric oncology units require a dedicated nursing team with knowledge and experience in administering chemotherapy, monitoring side effects, managing oncology emergencies, and providing patient/family education. Developing this unique skill set is an inefficient investment unless arbitrary rotation of nurses is stopped, because knowledge and expertise is lost when nurses leave the unit. Nurse rotation also threatens retention and is a serious issue in LMIC[37] where nursing shortages are acute,[38,39] specifically in pediatric oncology units.

## 3 | ETHICAL ARGUMENTATION FOR MORAL ACTION

Historically, clinician exposure to health risks has been inherent to communicable disease treatment and guiding ethical principles have

**TABLE 2** Ethical values as arguments for moral actions in supporting health professionals in childhood cancer care, adapted from Kass et al.[40]

| Ethical values | Moral actions |
|---|---|
| Respect | It is imperative to acknowledge health professionals for their willingness to undertake emotionally distressing, highly advanced care, and potentially risky tasks. The role of the specialist nurse in the multidisciplinary childhood cancer care team needs to be acknowledged and respected. |
| Protect from harm | It is a duty to do no harm and to protect health professionals, as well as patients/families, from avoidable and preventable harm by providing nurses and pharmacists with adequate training and proper protective equipment. |
| Justice | Imposition of reciprocal employer obligations to protect employees from harm because health professionals accept heightened risks as part of their daily practice when handling hazardous drugs and when providing care for which they do not have proper training and education. |

been articulated. Kass et al.[40] write about key ethical concepts for Ebola that are relevant for cancer care (Table 2).

Children/adolescents suffering from cancer in LMIC have the right to curative treatment. However, it would be ethically questionable to scale up diagnosis and treatment of childhood cancer as part of the WHO Global Initiative for Childhood Cancer in LMIC, if the ability of nurses and other health professionals to deliver such services safely is ignored. Access to PPE for safe handling of chemotherapy and the appropriate education and skills to deliver safe pediatric cancer care are *sine qua non*. WHO Global Initiative for Childhood Cancer has a crucial role in improving global access to appropriate childhood cancer care; we argue it is an ethical imperative to ensure (a) adequate protective equipment for all those handling hazardous drugs and (b) that specialized pediatric oncology nursing education and nonrotation of nurses is officially recognized, prioritized, and locally integrated worldwide.

There has been a strong focus on standards of accountability for health care in LMIC,[9,41] but historically, a lack of prioritization, or even neglect, of protective measures for nurses and others has been evident. We must promote standards, identify incentives, and provide a solid rationale to institutions and governments to prioritize access to PPE for all those handling hazardous drugs, and, in parallel, advance specialized nursing roles and education to develop proficiency in pediatric oncology nursing care and optimize patient outcomes.[42]

## 4 | IMPLICATIONS

The Nurse Specialists of WHO Global Initiative for Childhood Cancer urge WHO Member States and facilities delivering cancer treatment to prioritize safe nursing work environments and specialized education to improve overall population health. Health policy makers and hospital administrators can improve nurse recruitment and retention by creating a positive practice environment ensuring nurse occupational health and safety.[43] Promoting such environments through safe chemotherapy handling, specialized education, and nonrotation of nurses in WHO Member States is essential to improve the safety and outcomes of children/adolescents with cancer globally.

## CONFLICTS OF INTEREST

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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# Disparities in the delivery of pediatric oncology nursing care by country income classification: International survey results

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## Abstract

**Background:** In 2014, a task force of the International Society of Paediatric Oncology (SIOP) Paediatric Oncology in Developing Countries Nursing Workgroup published six baseline standards to provide a framework for pediatric oncology nursing care in low- and lower-middle income countries (L/LMIC). We conducted an international survey in 2016–2017 to examine the association between country income level and nurses' resporting of conformity to the standards at their respective institutions.

**Procedure:** Data from a cross-sectional web-based survey completed by nurses representing 54 countries were analyzed (N = 101). Responses were clustered by relevance to each standard and compared according to the 2017 World Bank–defined country income classification (CIC) of hospitals.

**Results:** CIC and nurse-to-patient ratios in inpatient wards were strongly associated ($P < 0.0001$). Nurses in L/LMIC prepared chemotherapy more often ($P < 0.0001$) yet were less likely to have access to personal protective equipment such as nitrile gloves ($P = 0.0007$) and fluid-resistant gowns ($P = 0.011$) than nurses in high-resource settings. Nurses in L/LMIC were excluded more often from physician/caregiver meetings to discuss treatment options ($P = 0.04$) and at the time of diagnosis ($P = 0.002$). Key educational topics were missing from nursing orientation programs across all CICs. An association between CIC and the availability of written policies ($P = 0.009$) was found.

**Conclusions:** CIC and the ability to conform to pediatric oncology baseline nursing standards were significantly associated in numerous elements of the baseline standards, a likely contributor to suboptimal patient outcomes in L/LMIC. To achieve the goal of high-quality cancer care for children worldwide, nursing disparities must be addressed.

KEYWORDS

disparities, global, low- and middle-income countries, nursing, pediatric oncology

## 1 | INTRODUCTION

A robust body of scientific evidence linking nursing care and patient outcomes has emerged over the past two decades. Factors such as nurses' workload, educational preparation, and work environments are associated with a decrease in mortality, infection rates, and cost of care in hospitalized patients.[1–5] Although studies specific to the pediatric population are limited, evidence indicates that nursing resources vary significantly across institutions caring for children and that inadequate nursing resources in pediatric wards are associated with surveillance left undone and missed changes in patients' condition.[6]

Approximately 300 000 children aged 0–19 are diagnosed with cancer per year.[7] The vast majority of those children live in countries with limited resources, which account for more than 90% of childhood cancer deaths.[8] The burden of treatment abandonment, defined

Abbreviations: BMT, bone marrow transplant; CIC, country income classification; HIC, high-income countries; IV, intravenous; LIC, low-income countries; LMIC, lower-middle income countries; L/LMIC, low- and lower-middle income countries; PICU, pediatric intensive care unit; PODC, Paediatric Oncology in Developing Countries; UMIC, upper-middle income countries; WHO, World Health Organization

  

as failure to start or complete curative treatment,[9] falls heavily on lower-middle income countries (LMIC). An international survey by Friedrich et al suggests that 83% of new childhood cancer cases and 99% of treatment abandonment were attributable to LMIC.[10]

In 2012, the International Society of Paediatric Oncology (SIOP) Paediatric Oncology in Developing Countries (PODC) Nursing Working Group convened a workshop to address pediatric oncology nursing needs, with nurse representatives from low-, middle-, and high-income countries (LIC, LMIC, and HIC, respectively). A cross-sectional sample of LMIC nurses caring for children with cancer was surveyed to identify their educational priorities.[11] As LMIC nurses described the challenges faced in their work environments, it became apparent that educational curriculums could not be addressed until standards for pediatric oncology nursing care were established. Standards were drafted, reviewed, and refined through consultation with the PODC nursing community over the following 2 years to achieve consensus. In 2014, Baseline Standards for Paediatric Oncology Nursing in Low- and Middle-Income Countries were published as a position statement in Lancet Oncology[12] and as an article in Cancer Control in 2015.[13] Although many hospitals in low- and lower-middle income countries (L/LMIC) are currently unable to meet the nursing standards due to factors such as hospital overcrowding, lack of funding, and shortage of nurses with specialized education and clinical training, the standards provide a framework to strive for as efforts are made to build infrastructure and improve work environments of pediatric oncology programs worldwide.

To date, no international standards for pediatric oncology nursing are recognized. In 2014, the Association of Pediatric Hematology/Oncology Nurses published "Scope and Standards of Pediatric Hematology/Oncology Practice."[14] Likewise, quality standards were created in England based on the National Institute for Health and Care Excellence publication "Improving Outcome in Children and Young People with Cancer,"[15] which included recommendations for nurse staffing. However, adoption of these and other country-based standards varies at the institution level, and none have been disseminated internationally.

The six baseline standards identify the core components recommended for pediatric oncology nursing programs. The standards address the following: (1) acuity-based staffing plans, with recommended nurse-to-patient ratios of maximum 1:5 in pediatric oncology units and 1:2 for critical care and bone marrow transplant (BMT) units, (2) formal pediatric oncology orientation for new nurses with specific learning objectives in theory and clinical skills, followed by 3–4 weeks of supervision by a skilled nurse, (3) minimum 10 h per year of continuing education, (4) acknowledgement of nurses as core members of the multidisciplinary team, with inclusion of nurses in patient rounds and meetings relevant to patient care, (5) access to resources for the provision of safe care including administration of chemotherapy, and (6) access to evidence-based policies and procedures to guide the delivery of nursing care, along with funding for locally directed nursing research. The standards have been well received by the international pediatric oncology community and endorsed by key academic pediatric cancer institutions, professional and parent groups, and nongovernmental organizations.[16]

After the publication of the baseline nursing standards, a PODC Nursing Baseline Standards Taskforce formed to develop a web-based survey to evaluate the extent to which hospitals providing pediatric cancer care worldwide are meeting these standards. This study presents the results of the survey and highlights the nursing disparities that must be addressed to improve outcomes of children with cancer in low- and middle-income countries.

## 2 | METHODS

A web-based survey was developed by the SIOP PODC Nursing Baseline Standards taskforce to offer nurses who care for children with cancer the opportunity to self-report on elements related to the six standards. To develop the survey instrument, specific criteria used to measure each standard were established using a modified Delphi technique. To establish content validity, eight expert pediatric oncology nurses representative of the six regions of the World Health Organization (WHO) member states reviewed the survey. A content validity index of 0.98 was achieved, with minor changes to the survey made on the basis of reviewer recommendations. The web-based REDCap™ survey was used to administer the questions and capture data. The survey consisted of a minimum of 32 questions and a maximum of 53 questions, depending on branching logic. Questions were nonsubjective. The survey began with a demographic section that focused on nurse responder and hospital characteristics, followed by questions grouped into six sections to address the components of each standard. Key educational and policy topics are not defined in the baseline standards; thus, the authors developed a list of educational and policy topics deemed most relevant to pediatric oncology nursing care for the purpose of the survey.

The survey was translated from English to Spanish, French, and Mandarin Chinese. The survey was emailed in August 2016 with a follow-up mailing in January 2017 to a convenience sample of 208 nurses caring for children with cancer. Email addresses were obtained from selected pediatric oncology–specific mailing lists and via professional contacts of taskforce members. A cover letter that described the intent of the research and the goal to publish the results (with data identifiable by country only) was also attached. Responses were accepted between August 2016 and February 2017. Responses were deemed ineligible if they were incomplete, or if there was a previous complete response received from a given institution (only one complete response per hospital was included to avoid duplication). A limited number of email contacts for nurses from LIC were available to our taskforce, resulting in a disproportionately low number of survey responses from nurses in LIC (Section 4). Thus, the LIC and LMIC's income responses were combined into one category (L/LMIC) at the statistician's recommendation.

## 3 | STATISTICAL ANALYSIS

Data were analyzed by using SAS v.9.4 (Cary, NC). The objective was to determine whether the institution's country income classification

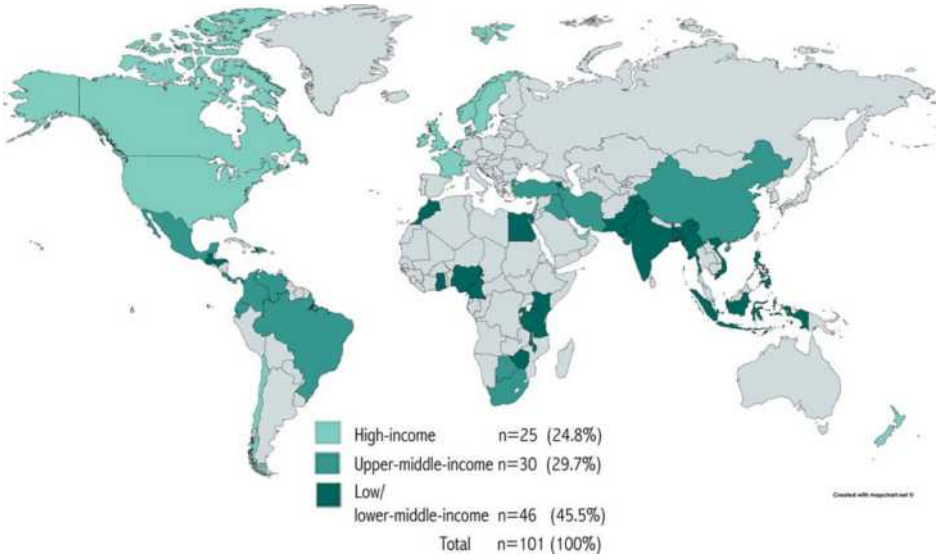


**FIGURE 1** Participating countries by World Bank income classification

(CIC) was associated with components of each of the six baseline standards. Surveys were classified as per The World Bank new country classifications by income level 2017 into three income categories according to the hospital's country—L/LMIC, upper-middle income countries (UMIC), and HIC.[17]

Fisher's exact test was used throughout to test for association between the hospital characteristic and the three income levels. A *P*-value of less than 0.05 was used as the cut-off for statistical significance.

## 4 | RESULTS

Of the 208 surveys sent, 129 responses were returned (62%) and 101 met the eligibility criteria (48.6%) for inclusion. By CIC, the eligible responses per number of survey invitations were as follows: LIC = 5/13, LMIC = 41/79, UMIC = 30/66, and HIC = 25/50. The survey responses represented 54 countries and were categorized into three CIC categories—46 (45.5%) from L/LMIC, 30 (29.7%) from UMIC, and 25 (24.8%) from HIC (Figure 1). By hospital type, 42 participating hospitals were categorized as general hospitals, 41 as pediatric hospitals, and 18 as cancer specialty/national cancer institutes. A dedicated pediatric oncology ward was present in 92% of hospitals; a pediatric intensive care unit (PICU) was present in 69.3%, and a pediatric BMT unit in 43.6%. By years of experience, 1% of nurse responders had less than 1 year, 14% had 1–5 years, 21% had 6–10 years, and 64% had more than 10 years of experience. By educational background, 77% of nurse responders had a university nursing degree, 5% had a technical degree, 2% had auxiliary training, and 16% had "other degrees." (Table 1). By language, 72% of surveys were completed in English, 19% in Spanish, 3% in French, and 6% in Mandarin Chinese.

### 4.1 | Standard 1—Acuity-based staffing plans

For inpatient wards, the association between the number of patients assigned per nurse and CIC was a significant factor in all shifts, including weekdays and weekends ($P < 0.0001$; Table 2). In the day shift, 13/46 (28%) of respondents in L/LMIC met the staffing standard of maximum five patients per nurse compared with 11/30 (37%) for those in UMIC and 21/25 (84%) in HIC. Presence of a PICU at the hospital was significantly associated with CIC ($P = 0.03$), as was the presence of a BMT unit ($P = 0.002$). Conformity to the PICU staffing standard of maximum two patients per nurse neared but did not reach significance. In hospitals with a pediatric BMT unit, there was no association between CIC and the ability to meet the standard of maximum two patients per nurse. One-third (33%) of nurses in L/LMIC reported that they were rotated between units, compared with 20% in UMIC and 4% in HIC ($P = 0.015$). Less than half (46%) of all pediatric oncology nurses reported that they used an instrument to assess patient acuity; this did not vary significantly by CIC.

### 4.2 | Standard 2—Formal orientation program

Table 3 shows that although this standard did not reach significance, the trend indicated that nurses from hospitals in HIC were more likely than those in L/LMIC or UMIC to report a formal orientation program (52% in L/LMIC, 63% in UMIC, and 80% in HIC, $P = 0.19$). Orientation of greater than two weeks was reported 30% of the time in L/LMIC and 37% in UMIC, compared with 60% in HIC ($P = 0.52$). The presence of defined learning objectives approached but did not reach significance by CIC ($P = 0.076$). The PODC Nursing Taskforce identified 12 topics essential for comprehensive pediatric oncology nurse education (Table 3). There was a significant association between CIC and the exclusion of critical topics such as overview of pediatric cancers ($P = 0.026$), neutropenic sepsis management ($P = 0.026$), pain assessment and management ($P = 0.012$), early detection and management of oncology emergencies ($P = 0.047$), and venous access management ($P = 0.029$). Other topics, such as safe chemotherapy administration, managing the side effects of cancer treatment, nutritional support, administration of blood products, infection prevention

**TABLE 1** Characteristics of hospitals and nurse responders

| | L/LMIC, n (%) | UMIC, n (%) | HIC, n (%) | Total, n (%) |
|---|---|---|---|---|
| Hospital characteristics | n = 46 | n = 30 | n = 25 | n = 101 |
| Hospital type | | | | |
| Cancer specialty hospital/national cancer institute | 10 (21.7) | 3 (10) | 5 (20) | 18 (17.8) |
| Pediatric hospital | 10 (21.7) | 16 (53.3) | 15 (60) | 41 (40.6) |
| General hospital | 26 (56.5) | 11 (36.7) | 5 (20) | 42 (41.6) |
| Hospital funding source | | | | |
| Public or government hospital | 30 (65.2) | 24 (80) | 18 (72) | 72 (71.3) |
| Private | 10 (21.7) | 3 (10) | 5 (20) | 18 (17.8) |
| Other | 6 (13) | 3 (10) | 2 (8) | 11 (10.9) |
| "Yes" response to the presence of: | | | | |
| Separate unit for children with cancer | 40 (87) | 28 (96.7) | 25 (100) | 93 (92.1) |
| Pediatric intensive care unit for children with cancer | 27 (58.7) | 21(70) | 22 (88) | 70 (69.3) |
| Pediatric bone marrow transplant unit | 13 (28.3) | 13 (43.3) | 18 (72) | 44 (43.6) |
| Nurse responder characteristics | | | | |
| Years of nursing experience | | | | |
| <1 | 1 (2.2) | 0 (0) | 0 (0) | 1 (1) |
| 1–5 | 12 (26.1) | 2 (6.7) | 0 (0) | 14 (13.9) |
| 6–10 | 13 (28.3) | 5 (16.7) | 3 (12) | 21 (20.8) |
| >10 | 20 (43.5) | 23 (76.7) | 22 (88) | 65 (64.4) |
| Educational background | | | | |
| Auxiliary/assistant | 2 (4.4) | 0 (0) | 0 (0) | 2 (2) |
| Technical | 2 (4.4) | 0 (0) | 0 (0) | 5 (5) |
| Professional (university degree) | 36 (78.3) | 22 (73.3) | 20 (80) | 78 (77.2) |
| Other | 6 (13) | 8 (26.7) | 2 (8) | 16 (15.8) |

HIC, high-income countries; L/LMIC, low- and lower-middle-income countries; UMIC, upper-middle-income countries.

and control, and patient and family education were more frequently absent from orientation programs in L/LMIC, and often missing in UMIC and HIC as well. Palliative care education was reported by 45% of nurses overall. Respondents in L/LMIC, with the highest burden of mortality, reported that palliative care education was included in orientation 35% of the time compared with 43% for those in UMIC and 64% in HIC ($P = 0.067$) (Table 3).

### 4.3 | Standard 3—Continuing education

Table 3 shows that overall, 50% of responders met the minimum standard of 10 h per year of continuing education. This minimum standard was met by 46% of nurses in L/LMIC compared with 47% of nurses in UMIC and 60% in HIC ($P = 0.58$).

### 4.4 | Standard 4—Nurses as core team members

The survey had questions about inclusion of nurses on patient rounds, during treatment plan and consent discussions, and at multidisciplinary team and committee meetings, referring to institution-based committees where decisions about patient care are made. Table 4 shows the presence of nurses at patient rounds was consistent across CICs. However, the association between CIC and the inclusion of nurses in all other meetings was highly significant. In LMIC, 41% of nurses reported being present in meetings with patients at the time of diagnosis or relapse compared with 63% in UMIC and 84% in HIC ($P = 0.002$). Similar associations were found between CIC and inclusion of nurses in meetings to discuss treatment plans and consent ($P = 0.038$) and at multidisciplinary team ($P < 0.0001$) and committee ($P = 0.0007$) meetings.

### 4.5 | Standard 5—Access to resources for safe care

The provision of safe care relies on consistent access to materials that protect patients and caregivers from harm, such as hand-hygiene supplies, personal protective equipment to limit exposure to hazardous drugs and infected materials, and equipment such as intravenous (IV) infusion pumps for safe administration of medications. Table 5 shows that a significant correlation between CIC and access to resources for providing safe care was reported almost uniformly. There was a significant association between CIC and availability of hand-washing supplies such as alcohol-based gels ($P = 0.012$) and paper towels ($P = 0.0002$). Striking differences were noted in resources for safe administration of chemotherapy. While 63% of nurses in L/LMIC responded that they are responsible for preparing chemotherapy compared with 33% in UMIC and 12% of nurses in HIC ($P < 0.0001$), nurses in L/LMIC were significantly less likely to have access to

**TABLE 2** Standard 1: Acuity-based staffing

| Standard 1: Acuity-Based Staffing | L/LMIC, n (%) | UMIC, n (%) | HIC, n (%) | Total, n (%) | *P*-value |
|---|---|---|---|---|---|
| Pediatric unit caring for children with cancer | n = 46 | n = 30 | n = 25 | n = 101 | |
| Nurses care for five or less patients | | | | | |
| Day shift (Monday-Friday) | 13 (28.3) | 11 (36.7) | 21 (84) | 45 (44.6) | <0.0001 |
| Afternoon shift | 11 (23.9) | 7 (23.3) | 22 (88) | 40 (39.6) | <0.0001 |
| Night shift | 11 (23.9) | 5 (16.7) | 18 (72) | 34 (33.7) | <0.0001 |
| Weekend shift | 13 (28.3) | 5 (16.7) | 22 (88) | 40 (39.6) | <0.0001 |
| Nurses rotate from oncology unit | 15 (32.6) | 6 (20) | 1 (4) | 22 (21.8) | 0.015 |
| Acuity tool is used | 18 (39.1) | 13 (43.3) | 15 (60) | 46 (45.5) | 0.35 |
| PICU at hospital | n = 27 | n = 21 | n = 22 | n = 70 | 0.03 |
| Nurses care for two or less patients | | | | | |
| Day shift (Monday-Friday) | 14 (51.9) | 10 (47.6) | 16 (72.7) | 40 (57.1) | 0.31 |
| Afternoon shift | 12 (44.4) | 9 (42.9) | 16 (72.7) | 37 (52.9) | 0.13 |
| Night shift | 11 (40.7) | 8 (38.1) | 16 (72.7) | 35 (50) | 0.11 |
| Weekend shift | 11 (40.7) | 8 (38.1) | 16 (72.7) | 35 (50) | 0.11 |
| Pediatric BMT unit at hospital | n = 13 | n = 13 | n = 18 | n = 44 | 0.002 |
| Nurses care for two or less patients | | | | | |
| Day shift (Monday-Friday) | 12 (92.3) | 9 (69.2) | 15 (83.3) | 36 (81.8) | 0.69 |
| Afternoon shift | 11 (84.6) | 9 (69.2) | 14 (77.8) | 34 (77.3) | 0.89 |
| Night shift | 8 (61.5) | 9 (69.2) | 11 (61.1) | 28 (63.6) | 0.92 |
| Weekend shift | 8 (61.5) | 9 (69.2) | 14 (77.8) | 31 (70.5) | 0.88 |

BMT, bone marrow transplant unit; HIC, high-income countries; L/LMIC, low- and lower-middle-income countries; PICU, pediatric intensive care unit; UMIC, upper-middle-income countries.

