

## Improving cancer care for children and young people 2

### Paediatric cancer in low-income and middle-income countries

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Patterns of cancer incidence across the world have undergone substantial changes as a result of industrialisation and economic development. However, the economies of most countries remain at an early or intermediate stage of development—these stages are characterised by poverty, too few health-care providers, weak health systems, and poor access to education, modern technology, and health care because of scattered rural populations. Low-income and middle-income countries also have younger populations and therefore a larger proportion of children with cancer than high-income countries. Most of these children die from the disease. Chronic infections, which remain the most common causes of disease-related death in all except high-income countries, can also be major risk factors for childhood cancer in poorer regions. We discuss childhood cancer in relation to global development and propose strategies that could result in improved survival. Education of the public, more and better-trained health professionals, strengthened cancer services, locally relevant research, regional hospital networks, international collaboration, and health insurance are all essential components of an enhanced model of care.

#### Introduction

Childhood cancer (defined here as cancer in children aged 0–14 years) constitutes only a small proportion of the global cancer burden, but 84% of childhood cancers occur in the low-income and middle-income countries, where nearly 90% of the world's children live and where access to care is poor (figure 1, table 1).<sup>1–3</sup> In 2010, 5·7 billion (83%) of the world's population of 6·9 billion people lived in low-income and middle-income countries. These countries have younger median ages and higher proportions of children in their populations than do high-income countries. Overall, 27% of the population of middle-income countries and 40% of the population of low-income countries are younger than 15 years, compared with 17% of the population of high-income countries.<sup>1</sup> In 2008, GLOBOCAN<sup>3</sup> estimated that about 148 000 cancers in children aged 0–14 years occurred in less-developed regions, a term that corresponds well to low-income and middle-income countries as defined by the World Bank<sup>2</sup> and includes Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia, and Polynesia—with a total population of 5·5 billion. The equivalent GLOBOCAN estimate for children with cancer in more-developed regions, defined as Europe, North America (excluding Mexico), Australia, New Zealand, and Japan, was 28 000. These regions have a total combined population of 1·2 billion people and differ little from high-income countries as defined by the World Bank.<sup>2</sup>

Relatively few countries, with only 15·9% of the world's population, fall into the high-income category, yet these countries account for 31·6% of deaths from cancer worldwide, largely because of the high proportion of older people in their populations.<sup>1,4</sup> WHO mortality data for the year 2008 (which is the latest available) shows that cancer is the most common cause of disease-related death in children aged 5–14 years in high-income countries (table 2), with roughly 5·4 times as many deaths from cancer as

from communicable diseases.<sup>4</sup> In low-income and middle-income countries, however, deaths from communicable diseases continue to outweigh cancer deaths in all childhood age groups, although the ratio between communicable and non-communicable diseases becomes progressively smaller as economic development increases; in children aged 5–14 years, 18 times as many deaths result from infections and parasitic diseases as from cancer in low-income countries, compared with about two times as many in upper-middle-income countries.<sup>4</sup>

In children aged 0–4 years, communicable diseases cause more deaths than cancer in countries of all income groups, including high-income countries. However, in high-income countries the number of deaths from infections and parasitic diseases in this age group is roughly twice the number of deaths from cancer, whereas in low-income and middle-income countries the numbers of deaths from infectious and parasitic

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Figure 1: African children with Burkitt's lymphoma

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For the **World Bank world development indicators database** see <http://databank.worldbank.org/ddp/home.do?Step=1&id=4>

diseases are about 150 and 60 times higher than the number of deaths from cancer, respectively (table 3).

