EUROPEAN JOURNAL OF CANCER 44 (2008) 2388–2396

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Global child health priorities: What role for paediatric oncologists?

Stewart J. Kellie[a,b,*], *Scott C. Howard*[c,d]

[a]*School of Public Health, University of Sydney, Sydney, Australia*
[b]*Department of Oncology, The Children's Hospital at Westmead, Sydney, Australia*
[c]*Department of Hematology–Oncology and International Outreach Program, St. Jude Children's Research Hospital, Memphis, TN, USA*
[d]*Department of Pediatrics, University of Tennessee College of Medicine, Memphis, TN, USA*

ARTICLE INFO

Article history:
Received 29 April 2008
Received in revised form
26 June 2008
Accepted 10 July 2008
Available online 15 September 2008

Keywords:
Paediatric
Oncology
Public health
Low income countries
Twinning programmes
Epidemiology

ABSTRACT

Despite increasing globalisation, international mobility and economic interdependence, 9.7 million children aged less than 5 years in low income countries will die this year, almost all from preventable or treatable diseases. Diarrhoea, pneumonia and malaria account for 5 million of these deaths each year, compared to about 150,000 deaths from childhood cancer in low- and middle-income countries. In high-income countries, 80% of the 50,000 children diagnosed with cancer each year survive, yet cancer remains the leading disease-related cause of childhood death. In low- and middle-income countries, where 80% of children live, the 200,000 children diagnosed with cancer each year have limited access to curative treatment, and only about 25% survive. Some might argue that death from paediatric cancer in poor countries is insignificant compared to death from other causes, and that scarce health resources may be better used in other areas of public health. Is there a role for the treatment of children with cancer in these regions? Do international partnerships or 'twinning' programmes enhance local health care or detract from other public health priorities? What is ethical and what is possible? This review examines the health challenges faced by infants and children in low-income countries, and assesses the role and impact of international paediatric oncology collaboration to improve childhood cancer care worldwide.

1. Introduction

Contemporary paediatric oncology research emphasises the discovery of novel therapies for refractory malignancy, analysis of late effects, assessment of quality of life and for addressing the special needs of adolescents and young adults with cancer. Survival rates in high-income countries average 80% and deaths attributable to toxicity are below 5%.[1–4] In 2006, the most recent year for which firm estimates were available, 9.7 million children aged less than five years died, mostly from preventable causes and almost all in low-income countries (LIC) or less privileged communities in middle-income countries (MIC).[5] Approximately 4 million newborn babies are included in this devastating total.[6]

* *Corresponding author*: Tel.: +61 2 9845 2141; fax: +61 2 9845 2171.
E-mail addresses: stewartk@chw.edu.au, kellies6@aapt.net.au (S.J. Kellie).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.07.022

2. The challenge of global child health

2.1. Morbidity and mortality amongst the world's children

Globally, the percentage of children dying before the age of 5 years (U5M) born in 1950, 1980, 1990 and 1999 was 25%, 12%, 9.6% and 6.7%, respectively; however, regional variations in the rate of decline are of concern to the international community.[5,7] In 2005, the U5M in sub-Saharan Africa averaged 169/1000 (i.e. 16.9% of children do not survive to age 5), and this figure does not include perinatal deaths (stillbirths and deaths in the first week of life) caused by asphyxia, preterm delivery, sepsis and tetanus.[8]

In 2000, 99% of under-five deaths occurred in the settings of poverty. Just six countries, India, Nigeria, China, Pakistan, Democratic Republic of Congo and Ethiopia, accounted for 50% of deaths. Forty-two low- and middle-income countries accounted for 90% of U5M and the remaining 150 countries for 10%.[7,8] Most of the 9.7 million deaths in this age group could have been prevented with simple proven public health services to reduce mortality from diarrhoea and pneumonia (approximately 2 million children each), malaria (almost 1 million), and measles, tuberculosis and HIV (hundreds of thousands)[9] (Fig. 1). One quarter of the world's children aged under two years have not been immunised against diphtheria, pertussis and tetanus; 40% do not receive appropriate antibiotics for pneumonia; 58% are not exclusively breast fed during the first four months of life; over half do not receive the needed vitamin A supplementation; one-third do not have access to iodised salt; and one quarter have malnutrition, a major contributor to childhood death.[8,10–12]

Mosley and Chen proposed a policy framework for understanding childhood illness comprising 'distal' socioeconomic factors such as education and income, which influence incidence and outcomes through five groups of 'proximal' causes (maternal factors, nutrient deficiency, environmental contamination, injury and personal illness control), determined by availability and access to health care services.[13–17] Interventions that have addressed specific elements of the Mosley-Chen framework have contributed to the declines in childhood mortality; however, the greatest declines have occurred in countries using the broadest range of interventions against the causes listed above.

2.2. Millennium development goals and international organisations

The Millennium Development Goals (MDGs) reflect the ambitious commitments of all 189 United Nations member states to reduce poverty, illiteracy and inadequate public health by 2015 (Table 1). A compact was reached between rich and poor countries in 2002 at the International Conference for Development, in which LIC accepted the responsibilities of good governance, serious health policy design and implementation and transparency whilst high-income countries (HIC) committed to increase donor financing from 0.25% of GDP to 0.7%.[18,19]

The MDGs specify strategies to break the cycle of poverty, ill-health and premature death that traps so many of the world's poorest in poverty.[19] Three of the eight Development Goals, eight of 18 targets and 18 of 47 indicators are health-related. Representatives of several development agencies, including the World Health Organisation (WHO), the World Bank and the Bill and Melinda Gates Foundation met in Ottawa in 2003 because progress in achieving health-related MDGs had been slower than in the areas of education or poverty reduction.[20]

Bhutta highlighted the alarming lack of progress in maternal and child health in South Asia despite a modern industrial infrastructure, a massive investment in nuclear and conventional arms and many people with computer software and information technology expertise. He argues that the region's indicators of maternal and child health rank amongst the worst in the world as a consequence of poor governance, poor planning, poor accountability and failure to conduct research into the underlying determinants of health in the region.[21,22] In the light of these pressing global needs, one might wonder whether paediatric cancer care should even be considered in LIC.