**TABLE 3** Standards 2 and 3: Educational preparation of pediatric oncology nurses

| | L/LMIC n (%) | UMIC n (%) | HIC n (%) | Total n (%) | *P*-value |
|---|---|---|---|---|---|
| Standard 2: Formal orientation program | n = 46 | n = 30 | n = 25 | n = 101 | |
| Orientation characteristics: "Yes" response to: | | | | | |
| New nurses receive protected time for orientation | 24 (52.2) | 19 (63.3) | 20 (80) | 63 (62.4) | 0.19 |
| Theory/clinical skills >2 weeks | 14 (58.3) | 11 (57.9) | 15 (75) | 40 (63.5) | 0.52 |
| Defined learning objectives present | 20 (83.3) | 18 (94.7) | 18 (90) | 56 (88.9) | 0.076 |
| Educational topics included in orientation program | | | | | |
| Overview of pediatric cancers | 22 (47.8) | 16 (53.3) | 20 (80) | 58 (57.4) | 0.026 |
| Neutropenic sepsis management | 22 (47.8) | 16 (53.3) | 20 (80) | 58 (57.4) | 0.026 |
| Early detection of oncology emergencies | 21 (45.7) | 17 (56.7) | 19 (76) | 57 (56.4) | 0.047 |
| Pain assessment and management | 18 (39.1) | 17 (56.7) | 19 (76) | 54 (53.5) | 0.012 |
| Palliative care education | 16 (34.8) | 13 (43.3) | 16 (64) | 45 (44.6) | 0.067 |
| Venous access management | 19 (41.3) | 19 (63.3) | 18 (72) | 56 (55.5) | 0.029 |
| Safe chemotherapy administration | 24 (52.2) | 19 (63.3) | 18 (72) | 61 (60.4) | 0.25 |
| Managing side effects of cancer treatment | 24 (52.2) | 18 (60) | 19 (76) | 61 (60.4) | 0.14 |
| Infection prevention and control | 24 (52.2) | 18 (60) | 19 (76) | 61 (60.4) | 0.14 |
| Blood product administration | 23 (50) | 18 (60) | 18 (72) | 59 (58.4) | 0.19 |
| Nutritional support | 20 (43.5) | 13 (43.3) | 16 (64) | 49 (48.5) | 0.22 |
| Patient and family education | 22 (47.8) | 16 (53.3) | 17 (68) | 55 (54.5) | 0.29 |
| Standard 3: Continuing education | | | | | |
| Nurses offered ≥10 h per year | 21 (45.7) | 14 (46.7) | 15 (60) | 50 (49.5) | 0.58 |

HIC, high-income countries; L/LMIC, low- and lower-middle-income countries; UMIC, upper-middle-income countries.

**TABLE 4** Standard 4: Inclusion of nurses as core team members

| | L/LMIC | UMIC | HIC | Total | *P*-value |
|---|---|---|---|---|---|
| Standard 4: Nurses as core team members | n = 46 | n = 30 | n = 25 | n = 101 | |
| Nurse participation in: | | | | | |
| Physician/caregiver meetings at diagnosis or relapse | 19 (41.3) | 19 (63.3) | 21 (84) | 59 (58.4) | 0.002 |
| Physician/caregiver meetings to discuss treatment plan or consent | 21 (45.7) | 21 (70) | 18 (72) | 60 (59.4) | 0.038 |
| Daily rounds with physicians | 42 (91.3) | 26 (86.7) | 22 (88) | 90 (89.1) | 0.78 |
| Multidisciplinary team meetings | 23 (50) | 24 (80) | 24 (96) | 71 (70.3) | <0.0001 |
| Multidisciplinary committees | 15 (32.6) | 15 (50) | 18 (72) | 48 (47.5) | 0.007 |

HIC, high-income countries; L/LMIC, low- and lower-middle-income countries; UMIC, upper-middle-income countries.

**TABLE 5** Standards 5 and 6: Resources for the provision of safe care

| | L/LMIC | UMIC | HIC | Total | *P*-value |
|---|---|---|---|---|---|
| | n = 46 | n = 30 | n = 25 | n = 101 | |
| Standard 5: Safety resources | | | | | |
| Intravenous infusion pumps | 36 (78.3) | 30 (100) | 25 (100) | 91 (90.1) | 0.0006 |
| Soap and running water for hand washing | 44 (95.7) | 30 (100) | 25 (100) | 99 (98) | 0.5 |
| Paper towels for hand washing | 30 (65.2) | 27 (90) | 25 (100) | 82 (81.2) | 0.0002 |
| Alcohol-based hand sanitizer gel | 45 (97.8) | 24 (80) | 25 (100) | 94 (93.1) | 0.012 |
| Powder-free gloves | 41 (89.1) | 27 (90) | 23 (92) | 91 (90.1) | 1 |
| Nitrile gloves for handing chemotherapy | 16 (34.8) | 12 (40) | 20 (80) | 48 (47.5) | 0.0007 |
| Fluid-resistant aprons (gowns) | 25 (54.4) | 22 (73.3) | 22 (88) | 69 (68.3) | 0.011 |
| Masks | 42 (91.3) | 29 (96.7) | 20 (80) | 91 (90.1) | 0.16 |
| Eye protectors and face shields | 24 (52.2) | 24 (80) | 20 (80) | 68 (67.3) | 0.013 |
| Chemotherapy preparation | | | | | |
| Nurse prepares chemotherapy | 29 (63) | 10 (33.3) | 3 (12) | 42 (41.6) | <0.0001 |
| Pharmacist prepares chemotherapy | 12 (26.1) | 16 (53.3) | 20 (80) | 48 (47.5) | <0.0001 |
| Physician prepares chemotherapy | 6 (13) | 4 (13.3) | 0 (0) | 10 (9.9) | 0.15 |
| Chemotherapy prepared in Class II biological safety cabinet | 28 (60.9) | 29 (96.7) | 21 (84) | 78 (77.2) | <0.0001 |
| Standard 6: Access to evidence-based policies and procedures to guide care | | | | | |
| Hospital provides written policies | 33 (71.7) | 27 (90) | 24 (96) | 84 (83.2) | 0.009 |
| Policies relevant to pediatric cancer care: | | | | | |
| Chemotherapy | 27 (58.7) | 25 (83.3) | 24 (96) | 76 (75.2) | 0.0009 |
| Medication administration | 29 (63) | 25 (83.3) | 23 (92) | 77 (76.2) | 0.013 |
| Narcotics or high-alert medications | 24 (52.2) | 19 (63.3) | 22 (88) | 65 (64.4) | 0.008 |
| Transfusion of blood products | 31 (67.4) | 27 (90) | 24 (96) | 82 (81.2) | 0.004 |
| Infection control or hand hygiene | 31 (67.4) | 27 (90) | 24 (96) | 82 (81.2) | 0.004 |
| Management of febrile neutropenia | 23 (50) | 22 (73.3) | 22 (88) | 67 (66.3) | 0.003 |
| Care of venous access devices | 23 (50) | 26 (86.7) | 24 (96) | 72 (72.3) | <0.0001 |
| Managing emergency situations | 25 (54.4) | 20 (66.7) | 22 (88) | 67 (66.3) | 0.012 |
| End-of-life care | 23 (50) | 19 (63.3) | 22 (88) | 64 (63.4) | 0.005 |

HIC, high-income countries; L/LMIC, low- and lower-middle-income countries; UMIC, upper-middle-income countries.

personal protective equipment (PPE) such as nitrile gloves ($P = 0.0007$), fluid-resistant gowns ($P = 0.011$), and protective eyewear/face shields ($P = 0.013$) than those in HIC. A significant association was found between CIC and consistent access to IV infusion pumps (L/LMIC 78% vs UMIC and HIC 100%; $P = 0.0006$). Further, 26% of respondents in L/LMIC and 53% in UMIC compared with 80% of respondents in HIC reported that a pharmacist was available to prepare chemotherapy ($P < 0.0001$). There was a strong significant association between CIC and preparation of chemotherapy in a Class II biological safety cabinet[18] ($P < 0.0001$).

### 4.6 | Standard 6—Evidence-based policies and procedures

Safe pediatric oncology nursing care is guided by evidence-driven policies and procedures that are readily available in the care environment. There was a significant association between CIC and the presence of written policies and procedures ($P = 0.009$; Table 5). Compared with hospitals in UMIC and HIC, those in L/LMIC were significantly less likely to have policies and procedures for medication administration ($P = 0.013$); chemotherapy administration ($P = 0.0009$); transfusion of blood products ($P = 0.004$); administration of high-alert medications, defined by the Institute for Safe Medical Practice as drugs that bear a heightened risk of causing patient harm when used in error[19] ($P = 0.008$); infection control, including hand hygiene, ($P = 0.004$); management of febrile neutropenia ($P = 0.003$); care of venous access devices ($P < 0.0001$); management of clinical emergencies ($P = 0.012$); and end-of-life care ($P = 0.005$).

## 5 | DISCUSSION

The findings from our survey clearly demonstrate the disparity in pediatric oncology nursing practices in resource-rich and resource-poor regions of the world. Nurses in L/LMIC consistently reported working in environments that do not comply with the baseline standards. They reported inadequate staffing, gaps in pediatric oncology education, lack of recognition of nurses as core team members, limited resources for providing safe care, and the absence of essential written policies and guidelines. Nurses in L/LMIC are often tasked with responsibilities that are performed by other disciplines in HIC and are less likely to be given protection against exposure to chemical and biological hazards in the workplace. It is important to note that nurses in HIC also reported not meeting the standards in several instances. For example, 18/25 (72%) of nurses in HIC reported meeting the staffing standard for pediatric inpatient wards on the night shift; (Table 2), key educational content was missing from curriculums across all income levels (Table 3), and only 60% of nurses from HIC reported meeting the standard of minimum 10 h per year of continuing education. This implies variation by institution within all income categories.

With regard to staffing, pediatric oncology nurses in L/LMIC were less likely to meet the recommended nurse-to-patient ratio of one nurse to maximum five patients. This is not surprising, considering the global nursing shortage and expense related to nursing personnel.[20] Hospital administrators often target nursing budgets in an effort to cut costs, despite evidence showing that inadequate nurse staffing levels are associated with increased healthcare costs due to adverse events and longer hospitalizations.[21] Investing in nursing can improve the quality of care and reduce turnover rates and burnout.[22,23] However, the mere addition of nurses to the workforce is not sufficient. Aiken et al recommended that nursing characteristics such as nurse workload, education, and work environment be considered in combination.[24] Lowering the patient-to-nurse ratio has markedly improved patient outcomes in hospitals with good work environments but not in those with average or poor work environments.[25] The educational level of nurses also affects patient mortality and failure-to-rescue rates in patients undergoing surgery.[26] Nurses in L/LMIC and UMIC report that formal education in core pediatric oncology topics is often lacking when they enter the service.[27] Inadequacy in educational preparation coupled with the high workload of nurses and inadequate medical resources raise grave concerns about patient safety, considering the vulnerability of the patient population and the complex treatment setting. The absence of evidence-based policies and procedures to guide pediatric oncology nursing care worsens this concern. Day et al note that education departments in L/LMIC are often staffed with few nurses but are responsible for educating hundreds of employees, which reduces the feasibility of providing orientation programs in specialty areas. Nurses may receive "on-the-job" training as opposed to a structured program based on learning outcomes and competency verification. This deficit highlights the need for improved hospital-based education programs focused on subspecialties in all settings.[28]

By introducing a pediatric oncology nurse educator, some hospitals in Latin America have addressed the lack of specialized orientation and continuing education. Dedicated nurse educators provide instruction in core pediatric oncology nursing theory and clinical skills to new nurses as well as ongoing education for all staff. This model has proven to be sustainable for more than 10 years in Latin America and has been replicated in other resource-limited countries such as Pakistan.[29–31] Rotation of nurses is another major impediment to delivering quality care. Children undergoing cancer therapy require highly specialized treatment and close monitoring for life-threatening adverse effects. To build competency, nurses require educational preparation supplemented with clinical experiences.[32] Rotation hinders nurses from developing knowledge and skills through experience and practice.

The survey also revealed that nurses in limited-resource regions are less likely to be included in patient meetings, treatment plan and consent discussions, and multidisciplinary team and committee meetings related to patient care. Exclusion as core team members prevents nurses from being well informed about their patients, thereby limiting the nurses' ability to serve as patient advocates and educators. Nurses are well positioned to teach patients and families important topics such as recognizing treatment complications and the importance of treatment adherence. This has critical implications in L/LMIC, where toxicity-related deaths and treatment abandonment are disproportionately high. Factors such as parental socioeconomic status, literacy, and beliefs about cancer are determinants of treatment abandonment in low-resource settings, which highlights the need for education and reinforcement of treatment goals in these settings.[33]

Our study has limitations. Despite a nearly 50% survey response rate, data were obtained by using a convenience sample and are therefore not entirely representative of the settings for nurses caring for children with cancer globally. Underrepresentation from nurses in LIC may be related to factors including the following: (1) fewer nurse contacts in LIC were known, indicating that nurses caring for children with cancer in LIC are less likely to have professional/organizational connections outside of their hospital, (2) only nurses with access to email, a computer with reliable internet, and protected time could complete the survey, and (3) many LIC do not have recognized, formal pediatric oncology programs. Of interest is that when the five LIC were analyzed separately, none met the staffing standard for pediatric wards

of one nurse to maximum five patients. None have an intensive care unit or BMT unit, and three out of five reported no formal orientation program for new nurses caring for children with cancer. Four out of five reported that nurses are responsible for preparing chemotherapy without pharmacy support. These results indicate that nurses in LIC may be even less likely to achieve the baseline standards than reported in the combined L/LMIC results. Translations of the survey were available in English, Spanish, French, and Mandarin Chinese, but many nurses do not speak one of these as their primary language. Institutional data were reported by one nurse leader from each hospital, and therefore may be limited to a single person's knowledge of the pediatric oncology program. Nurses are reliable informants of the quality of hospital care, given the amount of time they are present at the bedside[34]; however, surveys in general are limited because of the nature of self-reporting. In addition, the classification of hospitals into one of three categories on the basis of CIC of the country provided a useful but highly simplified measure of the actual level of resource scarcity or abundance in these hospitals. Given our findings, future studies need to analyze in detail the quality of orientation programs, policies and procedures, continuing education, and details regarding resources for safe care.

In conclusion, safe delivery of nursing care is an essential component of a successful pediatric oncology program. Despite the limitations, our findings build on the evidence that nurses in low-resource regions encounter serious obstacles in the care of children with cancer and their families, providing information that was previously lacking in the literature and offering directions for ongoing research. This work is relevant to hospital administrators, policy makers, ministries of health, and other healthcare professionals who strive to improve access to high-quality care for children with cancer. The WHO Global Initiative for Childhood Cancer launched in 2018 with the aim of reaching at least a 60% survival rate for children with cancer by 2030.[35] Our findings will be useful to this initiative, which strives to expand the capacity of countries to deliver best practices in pediatric oncology care. We advocate a pediatric oncology nursing workforce supported by adequate staffing, specialized and ongoing education, inclusion in decision making, sufficient resources for safe care, and availability of evidence-driven patient care policies. Future directions include the development of a standards-based assessment tool that will help nurse leaders in LMIC identify strengths and weaknesses of their individual programs and develop actionable and realistic goals. Assessing the feasibility of achieving the baseline standards in low resource settings must be based on observation of nursing practice within the context of local resources and culture. Further research is needed to analyze the link between achieving the nursing standards and better patient outcomes in children with cancer. These interventions will move this work beyond surveys and into interventional studies, building the case that promoting core standards for pediatric oncology nursing will contribute to improved survival of children with cancer in LMIC.

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## CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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# Burkitt lymphoma: Trends in children below 15 years reveal priority areas for early diagnosis activities in north-west Cameroon

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**Background:** Burkitt lymphoma is one of the most common childhood cancers in Cameroon. Incidence rates of 5.9/100 000 and 2.58 per 100 000 have been reported in two studies in 2005 and 2012 amongst children below 15 years in the North-West Region.

**Aim:** This study seeks to examine how Burkitt lymphoma incidence has varied between the various health districts of north-west Cameroon from 2003 to 2015.

**Setting**: North-West region of Cameroon.

**Method:** Ethics approval was obtained from the relevant university and Health Services Institutional Review Board. Population data was obtained from the regional delegation of public health. The Paediatric Oncology Networked Database registry from two hospitals and two pathology-based registries were reviewed for cases per year from the various districts. Age-standardised incidence rates were computed for all districts by year using the World Health Organizaion world standard populations.

**Results:** A total of 317 cases were registered. Overall age-standardised incidence rate was 3.07 per 100 000. Annual incidence ranged from 0.09 in 2003 to 6.12 in 2010. The districts with the highest incidence rates for the entire study period include Nwa with 10.54; Ndop with 5.63; Benakuma with 5.48; Ako with 4.97; and Nkambe with 4.73.

**Conclusion:** Clustering of Burkitt lymphoma is seen in the region, with the highest incidence in Nwa, Ndop, Benakuma, Ako and Nkambe. These districts should be prioritised for awareness creation campaigns. There is need for a population-based childhood cancer registry in the region, which will use both active and passive surveillance methods to record all childhood cancer cases.

## Introduction

Burkitt lymphoma (BL) is a malignant neoplasm of lymphoid tissue, affecting the B-lymphocytes.[1] It mostly affects children between 2 and 15 years of age and is known to affect more boys than girls in the ratio of 1.5:1.[2] Burkitt lymphoma is a clinically aggressive and rapidly growing tumour with a reported tumour doubling time of less than 3 days.[3] Burkitt lymphoma development has been linked to Epstein-Barr virus infection and malaria,[4] and higher incidence rates have been reported amongst populations with higher burden of malaria, Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV).[5,6,7] The most common sites of presentation of the disease as seen in Cameroon include the following: abdomen (76%), face (50%), spleen (36%), liver (20%), kidney (18%), paraspinal (9%), bone marrow (9%), external lymph nodes (7%), chest wall (4%), cerebrospinal fluid (4%), cranial nerves (3%), femur (2%) and testis (2%).[8] Diagnosis of BL is confirmed by histological and immunocytological demonstration of BL cells in tissue specimens.[3] Cytological examination of cerebrospinal fluid and bone marrow specimens is essential to ascertain metastasis and facilitate staging.[8]

Burkitt lymphoma makes up about 30%–50% of all childhood cancers recorded in tropical Africa.[1,9] Burkitt lymphoma treatment is available in a few treatment centres operating independently in different regions of Cameroon. A population-based cancer registry in the capital city Yaoundé reported an age-standardised incidence rate (ASIR) of 46.8 per million person years.[10] Hospital-based paediatric cancer registries exist in two centres in the North-West Region centres, including Banso and Mbingo Baptist Hospitals. Pathology laboratories also each keep a pathology-based cancer registry, including the pathology laboratories at Mezam Polyclinic Bamenda and Mbingo Baptist Hospital, both in the North-West Region.

Two earlier studies have described the epidemiology of BL in north-west Cameroon. Wright et al.[11] reported an incidence of 5.9/100 000 in 2005, while Lewis et al.[12] revealed an average incidence of 2.58 per 100 000 children under 15 years. As paediatric oncology care develops in the North-West Region of Cameroon, this study seeks to examine how the trends of BL incidence have varied between the various health districts of the region from 2003 to 2015, with the goal of identifying hot spots of the disease, which would be priority areas for awareness creation and early diagnosis initiatives.

# Methods

This is a descriptive cross-sectional study. This study involved children under the age of 15 years living in the North-West Region of Cameroon between 2003 and 2015. Cameroon is classified by the World Bank as a lower middle income country in central Africa and holds a total population of 24 million inhabitants, of which 43% are younger than 15 years.[13] The North-West Region of Cameroon has a total population of about 1 950 000 people[14] divided into 19 health districts, namely Ako, Bafut, Bali, Bamenda, Batibo, Benakuma, Fundong, Kumbo East, Kumbo West, Mbengwi, Oku, Njikwa, Nkambe, Ndop, Ndu, Nwa, Santa, Tubah and Wum.[15]

The population data for the various years of the study was obtained from the regional delegation of public health. This is updated as per the 2007 national population census, and it is the population figures used for healthcare planning in the region. The population for the age group 0–14 years was calculated as 42.47% of the total population for each district, as suggested in the National Demographic Health Survey.[16] The World Health Organization (WHO) world standard populations were used to calculate ASIRs.[17]

Two hospital-based children's cancer registries were reviewed for extraction of data for BL in the age group 0–14 years from 2003 to 2015. These are the registries of Banso Baptist Hospital and Mbingo Baptist Hospital, all using the Paediatric Oncology Networked Database (POND) – an online paediatric cancer registration platform developed by St Jude's Children's Hospital in the USA.[18] In these hospitals children clinically suspected of having BL are subjected to a fine needle tumour aspirate, bone marrow and cerebrospinal fluid cytopathology and an abdominal ultrasound to confirm the diagnosis. Two pathology-based registries in the region were also explored. Patient names and medical record numbers were cross-checked to avoid duplication of cases during data extraction from the various registries.

# Data analyses

Data extracted from the hospital-based and pathology registries included demographics (age, sex, district of residence), diagnosis information (disease name, method of diagnosis, date of diagnosis) and tumour site. Data were collected in Microsoft Excel 2016 and analysed using SPSS version 25. Calculations of ASIR using WHO standard populations were done by inserting formulas into the Excel spreadsheets. Means and standard deviations were used to describe continuous variables. Age-standardised incidence rates were computed for all districts by year.

## Ethical considerations

This study used secondary data form. Ethics approval was obtained from the relevant Health Services Institutional Review Board (ethical clearance number: IRB2016-28). Permission was obtained from the administrators of all the health units and laboratories from which data were obtained.

# Results

## Clinical profile of cases

From 2003 to 2015, there were 317 registered children with BL in the North-West Region of Cameroon. A total of 279 cases were registered in the two hospital-based registries; while 38 more were only recorded in the pathology-based registries. There were 136 (42.9%) females and 181 (57.1%) males, making a female:male ratio of 1:1.3. The age at diagnosis ranged from 1 to 14 years, with a mean of 8.02 years (standard deviation[SD] = 2.76).

Of all cases, 252 (79.5%) had cytological confirmation of BL while 57 (18%) were diagnosed only on a clinical basis, mostly with the use of ultrasound scan. One hundred and seventy one (54%) of the cases had only abdominal disease, 95 (30%) had facial disease, while 45 (14%) had both abdominal and facial tumours.

## Burkitt lymphoma distribution by year and district

The overall ASIR was 3.07 per 100 000 for children below 15 years in the region in the study period from 2003 to 2015. Annual incidence ranged from 0.09 to 6.12. Age-standardised incidence rates generally increased over the study period, with a peak ASIR of 6.12 per 100 000 in 2010. From 2010 the BL incidence rate dropped steeply and has been fairly constant between 2.57 and 3.17 per 100 000 from 2013 to 2015 (Figure 1).

The average ASIR in individual districts of the region for the entire study period ranged from 0/100 000 in Bali and Njikwa health districts to 10.54/100 000 in Nwa health

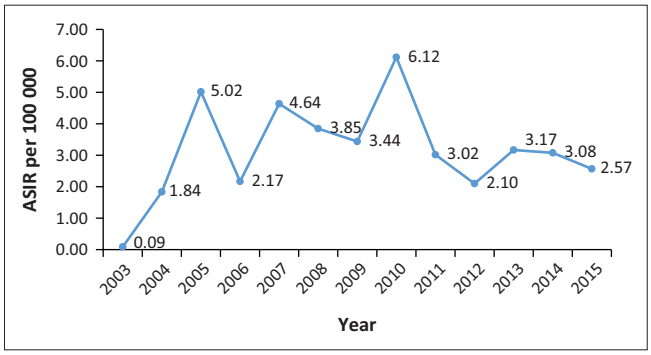
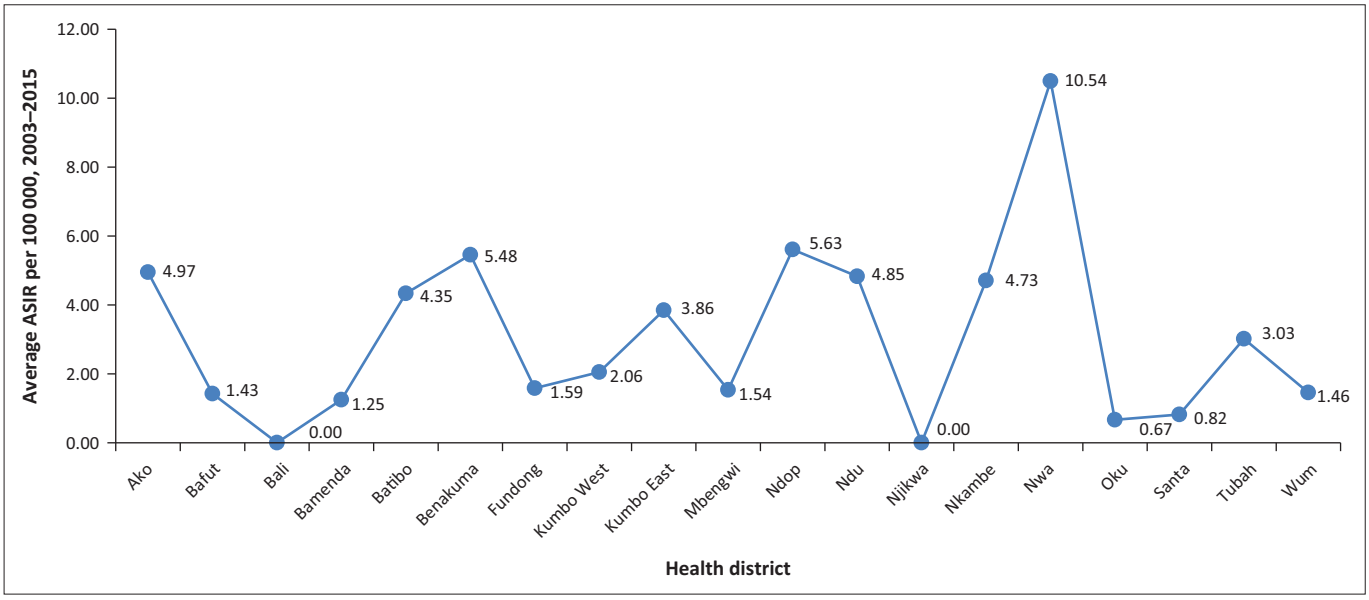



**FIGURE 1:** Trend of age-standardised incidence for Burkitt lymphoma in the North-West Region, 2003–2015, for children aged 0–14 years.