### Development and demographic transition

The age structures of developing countries arise from high birth rates, fairly high death rates, and low life expectancies. This description is consistent with a model of change in population structure that results from the demographic transition brought about by industrialisation and economic development (figure 2). The UK, where the industrial revolution began, had by 1850 made the transition from an economy based on agriculture to one based on manufacturing, with its attendant and progressive urbanisation, new lifestyles, and new exposures to various chemicals, cheap manufactured cigarettes, increased food production (often processed or chemically preserved) and, at least initially, massive pollution. These changes were factors in the rapid increase in cancer that occurred in people of all ages, even while improved living conditions, safe water, improved sanitation, and, eventually, substantially improved health care (including cancer care) led to an increased lifespan. However, most countries are still undergoing a demographic transition, although many of the features of industrial development have reached them as global trade has increased.

The extent of development can therefore be seen largely as a reflection of the extent to which countries have undergone a demographic transition, although many local factors, political and otherwise, have also affected socioeconomic progress. In turn, the extent to which countries have progressed through the demographic transition affects their patterns of disease, with development creating, in addition to the already high (although falling) burdens of communicable diseases,<sup>2</sup> an additional increasing mortality from cancer and other non-communicable diseases—the so-called double burden of disease. However, although the global cancer burden is projected to increase as populations grow and age, the childhood cancer burden is expected to increase only marginally, on the assumption of medium population growth. This expectation is based on the fact that fertility is falling (the global childhood population has, according to the UN,<sup>3</sup> reached a peak) and that the disease burden of age does not apply to childhood populations. However, although demographic factors that affect the cancer burden are likely to have only a small effect on childhood cancer, development could result in increased exposure to risk factors and therefore a larger than anticipated increase in childhood cancers.

### Burden and range of childhood cancers

Deaths from infection and parasitic diseases predominate in the 0–4 years age group in all countries, irrespective of income, such that the percentage of disease-related deaths caused by cancer in this age group worldwide is very small compared with the equivalent percentage for children in the 5–14 years age group (0.5% in children aged 0–4 years vs 5.8% in those aged 5–14 years). However, because cancer mortality is higher in the younger age group, the overall numbers of deaths in children aged 0–4 years and those aged 5–14 years are of the same order of magnitude, despite the population of the younger age group being roughly half that of the older children (tables 2, 3). Children in the 0–4 years age group have a somewhat different range of cancers than do older children; most cases of retinoblastoma, neuroblastoma, Wilms' tumour, embryonal rhabdomyosarcoma, hepatoblastoma, and yolk-sac tumours occur in the younger age group.<sup>5</sup> Some of these tumours can originate from embryonic cells that persist after birth, or from oncogenic events in utero. In children aged 5–14 years, sarcomas are more common. Haematological malignancies and brain tumours (both of which encompass many different cancers), which are the most common tumour types in children, occur in both age groups.

Although cancer incidence in children aged 0–14 years is higher in more-developed countries than in less-developed countries (table 4), the number of cancers in the childhood age group as a proportion of the total number of cases in the population is higher—often substantially so—in the less-developed countries, because of the higher proportion of children in these countries' populations.<sup>1</sup> On average, 2% of cancers in less-developed

	OECD countries	High income	Upper-middle income	Lower-middle income	Low income
Number of countries or economies in income group	31	70	54	54	36
GNI per head (US\$)	40 142	38 764	5865	1595	534
GDP per head (US\$)	42 220	41 062	7326	1882	579
Population (millions)	1033	1127	2472	2494	799
Rural population (%)	20%	19.7%	40.2%	61.6%	72.4%
Population aged 0–14 years (%)	17.0%	17.3%	21.9%	31.9%	39.25%
Non-working-age population (%)	49.7%	49%	42.9%	59.2%	77.0%
Population in poverty (<US\$1.25 per day)	..	..	9%	30%	48%
Health expenditure per head (US\$)	5093	4876	379	70.9	26.9
Total health expenditure (% of GDP)	12.9%	12.5%	6.0%	4.3%	5.3%
Public health expenditure (% of GDP)	8.4%	8.2%	3.3%	1.7%	2.1%
Private health expenditure (% of GDP)	4.5%	4.4%	2.8%	2.6%	3.2%
Public health expenditure (% of total health expenditure)	65%	65%	54.4%	39.5%	38.8%
Out-of-pocket health expenditure (% of total health expenditure)	13.6%	13.7%	33.3%	52.8%	48.1%
Number of physicians per 1000 people	2.8	2.7	1.7	0.8	0.2
Number of nurses or midwives per 1000 people	7.2	7.0	2.6	1.5	0.5
Female literacy (aged 15 years and older)	..	97.9%	91.3%	62.3%	56%
Male literacy (aged 15 years and older)	..	98.7%	93.5%	80%	69.7%