3. Epidemiology of paediatric cancer

Cancer is the leading cause of death from illness in children and teenagers in HIC. Mortality data from the United Kingdom show that cancer accounted for almost one quarter of all childhood deaths in the age range of 5–14 years.[23] (Table 2) Although childhood cancer only accounts for about 1% of

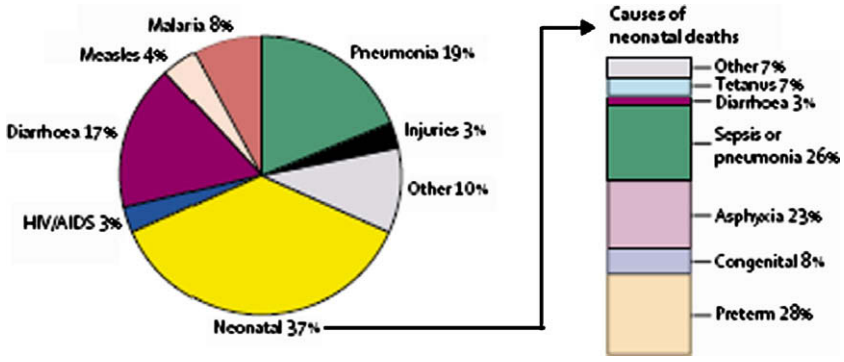

Fig. 1 – Major causes of death in children younger than 5 years and in neonates (yearly average for 2000–03) (Reprinted from[9], with permission from Elsevier).

Table 1 – Key economic indicators for sub-Saharan Africa and industrialised countries (adapted from Ref. [51])

Indicator	Low-income countries	Sub-Saharan Africa	High-income countries
Total population (2006)	2,353,000,000	741,000,000	1,011,000,000
Average growth 2000–2005	1.9	2.3	0.7
Population 0–14 years (2005)	36%	44%	18%
Life expectancy at birth in years, males (2005)	58	46	76
Infant mortality rate (younger than 1 year), per 1000 live births (2001)	61[a]	105	5
Under-5 mortality rate, per 1000 live births (2004)	122	168	7
Maternal mortality ratio, per 100,000 live births (2000, adjusted)	684	921	14
Percentage of children younger than 5 years who are moderately or severely malnourished(1996–2005[a])	39	29	3
Gross national income *per capita* (US$, 2005)	580	745	35,131
HIV prevalence, 15–49 years, (2005)	1.7%	6.2%	0.4%
Births attended by skilled health staff (2000–2004)	41%	42%	99%
Lifetime risk of maternal death (2000)	N/A	1 in 16	1 in 4,000

[a]Combined figure for MIC and LIC.
N/A: not available.

Table 2 – Main causes of child mortality, ages 1–14 years by sex and age group in England and Wales, 2000–2002

	Male mortality		Female mortality	
	1–4 years *n* (%)	5–14 years n (%)	1–4 years *n* (%)	5–14 years *n* (%)
Cancers	136 (14)	332 (23)	98 (13)	252 (24)
Infections	106 (11)	43 (3)	53 (7)	52 (5)
Nervous system	136 (14)	217 (15)	90 (12)	147 (14)
Circulatory system	39 (4)	72 (5)	53 (7)	63 (6)
Respiratory system	87 (9)	72 (5)	60 (8)	84 (8)
Congenital anomalies	136 (14)	101 (7)	113 (15)	94 (9)
Accident	164 (17)	433 (30)	120 (16)	199 (19)
Other	164 (17)	174 (12)	165 (20)	157 (16)
All deaths	968 (100)	1,444 (100)	752 (100)	1,049 (100)

Adapted (Reprinted with permission from Cancer Research, UK http://info.cancerresearchuk.org/cancerstats/childhoodcancer/mortality Accessed March 2008).

all cancer, in high-income countries it is the third most common cause of potential years of life lost after breast and lung cancer and ranks second in the total number of person-years saved by curative therapy (after breast cancer).[24]

Little is known about the epidemiology of paediatric cancer in MIC and LIC. Cancer mortality statistics in LIC suffer from predictable sources of error: inaccurate death certificates, misdiagnosis and under-reporting.[25,26] Children's cancer registries differ from the adult registries because of the relative rarity of paediatric cancer, the different spectrum of tumours, the use of histology-based classifications (e.g. leukaemia, neuroblastoma, and Ewing sarcoma), as opposed to site-specific classification used to estimate cancer mortality and incidence in the Global Burden of Disease studies.[27–30] Parkin and colleagues,[28] conducted a systematic review of geographic and ethnic variations in childhood cancer incidence from 64 countries and grouped cases into 12 diagnostic categories defined primarily by morphology. They demonstrated geographic and ethnic variation of age-standardised incidences but noted difficulties, such as incomplete ascertainment and unreliable population data. They reported an average annual incidence of 112/1,000,000, similar to the Surveillance, Epidemiology and End Results (SEER, USA) and European Automated Childhood Cancer Information System (ACCIS) age-standardised incidence rates of approximately 140/1,000,000/year.[31] The ACCIS project, used to estimate patterns and trends of incidence and survival in European countries, demonstrated differences between East and West survival in virtually every tumour category, providing a possible indicator of public health.[32]