**TABLE 1:** Annual age-standardised incidence (0–15 years) of Burkitt lymphoma in various districts of the North-West Region, 2003–2015.

| Health district | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | Average |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ako | - | - | - | 0.00 | 8.63 | 0.00 | 0.00 | 11.52 | 16.82 | 6.31 | 0.00 | 5.39 | 6.00 | 4.97 |
| Bafut | 0.00 | 0.00 | 6.77 | 0.00 | 6.03 | 0.00 | 0.00 | 4.01 | 0.00 | 0.00 | 3.14 | 0.00 | 0.00 | 1.43 |
| Bali | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Bamenda | 0.00 | 0.96 | 1.81 | 0.00 | 4.76 | 1.06 | 2.74 | 1.82 | 0.71 | 2.37 | 0.00 | 0.68 | 0.57 | 1.25 |
| Batibo | 0.00 | 6.22 | 5.20 | 2.53 | 12.41 | 7.47 | 0.00 | 8.06 | 3.15 | 7.00 | 0.00 | 2.46 | 6.48 | 4.35 |
| Benakuma | - | - | - | - | - | 13.90 | 12.79 | 0.00 | 4.63 | 3.80 | 0.00 | 0.00 | 14.79 | 4.86 |
| Fundong | 0.00 | 0.00 | 0.00 | 0.00 | 1.35 | 0.00 | 1.17 | 10.07 | 5.96 | 0.00 | 3.70 | 0.00 | 0.00 | 1.59 |
| Kumbo West | 1.31 | 0.00 | 5.81 | 2.98 | 3.24 | 5.34 | 8.67 | 1.42 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 2.06 |
| Kumbo East | 0.00 | 7.88 | 7.81 | 2.96 | 9.20 | 4.19 | 2.72 | 2.70 | 9.09 | 0.00 | 4.43 | 0.00 | 3.06 | 3.86 |
| Mbengwi | 0.00 | 0.00 | 3.51 | 0.00 | 2.45 | 0.00 | 2.77 | 0.00 | 0.00 | 0.00 | 0.00 | 8.62 | 4.25 | 1.54 |
| Ndop | 0.00 | 7.37 | 21.37 | 6.00 | 3.33 | 5.67 | 7.74 | 12.70 | 5.00 | 2.56 | 5.90 | 1.17 | 0.00 | 5.63 |
| Ndu | 0.00 | 0.00 | 8.53 | 1.38 | 2.19 | 2.13 | 0.00 | 17.52 | 6.59 | 0.00 | 26.38 | 0.00 | 3.14 | 4.85 |
| Njikwa | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Nkambe | 0.00 | 3.34 | 3.00 | 8.70 | 9.47 | 1.13 | 3.40 | 7.38 | 0.00 | 7.73 | 7.87 | 10.33 | 3.90 | 4.73 |
| Nwa | - | - | - | - | 0.00 | 17.30 | 23.89 | 17.48 | 4.31 | 13.83 | 2.81 | 15.13 | 10.65 | 10.54 |
| Oku | - | - | - | - | - | - | - | - | 0.00 | 0.00 | 1.38 | 0.00 | 2.66 | 0.67 |
| Santa | 0.00 | 0.00 | 0.00 | 2.43 | 2.03 | 0.00 | 0.00 | 3.61 | 0.00 | 0.00 | 0.00 | 0.00 | 3.35 | 0.82 |
| Tubah | - | - | - | 4.69 | 4.55 | 12.28 | 0.00 | 7.30 | 0.00 | 0.00 | 4.55 | 0.00 | 0.00 | 3.03 |
| Wum | 0.00 | 0.00 | 6.48 | 3.11 | 0.00 | 0.00 | 8.83 | 0.00 | 2.03 | 0.00 | 0.00 | 0.00 | 0.00 | 1.46 |
| Average | 0.09 | 1.84 | 5.02 | 2.17 | 4.64 | 3.85 | 3.44 | 6.12 | 3.02 | 2.10 | 3.17 | 3.08 | 2.57 | 3.07 |




ASIR, age-standardised incidence rate.

**FIGURE 2:** Variation of Burkitt lymphoma incidence across health districts.

district (Table 1). Spatial clustering of BL cases was noticed within the region. The districts that recorded the highest incidence rates for the entire study period include Nwa with 10.54/100 000; Ndop with 5.63 per 100 000; Benakuma with 5.48 per 100 000; Ako with 4.97 per 100 000; and Nkambe with 4.73 per 100 000. Despite fluctuations in ASIR over the years, with a remarkable drop from 2010, these districts consistently have higher incidence rates (Figure 2).

## Discussion

The 317 patients included in this study were all the patients diagnosed and registered within the two pathology laboratories, two childhood cancer units in the North-West Region. It is likely that patients who travelled to other provinces for treatment were not recorded. The male predominance in Burkitt lymphoma amongst children under 15 years has been reported in other population studies across Africa.[4,5,19,20] The ratio of 1.3:1 in this study is the same as that reported by Lewis et al. in the North-West Region of Cameroon[12] and not much lower than the ratio of 1.8 reported by Enow-Orock and colleagues in Yaoundé, Cameroon.[21] Pierce and Parker report a larger number of boys than girls for all childhood cancers put together.[22] They suggest that this might be because of a prioritisation of the health of males over females amongst poor populations. The modal age group of 5–9 with mean of 8 years corresponds to expert suggestions and what has been reported in Yaoundé,[21] and in other population studies.[4,19]

All the cytological diagnoses were done by use of fine needle aspiration cytology. This method has been shown to be safe,

cheap and fast[23] and has been recommended for use in the diagnosis of BL in developing countries, where there is a limited number of surgeons and pathologists.[24] In the absence of pathology, clinical diagnosis is accepted if the patient responds to BL treatment and if there is no contrary pathology diagnosis.[24] Ultrasound scan has been shown to be helpful in the diagnosis of BL, by describing the nature of the tumours, which are typically hypoechoic.[25] This is also useful for staging the disease.[24]

The dominance of abdominal involvement in this study supports what has been reported previously in Cameroon[12,21,25] and in Nigeria.[19] Historically, facial presentation has been described as most common in BL in sub-Saharan Africa,[26] but with advancement in imaging technology and increasing availability of ultrasound, early abdominal involvement is now detectable, which would otherwise be missed on clinical evaluation.[25] As more developing countries use ultrasound as a routine clinical investigation for BL patients, there is increasing predominance of abdominal presentation of BL over facial presentation.[27]

The average BL incidence rate of 3.07/100 000 over the 13-year period was a little higher than the rate of 2.58/100 000 reported by Lewis et al. in the North-West Region of Cameroon[12] but lower than the 4.68/100 000 reported from the Yaoundé Cancer Registry.[10] The case ascertainment in this study and the study by Lewis and colleagues is likely to be less complete than that of Enow-Orock et al. because the data was extracted from hospital-based registries, while the Yaoundé Cancer Registry is a population-based registry, which is more complete in nature. Higher incidence rates have been reported elsewhere, with rates as high as 8.4/100 000 children below 15 years in Ibadan, Nigeria.[28] Reported rates elsewhere in Africa include 2.15/100 000 in Kenya[14]; 5.7/100 000 in Tanzania[29]; and 4.3/100 000 in Uganda.[30]

The drop in ASIR for the region from 2010 raises a question on whether there is a challenge with identifying and referring cases to the treatment centres or whether there is indeed a drop in the incidence rate of childhood cancer. One major issue surrounding childhood cancer care in Cameroon in general is the low level of community awareness about cancers in children and the availability of care.[31] With the creation of the childhood cancer centre in the region in 2003 at Banso Baptist Hospital, followed by another centre at Mbingo Baptist Hospital in 2006, childhood cancer care team members embarked on community sensitisation, leading to increased childhood cancer awareness in the region. This could arguably explain why BL diagnosis increased with a steep gradient between 2003 and 2005 and remained fairly high until 2010. However, the drop in registered number of BL patients below 15 years from 2010 despite continuous and intensified community sensitisation remains unexplained. A decline in BL incidence has been shown in Ibadan, Nigeria, a neighbouring country, by two different researchers, with incidence consistently decreasing with time.[20,32] Babatunde et al. warn that the decreased number of registered BL cases might be because of economic crisis, as many children are left to die at home with disease without being brought to the hospital.[20]

We identified the districts with the highest incidence rates of BL to include Nwa, Ndop, Benakuma, Ako and Nkambe. Clustering, which refers to the concentration of cases in particular areas, in the region has been reported in the past.[11,12] Previous studies highlight only the Ndop District as a cluster zone for BL in the region, with an incidence rate as high as 21.5 per 100 000 reported from 2003 to 2005[11] and 10.3 per 100 000 for the period from 2003 to 2010,[12] in contrast to this study, which found an incidence rate of 5.63 per 100 000 in Ndop. This study did not investigate the disease stage for cases nor the delay from onset of disease to diagnosis, but Hesseling et al. report a predominance of late stage disease in this population with 72% Stage III and 12% Stage IV at diagnosis.[8] This indicates a change in the high-risk areas for BL in the region and calls for refocusing of awareness creation and early diagnosis trainings to the new areas of high incidence to ensure that all patients are promptly diagnosed and referred for treatment. Clustering was also noticed in western Kenya[5] and has been reported to be associated to malaria endemicity.[4,5,6,7] The two districts with the highest ASIR of BL are also the districts of highest malaria incidence in 2015.[33] Investigating the association of BL with malaria in this region might provide some explanation for the observed clustering. Earlier studies in Kenya[5,34] and Malawi[7] have reported an association between BL and malaria incidence.

## Limitations

Cancer registration in Cameroon is not well developed. Until now BL registration in north-west Cameroon has only been in the form of hospital-based childhood cancer registries and pathology-based cancer registries. It is purported that many children with cancer in developing countries like Cameroon go unrecorded for several reasons including paucity of cancer registries.[35] In addition, there is the issue of non-identification of paediatric cancer patients, because of low paediatric cancer awareness in communities.[31]

## Conclusion

This study has provided information about the trends in incidence rate of BL in children below 15 years between 2003 and 2015. We have identified districts with high ASIR for BL, which should be targeted for awareness creation and early diagnosis trainings. The authors observe the possibility of incomplete case ascertainment in this study, which relied only on data from hospital-based and pathology registries. There is therefore need for a population-based childhood cancer registry in the region, which will use both active and passive surveillance methods to capture all the cases in the region. Further research is required to establish reasons why the ASIR is higher for some districts than others, as well as reasons for the drop in BL incidence in the region.

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### Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

### Authors' contributions

G.M.A. designed the study, collected and analysed data and wrote the manuscript. P.B.H. established the hospital-based registries, provided supervision to the principal investigator and contributed to the study design, data analysis and writing of the manuscript. P.A. contributed pathology registry data and contributed to the writing of the manuscript. R.B. contributed pathology registry data and contributed to the writing of the manuscript. K.F. contributed to data collection and writing of the manuscript.

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# Burkitt lymphoma – Nutritional support during induction treatment: Effect on anthropometric parameters and morbidity of treatment

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**Background:** Malnutrition is common in children diagnosed with cancer in Africa, and it adds to the morbidity and mortality of treatment. Nutritional support is known to reduce morbidity and mortality of treatment.

**Aim:** The aim of this study was to record changes in anthropometric parameters, morbidity and mortality in patients admitted with Burkitt lymphoma (BL) whose diet was supplemented with protein, vitamins and minerals during induction chemotherapy.

**Methods:** Seventy consecutive newly diagnosed BL patients were enrolled. The diet was supplemented with a daily egg, 200 mL F-75 formula and vitamins. Guardians received 3 cups of dry rice and $1 daily to buy and prepare meals for the patient and themselves whilst in the hospital. Height, weight, triceps skinfold (TSF) and mid-upper arm circumference (MUAC) were recorded on days 1 and 28. Co-morbidities at diagnosis were treated, and neutropenia and febrile episodes managed with a standard protocol. Two patients who died within 24 h after admission were excluded from the anthropometric analyses.

**Results:** The mean age was 8 (range 2–16) years and the male:female ratio was 42:28. The St Jude stage distribution was as follows: Stage I = 6%, II = 4%, III = 69%, IV = 21%. Weight for age was < 10th centile at diagnosis in 18% (but influenced by tumour mass). Weight was unchanged or increased by ≥ 5% in 66% of patients on Day 28. The TSF was < 3rd centile in 47% of patients and increased by ≥ 0.5 cm in 57%. The MUAC was < 3rd centile in 16% of patients at diagnosis and in 10% of patients on Day 28. Febrile episodes in 60% and neutropenia in 18% of patients were successfully treated. Two patients died from presumed renal failure. The overall death rate (including the two deaths within 24 h after admission before chemotherapy was started) was 5.5% ($n$ = 4).

**Conclusion:** The TSF improved in the majority and the MUAC improved in some patients. Febrile neutropenia and febrile episodes could be successfully managed. The death rate during induction was lower than in our previously published results with the same chemotherapy protocol. Dietary supplementation should be a standard component of treatment in paediatric patients with cancer.

## Introduction

Endemic Burkitt lymphoma (BL), a highly aggressive lymphoma, is the most common childhood cancer in sub-Saharan Africa. The age standardised rate is 3.3 in the sub-Saharan region and 2.6 in the north-west region of Cameroon.[1,2]

Limited resources, such as unaffordable or unavailable drugs and limited supportive care, have led to the development of treatment with high frequency cyclophosphamide (CPM) during induction therapy. A 61% one-year disease-free survival rate was recorded in Cameroon with this treatment protocol, compared to survival rates of ≥ 80% in developed countries.[3,4,5]

Families in north-west and south-west Cameroon are mainly poor subsistence farmers and often live far away from the treatment centre. Guardians have to stay in hospital with the patient, provide meals for their child and pay the hospital bills. In this study free treatment was provided.

Malnutrition (weight for age < 5th centile) was present in 50% of patients with BL in Malawi and in 30% of patients with BL in Cameroon on admission.[3,6] Tolerance for chemotherapy and survival

rates are influenced by the nutritional status.[7,8,9,10] Malnutrition is associated with a higher rate of neutropenia and serious infections, treatment delays, reduced chemotherapy tolerance and a poorer outcome.[8] The impact of nutritional status on outcomes in children with cancer is an important but neglected area of research.[11] Prevention of early deaths during the induction phase of treatment is important to improve the overall survival rate.

The majority (85%) of BL patients have advanced disease and a large abdominal facial tumour burden, and they may eat and drink poorly during the first 3 days of treatment.[3,6]

Weight for age (W/A) is an inaccurate parameter of nutrition in the acute setting. Weight for height (W/H) is a better parameter of nutrition but may be influenced by factors such as tumour mass, oedema and ascites on admission in children with large tumours. The triceps skinfold (TSF), an indicator of body fat, and the mid-upper arm circumference (MUAC), an indicator of lean body mass, correlate with the golden standard of body composition, the DEXA scan, and are more appropriate objective measurements of nutrition.[11,12,13] The 5th centile for TSF in patients aged 4 to 14 years ranges from 5 mm to 6 mm in boys and from 6 mm to 8 mm in girls. The 5th centile for MUAC ranges from 126 mm to 172 mm in boys and 115 mm to 174 mm in girls.[14]

The objective of this descriptive prospective study was to document the anthropometric parameters and co-morbidities in newly diagnosed BL patients, to record morbidity of treatment and to measure the changes in anthropometric parameters during the 28-day induction treatment period in patients who received a standardised treatment protocol and a daily dietary supplement of protein, minerals and vitamins.

## Methods

The study was supervised by a resident paediatrician (MT). Seventy-two consecutive patients were admitted with BL between April 2010 and March 2011 to the Banso, Mbingo and Mutengene Baptist Hospitals in the north-west and south-west regions of Cameroon. Two patients who died of advanced disease within 24 h of admission were excluded from anthropometric analysis. Standard diagnostic procedures on admission included fine needle aspiration (FNA), an abdominal ultrasound (US) with measurement of the largest intra-abdominal mass, bone marrow aspiration (BM), cerebrospinal fluid (CSF) cytology, a full blood count (FBC), malaria smear, sickle cell test, human immunodeficiency virus (HIV) screening test, urinalysis and microscopy of faeces. The FBC was repeated before every chemotherapy pulse on days 8 and 14 and when fever occurred. The St Jude staging system was used.[15]

All patients were treated with the 2008 Cameroon BL protocol. Induction therapy commenced with 48 h of parenteral hydration at 3L/M$^2$ and oral allopurinol to prevent tumour lysis. A metoclopramide tablet was given 2 h before and 4 h after chemotherapy to prevent vomiting. Furosemide was used when needed to achieve a target urinary output of ≥ 3 mL/kg/h during the first 48 h. Chemotherapy was started 24 h after the onset of hydration and consisted of 40 mg/kg CPM (oral or intravenous), 12.5 mg intrathecal methotrexate and 12.5 mg intrathecal hydrocortisone on days 1, 8 and 15. The response to treatment was assessed on Day 28 by clinical assessment and abdominal US prior to starting maintenance chemotherapy. The response to and outcome of treatment will not be discussed in this article.

Every patient received a boiled egg, 200 mL of World Health Organization (WHO) F-75 formula and a multivitamin tablet as inpatients every day during the first 14 days, and guardians were provided with eggs and multivitamin tablets on discharge to be given daily at home until the follow-up visit on Day 28. Guardians, who have to stay with the patient in the ward, received a daily ration of three cups of dry rice and $1 in cash to buy and prepare local food for their child and themselves. Parenteral nutrition was not available. Parents in general strongly object to nasogastric tube feeding, and this was rarely used.

Anthropometric observations included measurement of weight (W) in kg and height (H), MUAC and TSF in cm, with a standardised scale, Harpenden calliper and a United Nations Children's Fund (UNICEF) measuring tape on days 1 and 28. Nurses were trained to perform these measurements. Two successive measurements were performed and the average value was recorded. Percentiles of W/A, H/A and body mass index (BMI) were determined with WHO Anthroplus software. Weight-for-age percentiles were only determined in children ≤ 10 years because WHO standards above age 10 years are not available.[14,15]

Coexisting diseases such as malaria and urinary or intestinal parasites were treated. A blood transfusion was considered when the haemoglobin dropped ≤ 7 g/dl. Neutropenia was defined as a total white blood cell count of ≤ 1.0 × 10$^9$/L. Fever was defined as a single episode of a temperature of ≥ 38.5°C or two episodes ≥ 38°C within a 24-hour period. A malaria smear was performed immediately, and treatment was given if found positive. If negative, first-line antibiotic treatment with intravenous gentamicin and ampicillin was started immediately irrespective of the white cell count. Blood cultures were not available. A cephalosporin was added if fever persisted > 48 h. Mucositis was treated with oral nystatin and acyclovir. The full cost of treatment, including hospitalisation, investigations, all medicines and transport for follow-up visits, was provided at no cost to the guardians.

The treatment protocol was approved by the Institutional Review Board of the Cameroon Baptist Convention and parents gave informed signed consent.

## Results

The 70 study patients included 42 boys and 28 girls with a mean age of 8 (range 2 to 16) years. Burkitt lymphoma was

confirmed on FNA in 76% and in the remainder on BM, CSF, abdominal US and clinical presentation. A marked reduction in tumour volume within 48 h was accepted as confirmation of the diagnosis in patients with a clinical diagnosis. The St Jude stage distribution was as follows: Stage I = 4 (6%), Stage II = 3 (4%), Stage III = 48 (69%) and Stage IV = 15 (21%). The US volume of the largest single abdominal mass (there usually are multiple masses) was > 400 mL in 32% of patients and < 400 mL in 49% of patients. The volume of the largest abdominal mass recorded exceeded 3000 mL. Abdominal US indicated ascites in two patients and a small pleural effusion in one patient.

On admission H/A was less than the 10th centile in 28 (42%), W/A less than the 10th centile in 12 (18%), and BMI less than the 10th centile in 50% of patients aged > 10 years. The TSF was less than the 3rd WHO centile in 46%, and the MUAC less than the 3rd WHO centile in 16% of patients.[16] On Day 28 the TSF had increased by 0.5 cm in 69%, and the MUAC was now less than or equal to the 3rd centile in 10% of patients (Table 1). Weight loss of ≥ 5% of body weight was recorded in 42% of patients, and weight gain in 24% of patients. Fifty per cent of patients, with a largest recorded single abdominal tumour of < 400 mL in volume, gained weight during induction therapy. Five of seven patients without abdominal masses (St Jude Stages I and II) gained > 1 kg in weight, and six of these patients had an increase in TSF of > 5 mm. Anthropometric data are summarised in Table 1, and individual patients' changes in TSF and MUAC are illustrated in Figure 1. Weight and height were not recorded in two and four patients, respectively, on admission, and height on Day 28 was not recorded in 11 patients.

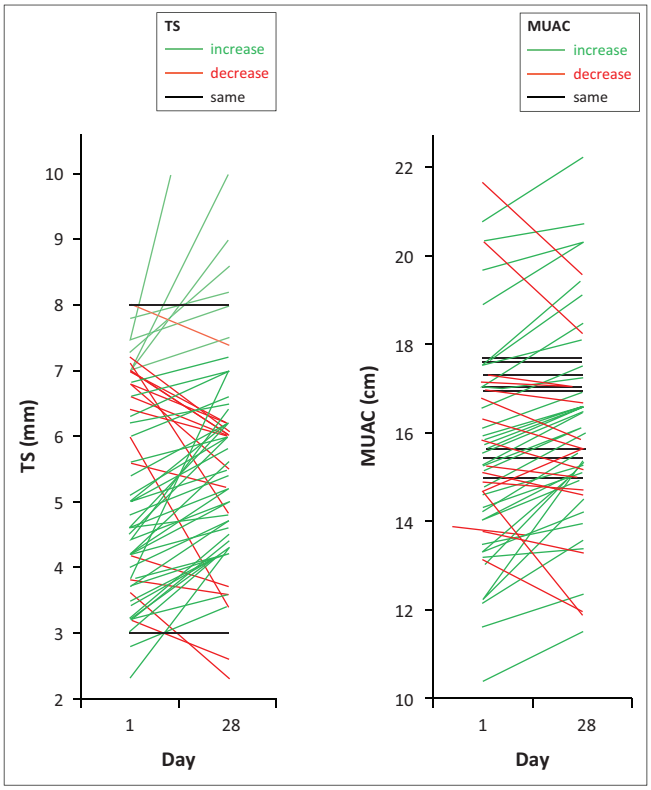
Two patients (3%) died from presumed tumour lysis and renal failure shortly after the first course of chemotherapy. Co-morbidities at diagnosis included malaria, sickle cell trait, intestinal parasites, schistosomiasis and HIV sero-positivity and are listed in Table 2. Three patients developed renal failure after the first dose of chemotherapy, of whom two died within the first week. Neutropenia occurred in 12 (18%), febrile episodes in 42 (60%) and prolonged fever in 17 (24%) of patients. Fourteen patients (20%) received a blood transfusion. Other complications observed were diarrhoea and vomiting, mucositis, cough, dental problems, wound infection, chickenpox, skin infection and anal prolapse (which corrected spontaneously) (see Table 3). No other deaths occurred during the 28-day induction treatment period.