Data are from the World Bank world development indicators database and are for 2010. Income groups are based on the 2011 gross national income (GNI) per head calculated according to the World Bank Atlas method.<sup>2</sup> Low income=US\$1025 or less; lower-middle income=\$1026–4035; upper-middle income=\$4036–12 475; high income=\$12 476 or more. OECD=Organisation for Economic Cooperation and Development. GDP=gross domestic product.

**Table 1: Selected development indicators in countries grouped according to World Bank income group**

	World	High income	Upper-middle income	Lower-middle income	Low income
Population aged 5–14 years	1 214 358 100	127 027 460	166 083 070	715 046 100	206 201 000
Deaths from all causes	1 265 306	17 396	66 973	721 871	459 065
Disease-related deaths	922 035	10 250	42 987	508 492	360 306
Infectious and parasitic diseases	496 605 (53.9%)	608 (5.9%)	14 738 (34.3%)	269 782 (53.1%)	211 476 (58.7%)
Non-communicable diseases (including cancers)	222 784 (24.2%)	9126 (89.0%)	24 030 (55.9%)	136 271 (26.8%)	53 357 (14.8%)
Cancers alone	53 464 (5.8%)	3317 (32.4%)	7984 (18.6%)	30 541 (6.0%)	11 622 (3.2%)

Based on WHO mortality data for 2008.<sup>4</sup> Percentages given are of disease-related deaths (the table does not show deaths from maternal, perinatal, and nutritional illness, and cancers are included in the non-communicable diseases category, so percentages do not add up to 100%).

**Table 2: Causes of death in children aged 5–14 years, by World Bank income group**

	World	High income	Upper-middle income	Lower-middle income	Low income
Population aged 0–4 years	634 176 000	62 609 870	83 257 710	366 776 700	121 531 770
Deaths from all causes	8 327 552	85 237	406 129	4 586 599	3 249 587
Disease-related deaths	8 044 722	77 730	385 484	4 441 084	3 140 423
Infectious and parasitic diseases	3 152 674 (39.2%)	3849 (5.0%)	82 903 (21.5%)	1 568 201 (35.3%)	1 497 720 (47.7%)
Non-communicable diseases (including cancers)	614 759 (7.6%)	31 769 (40.9%)	87 542 (22.7%)	347 009 (7.8%)	148 439 (4.7%)
Cancers alone	40 061 (0.5%)	1901 (2.4%)	4728 (1.2%)	23 341 (0.5%)	10 092 (0.3%)

Based on WHO mortality data for 2008.<sup>4</sup> Percentages given are of disease-related deaths (the table does not show deaths from maternal, perinatal, and nutritional illness, and cancers are included in the non-communicable diseases category, so percentages do not add up to 100%).