The higher incidence rate of ALL amongst children aged 2–5 years in HIC and the absence of such an age peak in LIC have supported two parallel infection-based theories of leukaemogenesis: infectious agent and hygiene conditions hypothesis,[33] and a population-mixing hypothesis;[34] however, under-diagnosis and under-registration are much more likely explanations for the very low reported incidence rates in the poorest countries.[26,35] Calculation of cancer incidence requires estimates of the population of interest and is influenced by the frequency and accuracy of census data and subsequent shifts in population and also by the accuracy of diagnosis, which may be lower for cancers with protean manifestations (e.g. acute leukaemias) than for solid tumours. Metzger and colleagues reported an incidence of ALL in the capital city of Honduras (the location of the country's only paediatric cancer unit) of 20 per million compared to 10 per million in distant and rural areas.[36] In another study, the mean annual leukaemia incidence per million children was

16.4 (standard deviation [SD] 13.6) in LIC, 36.5 (SD 11.6) in MIC and 40.9 (SD 6.1) in HIC. In contrast, the incidences of non-leukaemia cancers in LIC, MIC and HIC were similar, a finding that argues against systematic underestimation of the incidence of non-leukaemias in LIC.[26]

4. Paediatric cancer in low income countries (LIC)

Approximately 250,000 children develop cancer each year, of whom 200,000 live in MIC or LIC, where cancer therapy is not a public health priority. The International Union against Cancer (UICC) initiated a world cancer campaign in 2005 to increase awareness, improve care and coordinate the training of professionals, using the support offered by the National Cancer Institute (USA), the International Society of Paediatric Oncology (SIOP), the International Confederation of Childhood Cancer Parent Organisations (ICCCPO), and Sanofi-Aventis.[35,37] This project promotes twinning programmes to transfer information, technology and other supports required to improve cancer care for those children with inadequate access to curative or palliative care.[38]

5. Human rights, intellectual property rights and 'Essential medicines'

The WHO regularly updates a 'Model List' of 'Essential medicines' selected to meet the priority health care needs of the population with regard to disease prevalence, evidence of efficacy and safety, and comparative cost effectiveness.[39] To date, 156 countries have adopted an essential medicine list.[39] The WHO list comprises a *core list* representing a list of minimum needs for a basic health care system. Chemotherapy drugs are listed in the *complementary list* for which the provision of adequate or specialist resources are required.[40] The WHO list guides many international organisations including UNICEF, UNHCR, and UNFPA as well as non-government organisations such as the International Dispensary Association (www.idafoundation.org) and charities who have adopted the list as the basis for their medicine supply.[39] A number of LIC restrict drug importation to those drugs specified on the WHO 'Essential Medicines' list.

The specific constraints on access to cancer chemotherapy drugs for adults and children were first reviewed by WHO in 1985,[41] and updated by its Expert Committee in 1994.[42] The majority of the conditions for which chemotherapy was likely to prolong survival or cure belonged to the paediatric category, and the Expert Committee initially listed 10 chemotherapy agents considered essential for children with cancer. A decade later, WHO noted 'it is inappropriate to acquire drugs which are required to treat these cancers' unless 'adequate resources and facilities are available' to administer them effectively.[40] In 2007, the WHO launched a parallel essential medicines list for children, including an expanded list of chemotherapy drugs in the complementary section of the list[39] (Table 3).

The Essential Medicines list has been incorporated into the UN Committee on Economic, Social and Cultural Rights defining the right to health.[43] Article 12 of the Covenant states, 'the right of everyone to the enjoyment of the highest attainable standard of physical and mental health', and 'the creation of conditions which would assure to all medical service and medical attention in the event of sickness'.[44]

Table 3 – Chemotherapy drugs on the WHO (2007) model list of essential medicines for children (Complementary list)

Drug	Formulation
Allopurinol	*Tablet:* 100–300 mg
Asparaginase	*Powder for injection:* 10,000 IU in vial
Bleomycin	*Powder for injection:* 15 mg (as sulfate) in vial
Calcium folinate	*Injection:* 3 mg/ml in 10 ml ampoule, *Tablet:* 15 mg
Chlorambucil	*Tablet:* 2 mg
Cisplatin	*Powder for injection:* 10 mg; 50 mg in vial
Cyclophosphamide	*Powder for injection:* 500 mg in vial *Tablet:* 25 mg
Cytarabine	*Powder for injection:* 100 mg in vial
Dacarbazine	*Powder for injection:* 100 mg in vial
Dactinomycin	*Powder for injection:* 500 micrograms in vial
Daunorubicin	*Powder for injection:* 50 mg (as hydrochloride)
Doxorubicin	*Powder for injection:* 10 mg; 50 mg (hydrochloride) in vial.
Etoposide	*Capsule:* 100 mg, *Injection:* 20 mg/ml in 5 ml ampoule
Fluorouracil	*Injection:* 50 mg/ml in 5 ml ampoule
Mercaptopurine	*Tablet:* 50 mg
Methotrexate	*Powder for injection:* 50 mg (as sodium salt) in vial. *Tablet:* 2.5 mg (as sodium salt)
Procarbazine	*Capsule:* 50 mg (as hydrochloride).
Vinblastine	*Powder for injection:* 10 mg (sulfate) in vial
Vincristine	*Powder for injection:* 1 mg; 5 mg (sulfate) in vial

The Ponte di Legno Working Group emphasised 'the right of all children in the world to full access to the essential treatment of ALL and other cancers, and call upon all authorities concerned to recognise and support all measures that promote this right to a chance of cure'.[45] This position aligns with Target 17, Goal 8 of the United Nations Millennium Declaration in 2000, 'in cooperation with pharmaceutical companies provide access to affordable essential drugs in developing countries'.[46]

Global trade agreements could threaten access to newer essential drugs in LIC and MIC.[47] Trade Related Intellectual Property Rights (TRIPS) is a World Trade Organisation agreement designed to strike a balance between protecting patents and allowing governments to 'fine tune' trade protection to respond to anti-competitive practices or national requirements if the patent holder does not supply the invention.[48] The WTO Ministerial Conference in Doha in 2001 (*The Doha Declaration*) is essentially a waiver of the export provisions of TRIPS allowing nations to produce generic drugs under 'compulsory license' and export beyond their borders in the situations of public health need.[49,50] Although such measures may be used to acquire newer agents, patent protection has expired on virtually all highly efficacious chemotherapy agents listed in the WHO Essential medicines list,[51] so lack of access to effective chemotherapy in some LIC should not necessarily be attributed to over-protective trade policies.