The limitations of this study, such as the unavailability of microbiological cultures, an intensive care unit, renal dialysis and parenteral feeding, were a result of the limited resources that were available in this setting at the time. We did not record the type and quantity of food that the parents gave to their children in addition to the daily dietary supplements.

**TABLE 1:** Anthropometric parameters on days 1 and 28.

| Parameters | Day 1 (%) | Day 28 (%) |
|---|---|---|
| Weight for age < 10th centile | 18 | - |
| Weight gain ≥ 5% | - | 21 |
| Weight loss ≥ 5% | - | 34 |
| Weight unchanged | - | 45 |
| Height for age < 10th centile | 42 | - |
| Body mass index < 10th centile | 50 | - |
| MUAC < 3rd centile | 16 | 10 |
| TSF increase > 0.5 cm | - | 57 |
| TSF < 3rd centile | 47 | - |

MUAC, mid-upper arm circumference; TSF, triceps skinfold.




MUAC, mid-upper arm circumference; TSF, triceps skinfold.

**FIGURE 1:** Changes in triceps skinfold and mid-upper arm circumference.

**TABLE 2:** Co-morbidities on admission in 70 patients.

| Co-morbidity | Number | Percentage |
|---|---|---|
| Malaria | 6 | 9 |
| Sickle cell trait | 5 | 7 |
| Intestinal parasites | 7 | 10 |
| Schistosomiasis | 1 | 1 |
| HIV seropositive | 2 | 2 |

HIV, human immunodeficiency virus.

**TABLE 3:** Morbidity during treatment.

| Event | Number | Percentage |
|---|---|---|
| Febrile episode | 42 | 60 |
| Fever > 48 h | 17 | 24 |
| Neutropenia | 12 | 18 |
| Diarrhoea, vomiting, gastroenteritis | 9 | 13 |
| Blood transfusion | 14 | 20 |
| Mucositis | 4 | 6 |
| Cough | 2 | 3 |
| Dental problems | 2 | 3 |
| Varicella | 1 | 1 |
| Skin infection | 1 | 1 |
| Wound infection | 2 | 3 |
| Anal prolapse | 1 | 1 |

## Discussion

The H/A was less than the 10th centile in 42% and the W/A less than the 10th centile in 18% of patients. This confirms the high prevalence of poor nutrition in patients with BL at diagnosis. However weight reflects the short-term nutritional status at diagnosis and is overestimated in patients who have a large total tumour mass at diagnosis. Weight gain by Day 28 was recorded in 21% of all the patients but in 71% (5/7) of patients who had no abdominal masses (Stage I and II disease) and in 50% of children who presented with smaller abdominal tumours. Co-morbidities such as malaria and intestinal parasites, which may adversely affect the nutritional state, were identified and fully treated on admission.

The egg, 200 mL of F75 and multivitamin tablet, which provided a minimum daily intake of 8 g of good quality protein and additional vitamins, minerals and trace elements, was supplemented by the food (mainly rice, maize, vegetables and fruit) that the parents prepared.

An increase of the TSF in 57% of patients, and a reduction in the number of children with a MUAC less than the third centile from 16% to 10%, indicates that the nutritional support had a positive effect. Fever, febrile episodes and co-morbidities were managed without serious consequences. Laboratory facilities were too limited to accurately quantify renal function.

There were two deaths during induction treatment, constituting a 2.8% death rate during treatment. If the two patients who died before chemotherapy was commenced are added, the overall death rate was 5.5% (4/72). No patients abandoned treatment. This death rate is significantly lower ($P = 0.009$, $p < 0.5$) than the 8.5% (24/129) rate recorded in a cohort of patients who had previously been treated with the same chemotherapy protocol at the same hospitals, but for whom the nutritional support provided was limited.[3] The French–African Paediatric Oncology Group reported a 5.1% death rate with CPM induction treatment in 178 patients, but their exclusion of 79 patients from the analysis for unspecified reasons does not allow for a fair comparison.[17] In a recent Malawian study, doxorubicin was added to CPM during induction, and a 12% death rate was reported during the first 28 days. Ten of the seventy-eight Malawian patients, however, died before treatment was instituted and were not included as early deaths.[18] All episodes of neutropenia and fever were successfully treated. The two deaths from renal failure may have been prevented if renal dialysis had been available.

We could find no publications on the changes in nutritional status and the effect of dietary support during the first month of treatment in children with endemic BL with which to compare our findings.

Although supplements of protein, vitamins and trace elements were provided, we did not record the type and quantity of food that the parents prepared and gave to their children. We intend to provide an optimal diet to our patients in the future and to educate parents how best to prepare available and affordable local food with the help of trained dieticians.

## Conclusion

We have demonstrated that good enteral nutritional support during induction chemotherapy in a malnourished population of patients with BL resulted in an improvement in nutritional parameters in the majority of patients and was associated with a low morbidity and death rate during induction treatment. Nutritional support should be a standard component of treatment in all children with cancer.

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### Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

### Authors' contributions

P.B.H. was the principal investigator. M.T. was the physician conducting study at the Banso Baptist Hospital. E.L. was responsible for expert advice on nutrition. G.A. was responsible for the data collection and management. F.K. was the physician conducting study at the Mbingo Baptist Hospital. E.K. was the physician conducting study at the Mutengene Baptist Hospital.

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HEALTHCARE DELIVERY

# Burkitt's lymphoma: The prevalence of HIV/AIDS and the outcome of treatment

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The prevalence of HIV in Burkitt's lymphoma (BL) patients and the outcome of treatment in Cameroon were unknown. Records of all patients diagnosed with BL at three Cameroon Baptist Convention hospitals were reviewed to ascertain the recorded HIV status and outcome of treatment. Of 979 patients diagnosed with BL, 717 were tested for HIV and 11 (1.5%) were HIV-positive. Three of eight patients treated with both cyclophosphamide (CPM)-based chemotherapy and antiretrovirals were alive at 62, 96 and 111 months, respectively. The HIV rate was comparable to that of 1% for the general population of children aged <15 years. Low-cost high-frequency CPM was the only available treatment option for BL and was associated with 37.5% long-term survival in a resource-limited setting.

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The population of Cameroon in 2014 was 22 773 014, of whom ~40% (9 109 205) were aged <15 years. It was estimated that 94 000 of these children (1%) were infected with HIV, and only 11% of these received antiretroviral (ARV) therapy.[1] In 2013, the prevalence of HIV infection in pregnant women in the north-west and south-west regions was 4.6% and 6.8%, respectively, and the mother-to-child transmission rate in 18-month-old breastfed infants was 25%.[1] Children diagnosed with Burkitt's lymphoma (BL) between 2003 and 2015 at Banso and Mbingo Baptist hospitals in the north-west and Mutengene Baptist Hospital in the south-west were all treated with cyclophosphamide-based chemotherapy regimens, with an overall long-term survival rate of 55%.[2]

## Objective

To record the prevalence of HIV and the outcome of treatment in a large cohort of patients with BL.

## Methods

Our database is a Pediatric Oncology Network Database (POND) cancer registry for the period 2003 - 2013. The number of patients in whom enzyme-linked immunosorbent assay was positive for HIV, the CD4+ count when available, and whether ARV treatment was given or not were extracted from the database. The diagnosis of BL was based on a fine-needle tumour aspirate, a bone marrow aspirate, a cytological cerebrospinal fluid examination and an abdominal ultrasound scan. The long-term outcome was established by personal follow-up of every HIV-positive patient or their families. Chemotherapy induction treatment consisted of cyclophosphamide (CPM) 40 mg/kg on days 1, 8 and 15, followed by consolidation chemotherapy with 1 - 3 more doses of CPM with or without intravenous (IV) vincristine 1.5 mg/m$^2$ and IV methotrexate 1.0 g/m$^2$ for advanced or non-responsive disease. The duration of chemotherapy was 2 months. Rescue treatment of early relapses consisted of 3 weekly pulses of CPM and vincristine, and relapses beyond 1 year were treated in full again.[3] ARV treatment was not freely available in the early years of the study. More recent treatment always consisted of three drugs, based on World Health Organization guidelines and the national protocol. Examples of first-line treatment are as follows: age <3 years – abacavir + lamivudine + lopinavir/ritonavir; age 3 - 10 years and adolescents weighing <35 kg – abacavir + lamivudine + efavirenz; and age 11 - 19 years or weight >35 kg – tenofovir + lamivudine (or emtricitabine) + efavirenz.

Ethical approval for the BL treatment protocols was obtained from the Institutional Review Board of the Cameroon Baptist Convention Health Board.

## Results

Of 979 patients diagnosed with BL, 717 (73.2%) were tested for HIV and 11 (1.5%) tested positive. Their ages ranged from 2 to 13 years (median 7 years). The age at diagnosis of BL, St Jude stage of the BL, CD4+ count if done, ARV treatment given, current status and duration of long-term survival are listed in Table 1. On 30 October 2016, three of eight patients (37.5%) who had received the recommended ARV treatment and were still on ARV maintenance treatment were long-term survivors at 111, 96 and 62 months, respectively. Three patients who were not treated with ARVs died within 3 - 15 months, and five patients treated with ARVs died within 3 - 39 months after the onset of treatment from progressive disease. There was no chemotherapy-related death. The CD4+ count at diagnosis was recorded in only four patients.

## Discussion

Children with HIV have an increased risk of developing malignancies, and BL accounted for 21% of malignancies in HIV-positive children in South Africa, with a projected cure rate of 54.6% at 60 months using modern chemotherapy.[4] Modern chemotherapy for BL has a potential cure rate of >90% in HIV-negative patients,[5] but at considerable cost and the risk of significant morbidity. Our BL

**Table 1. Patient details and outcome**

| Patient no. | Age (years) | St Jude stage | CD4+ count (cells/μL) | ARV treatment | Current status | Length of survival (months) |
|---|---|---|---|---|---|---|
| 1 | 5 | III | No record | No | Dead | 15 |
| 2 | 12 | III | 145 | Yes | Dead | 6 |
| 3 | 7 | III | No record | Yes | Alive | 96 |
| 4 | 3 | III | 559 | Yes | Alive | 111 |
| 5 | 9 | III | No record | No | Dead | 3 |
| 6 | 2 | III | No record | Yes | Alive | 62 |
| 7 | 4 | II | No record | Yes | Dead | 4 |
| 8 | 3 | III | No record | No | Dead | 3 |
| 9 | 8 | III | No record | Yes | Dead | 39 |
| 10 | 12 | IV | 80 | Yes | Dead | 39 |
| 11 | 13 | III | 30 | Yes | Dead | 3 |

ARV = antiretroviral.

patients were treated with chemotherapy of much lower intensity because of limited access to drugs and supportive care.[6] Long-term survival of 5 - 9 years in three of eight patients (37.5%) who received both chemotherapy and ARVs is encouraging. The documented HIV prevalence rate of 1.5% in this large cohort of BL patients is comparable to the 1% HIV prevalence rate for the general population of children in Cameroon.

## Conclusion

HIV-positive children with BL are best treated with a context-appropriate chemotherapy regimen.

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**Author contributions.** PBH: Principal investigator, FK: physician in charge of the children's cancer service, EK: physician in charge of the HIV service of the Cameroon Baptist Convention Health Board, GM: research assistant responsible for the cancer registry and data co-ordination, PW: involved in planning and follow-up.

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# Improved outcome at end of treatment in the collaborative Wilms tumour Africa project

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## Abstract

**Background:** The Collaborative Wilms Tumour (WT) Africa Project has implemented an adapted WT treatment guideline in sub-Saharan Africa as a multi-centre prospective clinical trial. A retrospective, baseline evaluation of end-of-treatment outcome was performed for a 2-year period prior to the introduction of this guideline. The collaborative project aims to reduce both treatment abandonment and death during treatment to less than 10% for improving survival.

**Procedure:** All participating centres obtained local Institutional Research Board (IRB) approval and implemented the adapted WT treatment guideline. End-of-treatment outcome was documented for 2 years. It was divided into alive without evidence of disease, treatment abandonment, death during treatment and persistent disease. The outcome of children enroled in the first 2 years of the prospective clinical trial has been compared to the outcome before the start of the project.

**Results:** One hundred twenty-two patients were included in the baseline evaluation (2011–2012) and 133 in the first 2 years of the collaborative clinical trial (2014–2015). The percentage of patients alive without evidence of disease at the end of treatment increased from 52% (63/122) to 68% (90/133; $P = 0.01$). Treatment abandonment decreased from 23% (28/122) to 13% (17/133; $P = 0.03$). Death during treatment decreased from 21% (26/122) to 13% (17/133; $P = 0.07$).

**Conclusion:** This collaboration, using relatively simple and low-cost interventions, led to a significant decrease in treatment abandonment and increase in survival without evidence of disease at the end of treatment.

Abbreviations: EFS, event-free survival; PODC, Pediatric Oncology in Developing Countries; SIOP, International Society of Pediatric Oncology; WT, Wilms tumour

KEYWORDS
adapted treatment guideline, Africa, low-income countries, regional network, survival, Wilms tumour

## 1 | INTRODUCTION

Wilms tumour (WT) is a relatively common childhood renal cancer.[1] In high-income countries, survival of children with WT has improved over the last half century from around 30% to over 85%.[2,3] WT is treated with a combination of surgery and chemotherapy, with radiotherapy for a small group of children with higher risk tumours.[4]

In sub-Saharan Africa, reported survival rates are much lower, ranging from 11% in Sudan in 1990, where most children did not complete treatment, to 46% in Malawi and the French African Paediatric Oncology Group (GFAOP).[5–8]

In Blantyre, Malawi, an adapted WT treatment guideline with International Society of Paediatric Oncology (SIOP) based preoperative chemotherapy adapted supportive care and nutritional and social support was introduced in 2007.[9,10] Two-year event-free survival (EFS) improved from <25% to 46%.[7,11,12] Treatment abandonment decreased from over 60% to 6%.[7,11]

The Paediatric Oncology in Developing Countries (PODC) committee of SIOP published a consensus-adapted treatment guideline for WT and concomitant supportive care in low-income countries.[13,14] This WT treatment guideline is based on the SIOP WT 2001 protocol and on previous experience in Malawi and other low-income countries. It includes preoperative chemotherapy with a reduced dosage of doxorubicin compared to the SIOP main protocol – optional chemotherapy prolongation for large, localised tumours and a simplified postoperative chemotherapy stratification which allows for the absence of radiotherapy. There is a detailed section on adapted supportive care with recommendations for nutritional support, pain management and febrile neutropenia based on SIOP PODC guidelines.[14] The treatment guideline also includes a chapter on strategies and recommendations to prevent abandonment.[15] These strategies included free treatment for poor families to enable them complete treatment, social support which included meals for patients and travel costs, and if possible a place to stay for poor families. Counselling of parents about the nature of the disease and the importance of completing treatment was an integral aspect of management.[15] The SIOP Africa/PODC Collaborative WT Africa Project has implemented this comprehensive WT guideline in eight centres in five sub-Saharan African countries as a prospective clinical trial with uniform outcome evaluation (Supplementary Fig. S1 shows a map of Africa and participating centres).[16,17]

The aim of the collaborative project is to reduce both treatment abandonment and death during treatment to less than 10% and to increase 2-year EFS to 50%.[16,18] Enrolment started in January 2014 and is still continued. In this paper, we review the rate of treatment abandonment or death during treatment by comparing the end-of-treatment outcome of patients enroled in the first 2 years of the collaborative clinical trial to the outcome of patients for 2 years before the start of the project.

## 2 | METHODS

A baseline evaluation was carried out in participating centres prior to the implementation of the treatment guideline.[19] This baseline evaluation documented the end-of-treatment outcome of patients and existing facilities and practices in each centre, including details on supportive care and abandonment-related aspects.[19]

All participating centres obtained local Institutional Research Board (IRB) approval and implemented the adapted SIOP PODC treatment guideline with a uniform outcome evaluation (clinical trial registration number NCT01991652). Patients were included prospectively from January 2014 for a 2-year period in centres in Malawi (Blantyre), Cameroon (Mbingo, Banso, Mutengene) and Ghana (Accra and Kumasi). The National Cancer Institute in Uganda, Kampala, was included in the baseline outcome data but is not participating in the clinical trial, so the data from this institute were excluded from analyses. The centres – in Harare, Zimbabwe and Addis Ababa, Ethiopia – only joined the collaboration in 2016 and the data from these centres are also not included.

Patient data were collected locally from patient registration forms, sent to the coordinator and entered into a central SPSS database. Outcome of the patients at the end of treatment was documented and divided into four categories: (i) alive without evidence of disease, (ii) treatment abandonment (incomplete treatment), (iii) death during treatment and (iv) persistent disease (unresectable disease, relapse of disease, persistent disease after the completion of the full treatment). Evaluation in the baseline evaluation was performed through a retrospective file which made it infeasible to collect more detailed characteristics of patient and tumour, such as tumour size, metastatic disease and pathology reports. The outcome data are compared with the end-of-treatment outcome in the baseline evaluation. Statistical analysis was performed using IBM SPSS statistics 22.0; a $P$-value of $<0.05$ was considered significant.

All children younger than 18 years who presented at the participating centres with an abdominal mass compatible with a clinical and ultrasound diagnosis of a renal (Wilms) tumour were included in the prospective collaborative clinical trial. They all had a chest X-ray and ultrasound of the liver to document metastases. Patients were excluded later when findings during treatment, for example, at pre-operative imaging, surgery or histology, were incompatible with WT. The baseline evaluation documented the existing treatment

practices in each centre. In summary, the centres in Ethiopia, Malawi and Cameroon were already using the SIOP PODC treatment guideline, centres in Ghana were using the standard SIOP WT protocol and reduced preoperative doxorubicin dosage when adopting the collaborative protocol. Both centres in Ghana (Kumasi and Accra) have access to radiotherapy and used this therapy for post-operative treatment in the collaborative protocol, the centres in Malawi (Blantyre) and Cameroon (Mbingo, Banso, Mutengene) do not.

The baseline evaluation documented some information about the estimated cost of different aspects of treatment and which cost were covered by the government, by health insurance (if available) and by the oncology programme with external support (if available).[19] Estimated remaining costs of treatment for parents ranged from US$ 100 to 1,100 and was considered an important cause of failure to complete treatment. Aspects of associated costs (money for travel, board and lodging, food during stay in the hospital) were also documented. In the collaborative project, part of the funding was used to decrease costs for parents. The way this was performed differed from centre to centre. Some used it to pay treatment costs (centres in Ghana), others used it to improve social support (centres in Malawi, Cameroon). The baseline evaluation documented who was involved in counselling, and in the collaborative project we agreed to continue to aim for adequate counselling on the nature of the disease and the importance of completing treatment.[15] All relevant and available contact information is documented at admission and kept in the file, preferably on a sheet with a different colour. A diary with an overview of scheduled patient visits was maintained and patients are called or contacted if they fail to attend.

The analysis includes 2 years before and 2 years after the start of the collaborative clinical trial and evaluates and compares the end-of-treatment outcome of patients with a focus on treatment abandonment and death during treatment.

## 3 | RESULTS

### 3.1 | End-of-treatment outcome—Baseline (2011 and 2012)

A total of 122 children were included in the baseline evaluation, 22 from Kumasi, 24 from Accra, 59 from Blantyre and 17 from Cameroon. Sixty-three (52%) patients were alive without evidence of disease at the end of treatment, 28 (23%) abandoned treatment and 26 (21%) died during treatment. Five (4%) children had persistent disease (Table 1).

### 3.2 | End-of-treatment outcome—Prospective clinical trial (2014 and 2015)

Patient enrolment started in January 2014 and all children who were diagnosed in the first 2-year period of the collaboration are included in the analysis. A total of 144 patients were enroled initially. Eleven (8%) were later found to have another diagnosis, five of whom had the Burkitt lymphoma. The end-of-treatment outcome was evaluated

**TABLE 1** Outcome at the end of treatment in the different centres at baseline evaluation and in the prospective clinical trial during a 2-year period

| | KATH[a] | | KBTH[b] | | QECH[c] | | MM&B[d] | | All centres | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2011–2012 | 2014–2015 | 2011–2012 | 2014–2015 | 2011–2012 | 2014–2015 | 2011–2012 | 2014–2015 | 2011–2012 | 2014–2015 |
| Alive, no evidence of disease | 7 (32%) | 6 (55%) | 11 (46%) | 34 (77%) | 36 (61%) | 29 (60%) | 9 (53%) | 21 (70%) | 63 (52%) | 90 (68%), $P = 0.01$ |
| Abandonment of treatment | 7 (32%) | 3 (27%) | 10 (42%) | 5 (11%) | 8 (14%) | 6 (13%) | 3 (18%) | 3 (10%) | 28 (23%) | 17 (13%) $P = 0.03$ |
| Death during treatment | 7 (32%) | 1 (9%) | 3 (13%) | 2 (5%) | 12 (20%) | 10 (21%) | 4 (24%) | 4 (13%) | 26 (21%) | 17 (13%) $P = 0.07$ |
| Persistent disease or relapse | 1 (5%) | 1 (9%) | 0 (0%) | 3 (7%) | 3 (5%) | 2 (4%) | 1 (6%) | 2 (7%) | 5 (4%) | 8 (6%) N.S. |
| Death other cause | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%), N.S. |
| Total | 22 (100%) | 11 (100%) | 24 (100%) | 44 (100%) | 59 (100%) | 48 (100%) | 17 (100%) | 30 (100%) | 122 (100%) | 133 (100%) |

N.S., not significant.
[a]Komfo Anokye Teaching Hospital, Kumasi, Ghana.
[b]Korle Bu Teaching Hospital, Accra, Ghana.
[c]Queen Elizabeth Central Hospital, Blantyre, Malawi.
[d]Mbingo, Mutengene & Banso Baptist Hospitals, Cameroon.

for the remaining 133 patients, all of whom had received treatment according to the SIOP PODC adapted treatment guideline. Ninety patients (68%) were alive without evidence of disease at the treatment completion, 17 (13%) had abandoned treatment and 17 (13%) died during treatment. Eight children (6%) had persistent disease (Table 1). One child died of an accident during post-operative chemotherapy.

### 3.3 | Comparison of end-of-treatment outcome before and after the start of the collaborative Wilms tumour Africa project

The percentage of patients alive without evidence of disease at the end of treatment increased from 52% to 68% ($P = 0.01$). The treatment abandonment decreased from 23% to 13% ($P = 0.03$). Death during treatment decreased from 21% to 13% ($P = 0.07$, not significant). The percentage of patients with persistent disease at the end of treatment was 4% in the baseline and 5% in the current evaluation.

## 4 | DISCUSSION

This paper is a report of one of the few multicentre, prospective, clinical trials in childhood cancer in Anglophone sub-Saharan Africa.[6,17,20] It is relevant and useful to analyse the end-of-treatment outcome in low-income countries. Reliable outcome data with longer follow-up are often not available and are difficult to obtain. Treatment abandonment and death during treatment are often major causes of treatment failure. The end-of-treatment outcome can help evaluating and direct interventions aimed at reducing these two causes.

In our study, the percentage of patients alive without evidence of disease at the end of treatment increased from 52% to 68% ($P = 0.01$). This significant increase was achieved by relatively simple and low-cost interventions which helped to decrease incomplete treatment and toxic deaths.

Treatment abandonment decreased from 23% to 13% ($P = 0.03$). Financial support for medical treatment and associated costs combined with careful parental counselling about the need to complete treatment may have led to decreased abandonment. In the baseline evaluation, estimated cost of treatment for parents ranged from US$ 100 to 1,100 and was considered an important cause of incomplete treatment.[19] Treatment abandonment is the most common cause of treatment failure in low-income countries and largely preventable with financial support.[21–23] The aim of the project is to decrease abandonment to below 10%.[16] We know from previous experience in Malawi, where it was reduced to 6%, that this is possible with these simple but appropriate interventions.[7]

Death during treatment – assumed to be treatment related – decreased from 21% to 13%. This reduction was of borderline statistical significance, possibly because of small sample size. Improved supportive care and monitoring, and by simply being in a study, may have contributed to this decrease. The reduced preoperative doxorubicin dose (from doses of 50 to 30 mg/m$^2$) probably has also contributed to this decrease. The doxorubin dose was reduced because of the high rate of neutropenia and treatment-related mortality in malnourished Malawian children who received the higher dose (50 mg/m$^2$) before the start of the collaborative project.[9,24] The collaborative WT Africa project aims to reduce deaths during treatment to less than 10%.