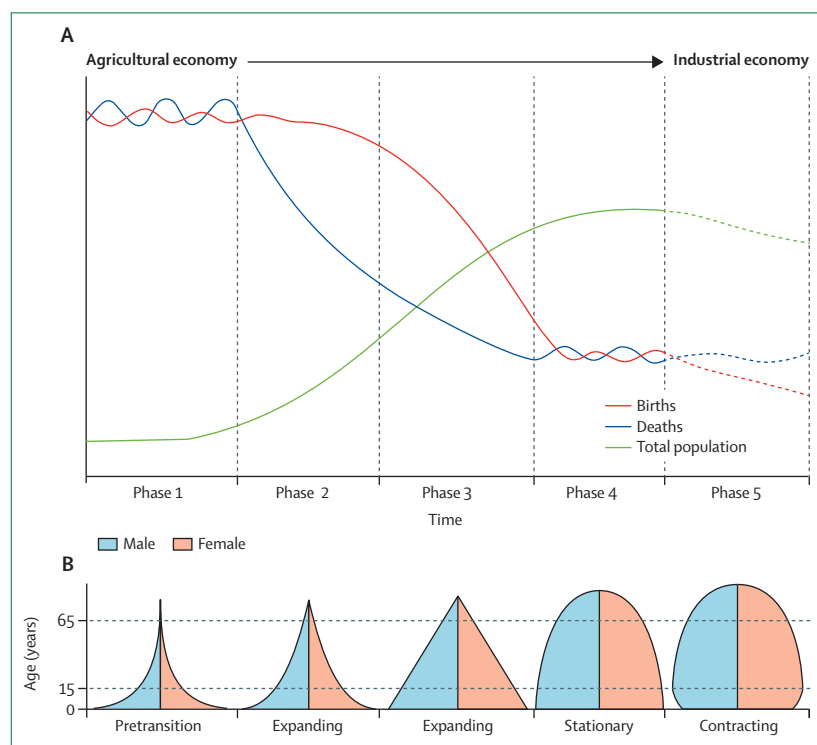
**Table 3: Causes of death in children aged 0–4 years, by World Bank income group**

countries and 0.5% of cancers in more-developed countries are in the 0–14 years' age group,<sup>3</sup> but these proportions vary between different countries and regions. In Africa as a whole, 4.8% of cancers are in children younger than 15 years, compared with 0.4% in Europe, which suggests that the proportion of cancers that occur in children is roughly 12 times higher in Africa than in Europe (figure 3). Such information is important for the planning of cancer control programmes.

### Incidence of childhood cancers

Based on GLOBOCAN estimates,<sup>3</sup> the incidence of childhood cancer varies between 50 and 200 cases per million children per year in different countries (figure 3). Because of the scarcity of cancer registries in low-income and middle-income countries, GLOBOCAN estimates might not be of adequate quality, particularly with respect to childhood cancer. However, these estimates (which also incorporate WHO mortality data) are still of unique importance, since they are often the only unbiased source of incidence and mortality data available in these countries. Nonetheless, more cancer registries are urgently needed in low-income and middle-income countries, and particularly in rural regions, since most cancer registries are in urban areas and so might not accurately reflect the national situation, particularly in countries with predominantly rural populations (eg, in equatorial Africa).<sup>7</sup>

The reason for the variability in total childhood cancer incidence across the world is largely unknown, although it is probably related to exposure to risk factors. In some cases, the very high incidence of one cancer can be enough to account for an unexpectedly high overall incidence. In equatorial Africa, for example, Burkitt's lymphoma accounts for roughly half of all childhood cancers,<sup>8,9</sup> and the AIDS epidemic in many African countries has led to a substantial increase in Kaposi's sarcoma, even to the point at which its incidence exceeds that of Burkitt's lymphoma.<sup>9</sup> Other countries seem to have very low overall incidences of childhood cancer, particularly countries in the southern and western parts of Africa.<sup>3</sup> One reason for this finding could be that many childhood cancers are not diagnosed, particularly leukaemias and brain tumours, which seem from the little registry data available to be uncommon in low-income countries.<sup>5,10</sup> However, although underdiagnosis and under-reporting doubtless occur, the extent of the incompleteness of the data is difficult to estimate because a source of independent data, such as death certificates, is not available. Moreover, under-reporting is unlikely to be the only reason for low overall incidences, since some cancers such as retinoblastoma and Wilms' tumour could have similar incidences irrespective of national income classification, or might have even higher incidences in low-income and middle-income countries than in high-income countries. Diseases with similar



**Figure 2: Demographic transition**

(A) Population change and economic development. Phase 1=high birth rates and death rates (pre-industrial); phase 2=fall in death rate (improved food and water supply, improved public health and hygiene), with consequent population growth; phase 3=fall in birth rate (urbanisation), with slowing of population growth; phase 4=low birth and death rates, with stabilisation of population growth; phase 5=contraction (birth rate lower than death rate). Developing countries are in phases 2 and 3, whereas developed countries in phases 4 and 5. (B) Population pyramids show demographic changes that accompany economic development.