Responsibility for sustainable advances in paediatric oncology in LIC belongs to the whole world and a failure to treat life-threatening disease represents a violation of the human rights of children and the professional duties of the health care community.[52] A recent editorial from the WHO argued that cost-effective medicines for 'rare' conditions should be considered essential on the principle of 'distributive justice' where the rights of one patient to receive treatment should not differ from another based only on the prevalence of their illness.[53] However, if the cost of care for 100,000 children with potentially fatal diarrhoea is the same as that for one child with leukaemia, the issue of resource allocation becomes paramount.

6. Barriers to Successful Paediatric Oncology Care

6.1. *Overcoming poverty*

Extreme poverty is a barrier to effective intervention against the major killers of children worldwide – malnutrition, hygiene/sanitation or vaccine-preventable infectious diseases and accidental death. Developing cancer services in these areas is not a priority in the context of an ongoing humanitarian crisis. Poverty density (poor or disadvantaged people per square kilometre), population density and transport costs contribute to regional inequalities within countries which further complicate the implementation of health policy and delivery of cancer care.[54,55]

The costs of transport, accommodation and treatment combined with the economic impact of an absent relative accompanying the patient threaten the viability of many subsistence-level families. Reliance on traditional or local 'healers' may delay diagnosis and result in more patients from LIC presenting with advanced disease. A lack of understanding the need for treatment is one of the major barriers associated with poverty.[55–60]

6.2. *Developing centres of excellence*

The International Outreach Program of St Jude Children's Research Hospital (SJCRH) has been instrumental in developing paediatric cancer services in LIC.[55,61] The creation of a paediatric cancer unit is a critical first step to optimise local resources and to act as a nidus for training and future development.[57,58] Successful paediatric cancer programmes have been developed in many LIC and MIC.[52,58,60–67]

6.3. *Therapeutic protocol development*

Treating children with cancer using protocols positively influences the collective discipline of care.[57] Protocol-based treatment provides a means for assessing the impact of treatment on survival, an assessment of toxicity, and treatment compliance. Links between established and developing units facilitate protocol development adapted to local conditions.[59,61,68] Cancer centres in LIC face the added difficulties of high toxic death rates, often in excess of 20% for ALL (compared to 1% in HIC), more extensive disease at presentation and high rates of abandonment because of hospital charges, drug costs, family economic impact, lack of affordable accommodation and distance and transport costs.[36,60–63,68,69]

The web-based resource 'Cure4Kids' (www.cure4kids.org) is a comprehensive interactive platform providing real time access to protocols, education and professional development opportunities. Participants in LIC can interact with colleagues in other centres or countries in real time to discuss patients and protocols, and access a library of pre-recorded lectures and tutorials on a comprehensive range of medical, nursing and supportive care topics.[70]

6.4. *Training programmes for health care workers*

Training physicians and nurses who practice in LIC is a priority of programmes aimed at developing sustainable paediatric cancer care.[55,63,71–74] A long-term commitment is required to develop oncology staff, mostly within their country of origin in the circumstances directly relevant to future practice.[57,59] Short-term visiting fellowships to HIC for specific training are encouraged, but the avoidance of lengthy absences is preferred because trainees may be forgotten, lose their place or simply never return.[59]

SJCRH established the International Training Centre for Paediatric Oncology Nurses in San Salvador in conjunction with a local nursing society and multispeciality children's hospital. The training programme was open to nurses from other Latin American countries.[72,74] Prospective and retrospective analyses were a core component of the project that demonstrated cost effectiveness, high retention rates, satisfaction from the institutions that sent nurses and improved nursing practice. The scheme was extended to Morocco in 2000 to include a 'teach the teacher' programme at the partner sites, and recently a training centre has been established in Santiago, Chile where experienced nurses can gain specific oncology nursing experience.

6.5. *Developing laboratory and information transfer facilities*

The importance of 'twinning' to improve the outcome of children with ALL in LIC is evident in Dutch partnerships with Indonesian physicians, Italian partnerships with Central Americans, the NCI (USA) programme in India and the SJCRH International outreach programme.[60,62,66,68] Cancer treatment requires access to basic microbiologic, haematologic and safe blood banking facilities, as well as pathology and diagnostic imaging. SJCRH explored the development of regional immunophenotyping of leukaemic blasts in Latin America because of the clinical value of the technique and problems sending samples to the USA.[75] Using a simplified technique, they showed that children with more than 0.01% residual B-lineage leukaemia cells by day 19 of induction had a 10-year risk of relapse or remission failure of 29% compared to 5% in children with lower levels.[76] This simplified method is now being used to identify very low-risk patients with ALL in Recife, Brazil, who may benefit from reduced-intensity therapy (with lower toxicity), and highlights the value of developing simplified methods that can be implemented and sustained using local resources.

Recently, Chauvenet et al. reported excellent results in 650 patients with lesser-risk B-lineage ALL treated with antimetabolite therapy only.[77] The 6-year event-free survival (EFS) was 86.6% and the overall survival (OS) was 97.2% – results that offer hope to some children with ALL from LIC, where lesser-intensity therapy would increase compliance and decrease treatment-related mortality and costs.