The study has several limitations. The baseline evaluation of outcome was based on a retrospective file analysis, and files may have been incomplete. Files may have been lost, as may have been the case in Accra where patient numbers increased. In our experience, losing files is more likely for children who die or do not complete treatment than for children who do well. The retrospective nature of the baseline study also limited the details of data we could reliably collect making clinical and histological comparisons difficult.

Five percent of children had persistent disease at the end of treatment. With longer follow-up, more children will relapse. In Malawi (2009–2010), 15% of children relapsed after treatment, with 46% EFS after a median follow-up of 18 months.[7] Long-term follow-up, as planned in this collaborative project, will reveal post-treatment relapses time of disease-related mortality, long-term survival and the effects of surgical stage of disease, metastatic disease and intensity of treatment can be assessed. At present, the estimated 2-year EFS has increased from about 35% to 50% based on the end-of-treatment outcome and previously documented relapse rate in Malawi.[7] But this result must be interpreted with caution and we await long-term follow-up.

About 10% of patients who were initially enroled with a renal tumour were not diagnosed as WT after imaging or surgery. This is similar to the rate of misdiagnosis in Malawi.[7] Misdiagnosis is rare in high-income countries. Expert ultrasonography can differentiate a renal tumour from other malignancies, though this can be difficult in very large tumours.[13] A good-quality fine-needle aspirate (FNA, cytology) can help to exclude endemic Burkitt lymphoma which was the final diagnosis in half of the patients who were initially thought to have a renal tumour. A regional ultrasonography training meeting is planned in May 2018 to help improve ultrasound diagnosis.

## 5 | CONCLUSION

Relatively simple, low-cost interventions have led to a significant decrease in the treatment abandonment and increase in survival at the end of treatment. Sharing similar local challenges in this regional collaborative project helps to identify feasible, sustainable and successful strategies to improve outcome.

### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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# Data collection in the Collaborative Wilms Tumour Africa Project

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## 1. Introduction

Data matters. Carefully collected and documented evidence gives confidence to clinical management, is essential for the planning of future health needs and forms the basis of a cancer registry. Data are the foundation on which protocols, prognostications, follow up and supportive care are based; and data are only relevant if appropriate to the children from the settings where the data are collected. Evidence is also helpful in international collaborations to inform others who have not worked in a similar setting. Proper data is essential for adequate resource mobilization and distribution. (see Figs. 1–5).

All clinical trials require careful documentation and can help improve the care of children with cancer, including in sub-Saharan Africa [1]. The Collaborative Wilms Tumour Africa Project is implementing a consensus-adapted treatment guideline as a prospective clinical trial with uniform outcome evaluation. This is being undertaken in eight centres in Malawi, Cameroon, Ghana, Zimbabwe and Ethiopia. Enrolment started in 2014. The project is funded by World Child Cancer and the International Society of Pediatric Oncology (SIOP). The overall aim is to increase survival to more than 50% and to decrease both abandonment of treatment and death during treatment to less than 10%. To understand and thereby reduce deaths and decrease abandonment requires careful and detailed documentation of the problems faced by families and children with cancer in the setting in which the children are treated. This project is collecting hospital-based data which can answer questions about patient presentation to hospital and outcomes of treatment. Population-based cancer registration is necessary to understand the prevalence of cancers. Knowing how common a cancer is would help us understand the lack or otherwise failure of access to care. Unfortunately these registers are very limited in sub-Saharan Africa.

We aim to achieve improved, long-term results by giving priority to interventions with most impact on childhood cancer care and survival. Local teams decide on which interventions to prioritise and how to assess feasibility. We try to keep things as simple as possible and to do 'simple things' well. Additionally, we realize we can only improve and implement interventions step by step. We applied these same 'principles' when developing and implementing the data collection and management structure. Our systems for data collection and data entry are simple but could be improved. Data entry has to be checked centrally as double entry cannot be done locally and data are transferred in a password controlled dropbox. Improvements are possible in data monitoring, control and electronic data entry; all require funding.

In March 2013, at the beginning of the collaborative project, a three-day work meeting was held in Blantyre, Malawi. Team leaders and the principal co-ordinator attended from Cameroon, Accra (Ghana), Blantyre (Malawi) and Kampala (Uganda). Together, we developed the treatment guideline, defined locally relevant clinical questions and designed the case registration forms (CRFs). Each individual item on the CRF was checked to decide whether it should be included, and conclusions were by consensus agreement.

As a draft template we used the case record form of the SIOP renal tumour study group that had been modified (simplified) for use in Malawi. Pathologists and surgeons from each local centre were asked to modify their sections as they saw fit. For example, at the surgeons' suggestion, the surgical section starts with a simple question: 'At operation does it look like a Wilms tumour: yes/no, if

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**Fig. 1.** Archive of medical files in Blantyre, Malawi.

**Fig. 2.** The person is more important than the system - Dalida Pidini, data manager in Blantyre, Malawi.

no – please specify'.

We sometimes had to find a good compromise. For example, we wanted to document the size of the tumour at diagnosis and after preoperative chemotherapy to assess the response. It was expected that imaging techniques (ultrasonography, CT scan or MRI) with reliable measurement of size would not always be available. Since size was considered important enough to document we decided to include an estimation of tumour size, as measured with a ruler, and the clinician's assessment of response, although subjective.

The time spent together in designing the data entry form has been a good investment. No data field is redundant and through discussion we obtained better insight into which data were feasible to collect and what was too ambitious. Additionally, it enhanced local ownership and active participation of individual centres and their leaders.

We want to keep data entry simple and accessible. The CRFs are in Microsoft Word. The local data entry person can complete the form with pen and paper or complete a computerised soft copy. Thereafter the forms are copied and collected centrally. Hard copies can be sent by ordinary mail and soft copies can be sent by email or placed in a dropbox. Transmitting soft copies by email or to a dropbox are preferred. Site clinicians supervise and check the data entry.

The person entering the data is more important than the data collection system. Training is important, but it is mostly the dedication and interest of the person entering the data that determines its quality and completeness. In our project the local clinical leaders arrange who will enter the data. The local lead supervises and checks all the forms before they are sent to the central co-ordinator. In Blantyre the data entry person joins the ward rounds, knows all the patients and coordinates the follow up.

Follow-up is challenging in low-income countries and especially in sub-Saharan Africa. Parents have other priorities than returning to the hospital with a healthy-looking child; funds are often lacking for follow up and when they are available, bad roads and lack of home addresses hamper outreach visits to the homes of patients. Mobile phones are not always available and there is limited facility for charging, as well as limited mobile phone network coverage in

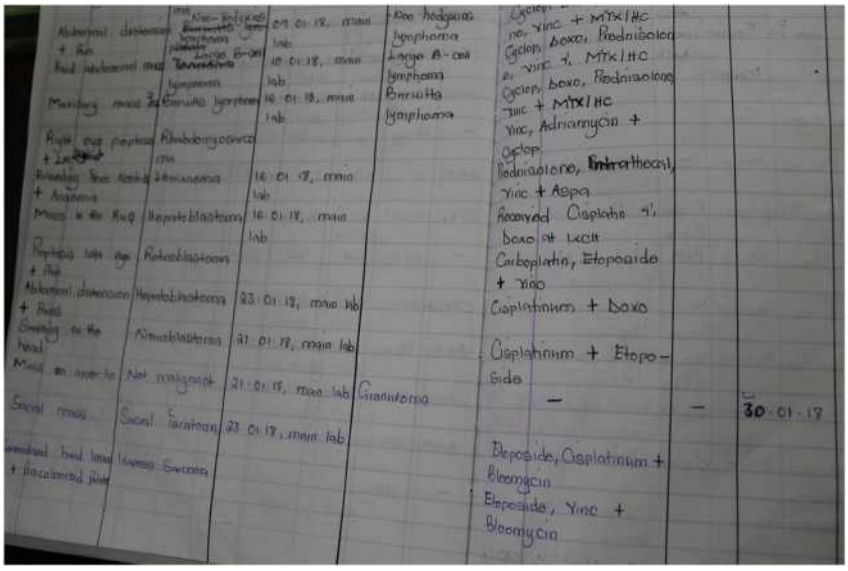


**Fig. 3.** A simple pen and paper system can work - admission book in Blantyre, Malawi.

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| | | |
|---|---|---|
| | **SIOP AFRICA / PODC Collaborative Wilms Tumour Project** | **PATIENT REGISTRATION FORM** |

| | |
|---|---|
| **Patient Identifier** (e.g. John Smith, male, born 15/12/1980 = JSM15121980) F S M/F D D M M Y Y Y Y | **SIOP Sequence No:** |
| | **Centre:** Queen Elizabeth Central Hospital, Blantyre, Malawi |

| **1. At Admission / Diagnosis** | | | |
|---|---|---|---|
| **1.1 Patient Details** | | | |
| Date of admission | xx | M / F | |
| First Name | | | |
| Family Name | | | |
| Date of Birth or Age (if known) | | | |
| Home address | | | |
| Town / Village | | District | |
| Distance home – treatment centre (km) | | | |
| Contact (phone no.) | | Phone owner | |
| Alternative phone no. | | | |
| Nearby church / school / landmark | | | |
| Map | | | |
| **1.2 Patient Medical History** | | | |
| Duration of symptoms | | | |
| Previous surgery / chemotherapy for this disease | | | |

**Fig. 4.** Two pages of the case record form as an example.

| | | |
|---|---|---|
| | **SIOP AFRICA / PODC Collaborative Wilms Tumour Project** | **PATIENT REGISTRATION FORM** |

| | |
|---|---|
| **Patient Identifier** (e.g. John Smith, male, born 15/12/1980 = JSM15121980) F S M/F D D M M Y Y Y Y | **SIOP Sequence No:** |
| | **Centre:** Queen Elizabeth Central Hospital, Blantyre, Malawi |

## 2. Surgery

| | | | |
|---|---|---|---|
| Surgeon | | Date of surgery | |
| Tumour looks like Wilms tumour | Yes | No | Not sure |
| Suspect different condition | Yes / No | If yes please specify | |
| Did you see any metastases | Yes / No | If yes please specify where | |

| | Did the following structures look: | | | Did you perform: | | |
|---|---|---|---|---|---|---|
| | Normal | Suspicious | Obviously infiltrated | Complete resection | Incomplete resection | No resection |
| Renal vein | | | | | | |
| Vena Cava | | | | | | |
| Tumour capsule | | | | | | |
| Lymph nodes | | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Did you see a Tumour Capsule Rupture | Yes / No | If yes do you think this occurred | Preoperatively | During surgery | Do not know |
| Is this a | Major rupture | Minor rupture | Did you do a | Biopsy only | Total nephrectomy |
| If nephrectomy was is | Complete resection of an intrarenal tumour (surgical stage 1) | Complete resection of a tumour with extra renal extension (surgical stage 2) | | | Incomplete resection (surgical stage 3) |

| | | | |
|---|---|---|---|
| Any complications during surgery (please specify | | | |
| Was the surgery | Difficult / complicated | Simple, complete resection | |
| Did you have to (partially) resect organs (due to injury) | Yes / No | If yes which organ(s) | |
| Tumour weight | grams | Largest tumour diameter | cm |

**Fig. 4.** (*continued*).

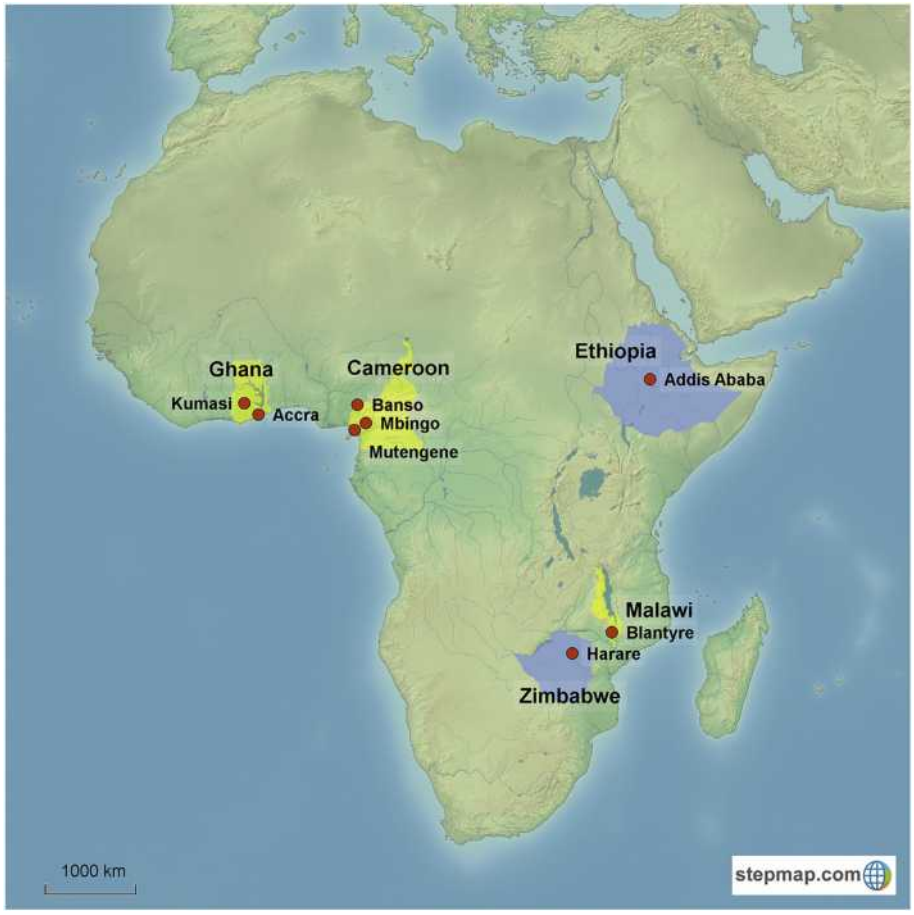


**Fig. 5.** Map showing the centres participating in Collaborative Wilms Tumour Africa Project.

rural areas. All of this means that survival data from low income countries with longer term follow-up are rare. However long-term follow-up is needed to record late relapses and establish the true survival rate.

At the work meeting in 2013 we discussed and agreed on the strategies to facilitate adequate long-term follow up in our project. Personal details of the patient and his or her parents are carefully documented at diagnosis. These include the home village, traditional authority and region. A home address is noted if available, but many homes do not have an address and it is more important to record landmarks near the home (e.g. a church, or a school) and relevant mobile phone numbers, including phone numbers of relatives or officials in the village. These details are essential when active follow up by phone or by visiting the patient's home is needed.

Someone in each centre is tasked to keep track of the patient after active treatment is completed. An excel sheet is kept with the names of all enrolled patients, the date they were last seen and their condition (well or relapse of disease). This excel sheet showing an overview of follow up is sent to the central coordinator about every six months.

The central database is in SPSS. Two medical students are helping to enter the data. They are familiar with SPSS and were trained to understand the CRFs and the questions underlying the different data points.

There are several challenges. Data entry, cleaning, integrating and analysis all take time, and everyone involved in the project has other duties, most often of patient care. It is a challenge to find time to do the work. For a dedicated data manager, it is not always easy to get good clinical supervision. In some centres it is a challenge to get forms completed by other participating disciplines such as pathology or surgery. However, as originally hoped for, overall this multi-disciplinary project has strengthened local inter-disciplinary activities.

The quality and completeness of the collected data has been excellent; less than 10% of data points are unfilled and only a few need clarifications by the central co-ordinating team. Careful pre-project planning has meant that very few modifications or explanations have been needed to assist data entry and completeness. Good documentation will help to assess the true impact of interventions in this regional network and will thus help to find sustainable solutions for local challenges to benefit children with cancer. Many of the lessons learned such as access to care, the need for early and definitive diagnoses and the difficulty and cost of follow up are all relevant to other chronic non-communicable diseases that are of increasing concern and prominence in LMICs. Perhaps the Wilms Collaborative Team Project can help to forge a path for others to follow.

## Conflicts of interest

Authors declare no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.phoj.2018.09.001.

## Reference

[1] Israels T, Kambugu J, Kouya F, El-Mallawany NK, Hesseling PB, Kaspers GJ, et al. Clinical trials to improve childhood cancer care and survival in sub-Saharan Africa. Nat Rev Clin Oncol 2013;10(10):599–604.

Support Care Cancer
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REVIEW ARTICLE

# A systematic review of integrative clinical trials for supportive care in pediatric oncology: a report from the International Society of Pediatric Oncology, T&CM collaborative

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**Abstract**
*Purpose* Traditional and complementary medicine (T&CM) use in children with cancer is well established among high-income, upper middle-income, low-middle-income, and low-income countries (HIC, UMIC, LMIC, LIC, respectively). In HIC, a developing body of evidence exists for several T&CM therapies; however, evidence in other income settings is less well described despite a significantly higher use when compared to reports from HIC. The aim of this systematic review was to evaluate the evidence for T&CM for a variety of supportive care indications among children with cancer.
*Methods* We performed a systematic review following the PRISMA guidelines of randomized, controlled clinical trials from inception through September 2016. Our eligibility criteria were limited to T&CM studies performed in children and adolescents undergoing treatment for a pediatric malignancy.
*Results* Of 6342 studies identified, 44 met inclusion criteria. Two clinical trials reported on acupuncture, 1 reported on aromatherapy, 9 evaluated massage therapy, and 32 reported on dietary supplements. Twenty-two studies were performed in HIC, 15 in UMIC, and 7 in LMIC. T&CM therapies were most commonly investigated for the prevention or management of mucositis, weight loss, and febrile neutropenia. Encouraging results were reported for select interventions; however, the majority of studies were classified as poor to fair quality.
*Conclusion* Our search revealed numerous clinical studies investigating the use of T&CM for supportive care purposes in pediatric oncology in HIC, UMIC, and LMIC. Although limited, these results could inform supportive care resource allocation and indicate where T&CM may serve to fill gaps where access to care may be limited.

**Keywords** Traditional and complementary medicine · Integrative medicine · Pediatric oncology · Supportive care · Symptom management

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00520-017-3908-0) contains supplementary material, which is available to authorized users.

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## Background

The global incidence of childhood cancer has observed a steady increase in the last decade likely due to increased access to treatment and improved reporting of childhood cancer [1]. Traditional and complementary medicine (T&CM) is a globally utilized supportive care tool in children undergoing treatment for malignancies in countries of all income levels [2, 3]; however, there is a general consensus that the evidence supporting its efficacy remains unclear for most indications. The lack of demonstrated safety and efficacy, the potential for

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adverse interactions with prescribed therapy, the delays in seeking conventional treatment, and the risk of diminishing the high cure rate obtained for several pediatric malignancies have raised concerns about T&CM use [4–7].

T&CM has the potential be a low-cost adjunct to existing supportive care regimens and may be especially useful in low-middle-income countries (LMICs) where consistent access to supportive care medications may be limited [8]. There is a precedent of utilizing T&CM as a low-cost approach for closing gaps in medical care in LMICs, particularly in rural areas [9–12]. It is evident that additional research in T&CM is necessary prior to its inclusion into supportive care regimens in pediatric oncology. To this end, we describe the results of a systematic review of clinical trials that investigated the efficacy of T&CM therapies for supportive care indications in childhood cancer.

## Methods

### Literature search

Our methodology followed the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13]. Our search strategy included MeSH terms and text related to pediatrics, oncology, and T&CM (Online Resource 1). Our search was limited to studies of human subjects without any language restriction. All references were compiled into an EndNote (X7) library for review of titles and abstracts by two independent authors (AR and KT). Subsequent manual review of citations was performed with the inclusion of additional manuscripts that met the eligibility criteria below. Any disagreement was resolved by a final consensus (AR, KT, and EJL).

### Eligibility criteria

Published manuscripts that reported on randomized, controlled, clinical trials that evaluated a T&CM therapy for supportive care purposes, performed among children and adolescents from birth to 18 years of age (inclusive), and diagnosed with a pediatric malignancy were included. Clinical trials that included adults were included in the systematic review if at least 80% of study participants were 18 years of age or younger. Classification of countries by income level was defined by criteria set forth by the World Bank [14]. Studies performed after cessation of cancer therapy, among children receiving surgery only, and case reports/case series/non-controlled trials were excluded. There was no exclusion by study date or date of publication.

### Data extraction

Extracted data of interest included country of publication, year, demographic data (gender and age), diagnosis, study design, conventional cancer treatment, T&CM intervention (time in relation to phase of cancer therapy, dose, and duration of intervention), sample size, method of randomization, primary and secondary outcomes, statistical methods, and results. Data were extracted by one author (AR) and independently verified by a second author (EJL) using a standard data extraction sheet. Quality scores were calculated for eligible studies using the National Institute of Health's Quality Assessment Tool for Controlled Intervention Studies, a 14-point scale that identifies the quality of randomized, controlled trials (Online Resource 2) [15]. The criteria for assessing study quality were adapted from previously published studies [16, 17]. Two reviewers (AR and EJL) extracted data for determination of study quality.

### Data synthesis and analysis

Due to the heterogeneity of the data and a small number of clinical trials evaluating a single T&CM therapy, a formal statistical analysis was not feasible. Study descriptives were extracted and summarized in table format (Tables 1, 2, 3, and 4). Within each table, studies were further classified by study outcomes and by the income level of the country in which the study was performed.

## Results

### Search strategy

A total of 6342 studies were produced in the original search (Fig. 1). Forty-seven papers from the original search met inclusion criteria. Of these, 16 studies were removed entirely due to inability to contact the author to clarify study details [18–33]. Thirty-one papers from the original search were included in the review. We identified an additional 56 manuscripts following the original literature search through reference review and ongoing monthly searches. Thirteen were eligible and included in the review [34–46]. Our final search results included 44 papers (acupuncture ($N = 2$), aromatherapy ($N = 1$), dietary supplements ($N = 32$), and massage ($N = 9$)).