6.6. *Development of databases and cancer registries*

Hospital-based cancer registries are essential in LIC for evaluating the outcome of interventions aimed at improving the health of cancer patients in resource-poor settings. Establishing a cancer registry is a first step in a rigorous data management programme to monitor survival, abandonment, toxicity and also provide epidemiologic information.[28,78] Quality improvement activities rely on accurate data to assess the impact of interventions of treatment outcome and quality of care. Databases also provide information to hospital management, government, non-government and donor organisations for planning, prioritising and monitoring cancer treatment efforts and informing public health priorities. In this regard, the secure, online Paediatric Oncology Networked Database (www.POND4kids.org) is available in multiple languages at no cost to centres that wish to use it. The software permits the storage of patient information, facilitated analysis (e.g. Kaplan-Meier curves), and flexible reporting. Protocols can be implemented with the automatic generation of treatment maps and the calculations of chemotherapy doses.[79] POND is currently used by 52 centres in 27 countries; a demonstration area and an application for a site license are available at www.POND4kids.org.

6.7. *Clinical research and ethics in LIC*

Developing countries and international donors are encouraged to invest in health research capacity in LIC to narrow health inequalities, to inform sound health policy decisions and to provide a platform for collaborative clinical research protocols.[80,81] The design and conduct of clinical research initiatives in LIC should initially focus on the epidemiologic, clinical and biologic questions relevant to the advancement of local clinical care. Developing countries should determine priorities, regulatory frameworks and codes of ethics relating to research collaboration. Costello and Zumla,[82] listed four broad principles to enhance research partnerships, encourage national leadership and institutional involvement and use research partnerships to build academic infrastructure:

- Mutual trust and shared decision making,
- National ownership,
- Emphasis on getting research findings into policy and practice and
- Development of national research capacity.

Good governance of research influences decisions about what questions are to be asked, by whom, and to what end. It also provides oversight on ethical considerations such as differences in cultural values, availability of supportive care and informed consent. Ethical oversight of clinical collaboration in LIC can have far reaching benefits, as reported from El Salvador recently.[83] Twinning organisations should discourage wealthy families from transferring abroad for treatment, as the loss of every patient with the capacity to contribute financially weakens the development of local services.[84] This is best accomplished by assuring the quality of local care is at least adequate and eventually excellent.

7. Lessons from sub-Saharan Africa

Burkitt lymphoma is the commonest malignancy affecting children in sub-Saharan Africa and is potentially curable with relatively inexpensive therapy.[85] Between 1968 and 1972, 30 – 40% of patients were cured with cyclophosphamide only.[86] A tumour registry in Malawi indicates that endemic Burkitt lymphoma accounted for 59% of all childhood cancer in that country.[87] Various treatments between 1988 and 1992 resulted in a 25% 5-year survival: 40% of patients abandoned or died before completing the therapy.[88] Similar results were reported from an earlier Ugandan study.[89]

More recently, Kazembe and colleagues,[90] examined the long-term survival of children with Burkitt lymphoma in Malawi treated with cyclophosphamide alone for one or more courses. The authors emphasised the challenges presented by resource-poor settings. They showed no difference in the mean cumulative dose of cyclophosphamide in survivors or those who relapsed, suggesting that higher doses did not improve survival and death from toxicity or the emergence of drug resistance, which were the key determinants of survival.[90]

SIOP adapted a protocol for Burkitt lymphoma to the realities of supportive care, access and affordability in Malawi.[91] The study showed a 1-year survival of 59% of all patients including those who died from treatment-related complications. The authors addressed the social, tribal and cultural barriers to effective treatment and the Europe-based International Dispensary Association contributed drugs, supportive care medicines, and other treatment requirements. A follow-up study shortened the treatment duration to 42 days to reduce abandonment and costs; however, the overall outcome was inferior.[92] Registry data confirm that HIV prevalence has altered cancer epidemiology: Kaposi sarcoma now accounts for 11% of paediatric cancer in Malawi and 33% in Uganda.[93–95]

8. Paediatric oncology twinning partnerships in LIC and global child health priorities

Will the current collaborative efforts – 'twinning partnerships' – between institutions in developing countries and targeted partner institutions in LIC have an adverse effect on global child health priorities by diverting resources from critically important public health interventions? The answer appears to be 'no' and evidence suggests that subspeciality collaborations building on committed local hospital and health infrastructure present a sustainable model to improve childhood cancer care. These partnerships can enhance both paediatric cancer and general paediatric health care by

- training local medical, nursing and technical staff, using a combination of local training, 'teach the teacher' exposure and international fellowships;
- encouraging specialists to develop subspeciality practices in their national communities rather than becoming part of 'brain drain';
- developing clinical research adapted to local needs and resources;
- developing databases and hospital-based cancer registries;
- stimulating awareness of health care needs, delivery and policy in LIC;
- highlighting poor governance, poor planning, poor accountability and a lack of local research into health outcomes in middle income countries;
- introducing international donor organisations to sustainable and evidence-based healthcare delivery;
- providing an information base for regional and national health care priority setting in LIC;
- emphasising the partnership model of development and resist neo-colonial models of external health care delivery;
- reinforcing the fact that children have a fundamental right to treatment of potentially curable disease;
- emphasising the human rights framework of access to affordable essential medicines for all persons;
- provoking considerations of the role of economic, trade and national debt servicing policies in widening the inequality gap and compromising global child health;
- preparing and equipping personnel in LIC to respond to the changing demography of childhood mortality, as the relative impact of cancer in these communities increases.

In certain regions urgent unmet humanitarian needs or open conflict may preclude the development of paediatric cancer programmes,[55] but the experience in Malawi suggests that even in a very poor LIC, treatment of common, curable cancers with uncomplicated therapy is feasible where the conditions for collaboration exist.[96] Instead of diverting resources from basic healthcare services, international partnerships to treat children with cancer increase resources available to the local healthcare system by mobilising foreign aid and community support. Such efforts are complementary to government public health efforts and should be encouraged in all LIC and MIC.

Conflict of interest statement

None declared.

REFERENCES

1. Hargrave DR, Hann II, Richards SM, et al. Progressive reduction in treatment-related deaths in Medical Research Council childhood lymphoblastic leukaemia trials from 1980 to 1997 (UKALL VIII, X and XI). *Brit J Haematol* 2001;**112**(2):293–9.
2. Eden OB, Harrison G, Richards S, et al. Long-term follow-up of the United Kingdom Medical Research Council protocols for childhood acute lymphoblastic leukaemia, 1980–1997. Medical Research Council Childhood Leukaemia Working Party. *Leukemia* 2000;**14**(12):2307–20.
3. McGregor LM, Metzger ML, Sanders R, et al. Pediatric cancers in the new millennium: dramatic progress, new challenges [see comment]. *Oncology (Williston Park)* 2007;**21**(7):809–20 [Discussion 820].
4. Rubnitz JE, Lensing S, Zhou Y, et al. Death during induction therapy and first remission of acute leukemia in childhood: the St. Jude experience. *Cancer* 2004;**101**(7):1677–84.
5. UNICEF. Child survival. In: The state of the world's children 2008. Executive summary New York: United Nations Children's Fund (UNICEF); 2007. p. 1–42.
6. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? where? why?[see comment]. *Lancet* 2005;**365**(9462):891–900.
7. Ahmad OB, Lopez AD, Inoue M. The decline in child mortality: a reappraisal. *Bull World Health Org* 2000;**78**(10):1175–91.
8. Black RE, Morris SS, Bryce J, Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? [see comment]. *Lancet* 2003;**361**(9376):2226–34.
9. Bryce J, Boschi-Pinto C, Shibuya K, et al. WHO estimates of the causes of death in children [see comment]. *Lancet* 2005;**365**(9465):1147–52.
10. Black RE, Allen LH, Bhutta ZA, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 2008;**371**(9608):243–60.
11. The World's Forgotten Children. Lancet 2003;361(9351):1.
12. Bryce J, el Arifeen S, Pariyo G, et al. Reducing child mortality: can public health deliver? *Lancet* 2003;**362**(9378):159–64.
13. Mosley W, Chen LC. An analytical framework for the study of child survival in developing countries. *Popul Develop Rev* 1984;**10**(suppl):24–45.
14. Claeson M, Waldman RJ. The evolution of child health programmes in developing countries: from targeting diseases to targeting people. *Bull World Health Org* 2000;**78**(10):1234.
15. Victora CG, Bryce J, Fontaine O, Monasch R. Reducing deaths from diarrhoea through oral rehydration therapy. *Bull World Health Org* 2000;**78**(10):1246.
16. de Onis M, Frongillo EA, Blossner M. Is malnutrition declining? An analysis of changes in levels of child malnutrition since 1980. *Bull World Health Org* 2000;**78**(10):1222.
17. Rutstein SO. Factors associated with trends in infant and child mortality in developing countries during the 1990s. *Bull World Health Org* 2000;**78**(10):1256.
18. Sachs JD, McArthur JW. The Millennium Project: a plan for meeting the millennium development goals. *Lancet* 2005;**365**(9456):347–53.
19. Sachs JD. Health in the developing world: achieving the Millennium Development Goals. *Bull World Health Org* 2004;**82**(12):947–9.
20. Cahill K, et al. High level forum on the health millennium development goals: selected papers, 2003–2005. Geneva: World Health Organization, 2006.
21. Bhutta ZA. Why has so little changed in maternal and child health in south Asia. *BMJ* 2000;**321**:809–12.
22. Engaging with global health. BMJ 2000;321:54–55.
23. Mortality statistics. Childhood, infant and perinatal. Series DH3 no. 32. In: National Statistics: The Stationery Office, London; 1999.
24. Bleyer WA. The impact of childhood cancer on the United States and the world. *CA: Cancer J Clin* 1990;**40**(6):355–67.
25. Gajalakshmi CK, Shanta V, Rama R. Registration of cancer mortality data in a developing area: Chennai (Madras, India) experience. *Cancer Causes Contr* 1998;**9**(2):131–6.
26. Howard SC, Metzger ML, Wilimas JA, et al. Childhood cancer epidemiology in low-income countries. *Cancer* 2008;**112**(3):461–72.

27. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA: A Cancer J Clin* 2005;**55**(2):74–108.
28. Parkin DM, Stiller CA, Draper GJ, Bieber CA. The international incidence of childhood cancer. *Int J Cancer* 1988;**42**(4):511–20.
29. Cole C. Registering childhood cancers. *Lancet* 2004;**364**:2074–5.
30. Shibuya K, Mathers CD, Boschi-Pinto C, et al. Global and regional estimates of cancer mortality and incidence by site: II Results for the global burden of disease 2000. *BMC Cancer* 2002;**2**:37.
31. Cancer Statistics Review, 1973–1986. Bethesda MD, Division of Cancer Prevention and Control Surveillance program. NIH Publication No. 89-2789. Bethesda, MD, National Cancer Institute, May 1989.
32. Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study. *Lancet* 2004;**364**(9451):2097–105.
33. Greaves MF. An immunological window on leukaemia. *Immunol Suppl* 1989;**2**(56-63):64–5.
34. Kinlen L. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. *Lancet* 1988;**2**(8624):1323–7.
35. UICC 2005. World cancer campaign: the time to act is now. Geneva: International Union against Cancer (UICC); 2005.
36. Metzger ML, Howard SC, Fu LC, et al. Outcome of childhood acute lymphoblastic leukaemia in resource-poor countries. *Lancet* 2003;**362**(9385):706–8.
37. Burton A. My child matters initiative awards: combating cancer in children in the developing world. *Lancet Oncol* 2006;**7**:13–4.
38. UICC Global Cancer Control. Childhood cancer: rising to the challenge. Geneva: UICC; 2006.
39. World Health Organization. Essential medicines. <http://www.who.int/medicines/services/essmedicines_def/en/print.html>.
40. Sikora K, Advani S, Koroltchouk V, et al. Essential drugs for cancer therapy: a World Health Organization consultation. *Ann Oncol* 1999;**10**(4):385–90.
41. Anonymous. Essential drugs for cancer chemotherapy: memorandum from a WHO meeting. Bull World Health Org 1985;63(6):999–1002.
42. Anonymous. Essential drugs for cancer chemotherapy. WHO consultation. Bull World Health Org 1994;72(5):693–8.
43. Seuba X, Seuba X. A human rights approach to the WHO Model List of Essential Medicines. Bull World Health Org 2006;84(5):405–7 [Discussion 408–11].
44. World health Organization. Equitable access to essential medicines: a framework for collective action. In: WHO Policy Perspectives on Medicines. Geneva: WHO; 2004.
45. Pui CH, Schrappe M, Masera G, et al. Ponte di Legno Working Group: statement on the right of children with leukemia to have full access to essential treatment and report on the Sixth International Childhood Acute Lymphoblastic Leukemia Workshop. *Leukemia* 2004;**18**(6):1043–53.
46. 2004 World Bank Indicators. Washington: International Bank for Reconstruction and Development/The World Bank; 2004.
47. 't Hoen E. Report of the Commission on Intellectual Property Rights, Innovation and Public Health: a call to governments. *Bull World Health Org* 2006;**84**(5):421–3.
48. TRIPS and pharmaceutical patents: fact sheet. World Trade Organization, <http://www.wto.org/english/tratop_e/trips_e/factsheet_pharm00_e.htm> [accessed 29.03.2008].
49. The Doha declaration on the TRIPS agreement and public health. World Health Organization, <http://www.who.int/medicines/areas/policy/doha_declaration/en/print.html> [accessed 29.03.2008].
50. WTO decision on the implementation of paragraph 6 of the Doha declaration on the TRIPS agreement and public health. World Trade Organization, http://www.who.int/medicines/areas/policy/wto_impl_para6/en/print.html [accessed 29.03.2008].
51. World development report 2006: equity and development. The World Bank.http://www.wds.worldbank.org/external/default/WDSContentServer/IW3P/IB/2005/09/20/000112742_20050920110826/additional/841401968_2005082630000807.pdf.
52. Sala A, Barr RD, Masera G, Consortium M, Sala A, Barr RD, et al. A survey of resources and activities in the MISPHO family of institutions in Latin America: a comparison of two eras. *Pediat Blood Cancer* 2004;**43**(7):758–64.
53. Reidenberg M. Are drugs for rare diseases 'essential'? *Bull World Health Org* 2006;**84**:686.
54. World Development Report. Focus 6 on regional inequality. The role of public policy in addressing spatial inequalities. 2005:204-205.
55. Ribeiro RC, Marina N, Crist WM. St Jude Children's Research Hospital's International Outreach Program. *Leukemia* 1996;**10**(3):570–4.
56. Dang-Tan T, Franco EL, Dang-Tan T, Franco EL. Diagnosis delays in childhood cancer: a review. *Cancer* 2007;**110**(4):703–13.
57. Simone JV. Cancer care and clinical research for children in less developed countries: problems and promise. *J Pediat Hematol/Oncol* 2000;**22**(6):490–1.
58. Pui CH, Ribeiro RC, Pui C-H, Ribeiro RC. International collaboration on childhood leukemia. *Int J Hematol* 2003;**78**(5):383–9.
59. Eden T. Translation of cure for acute lymphoblastic leukaemia to all children. *Brit J Haematol* 2002;**118**(4):945–51.
60. Ribeiro RC, Pui CH, Ribeiro RC, Pui C-H. Saving the children-improving childhood cancer treatment in developing countries. *New Engl J Med* 2005;**352**(21):2158–60.
61. Howard SC, Ribeiro RC, Pui CH, Howard SC, Ribeiro RC, Pui C-H. Strategies to improve outcomes of children with cancer in low-income countries. *Eur J Cancer* 2005;**41**(11):1584–7.
62. Magrath I, Shanta V, Advani S, et al. Treatment of acute lymphoblastic leukaemia in countries with limited resources; lessons from use of a single protocol in India over a twenty year period. *Eur J Cancer* 2005;**41**(11):1570–83.
63. Antillon F, Baez FL, Barr R, et al. AMOR: a proposed cooperative effort to improve outcomes of childhood cancer in Central America. *Pediat Blood Cancer* 2005;**45**(2):107–10.
64. Ekenze SO, Agugua-Obianyo NEN, Odetunde OA. The challenge of nephroblastoma in a developing country. *Ann Oncol* 2006;**17**(10):1598–600.
65. Bonilla M, Moreno N, Marina N, et al. Acute lymphoblastic leukemia in a developing country: preliminary results of a nonrandomized clinical trial in El Salvador [see comment]. *J Pediat Hematol/Oncol* 2000;**22**(6):495–501.
66. Veerman AJP, Sumadiono S. Twinning: a rewarding scenario for development of oncology services in transitional countries. *Pediat Blood Cancer* 2005;**45**:103–6.
67. Madani A, Zafad S, Harif M, et al. Treatment of Wilms tumor according to SIOP 9 protocol in Casablanca, Morocco. *Pediat Blood Cancer* 2006;**46**(4):472–5.
68. Masera G, Baez F, Biondi A, et al. North–South twinning in paediatric haemato-oncology: the La Mascota programme, Nicaragua [see comment]. *Lancet* 1998;**352**(9144):1923–6.
69. Mostert S, Sitaresmi MN, Gundy CM, Sutaryo, Veerman AJ, Mostert S, et al. Influence of socioeconomic status on childhood acute lymphoblastic leukemia treatment in Indonesia. *Pediatrics* 2006;**118**(6):e1600–6.
70. Quintana Y, Nambayan A, Ribeiro R, et al. Cure4Kids – building online learning and collaboration networks. In: AMIA