### Acupuncture

Two studies reported on acupuncture, both investigating the effect on chemotherapy-induced nausea and vomiting (Table 1), one of poor [47] and one of good [48] quality [47, 48]. Both studies were performed in high-income countries (HIC) and with a small, heterogeneous population. Each study

**Table 1** Summary of studies in acupuncture

| Outcome | Author | Income level | Diagnosis | Sample size | Gender/age | Study design | Cancer t therapy | Intervention | Results | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|
| CINV | Gottschling (2008, Germany) [48] | HIC | Mixed | *N* = 23 | 13M, 10F, age = 13.6 ± 2.9 years | Multicenter randomized crossover study | VIDE, IP, I2VA, or I2VAd | Individualized acupuncture | ↓ Antiemetic use ($P = 0.001$)<br>↓ Episodes of retching/ vomiting ($P = 0.01$) | Good |
| | Reindl (2006, Germany) [47] | HIC | Mixed | *N* = 11 | 4M, 7F, median age = 15.2 years (10–16.8 years) | Randomized, multicenter, prospective crossover trial | VIDE, IP, I2VA, or I2VAd | Acupuncture | ↓ Antiemetic use ($P = 0.024$)<br>Episodes of vomiting NS<br>Nausea scores NS | Poor |

*CINV* chemotherapy-induced nausea and vomiting, *F* females, *HIC* high-income country, *I2VA* vincristine, ifosfamide, actinomycin D, *I2VAd* vincristine, ifosfamide, adriamycin, *IP* ifosfamide, cisplatin, *M* males, *NS* non-significant, *VIDE* vincristine, ifosfamide, doxorubicin, etoposide

**Table 2** Summary of studies in aromatherapy

| Outcome | Author | Income level | Diagnosis | Sample size | Gender/age | Study design | Cancer therapy | Intervention | Results | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|
| Anxiety | Ndao (2012, USA) [49] | HIC | Mixed | *N* = 37 | Intrvn 13M, 4F, mean age = 11.7 ± 4.2 years; Ctrl 14M, 6F, mean age = 12.8 ± 5.6 years | Double-blind, placebo-controlled randomized study | Intrvn group: autologous HCT: *N* = 7 (41%); allogeneic HCT: *N* = 10 (59%); Ctrl group: autologous HCT: *N* = 7 (35%); allogeneic HCT: *N* = 13 (65%) | Bergamot essential oil | ↑ State anxiety in the treatment group at T3 ($P = 0.01$) and T4 ($P = 0.05$)<br>↑ Nausea in intervention group at T3 ($P < 0.01$) and T4 ($P = 0.03$)<br>↑ Pain in intervention group at T1/T2 ($P = 0.04$) | Good |

*Ctrl* control, *F* females, *HCT* hematopoietic cell transplant, *HIC* high-income country, *Intrvn* intervention, *M* males, *T* timepoint

**Table 3** Summary of studies in massage

| Outcome | Author | Income Level | Diagnosis | Sample Size | Gender/age | Study Design | Cancer Therapy | Intervention | Results | Quality Score |
|---|---|---|---|---|---|---|---|---|---|---|
| Nausea and vomiting | Mazlum (2013, Iran) [50] | UMIC | ALL | $N = 74$ | Intrvn 60% M; Ctrl 51.4% M; mean age = 8.6 ± 3.3 years | 2-group randomized controlled clinical trial study | CT | Swedish massage | ↓ Incidence of nausea during 48 h post-chemo between groups ($P = 0.027$)<br>↓ Frequency of vomiting after therapy ($P = 0.001$)<br>↓ Duration of vomiting after therapy ($P = 0.002$)<br>↓ Severity of vomiting after therapy ($P = 0.002$)<br>↓ Frequency of total vomiting ($P = 0.014$)<br>↓ Duration of total vomiting ($P = 0.002$)<br>↓ Severity of total vomiting ($P = 0.011$) | Fair |
| | Miladinia (2015, Iran) [39] | UMIC | Mixed | $N = 45$ | Intrvn 12M, 10F, mean age = 11.46 ± 2.14 years; Ctrl 13M, 8F, mean age = 10.91 ± 1.93 years | 2-group randomized controlled double-blind trial, repeated measures design | CT | Slow-stroke back massage | ↓ Nausea severity ($P = 0.001$)<br>↓ Frequency of vomiting ($P = 0.001$) | Fair |
| Pain | Batalha (2013, Portugal) [51] | HIC | Mixed | $N = 52$ | Intrvn 76.9% M, median = 13.5 years; Ctrl 46.2% M, median age = 12 years | Prospective, longitudinal, randomized, controlled and single-blinded study | CT, antibiotics, or steroid corticoid therapy | Massage | ↓ Pain interference with ambulatory capacity between days 1 and 6 ($P < 0.05$) | Poor |
| Psychosocial outcomes | Field (2001, USA) [56] | HIC | ALL | $N = 20$ | 10M, 10F, mean age = 6.9 years | Randomized, wait-list control | Standard medical care (medical exams, RT, CT, other medical procedures) | Parent-administered massage | ↓ Parental anxiety ($P = 0.05$)<br>↓ Parental depressed mood ($P = 0.01$)<br>↓ Child anxiety ($P = 0.05$)<br>↓ Child depressed mood ($P = 0.01$)<br>↑ WBC ($P = 0.05$)<br>↑ Neutrophils ($P = 0.05$) | Poor |
| | Haun (2009, USA) [55] | HIC | Mixed | $N = 30$ | Intrvn 8M, 7F, mean age = 10.7 years; Ctrl 7M, 8F, mean age = 9.3 years | Randomized, non-blinded, prospective study | NR | Swedish massage | ↓ Muscle soreness ($P < 0.001$)<br>↓ Discomfort ($P < 0.001$)<br>↓ Respiratory rate ($P < 0.000$)<br>↓ Anxiety ($P < 0.000$) | Poor |

**Table 3** (continued)

| Outcome | Author | Income Level | Diagnosis | Sample Size | Gender/age | Study Design | Cancer Therapy | Intervention | Results | Quality Score |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Improvement in emotional symptoms ($P < 0.001$)<br>Improvement in clinical progress score ($P < 0.001$) | |
| Psychosocial outcomes (cont'd) | Phipps (2005, USA) [40] | HIC | Mixed | $N = 50$ | 20% < 6 years, 46% 6–12 years, 34% > 12 years | Randomized trial | Allogeneic HCT: $N = 38$, autologous HCT: $N = 12$ | Professional or parent massage | ↓ Child ($P = 0.004$) and parent ($P < 0.0001$) reported anxiety with professional massage<br>↓ Parent-reported discomfort ($P = 0.004$) with professional massage<br>↓ Days to engraftment in parent massage vs. control ($P = 0.04$) | Poor |
| | Phipps (2010, USA/Canada) [52] | HIC | Mixed | $N = 178$ | 59.1% M; 49.1% 6–12 years, 50.9% > 12 years | Multisite, prospective, controlled trial | Autologous HCT: $N = 31$ (18.1%), allo-matched sibling HCT: $N = 44$, 25.7%, allo-other HCT: $N = 96$, 56.1% | Massage and humor therapy | No significant findings | Fair |
| | Phipps (2012, USA) [53] | HIC | Mixed | $N = 171$ | 59.1% M, mean age = 12.8 years (6–18 years) | Randomized, multisite trial | Autologous HCT 18.1%, allogeneic-matched sibling HCT 25.7%, allogeneic-other HCT 56.1% | Massage and humor therapy | No significant findings | Poor |
| | Post-White (2009, USA) [54] | HIC | Mixed | $N = 25$ | 60% M, age range 1–18 years | Crossover | CT | Massage therapy vs. quiet time | ↓ HR ($P = 0.02$)<br>↓ RR ($P = 0.05$)<br>↓ Anxiety in children 1–13 at session 4 ($P = 0.04$)<br>Salivary cortisol NS | Poor |

*ALL* acute lymphoblastic leukemia, *cont'd* continued, *CT* chemotherapy, *Ctrl* control, *F* females, *HIC* high-income country, *HR* heart rate, *Intrvn* intervention, *M* males, *NS* non-significant, *RR* relative risk, *RT* radiation therapy, *UMIC* upper middle-income country, *WBC* white blood cell

**Table 4** Summary of studies in dietary supplements

| Outcome | Author | Income level | Diagnosis | Sample size[a] | Gender/age | Study design |
|---|---|---|---|---|---|---|
| Appetite/weight management | Bayram (2009, Turkey) [35] | UMIC | Mixed | *N* = 52 | Intrvn 63.6% M, Ctrl 52.6% M; mean age = 7.5 ± 3 years | Prospective, randomized, controlled, single-center, open-label design |
| | Consolo (2013, Brazil) [70] | UMIC | Mixed | *N* = 38 | 53% M; mean age = 9.9 ± 5.5 years | Double-blind, randomized, placebo-controlled trial |
| | Naderi (2014, Iran) [71] | UMIC | ALL | *N* = 34 | Intrvn 3M, 14F; mean age = 5.79 ± 3.97 years (1–13 years); Ctrl 11M, 6F, mean age = 7.17 ± 3.66 years (6 months–14 years) | Randomized controlled trial |
| Bone mineral density | Diaz (2008, Chile) [76] | HIC | ALL | *N* = 16 | 9M; mean age = 5.5 years (1.7–11.5 years) | Non-blinded, quasi-randomized trial |
| CINV | Pillai (2011, India) [75] | LMIC | Newly diagnosed bone sarcomas | *N* = 60 | Intrvn 24M, median age = 15.5 years (9–21 years); Ctrl 16M, median age = 15.83 years (9–21 years) | Prospective, double-blind, randomized, controlled, single institutional trial |
| CINV (cont'd) | Shi (2012, China) [74b] | UMIC | Mixed | *N* = 80 | Intrvn 20M, 20F, mean age = 3.0 ± 1.8 years; Ctrl 26M, 14F, mean age = 4.0 ± 2.3 years | Not reported |
| Fever and neutropenia | Abdulrhman (2016, Egypt) [38] | LMIC | ALL | *N* = 40 | 50% M; group A mean age = 5.1 ± 2.5 years (2.5–10 years); group B mean age = 5.65 ± 2.24 years (2.5–10 years) | Open-label, randomized crossover clinical trial |
| | Garami (2004, Hungary) [73] | HIC | Mixed | *N* = 22 | 8M; Intrvn mean age = 11 years (2–17 years); Ctrl mean age = 10.6 years (2–18) | Open-label, matched-pair pilot clinical trial |
| | Wada (2010, Japan) [45] | HIC | Mixed | *N* = 42 | Intrvn 7M, 11F, 1 year 2 months–13 years 2 months (mean/median age not specified); Ctrl 9M, 13F, 1 year 1 month—13 years 4 months (mean/median age not specified) | Single-blinded, placebo-controlled trial |
| Fever and neutropenia (cont'd) | Wada (2010, Japan) [45] (cont'd) | | | | | |
| Gastrointestinal | Dagdemir (2004, Turkey) [77] | UMIC | Mixed | *N* = 35 | Intrvn 12M, 10F, median age = 8.7 years (3–16 years); Ctrl 8M, 5F, median age = 9.2 years (2.5–16 years) | Randomized, otherwise not reported |
| Hepatic toxicity | Elbarbary (2016, Egypt) [41] | LMIC | ALL | *N* = 70 | Intrvn 18M, 17F, mean age = 8.4 ± 3.3 years (4–16 years); Ctrl 21M, 14F, mean age = 7.1 ± 3.1 years (3–15 years) | Double-blind, randomized placebo-controlled trial |
| | Hagag (2015, Egypt) [42] | LMIC | ALL | *N* = 40 | Intrvn 15M, 5F, mean age = 8.84 ± 3.56 years (5–12 years); Ctrl 13M, 7F, mean age = 9.34 ± 3.28 years (4–13 years) | Randomized controlled trial |
| Hepatic toxicity (cont'd) | Ladas (2010, USA) [72] | HIC | ALL | *N* = 50 | 58% M; Intrvn mean age = 8.7 ± 5.1 years; Ctrl mean age = 7.0 ± 3.2 years | Randomized, controlled, double-blind pilot trial |
| Mucositis | Abdulrhman (2012, Egypt) [34] | LMIC | ALL | *N* = 90 | 57M; mean age = 6.9 ± 3.8 years (2–18 years) | Randomized controlled clinical phase II trial |
| | Aquino (2005, USA) [57] | HIC | Mixed | *N* = 120 | | Double-blind randomized placebo-controlled trial |

**Table 4** (continued)

| Outcome | Author | Income level | Diagnosis | Sample size[a] | Gender/age | Study design |
|---|---|---|---|---|---|---|
| | | | | | Intrvn 65% M, mean age = 8.9 ± 1 years; Ctrl 57% M, mean age = 10.5 ± 0.6 years | |
| | El-Housseiny (2007, Egypt) [36] | LMIC | NR | *N* = 80 | Group A (topical vit. E) mean age = 5.75 years; group B (systemic vit. E) mean age = 9.30 years | Prospective randomized trial |
| Mucositis (cont'd) | Khurana (2013, Turkey) [58] | UMIC | Mixed | *N* = 72 | Group 1 19M, 5F, mean age = 8.98 ± 2.58 years; group 2 (vit. E) 18M, 6F, mean age = 9.29 ± 2.58 years; group 3 (pycnogenol): 20M, 4F, mean age = 9.48 ± 2.53 years | Single-blind controlled trial |
| | Kokkonen (2002, Finland) [59] | HIC | Mixed | *N* = 20 | Intrvn 5M, 5F, mean age = 7.7 ± 4.4 years; Ctrl 5M, 5F, mean age = 8.7 ± 5.2 years | Prospective, randomized trial |
| | Oberbaum (2001, Israel) [37] | HIC | Mixed | *N* = 30 | Intrvn 53% M, mean age = 10.1 ± 7.0 years; Ctrl 60% M, mean age = 9.7 ± 5.7 years | Randomized, placebo-controlled, double-blind clinical trial |
| | Okur (2006, Turkey) [60] | UMIC | Mixed | *N* = 21 | Mean age = 9.86 ± 5.38 years | Crossover trial |
| | Sencer (2010, USA) [61] | HIC | Mixed | *N* = 195 | Intrvn 56% M, median age = 12 years (3–24 years); Ctrl 70% M, median age = 11 years (3–25 years) | International multicenter, double-blind, placebo-controlled randomized trial |
| Mucositis (cont'd) | Sung (2007, Canada) [65] | HIC | Mixed | *N* = 16 | Median age = 12.7 years (6.4–15.1 years) | Series of *N* of 1, double-blinded, randomized controlled trials |
| | Tomazevic (2013, Slovenia) [62] | HIC | Mixed | *N* = 50 | Intrvn 11M, 8F, mean age = 6.7 ± 5.3 years (1.0–16.8 years); Ctrl 9M, 12F, mean age = 9.3 ± 6.6 years (1.0–18.8 years) | Double blind, randomized, placebo-controlled trial |
| | Uderzo (2011, Italy) [63] | HIC | Mixed | *N* = 120 | Intrvn 70% M, mean age = 8.0 years (0.9–18.6 years); Ctrl 67.2% M, mean age = 8.4 years (0.4–18.6 years) | Prospective, randomized, double-blind, controlled trial |
| | Yildirim (2013, Turkey) [64] | UMIC | B cell non-Hodgkin lymphoma | *N* = 12 | 10M, 2F; median age = 72 months (48–120 months) | Crossover trial |
| Neurotoxicity | Bradfield (2015, USA) [43] | HIC | Mixed | *N* = 250 | Intrvn: stratum 1 14M, 12F, mean age = 9.1 ± 5.6 years, stratum 2 67M, 34F, mean age = 8.4 ± 4.7 years; Ctrl: stratum 1 12M, 11F, mean age = 8.8 ± 5.5 years, stratum 2 57M, 42F, mean age = 8.5 ± 4.8 years | Randomized, placebo-controlled, double-blind clinical trial |
| Neurotoxicity (cont'd) | Mokhtar (2010, Egypt) [44] | LMIC | Mixed | *N* = 94 | Intrvn 37M, 17F, mean age = 7.42 ± 3.85 years; Ctrl 30M, 10F, mean age = 6.78 ± 4.21 years | Randomized, single-blinded, placebo-controlled clinical trial |
| Treatment-related toxicities | Tacyildiz (2010, Turkey) [66] | UMIC | Mixed | *N* = 8 | 3M, median age = 7 years (6–13 years) | Crossover trial |
| | Rocha (2016, Brazil) [46] | UMIC | Mixed | *N* = 34 | LL group 10M, 7F, mean age = 7.6 years; ST group 13M, 6F, mean age = 8.0 years | Randomized, double-blind, placebo-controlled, crossover trial |
| Treatment-related toxicities (cont'd) | Shi (2007, China) [68] | UMIC | Mixed | *N* = 60 | Intrvn 19M, 11F, mean age = 4.43 ± 2.47 years; Ctrl 20M, 10F, mean age = 2.80 ± 1.69 years | Prospective cohort trial |
| | Shi (2012, China) [67a] | UMIC | Mixed | *N* = 167 | Intrvn 45M, 38F, mean age = 3.7 ± 2.3 years; Ctrl 48M, 36F, mean age = 3.83 ± 2.61 years | NR |
| Treatment-related toxicities (cont'd) | Shi (2012, China) [67a] (cont'd) | | | | | |

**Table 4** (continued)

| Outcome | Author | Income level | Diagnosis | Sample size[a] | Gender/age | Study design |
|---|---|---|---|---|---|---|
| | Vieira (2015, Brazil) [69] | UMIC | Mixed | *N* = 39 | LL group 10M, 9F, mean age = 8.2 years; ST group 12M, 8F, mean age = 7.4 years | Randomized, double-blind, placebo-controlled, phase II crossover trial |

| Outcome | Cancer therapy[b] | Supplement/dose | Results | Quality Score |
|---|---|---|---|---|
| Appetite/weight management | CT | Protein and energy-dense EPA-containing oral supplement; 300 kcal, 16 g protein, 1.09 g EPA twice a day | ↓ Loss of body wt ($P = 0.001$) and loss of BMI ($P = 0.002$) at 3 months↓ Weight loss at 6 months ($P = 0.03$)↓ Body wt loss ($P = 0.006$) and BMI loss ($P = 0.018$)↑ Remission rate at 3 months ($P = 0.036$) | Fair |
| | CT | Zinc chelate; 2 mg/kg/day of zinc (max 60 mg/day) | ↑ Weight gain ($P = 0.032$)Significant difference between group A and group B regarding infectious episodes was observed ($P = 0.02$) | Fair |
| | CT | PediaSure (100–150 $cm^3$ every other day) and carnitine (50 mg/kg everyday) | NS effect on anthropometric measures | Good |
| Bone mineral density | Protocol 1 PINDA phase 1 | Calcitriol (< 30 kg: 0.25 mg/day; > 30 kg: 0.5 mg/day) | ↑ Lumbar spine BMD in children with lower initial BMD in the calcitriol group vs. higher initial BMD ($r = -0.78$, $P = 0.020$) | Poor |
| CINV | Combination of cisplatin 40 $mg/m^2$/day and doxorubicin 25 $mg/m^2$/day | Ginger root powder (≥ 20 and < 40 kg: 1000 mg; ≥ 40 and < 60 kg: 2000 mg) | ↓ Moderate to severe nausea ($P = 0.003$)↓ Moderate to severe vomiting ($P = 0.002$)↓ Moderate to severe delayed nausea ($P < 0.001$)↓ Moderate to severe delayed vomiting ($P = 0.022$) | Good |
| CINV (cont'd) | CT | Hewei Zhiou Recipe (fresh common reed rhizome 30 g, fresh bamboo shavings 4–6 g, fresh ginger 3 pieces, Chinese date 3 pieces) | ↓ Vomiting by end of second to sixth therapeutic course ($P < 0.01$) | Fair |
| Fever and neutropenia | Modified CCG 1991 protocol for standard-risk ALL and on maintenance therapy | Honey (2.5 g/kg body wt, twice weekly) | ↓ Number of patients with FN ($P = 0.037$)<br>↓ FN episodes ($P = 0.004$)<br>↓ Duration of hospital stay ($P = 0.006$)<br>↓ Number of patients who developed FN during intervention ($P = 0.00004$) | Fair |
| | Cerebral PNET: carboplatin, cyclophosphamide, dactinomycin, doxorubicin, epirubicin, etoposide, ifosfamide, vincristine; osteosarcoma: carboplatin, cisplatin, doxorubicin, ifosfamide, methotrexate; hepatoblastoma: cisplatin, doxorubicin; mesenchymal chondrosarcoma: cyclophosphamide, doxorubicin, etoposide, ifosfamide, vincristine | Avemar (6 $g/m^2$ dissolved in water, twice daily) | ↓ Neutropenic episodes ($P = 0.037$)↑ WBC counts ($P < 0.021$)↑ Lymphocyte counts ($P < 0.001$) | Fair |
| | CT | Bifidobacterium breve strain Yakult ($10^9$ in 1 g preparation, 3 times per day) | ↓ Frequency ($P = 0.02$) and duration ($P = 0.02$) of febrile episodes<br>↓ Proportion of patients who developed fever (RR 0.65)<br>↓ Cumulative length of parenteral antibiotic therapy ($P = 0.04$) | Fair |

**Table 4** (continued)

| Outcome | Cancer therapy[b] | Supplement/dose | Results | Quality Score |
|---|---|---|---|---|
| Fever and neutropenia (cont'd) | | | ↓ Proportion of those who used parenteral antibiotic (RR 0.75) | |
| Gastrointestinal | HDMTX | Vitamin A (180,000 IU/day) | ↓ D-Xylose absorption in control vs. intervention ($P = 0.033$)↓ D-Xylose in control group with lower RBP at baseline compared to trial group ($P = 0.004$) | Poor |
| Hepatic toxicity | MTX-including treatment protocols | Omega-3 fatty acids (1000 mg fish oil—180 mg EPA, 120 mg DHA) | ↓ Total and direct bilirubin, ALT, AST, ALP, GGT, MDA ($P < 0.001$)<br>↑ Uric acid ($P = 0.004$)<br>↑ TAC, SOD, and GPX ($P < 0.001$) | Good |
| | MTX-including treatment protocols | Black seed oil (80 mg/kg/day) | ↓ Total ($P = 0.000$) and direct ($P = 0.000$) bilirubin<br>↓ Indirect bilirubin ($P = 0.000$)<br>↓ Serum ALT ($P = 0.000$)<br>↓ Serum AST ($P = 0.000$)<br>↓ Alkaline phosphatase ($P = 0.000$)<br>↓ Prothrombin time ($P = 0.01$)<br>↓ Relapse and death ($P = 0.029$)<br>↑ Complete remission ($P = 0.029$) | Fair |
| Hepatic toxicity (cont'd) | MTX, 6-MP, VCR | Milk thistle (1:2 mixture of silibinin and soy phosphatidylcholine); 240 mg milk thistle (80 mg silibinin) | ↓ AST ($P = 0.04$)5 patients in MT group and no patients in placebo group had greater than a 50% reduction in total bilirubin during intervention period ($P < 0.007$) | Good |
| Mucositis | BFM-90 (standard risk, consolidaton phase) | Honey; 0.5 g/kg (max 15 g) 3 times daily × 10 days or until healedHOPE; 0.25 g/kg 3 times daily × 10 days or until healed vs. controls (benzocaine gel) | ↓ Grade 2 mucositis recovery time in honey group ($P < 0.05$)↑ Grade 3 mucositis healing time in honey and HOPE vs. control ($P < 0.01$)<br>↑ Healing time with honey alone in grades 2 and 3 mucositis vs. control ($P = 0.0005$) or HOPE ($P = 0.0056$) | Fair |
| | Autologous or allogeneic HCT with TBI or MTX | Glutamine; 2 g/m$^2$/dose (max 4 g); twice daily | ↓ Morphine use ($P = 0.03$)↓ TPN use ($P = 0.01$) | Good |
| | CT | Vitamin E; 100 mg twice daily | No significant findings | Poor |
| Mucositis (cont'd) | ALL: induction or delayed intensification; AML: induction or intensification; NHL: MCP-842 | Vitamin E; 200 mg/day, 3 times daily × 1 weekPycnogenol; 1 mg/kg per day, 3 times daily × 1 week | ↑ Number of patients who healed completely with vitamin E than pycnogenol or control (*P* value NR)<br>Significant difference in WHO mucositis grading between group 1 (control) and group 2 (vit. E) ($P < 0.0001$) | Fair |
| | Protocol of the NSPHO; MOPP, ABVD; LBM-89, BFM-90; IRS-III; NWTS-4 | Vitamin A; 10 mg/kg × first 3 weeks, 5 mg/kg × next 3 weeks | No significant findings | Fair |
| | Allogeneic or autologous HCT | Traumeel S; 2.2 mL five times daily | ↓ Symptom duration and severity ($P < 0.01$)↓ Time to worsening of symptoms ($P < 0.001$) | Good |
| | BEP; BB24, CC, mini-BEAM; ABVD; A3; P-IV; HDMTX; EVAII; HTP | Glutamine; 4 g/m$^2$/day | NS differences between gln course and non-gln course on first and fifth days↓ Need for antibiotic therapy in gln group vs. control ($P = 0.03$) | Poor |
| | Myeloablative HCT (allogeneic or autologous) | Traumeel S; 2.2 mL five times daily | Trend towards ↓ narcotic use in Traumeel group ($P = 0.02$)<br>No other significant findings | Good |
| Mucositis (cont'd) | Doxorubicin-containing CT | Topical vitamin E 800 mg | No significant findings | Good |

**Table 4** (continued)

| Outcome | Cancer therapy[b] | Supplement/dose | Results | Quality Score |
|---|---|---|---|---|
| | CT | Propolis; 0.38 g twice daily | No significant findings | Fair |
| | Allogeneic HCT | Glutamine; 0.4 g/kg/day | No significant findings | Good |
| | BFM-90 | Glutamine; 0.4 g/kg/day | No significant findings | Fair |
| Neurotoxicity | Stratum1: VCR; Stratum 2: VCR + steroids | L-Glutamic acid (250 mg capsules, 1 capsule for body surface < 1 $m^2$, 2 capsules for ≥ 1 $m^2$; 3 times daily | No significant findings | Fair |
| Neurotoxicity (cont'd) | VCR | Glutamic acid (1.5 g daily in 3 divided doses) | ↓ Reduction of tendon Achilles reflex at third ($P = 0.01$) and fourth visits ($P = 0.004$)<br>↓ Reduction in patellar reflex at third and fourth visits ($P = 0.008$)<br>↓ Paresthesias ($P = 0.01$)<br>↓ Constipation ($P = 0.02$)<br>↓ Rate of constipation development ($P$ value NR)<br>↓ Neurotoxicity sum score at second ($P = 0.01$), third ($P = 0.000$), and fourth ($P = 0.000$) visits<br>Changes in anxorexia and strength NS | Fair |
| Treatment-related toxicities | ICE, A5, A3, ACC, VCR-carbopolatin, CTX, paclitaxel, paclitaxel + RT, irinotecan + temozolamide, temozolamide + COPP + VCR-carboplatin, irinotecan + RT | Genistein (0.30 g/tablet: 82% soy isoflavone extract + 2.7% (8 mg) genistein) | No significant findings | Poor |
| | CT | Selenium glycinate (0–6 months, 27 μg/day, 7–12 months, 36 μg/day, 1–3 years, 36 μg/day, 4–8 years, 54 μg/day, 9–13 years, 72 μg/day, 14–18, 100 μg/day | ↑ Neutrophil count in ST group ($P = 0.0192$)<br>↑ IgA ($P = 0.0051$) and IgG ($P = 0.0055$) in ST vs. LL patients after Se use<br>↑ IgA production after Se in ST vs. LL group ($P = 0.0011$) | Poor |
| Treatment-related toxicities (cont'd) | CT ± RT: phase II: VCR, CTX, ADM, ACTD, 5-FU; phases III and IV: VCR, CTX, ADM, DDP, Vp16, BLM | Various Chinese herbs according to syndrome differentiation (decocted twice, 50 mL per time for children < 3 years, 100 mL per time for children > 3 years, BID | ↑ WBC ($P < 0.01$)<br>↓ PLT ($P < 0.05$)<br>↓ Clinical symptom scores ($P < 0.01$) | Fair |
| | Phase II: VCR, CTX, ADM, ACTD, 5-FU; phases III and IV: VCR, CTX, ADM, DDP, Vp16, BLM | Fuzheng Jianpi Decoction (50–100 mL BID) | ↓ Nausea and vomiting at 6 months ($P = 0.001$) and 1 year ($P = 0.001$)<br>↓ Anorexia at 6 months ($P = 0.000$) and 1 year ($P = 0.000$)<br>↓ Weakness at 6 months ($P = 0.014$) and 1 year ($P = 0.001$)<br>↓ Weight loss at 6 months ($P = 0.003$) and 1 year ($P = 0.017$)<br>↓ Constipation at 6 months ($P = 0.002$)<br>↓ Pain at 1 year ($P = 0.04$<br>↓ 2 and 3-year psychological ($P < 0.05$) and general symptom scores ($P < 0.01$) compared with 1 year<br>↓ 2 and 3-year somatic and psych functions and general symptom scores (all $P < 0.05$) | Fair |

**Table 4** (continued)

| Outcome | Cancer therapy[b] | Supplement/dose | Results | Quality Score |
|---|---|---|---|---|
| Treatment-related toxicities (cont'd) | CT | Selenium (0–6 months = 27 μg/day; 7–12 months 36 μg/day; 1–3 years= 36 μg/day; 4–8 years = 54 μg/day; 9–13 years = 72 μg/day; 14–18 years = 100 μg/day) | ↓ 2-year somatic and psych functions ($P < 0.05$)<br>↓ 3-year psych functions and general symptoms scores ($P < 0.05$)<br>↑ WBC ($P < 0.01$) and Hb ($P < 0.05$) at 6 months<br>↑ WBC ($P < 0.01$) and PLT ($P < 0.05$) at 1 year<br>↑ Physical function<br>↓ Nausea ($P = 0.0036$) and appetite loss ($P = 0.028$) in ST group<br>↓ Fatigue in ST group at 1 year ($P = 0.0289$)<br>↓ AST ($P = 0.0447$)<br>↓ Serum creatinine<br>↓ Serum urea | Fair |

*μg* micrograms, *5-FU* 5-fluorouracil, *6-MP* 6-mercaptopurine, *A3* vincristine, adriamycin, dacarbazine, iphosphamide, *A5* cisplatin, cyclophosphamide, etoposide, *ABVD* adriamycin, bleomycin, vinblastine, dacarbazine, *ACC* adriamycin, cisplatin, etoposide, mitotane, *ACTD* dactinomycin, *ADM* adriamycin, *ALL* acute lymphoblastic leukemia, *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *AML* acute myeloid leukemia, *AST* aspartate aminotransferase, *BB24* dexametasone, vincristine, methotrexate, cyclophosphamide, doxorubin, *BEP* bleomycin, etoposide, cisplatin, *BFM-90* Berlin-Frankfurt-Munster protocol, *BID* twice a day, *BLM* bleomycin, *BMD* bone mineral density, *BMI* body mass index, *CC* dexametosone, vincristine, citarabine, vepeside, *cc* cubic centimeters, *CCG 1991* Children's Cancer Group 1991, *cont'd* continued, *COPP* cyclophosphamide, vincristine, procarbazine, prednisone, *CT* chemotherapy, *Ctrl* control, *CTX* cyclophosphamide, *DDP* cisplatin, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid, *EVAII* etoposide, vincristine, adriamycin, iphosphamide, *F* females, *FN* febrile neutropenia, *g* grams, *GGT* gamma-glutamyl transpeptidase, *GPX* glutathione peroxidase, *Hb* hemoglobin, *HCT* hematopoietic cell transplant, *HDMTX* high-dose methotrexate, *HIC* high-income country, *HOPE* honey, olive oil-propolis extract and beeswax, *HTP* cisplatin, adriamycin, *gln* glutamine, *ICE* ifosfamide, carboplatin, etoposide, *IgA* immunoglobulin A, *IgG* immunoglobulin G, *Intrvn* intervention, *IRS-III* Third Intergroup Rhabdomyosarcoma Study, *IU* international units, *LBM-89* Lymphome Malins de Burkitt, *LL* leukemia/lymphoma, *LMIC* low-middle-income country, *kcal* kilocalories, *kg* kilograms, *M* males, *m* meters, *max* maximum, *MCP-842* mitoxantrone, chlorambucil, prednisolone, *MDA* malondialdehyde, *mg* milligrams, *mini-BEAM* carumustine, etoposide, citarabine, melphalan, *mL* milliliters, *MOPP* mustargen oncovin procarbazine prednisone, *MT* milk thistle, *MTX* methotrexate, *NHL* non-Hodgkin lymphoma, *NR* not reported, *NS* non-significant, *NSPHO* Nordic Society for Pediatric Hematology and Oncology, *NWTS-4* National Wilms' Tumor Study-4, *P-IV* actinomycin, vincristine, *PINDA* Programa Infantil de Drogas Antineoplásicas de Chile, *PLT* platelets, *PNET* primitive neuroectodermal tumor, *RBP* retinol-binding protein, *RR* relative risk, *RT* radiation therapy, *Se* selenium, *SOD* superoxide dismutase, *ST* solid tumor, *TAC* total antioxidant capacity, *TBI* total body irradiation, *TPN* total parenteral nutrition, *UMIC* upper middle-income country, *VCR* vincristine, *vit*. vitamin, *Vp16* etoposide, *WBC* white blood cell, *WHO* World Health Organization, *wt* weight

[a] Sample size = number randomized

[b] When indicated, protocol provided in table. Otherwise chemotherapy ± radiation

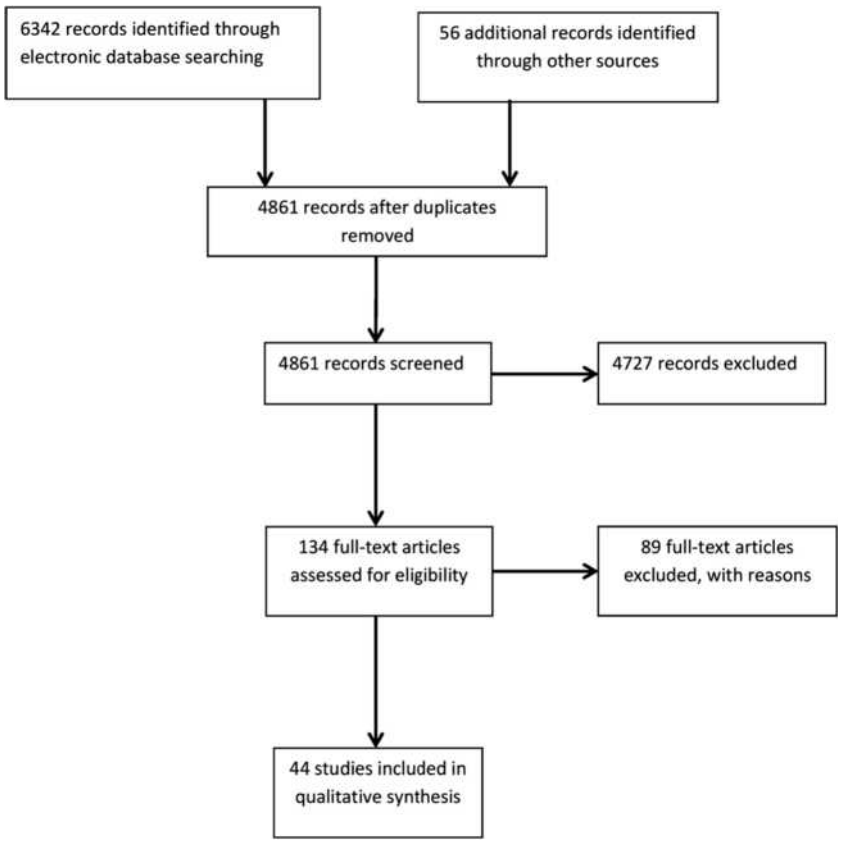


**Fig. 1** Results of search strategy

reported a significant decline in the use of antiemetics. One study reported a significant decrease in episodes of retching and/or vomiting [48].

### Aromatherapy

One good-quality study investigated aromatherapy among children undergoing hematopoietic stem cell transplantation (HCT) (Table 2) [49]. This trial, performed in an HIC, examined the effects of bergamot essential oil on anxiety in 27 children undergoing HCT for a variety of diagnoses. The authors found increased nausea and anxiety in the aromatherapy group compared with the control group.

### Massage

Nine studies, all performed in HIC and upper middle-income countries (UMIC), investigated the use of massage (Table 3) [39, 40, 50–56]. Six studies were of poor quality [40, 51, 53–56], and three were of fair quality [39, 50, 52]. Massage was administered in the inpatient [40, 50–55] and outpatient [54, 55] setting and at home [56]. One paper did not report the setting [39]. Various forms of massage therapy were provided and included massage therapy provided by parents [56], registered nurses [51], and licensed massage therapists [40, 50, 52–55]. One study did not report the provider of massage therapy [39]. Six of the studies examined the effect of massage on psychosocial outcomes [40, 52–56] and three studies on symptom management [39, 50, 51]. Three of the trials demonstrated a statistically significant reduction in child's anxiety [40, 54, 56]. One study found that Swedish massage was effective at reducing nausea and vomiting during 48 h post chemotherapy ($P = 0.027$) [50], and another found that slow-stroke back massage reduced nausea severity and vomiting frequency over the course of six chemotherapy infusions [39]. A third found that massage therapy reduced pain [51]. Swedish massage provided in the inpatient and outpatient settings reported beneficial effects on muscle soreness, discomfort, respiratory rate, anxiety, emotional symptoms, and clinical progress scores [55].

### Supplements

Thirty-two studies investigated the use of dietary supplements for several supportive care indications (Table 4). Twelve studies examined the effects of dietary supplements on mucositis, [34, 36, 37, 57–65], five studied treatment-related toxicities [46, 66–69], three examined appetite and weight management [35, 70, 71], three evaluated hepatic toxicity [41, 42, 72], three evaluated fever and neutropenia [38, 45, 73], two studies evaluated neuropathy [43, 44], two examined chemotherapy-induced nausea and vomiting [74, 75], and one study each

examined bone mineral density [76] and gastrointestinal symptoms [77]. Of the 32 studies, 12 studies were performed in HIC [37, 43, 45, 57, 59, 61–63, 65, 72, 73, 76], 13 in UMIC [35, 46, 58, 60, 64, 66–71, 74, 77], and 7 in LMICs [34, 36, 38, 41, 42, 44, 75]. Seven papers received a quality score of "poor" [36, 46, 60, 66, 76, 77], 17 "fair" [34, 35, 38, 42–45, 58, 59, 62, 64, 67–70, 73, 74], and 9 "good" [37, 41, 57, 61, 63, 65, 71, 72, 75]. Most studies included a wide range of diagnoses with few studies performed among homogenous patient populations.

The use of dietary supplements for the prevention or treatment of mucositis was the most commonly investigated supportive care indication. Glutamine ($N = 4$) was the most widely studied supplement for this indication; however, variable doses, routes, and duration were studied (Table 4) [57, 60, 63, 64]. Two studies were performed in children undergoing HCT; one showed decreased use of morphine and TPN in children receiving glutamine [57], and the other showed no benefit [63]. The other two studies found decreased antibiotic use in the glutamine group [60], while the other reported no significant findings [64].

Three studies evaluated vitamin E for the prevention [65] and treatment [36, 58] of mucositis. One study found a significant improvement in mucositis scores [58]; the other two reported no significant findings [36, 65]. Vitamin A was evaluated for the prevention of mucositis and did not report significant results [59]. Finally, honey was found to reduce the recovery time of mucositis when compared to a mixture of honey, olive oil-propolis extract and beeswax, or control [34]. The use of propolis, a bee resin, alone did not produce any significant results [62]. The first T&CM clinical trial conducted through Children's Oncology Group (COG) [61] administered Traumeel S or placebo to 200 children undergoing HCT. The authors did not find a significant effect on mucositis; however, a trend in the reduction in the administration of narcotics was observed.

Several studies examined T&CM therapies for a variety of treatment-related toxicities. Genistein [66] did not report significant effects, whereas beneficial effects were observed for selenium [46, 69]. One study examined Fuzheng Jianpi Decoction, a mixture of several different herbal remedies, and found improvement in anorexia, weakness, weight loss, constipation, pain, and somatic and psychological functioning [67]. Another study found a benefit on white blood cell (WBC) count and clinical symptom scores with various and individualized Chinese herbs [68].

Three studies addressed appetite and weight management [35, 70, 71]. Zinc chelate (2 mg/kg/day) significantly prevented weight loss, while also decreasing the number of infectious episodes [70]. An energy-dense eicosapentaenoic acid supplement (1 g BID) significantly decreased loss of body weight and body mass index [35]. A study evaluating PediaSure® and carnitine revealed no significant impact on anthropometric measures [71].

Three studies evaluated hepatic toxicity [41, 42, 72]. A small, multicenter pilot study found that milk thistle significantly decreased aspartate aminotransferase (AST) and total bilirubin among children with acute lymphoblastic leukemia in the maintenance phase of therapy [72]. Omega-3 fatty acids were found to reduce liver enzymes and increase antioxidants and uric acid [41]. Another study found that black seed oil decreased liver enzymes, alkaline phosphatase, and prothrombin time [42].

A study found that wheat germ extract significantly decreased neutropenic episodes and improved WBC and lymphocyte counts [73]. A Japanese study found that probiotics reduced the frequency and duration of febrile episodes and lowered the risk of developing fever [45]. In another study, administration of honey was associated with a reduction in the number of episodes of fever, number of children who developed febrile neutropenia, and reduced duration of hospital stays [38].

Glutamic acid was evaluated for neurotoxicity in two studies [43, 44]. One study found reduced severity of the tendon Achilles and patellar reflexes and decreased paresthesias, constipation, and neurotoxicity summary score [44]. In contrast, a multicenter consortium group study found that glutamic acid was not effective in the prevention of vincristine-induced neurotoxicity [43].

Two studies found improvement in nausea and vomiting with dietary supplements [74, 75]. A study examining vitamin A for D-xylose malabsorption found no significant effects [77]. Supplementation with calcitriol was found to improve lumbar spine bone mineral density [76].

## Discussion

To the authors' knowledge, we present the results from the first systematic review of clinical trials investigating T&CM interventions for supportive care indications in children and adolescents with cancer. Within each of the T&CM domains, the reported findings conflicted, identifying opportunities to further advance each of these domains within pediatric oncology. The widespread and persistent use of T&CM, particularly in LMICs, further endorses the need for additional research in pediatric oncology [3, 78, 79].

Several of the reviewed studies investigated the efficacy of massage therapy, a generally safe and accepted T&CM intervention [80]. We found encouraging evidence suggesting that massage therapy may be beneficial for several symptoms, which concurs with a recent consensus statement on non-pharmacologic approaches [81]. Evidence-based, non-pharmacologic T&CM interventions may be a cost-effective

approach to advance the provision of supportive and palliative care across all income settings.

The role of acupuncture has been one of the most thoroughly researched T&CM modalities with some translational data describing its role for the treatment of several disorders [82–86], including chemotherapy-induced nausea and vomiting and pain management [87]. Our review found that there are a limited number of studies in pediatric oncology despite documented safety and feasibility in pediatric oncology [88–90]. Acupuncture may be especially beneficial for clinicians, children, and adolescents seeking non-pharmacologic approaches to manage a specified indication or symptom clusters. Training and licensing guidelines set forth by HIC or countries with an established system for delivering Traditional Chinese Medicine may serve as a framework for the investigation of acupuncture in countries without an established body of legislation.

Our review found that the largest number of T&CM studies evaluated the role of a dietary or herbal supplement for symptom management. The role of dietary supplements has been one of the most controversial aspects of T&CM due to the risk of adverse interactions with cancer therapy together with the absence of governing bodies providing oversight on the manufacturing and processing of dietary supplements. We found that two large cooperative groups conducted multicenter studies thus providing a framework for the conduct of T&CM. While several studies have reported encouraging results, the quality of the trials precludes their integration into existing standards of practice. We found that for select T&CM supplements, a benefit may be evident. This may have a significant impact in LMICs where access to supportive care medications may be scarce. In these settings, the risks and benefits of T&CM supplements should be weighed prior to their incorporation into care.

The strengths of our systematic review were the clearly defined eligibility criteria, the inclusion of a research librarian for the conduct of a systematic search, the evaluation of evidence from both HIC and LMIC, and the consideration of a quality score for each study. However, there are several limitations to our review, many of which are inherent to the conduct of systematic reviews. Several of the screened studies were not obtained due to inability to contact the authors or inability to locate the published article. It is also plausible that due to limited resources in LMICs, not all clinical studies were submitted for peer review publication. Therefore, we cannot exclude publication bias in our study. We were unable to conduct a formal meta-analysis due to the limited number of studies investigating the same indication and the heterogeneity within the studies that reported on the same outcomes. While we were able to identify areas that appear to be encouraging for future research, it must be recognized that our recommendations evolved from a limited number of clinical studies. Moreover, many of the studies received a low-quality score; thus, our findings are not based upon high-quality clinical trials. Finally, most of the included studies were performed in HIC, thus limiting the generalizability of their findings to the resources available and clinical care delivered to pediatric cancer units in LMICs.

There has been significant scientific effort in advancing the science of T&CM among children with cancer in both HIC and LMIC. Although most studies in this systematic review were of poor quality, a body of literature exists to foster educational and research initiatives. Pediatric cancer units interested in incorporating T&CM into the supportive care needs of children with cancer should consider the existing evidence alongside national policies, barriers in delivering existing care, and indigenous resources to identify the modalities that may be readily integrated into institutional clinical care and whose research findings will have an impact on the quality of care delivered by the institution.

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APPENDIX

# CONFERENCE ABSTRACTS 2018 TO 2020

# NURSING IN WHO GLOBAL INITIATIVE FOR CHILDHOOD CANCER (GICC): – A REPORT FROM NURSE SPECIALISTS OF GICC IN THE YEAR OF THE NURSE (2020)

Oral presentation at the 52nd congress of the International Paediatric Oncology Society, virtual conference. October 2020

Rachel Hollis, United Kingdom Pernilla Pergert, Sweden Julia Downing, United Kingdom Courtney E. Sullivan, United States of America Glenn M. Afungchwi, Cameroon Melissa Adde, Belgium Lisa Morrissey, United States of America Rehana A. Punjwani, Pakistan Andre Ilbawi, Switzerland Julia Challinor, United States of America

## Background and aims

In 2020, the WHO/International Council of Nursing "Year of the Nurse and the Midwife" converges with the WHO GICC. The GICC aims to prioritize childhood cancer and support government capacity building to achieve 60% global survival by 2030. **Aims:** Create an informal coalition of expert paediatric oncology nurse representatives from countries of all income levels to guide health policy priorities to support activities for strengthening nursing and nursing leadership and to provide country assistance and regional planning as part of GICC and beyond.

## Methods

Specialist nurses engaged in WHO GICC working groups since 2018, created an informal coalition. Nurse leaders from the six initial WHO focus countries (Peru, Ghana, Zambia, Uzbekistan, Myanmar and Philippines) were nominated as GICC government-identified nurse focal point. Specialist nurses joined focus country workshops with local nursing leaders. Common challenges, advocacy needs and preliminary nursing priorities were identified through workshops and monthly conference calls with a WHO representative. Priorities were drafted into a position statement, and a survey developed and pretested to contribute to an analysis of the paediatric oncology nursing situation in each focus country in collaboration with the national nurse focal point for the Initiative.

## Results

Safety and specialization were identified as initial paediatric oncology nursing priorities for GICC focus countries. A publication from the specialist nurses amplified calls, particularly in resource-limited settings, for appropriate protective equipment when managing hazardous drugs and specialist training for optimal nursing care. These priorities were echoed in focus country workshops across diverse settings and informed survey development and local action planning.

**Conclusions**

Specialized paediatric oncology nursing education and safe work environments are tangible, cost-effective interventions aligned with existing GICC political commitments and focus countries' nurse priorities. Specialist nurses are now participating and leading elements of the GICC working groups to promote implementation of nursing priorities in the initiative. Future work includes contributing to GICC technical package development and advocating for the inclusion strategies to optimize the paediatric oncology nursing workforce.

# Outline for a foundation programme for nurses new to Pediatric Oncology in Sub-Saharan Africa: developed using a Delphi approach

Oral presentation at the 52nd congress of the International Paediatric Oncology Society, virtual conference. October 2020

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## Background and aims

The Sub-Saharan African nursing network builds on existing training initiatives across the region. It aims to develop harmonized tiered curricular for foundation and specialist level nurse training. A steering committee of nurse leaders, predominantly of African origin, oversees the activities of the network. It is affiliated to SIOP Africa for support and sustainability. The aim of this study was to develop an outline for a 'foundation' training programme.

## Methods

A three-round Delphi survey was conducted. A convenience sample of nurses from Sub- Sahara Africa with experience of at least one year caring for children with cancer was recruited. In the first round, participants were asked to identify a minimum of 10 and a maximum of 20 topic areas for inclusion in the programme. In the second round, participants were asked to rate the importance of each topic identified on a 5-point Likert scale with an aim of 80% consensus. In round three, participants were presented with a proposed outline framework and asked to express

agreement with wording and grouping of topics into modules. REDCap was used for data collection and analysis.

**Results**

Forty-six nurses participated in the first round whereby 57 different topic areas were identified. In the second round, 29 (63%) responded. All topic areas achieved consensus of 80% except 1. Nineteen nurses participated in the final round (41%), commenting on 12 modules encompassing the topics. There was 98% agreement for wording and 97% for grouping. The course outline was circulated to the steering committee for expert input and minor modifications were made before an outline framework was agreed.

**Conclusions**

The survey demonstrated a high level of consensus; suggesting a shared perception of essential knowledge and skills required for paediatric oncology nursing in Sub-Saharan Africa. The outline framework developed through this approach establishes the basis of a foundation/orientation programme in this setting.

# 'SUCCOUR' (SUPPORTIVE CARE FOR CHILDREN WITH CANCER IN AFRICA) - NURSING AT THE EPICENTRE OF A REGIONAL COLLABORATIVE TO IMPROVE SUPPORTIVE CARE

Oral presentation at the 52nd congress of the International Paediatric Oncology Society, virtual conference. October 2020.

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**Introduction:**

The 'SUCCOUR' project has as vision that every child in Africa gets the best possible supportive care required to be cured of cancer. The project builds on the Collaborative Wilms Tumour Africa Project which exists since 2014 and has led to improvement in survival rates, abandonment and death during treatment. Nurse retention and continuous education are essential for quality care in paediatric oncology. One of the specific objectives of the SUCCOUR project is to build local capacity for supportive care with emphasis on nursing.