2003, Annual symposium proceedings/AMIA symposium. p. 978.
71. Workman GM, Ribeiro RC, Rai SN, et al. Pediatric cancer knowledge: assessment of knowledge of warning signs and symptoms for pediatric cancer among Brazilian community health workers. *J Cancer Edu* 2007;**22**(3):181–5.
72. Wilimas JA, Donahue N, Chammas G, et al. Training subspecialty nurses in developing countries: methods, outcome, and cost. *Med Pediat Oncol* 2003;**41**(2):136–40.
73. Leander C, Fu LC, Pena A, et al. Impact of an education program on late diagnosis of retinoblastoma in Honduras. *Pediat Blood Cancer* 2007;**49**(6):817–9.
74. Donahue N, Wilimas J, Urbina C, et al. International hematology–oncology nursing education in Latin America. *J Pediat Oncol Nurs* 2002;**19**(3):79–83.
75. Howard SC, Campana D, Coustan-Smith E, et al. Development of a regional flow cytometry center for diagnosis of childhood leukemia in Central America. *Leukemia* 2005;**19**(3):323–5.
76. Coustan-Smith E, Ribeiro RC, Stow P, et al. A simplified flow cytometric assay identifies children with acute lymphoblastic leukemia who have a superior clinical outcome. *Blood* 2006;**108**(1):97–102.
77. Chauvenet AR, Martin PL, Devidas M, et al. Antimetabolite therapy for lesser-risk B-lineage acute lymphoblastic leukemia of childhood: a report from Children's Oncology Group Study P9201. *Blood* 2007;**110**(4):1105–11.
78. Ayoub L, Fu L, Pena A, et al. Implementation of a data management program in a pediatric cancer unit in a low income country. *Pediat Blood Cancer* 2007;**49**(1):23–7.
79. Quintana Y, Howard S, Norland M, Patel A, O'Brien R, Ribeiro R, et al. Pond4Kids – an multi-site online Pediatric Oncology Research Database for collaborative protocol research. In: AMIA 2005, Annual symposium proceedings/AMIA symposium. p. 1090.
80. Sitthi-Amorn C, Somrongthong R. Strengthening health research capacity in developing countries: a critical element for achieving health equity [see comment]. *BMJ* 2000;**321**(7264):813–7.
81. Sitthi-Amorn C, Somrongthong R, Janjaroen WS. Economic and health care restructuring – the need for better governance. *Int J Epidemiol* 2001;**30**(4):717–9.
82. Costello A, Zumla A. Moving to research partnerships in developing countries. *BMJ* 2000;**321**:827–9.
83. Caniza MA, Clara W, Maron G, et al. Establishment of ethical oversight of human research in El Salvador: lessons learned. *Lancet Oncol* 2006;**7**(12):1027–33.
84. Chandy M. An approach to the management of leukemia in the developing world. *Clin Lab Haematol* 2006;**28**(3):147–53.
85. Burkitt D. A sarcoma involving the jaws in African children. *Brit J Surg* 1958;**46**:218–23.
86. Nkrumah FK, Perkins IV. Burkitt's lymphoma: a clinical study of 110 patients. *Cancer* 1976;**37**(2):671–6.
87. Banda L. Patterns of the most common malignancies in Malawi. In: Proceedings of the first continental meeting of the international society of pediatric oncology in Africa, Stellenbosch, South Africa: University of Stellenbosch Printers; 1995. p. 12–13.
88. van Hasselt EJ, Broadhead R. Burkitt's lymphoma: a case file study of 160 patients treated in Queen Elizabeth Central Hospital from 1988 to 1992. *Pediat Hematol Oncol* 1995;**12**(3):277–81.
89. Olweny CL, Katongole-Mbidde E, Otim D, Lwanga SK, Magrath IT, Ziegler JL. Long-term experience with Burkitt's lymphoma in Uganda. *Int J Cancer* 1980;**26**(3):261–6.
90. Kazembe P, Hesseling PB, Griffin BE, Lampert I, Wessels G. Long term survival of children with Burkitt lymphoma in Malawi after cyclophosphamide monotherapy. *Med Pediat Oncol* 2003;**40**(1):23–5.
91. Hesseling PB, Broadhead R, Molyneux E, et al. Malawi pilot study of Burkitt lymphoma treatment. *Med Pediat Oncol* 2003;**41**(6):532–40.
92. Hesseling P, Broadhead R, Mansvelt E, et al. The 2000 Burkitt lymphoma trial in Malawi. *Pediat Blood Cancer* 2005;**44**(3):245–50.
93. Banda LT, Parkin DM, Dzamalala CP, Liomba NG. Cancer incidence in Blantyre, Malawi 1994–1998. *Trop Med Int Health* 2001;**6**(4):296–304.
94. Sinfield RL, Molyneux EM, Banda K, et al. Spectrum and presentation of pediatric malignancies in the HIV era: experience from Blantyre, Malawi, 1998–2003. *Pediat Blood Cancer* 2007;**48**(5):515–20.
95. Wabinga HR, Parkin DM, Wabwire-Mangen F, Nambooze S. Trends in cancer incidence in Kyadondo County, Uganda, 1960–1997. *Brit J Cancer* 2000;**82**(9):1585–92.
96. Kruger C. Childhood cancer in developing countries. *Lancet* 2005;**365**:752–3.