**Method:**

A clinical nurse role model for supportive care was appointed in each of the five centres across five countries (Ghana, Zimbabwe, Kenya, Malawi, and Cameroon). Salary support was provided to the nurses and monthly educational web meetings were conducted on supportive-care-related topics. Succour nurses teach the lessons from web meetings to colleagues at their various hospitals.

**Results:**

Between July 2019 and March 2020, nine educational web meetings have been held, including 7 case presentations from nurses, one teaching from a nurse and 6 from doctors. Priority topics were identified by nurses. In an evaluation in December 2019, the nurses were satisfied (67%) or very satisfied (33%) with the content and structure of the sessions and strongly agree (100%) that the leaning was relevant to their work in paediatric oncology nursing care. Ten teaching sessions have been conducted at local centres with total attendance of 118.

**Conclusion:**

Regional collaborative projects present a good opportunity for nursing capacity building. The SUCCOUR project harnesses local expertise and collective resources to develop nursing capacity necessary for optimal supportive care.

# SUCCOUR – SUPPORTIVE CARE FOR CHILDREN WITH CANCER IN AFRICA – A BASELINE ASSESSMENT

Oral presentation at the 52nd congress of the International Paediatric Oncology Society, virtual conference. October 2020.

Larissa Klootwijk, Festus Njuguna, Janna Weijers, George Chagaluka, Francine Kouya, Vivian Painstil, Lillian Sung, Inam Chitsike, Liz Molyneux, Glenn Mbah Afungchwi, Trijn Israels

## Background and aims

The Global Initiative for Childhood Cancer aims to achieve 60% survival by 2030. Survival in many countries in sub-Saharan Africa is below 20% and death during treatment is common . Improved supportive care can reduce treatment-related mortality and allow more intense anti-cancer treatment, thus increasing cure rates. SUCCOUR is a project launched in 2019 by the 'Wilms Africa' group to improve supportive care in Africa. The objective of this study was to evaluate current practices and outcomes in nutrition, febrile neutropenia and death during treatment.

## Methods

A prospective, observational study was conducted in five hospitals in sub-Saharan Africa (Kenya, Malawi, Cameroon, Zimbabwe, Ghana). Data were collected from September 2019 – March 2020. All children below 16 years with a newly diagnosed cancer treated with curative intent were included. Data were abstracted using standard case report forms by trained personnel. Uncertain data were confirmed by treating clinicians in real time.

## Results

256 patients were enrolled (median age 6.3 years, range 0.2 – 17 years, 54% male). Most common cancer was Burkitt lymphoma (65/256, 24%). 56 (22%) had a mid-upper-arm-circumference (MUAC) indicating acute malnutrition. 168 (68%) parents or guardians reported occasional insufficient food at home. 212 (82%) patients received nutritional support during their hospital stay. 103 (40%) had a documented febrile neutropenic (FN) episode, of whom 12 (12%) died. Median time of onset of fever to receiving antibiotics was

30 minutes (range 0 minutes to 76 hours). Overall 37 (14%) patients died during treatment of whom at least 81% (30) are considered to have died of a treatment related cause based on signs, symptoms and laboratory results in the week preceding death.

**Conclusions**

This baseline assessment of the current situation will facilitate the development and prioritisation of supportive care interventions, and provide a benchmark for evaluating future interventions.

# PSYCHOSOCIAL SUPPORT NEEDS ASSESSMENT AMONGST ADOLESCENTS WHO SURVIVED CHILDHOOD CANCER IN CAMEROON

E-Poster at the 52nd congress of the International Paediatric Oncology Society, virtual conference. October 2020.

Kouya Francine, Vera Njamnshi, Brian Jator, Bernard Njodzeka, Glenn Mbah Afungchwi

**Introduction/ Aims:**

The Cameroon Baptist Convention Health Services opened a paediatric oncology unit since 2003. Survival rates for common and curable cancers are about 50%. There is no psychosocial support service for survivors.

This study aimed at identifying the psychosocial support needs during treatment and survivorship from the perspective of adolescent and young adult survivors.

**Methods:**

A structured questionnaire was used to interview survivors aged 12 years and above through telephone call between November 1 2019 and January 31 2020.

**Results/Discussions:**

Fourty-two survivors were interviewed with median age of 20.50[IQR 16 – 22.5]. During treatment, only 10 (23.8%) participants got a clear explanation of their disease from the health care team and eleven (26.8%) got a clear explanation from their parents.

Eight (19%) were always anxious during the course of their treatment and five (13.2%) always felt depressed. Common concerns during treatment included pain from disease (n = 21, 50%), pain from procedures (n = 27, 64.3%), frequent hospital visits (n = 15, 35.7%), hair loss (n = 26, 61.9%), change in body shape (n = 11, 26.2%), fear of death (n = 18, 42.9%), and fear of loss of education (n = 2, 4.8%).

After treatment, 15 (35.9%) returned to school very easily, while 7 (18.4%) did not return to school. Eight (19.0%) faced difficulties in their life activities related to the physical effects of cancer and 9 (21.4%) faced difficulties related to emotional effects of cancer. Three (7.1%) reported difficulty getting a partner because of their history of cancer.

**Conclusion:**

Many adolescent and young adult survivors have a poor understanding of their disease, yet face significant physical and emotional problems resulting from it. Loss of education amongst childhood cancer survivors poses a threat to their survival and integration.

Psychosocial support during and post treatment should be integrated childhood cancer programmes in LMIC.

# THE SIOP AFRICA / PODC COLLABORATIVE WILMS TUMOUR PROJECT – MAKING PROGRESS

Oral presentation at the 52nd congress of the International Paediatric Oncology Society, virtual conference. October 2020.

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5. Stellenbosch University, Cape Town, South Africa University of Manchester, UK
6. Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia
7. Princess Maxima Center, Utrecht, The Netherlands
8. World Child Cancer UK
9. Max Super-Specialty Hospital, New Delhi, India
10. College of Health Sciences, University of Zimbabwe, Zimbabwe

## Background

The Collaborative Wilms Tumour (WT) Africa Project is implementing a published consensus adapted WT treatment guideline in Malawi, Cameroon, Ghana, Zimbabwe and Ethiopia. A baseline evaluation of outcome was done in currently participating centres for children diagnosed in 2011 and 2012. Mean survival of 176 children at the end of treatment was 52%; a quarter (23%) died during treatment and 20% did not complete ('abandoned') treatment. Treatment costs were considered an important cause of incomplete treatment. Overall 2-year survival was estimated at 35% based on the relapse rate after completion of treatment of children with a Wilms tumour in Malawi. The aim of the collaborative project is to reduce both incomplete treatment and death during treatment to below 10% and to increase 2-year survival to 50%.

## Methods

All participating centres obtained local IRB approval and implemented the adapted WT treatment guideline. The Collaborative helps fund treatment and associated costs such as travel to prevent abandonment.

**Results**

Patient enrolment started in 2014 and 108 patients have ended treatment. Eleven (10%) were misdiagnosed at admission; five of whom had a Burkitt lymphoma. Of the remaining 97 patients, 64 (66%) were alive and well at completion of treatment, 14 (14%) had abandoned treatment, 13 (13%) died during treatment, four children (4%) had unresectable disease and one (1%) had progression of disease during treatment. One child died during postoperative chemotherapy of another cause. Overall 2-year survival is estimated at 45 - 50%.

**Conclusion**

Relatively simple and low cost interventions have led to a reduction of incomplete treatment and treatment related deaths and an increase of survival at the end of treatment.

# RESEARCH PRIORITIES IN PAEDIATRIC ONCOLOGY NURSING: AN AFRICAN PERSPECTIVE

Oral presentation at the 51st congress of the International Paediatric Oncology Society, virtual conference. Lyon, France. October 2019.

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## Background/Aims

SIOP PODC baseline standards for paediatric oncology nursing in low- and middle-income countries (LMIC) recommend evidence-based policies/procedures to guide quality nursing care. LMICs often lack nursing policies/procedures for vital care including managing chemotherapy, clinical emergencies, and end-of-life care. Rigorous research is required for the development of evidence-based policies. The aim of this survey was to identify research priorities that are important to paediatric oncology nurses in Africa.

## Methods

Using a recognized approach to scope expertise of conference participants, a convenience sample of nurse attendees from Egypt, Tanzania, Morocco, Uganda, and Cameroon,

completed an exercise at the 13th African continental SIOP conference in Cairo, Egypt, March 2019. They were asked to discuss their priorities for research in small groups, and using post-it notes, submit two research priorities to share with the larger group. All submissions were collected, collated and duplicates removed. A thematic analysis was conducted to first, group by research priorities, and second, by target stakeholders.

**Results**

Participants submitted 54 research priorities, 46 were retained after eliminating duplicates. Themes were: psychosocial support and counselling (n=30); professional practice (n=30); clinical care (n=5); education (n=7); access to care (n=6); end-of-life care (n=2); research funding (n=1); and cancer prevention (1). The target stakeholders included: nurses (41.3%), parents (37%), or children and parents (13.4%).

**Conclusion**

African paediatric oncology nurses identified 8 research priority themes, targeted towards key stakeholders. These research priorities go beyond the scope of hospital care to include advocacy and sustainability. Identifying questions that matter the most is taking the first step in revealing gaps in knowledge yet to be filled. African nurses caring for children and adolescents with cancer have significant interest in conducting research, however, they require capacity building, mentoring and funding to engage in research and create guidelines for practice based on best evidence in consideration of local, resource-limited healthcare environments.

# HIV PREVALENCE AND DISEASE OUTCOME AMONG PATIENTS WITH CHILDHOOD CANCER IN MBINGO, BANSO, AND MUTENGENE BAPTIST HOSPITALS, CAMEROON

Oral presentation at the 51st congress of the International Paediatric Oncology Society, virtual conference. Lyon, France. October 2019.

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**Background/Objectives:**

Cameroon has a population of 23.3 million, with 42.2% below 15 years. The Human Immunodeficiency Virus (HIV) prevalence amongst children aged 0-14 years is 0.4%. HIV is routinely tested for every child with cancer treated in the Cameroon Baptist Convention Health Services (CBCHS) Childhood Cancer Programme at Mutengene, Mbingo and Banso Baptist Hospitals in the Southwest and Northwest regions. Childhood cancer patients with HIV are treated with the same protocol as HIV negative cases. Our aim is to evaluate the prevalence of HIV among children diagnosed with cancer and the outcome.

**Design/Methods:**

Retrospective review of patients records from 2003-2016 on our database (POND). We analyzed all HIV positive cases for cancer type, and length of survival. Records review was conducted for information on antiretroviral therapy (ART). Data was analyzed on SPSS Version 25. An alpha level of 0.05 was considered for statistical significance.

**Results:**

A total of 1,513 patients were registered, 1,204 (79.6%) were tested for HIV. Twenty two (1.8%) patients were positive for HIV, with a female to male ratio of 1:1.2 and the median age of 7 years. The HIV prevalence by cancer type was as follows: Burkitt lymphoma (1.3%), Kaposi sarcoma (38.9%) and Retinoblastoma (0.9%). The distribution of childhood cancer patients with HIV by stage was: stage I (9.1%), stage II (13.6%), stage III (45.5%) and stage IV (9.1%). There was record of ART for 68.8% of HIV positive cases. Fifty percent were alive with a follow up range of 1-120 months (median 16 months). Survival was better amongst patients on ART (Fisher's exact = 0.006).

**Conclusions:**

The prevalence of HIV (1.8%) was 4.5 times higher in cancer patients than in the general population (0.4%). Outcome is better amongst patients who receive ART.

# SURVEY ON USE OF TRADITIONAL AND COMPLEMENTARY MEDICINE (T&CM) IN PAEDIATRIC ONCOLOGY IN AFRICA: PRELIMINARY FINDINGS FROM CAMEROON

Poster presentation at the third scientific conference of the African Christian Health Associations Platform (ACHAP). Yaounde, February 2019

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## BACKGROUND

Use of T&CM is highly prevalent among children with pediatric malignancies and has been associated with delays in diagnosis, abandonment of conventional cancer therapy. The situation in Africa is poorly understood. The aim of this study is to document the prevalence of T&CM use and described associations of T&CM use in African children diagnosed with cancer and being treated in the participating centres.

## METHOD

This is a cross-sectional study. Questionnaire-based interviews were conducted with parents of childhood cancer patients aged below 15 years, by trained interviewers who were not directly part of the day-to-day care team. Data was entered into a central REDCap database and analyzed on SPSS. The questionnaire collected information on demographics, health beliefs, health behaviours and T&CM use.

## RESULTS

Sixty-two patients participated between October 2017 and November 2018, 54.8% males and 43.5% females. Traditional medicine (TM) is available to 92% of respondents. Twenty four percent think that TM may be good for cancer treatment. Seventy-six percent used T&CM before diagnosis. Fifty percent visited a traditional healer (TH) before diagnosis of cancer,

with 29% doing so as first choice. Herbs (38.7%) and prayers for healing purposes (37.1%) were also used. Thirty-three percent used T&CM after diagnosis; mostly prayers for healing purposes (24.4%), herbs (11.3%) and TH (4.8%). The reported side effects with T&CM include pain (56.4%) and worsening of symptoms (61.5%). Three percent delayed for scheduled treatment due to T&CM after diagnosis. T&CM was mostly paid for by cash (56.8%), from 1.7 to 226 USD or free of charge (34.1%). Fifty four percent report that they would not disclose the use of TM to their doctor.

**CONCLUSION**

Paediatric oncology patients use T&CM before and during treatment. These treatments have effects on their symptoms, finances and treatment adherence. More disclosure and discussion on T&CM is required. The African T&CM survey provides an opportunity to understand the nature and stakes of T&CM use in paediatric oncology across Africa.

# Outcome comparison of 2 Retinoblastoma treatment protocols for developing countries as per SIOP-PODC recommendations

Oral presentation at the 13th African continental congress of the International Paediatric Oncology Society. April, 2019.

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**Introduction**:

Members of the International Society of Paediatric Oncology (SIOP) and Paediatric Oncology in Developing Countries (PODC) provided recommendations for graduated-intensity treatment of children with retinoblastoma in developing countries.

**Aim**:

To compare the outcome of children treated with 2 SIOP-PODC recommended retinoblastoma treatment protocols respectively in South Africa (SA) and Cameroon (CA).

**Methods**:

All children diagnosed with retinoblastoma between 2012 and 2016, treated in 6 paediatric oncology units (POUs) in SA and 2 POUs in CA were included (n=281). Treatment in SA (upper-middle-income country) involved local intraocular therapy, or chemotherapy (including Vincristine, Carboplatin and Etoposide) and/or surgery and/or radiotherapy for more extensive disease versus local intraocular therapy or combination chemotherapy (including Vincristine, Adriamycin and Cyclophosphamide) and/or surgery in Cameroon (lower middle-income country). Survival data presented is for 12-month follow-up unless otherwise specified, Chi-square and p-values for Log Rank Mantel-Cox.

**Results**:

Twelve-month survival in SA was 78.2% (100 of 127) and 59.2% (45 of 76) in CA (Chi-Square=9.277, p=0.002), which was significantly affected by stage. All stage 0 patients had a 100% survival in SA (16/16) and CA (2/2). SA patients had a better survival for all other stages compared to CA patients except stage IV: Stage I – SA 92.7% (51/55) versus CA 58.8% (10/17) (Chi-Square=13.391, p=0.000); Stage II – SA 100% (14/14) versus CA 75% (9/12) (Chi-Square=3.833, p=0.050); Stage III – SA 70% (7/10) versus CA 40% (2/5) (Chi-Square = 1.207, no survival difference). Stage IV CA patients had a better 12-month survival of 67% 8/12) compared to SA with 26% (6/23). The differences in survival between the stages might indicate the difficulty in staging children in CA, with only one dedicated pathologist and not all histology reviewed.

**Conclusion**:

The SIOP-PODC recommendations for graduated-intensity treatment protocols in different settings in developing countries had an acceptable overall survival after 12 months.

# Burkitt Lymphoma (BL): Effect of Cyclophosphamide (CPM) on the Menarche and Fertility Rate in 113 Cameroonian patients.

Oral presentation at the 13th African continental congress of the International Paediatric Oncology Society. April, 2019.

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## Background

Delayed menarche and normal fertility was recorded in 24 BL patients treated with CPM in Ghana. The US Childhood Cancer Survivor Study reported a reduced fertility risk in girls treated with a high cumulative CPM dose. We treated BL patients with CPM and intrathecal methotrexate at three Baptist hospitals in Cameroon between 2003 and 2015. Some received intravenous vincristine and methotrexate 1000 mg/m$^2$.

## Objectives

To establish the age at menarche, outcome of pregnancy, and fertility rate in BL survivors treated with CPM.

## Methods

Our POND4Kids registry was used to identify girls aged ≥ 12 years. A questionnaire was applied by personal interview or telephone to establish age at menarche of the patient and her

mother, incidence and outcome of pregnancy and status of the new - born. Age specific fertility rate (ASFR) was calculated.

**Results**

113 survivors who had reached their menarche aged 3 – 17 years at diagnosis (median 8), currently aged 12 – 26 years (median 17) were interviewed in person or per telephone. Mean follow – up was 9.0 years (range 1.2 – 13.3). Median age at menarche was 14 years (range 10 – 17) and their mothers 15 years (range 10 – 19). Median time since menarche was 3 years (range 0.04 to 11). Twenty three patients (20.4%) were successfully treated for relapse(s). Thirty two pregnancies resulted in 23 normal babies, four still births, one abortion, one miscarriage, and three uncompleted pregnancies. The ASFR was 82% for age group 15 – 19 years and 863.6% for age group 20 – 24 years.

**Conclusions**

The patient's age at menarche was one year lower than that of their mothers. The ASFR in age group 15 – 19 years was lower, and in age - group 20 – 24 years higher than recorded in Cameroon. Patients treated before age 10 years had a markedly lower ASFR.

# The Banso Baptist Hospital Healthy Lifestyle Club: a preventive approach to Non-communicable disease control in Cameroon.

Poster presentation at the third scientific conference of the African Christian Health Associations Platform (ACHAP). Yaounde, February 2019

Njecko B[1], Afungchwi GM[2], Fanfon T[1], Ekeawah C[1], Ngong BD[1]

1 = Banso Baptist Hospital

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## BACKGROUND/AIM:

The world is waking to a rise of morbidity and mortality due to non-communicable diseases (NCD), with a lion share of the problem in developing countries. Forty three percent of the deaths in Cameroon in 2002 were due to NCDs. The annual admissions due to NCDs has been on the rise in the Cameroon Baptist Convention Health Services facilities. Most NCDs are preventable through conscious healthy lifestyle modifications. If detected early, they can be controlled by medical therapy and lifestyle modifications. The aim of the healthy lifestyle club is to provide a platform for individual and collaborative monitoring of vital health numbers and psychosocial support for the attainment of individual goals for healthy living with guidance from a multidisciplinary team of health professionals.

## METHOD:

A multidisciplinary team of health care professionals was set up to coordinate the club, including a doctor, nurse practitioner, nurses, physical therapists, nutritionist and social worker. Individuals were invited to join the club following assessment of their numbers at the 'Know Your Numbers' unit, if they desired to take active measures to maintain healthy numbers and reduce disease risk. An executive body was set up with leaders elected by club members and ground rules laid down for the functioning of the club. The club meets monthly in circular discussion forum. At every meeting, a health talk is given, followed by discussions and sharing of individual health improvement strategies by group members. At the end of meetings, each group member gets a one-on-one session with nurses and health practitioners to discuss changes in their health numbers, challenges and possible way out. Members with ill-health are referred to consult a doctor.

**RESULTS:**

The clinic was launched in April 2017 and now has 47 registered members, 10 (21%) of whom have chronic NCDs and 37(79%) are healthy. The club members are of various works of life, including nurses, teachers, traders and farmers. The group has held 17 monthly meetings up until December 2018, with an average attendance of 20 per meeting. The major health education topics covered include healthy feeding and drinking habits; alcohol abuse; exercise and health; careful use of firewood; diabetes; hypertension; stress prevention; personal goals settings; and mental hygiene. All club members have kept diaries of their monthly health numbers and those with diabetes and hypertension attend monthly disease clinics in addition to the club. Members of the club have participated in celebration of the international physical exercise day and world diabetes day.

**CONCLUSION:**

We have established a functional healthy life style club whose members include healthy persons and persons with chronic diseases. The healthy lifestyle club is a practical way by which health care professionals can empower patients, sick and well, to proactively monitor their health and guard against NCDs and their complications. It also constitutes a structure for advocacy on NCD control at the community level. This initiative can be easily replicated in other hospitals in Cameroon and Africa.

# FIVE YEAR EXPERIENCE OF OUTREACH PALLIATIVE CARE TO CHILDREN WITH CANCER AT BANSO BAPTIST HOSPITAL (BBH) AND MBINGO BAPTIST HOSPITAL (MBH), NORTHWEST CAMEROON

Poster presentation at the third scientific conference of the African Christian Health Associations Platform (ACHAP). Yaounde, February 2019

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## Background

Palliative care (PC) is an essential component of every comprehensive childhood cancer programme. The CBCHS CHC programme provides care to about 140 children with cancer every year. Majority of them are diagnosed at late stages of disease and only about 50% of them are cured. About 70% of our patients are from poor families and live in remote rural settings. In order to offer PC to these children in their own homes, a motorbike outreach palliative care service established at BBH in 2013 for BBH and MBH in 2014. Our aim is for all children with cancer dying at home to receive essential pain control and symptom management, psychosocial and spiritual care, with all parents/carers receiving appropriate support and counsel through disease process and bereavement.

## METHODS

Our specialist paediatric PC nurse spends two weeks at each of the hospitals for familiarization with the patients and to support and teach the nursing staff to provide adequate symptom management during admission. Motorbike outreach is conducted to every home on fortnightly basis, carrying medications along. Community support systems are identified and patients linked to them. Phone contact is maintained with the families. A spread sheet is kept and updated for their changing symptoms and overall status.

## RESULTS

Over five years, we have provided holistic care to 814 patients (103 patients at home) and their families in the hospital and at home from 2013 to 2017, 381 home visits, 26 bereavement visits, 671 phone contacts. A qualitative evaluation of the programme in 2015 showed that it significantly improved quality of life for children with terminal disease and their families.

## CONCLUSION

Our paediatric PC outreach service has improved psychosocial and spiritual support to children with cancer and their families throughout their cancer journey, and significantly improved symptom control and quality of life for terminal patients.

# DEVELOPMENT OF A COMPETENCY-BASED ORIENTATION PRGRAMME FOR PEDIATRIC ONCOLOGY NURSING IN RURAL CAMEROON

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2 = Leeds Children's Hospital, UK

Oral presentation at the 50th congress of the International Society of Paediatric Oncology. Kyoto, Japan. October 2018.

## BACKGROUND/AIM

The Cameroon Baptist Convention Health Services operates childhood cancer centers in three rural hospitals in Cameroon. The baseline standards of the SIOP PODC nursing group recommend formal nursing orientation programmes with both theory and skills training. . The aim of this project is to establish a competency-based pediatric oncology nursing induction programme which meets this standard.

## METHODS

The programme was developed following a needs analysis undertaken with the local nursing team. It consists of two theory based workshops, each followed by 6 months of observed clinical skills acquisition. It is led by an expert nurse from Leeds Children's hospital and a local lead nurse. The first workshop covered: Cancer and its treatment; Supportive Care; and Professional Issues part 1. The second workshop will cover: Outcomes of treatment (survivorship and palliative care) and further professional issues. Core competences have been developed with specific competencies for chemotherapy administration. A check list has been developed for validation of competency, through peer evaluation moderated by the lead pediatric oncology nurses in each of the three hospitals.

## RESULTS

Fifteen nurses are currently in training. First workshop held in November 2017. Average rating of the workshop structure and content by participants was 4.5 on a scale of 5. Graded assignments for submission in April 2018 include: a case study of a child with a commonly seen cancer; a presentation on a cancer and its treatment; and a policy or checklist for a

nursing procedure. The second workshop will be held in May 2018. Graded assignments for submission in October 2018 will include a further case study, a sample “elevator” speech for nursing advocacy; and a research proposal on a nursing care related topic.

## CONCLUSION

The SIOP PODC baseline standards recommend formal orientation programmes for pediatric oncology nurses. Twinning partnerships can facilitate the development of training programmes for nurses in Low and Middle Income Countries which respond to the needs of the local setting.