	New cases	Incidence (per million)	Cumulative risk*
World	175 058	94	0.14%
Very high HDI	24 855	142	0.21%
High HDI	25 080	113	0.17%
Medium HDI	110 027	86	0.13%
Low HDI	15 035	85	0.13%

Data are from GLOBOCAN.<sup>3</sup> The UN HDI is based on two educational indicators, life expectancy at birth, and the logarithm of income, all of which are aggregated into a single index.<sup>6</sup> \*Cumulative risk is the risk of developing cancer before age 15 years.

**Table 4: Incidence of childhood cancer (aged 0–14 years) in 2008, by human development index (HDI) classification**

clinical characteristics can also vary in incidence in different regions—eg, precursor B-cell and precursor T-cell acute lymphoblastic leukaemias.<sup>5,10,11</sup>

By contrast with incidence, cancer mortality is much higher in children in less-developed regions than in more-developed regions. For example, in 2008, cancer mortality in Africa was 69 per million children, compared with 31 per million children in Europe. In Africa, an average of 5.13% of cancer deaths were in children, whereas in Europe children accounted for only 0.2% of cancer deaths (figure 4). Although survival data are not available,

mortality-to-incidence ratios give an idea of the association between development and cancer survival (figure 5).

### Risk factors for childhood cancers

Differences in incidence of individual childhood cancers are caused by differences in exposure to risk factors, coupled with genetic factors that affect the likelihood of a cancer developing. Little recent data exist for the incidence of childhood cancer subtypes in low-income and middle-income countries, but data from the 1980s strongly suggested the presence of substantial geographical variability (figure 6).<sup>5,12</sup> Leukaemias and lymphomas are the most common childhood cancers throughout the world—acute lymphoblastic leukaemias account for about 30% of all cases of childhood cancer, although its incidence does seem to vary. In equatorial Africa, however, acute lymphoblastic leukaemia is uncommon, its place taken by Burkitt's lymphoma, except in regions where the HIV epidemic has led to a substantial increase in the incidence of Kaposi's sarcoma.<sup>13</sup>

Some cancers might vary in incidence according to the extent of socioeconomic development. Evidence for this suggestion is provided by the fall in incidence of Burkitt's lymphoma and the increase in incidence of acute lymphoblastic leukaemia in the Gaza strip that coincided with a period of rapid socioeconomic development.<sup>14</sup> Other evidence suggests that the incidence of common (precursor B) acute lymphoblastic leukaemia is low in low-income and middle-income countries and that it increases substantially as countries undergo socioeconomic development.<sup>14,15</sup> For example, acute lymphoblastic leukaemia has a low incidence in India, and several institution-based studies have shown that the proportion of T-cell disease is high, particularly in rural regions, but has been decreasing with time.<sup>11,14–17</sup> This finding is consistent with data from Egypt<sup>18,19</sup> and evidence from death certificates in England and Wales that precursor B-cell acute lymphoblastic leukaemia started to increase in incidence in the early 20th century, first in England and Wales, and then in various other population groups.<sup>15,19,20</sup> Retinoblastoma and Burkitt's lymphoma, by contrast, might be inversely associated with socioeconomic development and seem to be more common in rural regions.<sup>8,9,10</sup> Retinoblastoma is the most common solid tumour of childhood in some low-income and middle-income countries and can have a higher incidence in these countries than that of neuroblastoma, which is invariably more common in high-income countries.<sup>5,10</sup>

Epstein-Barr virus (EBV) is associated with several childhood cancers, particularly in low-income and middle-income countries.<sup>21,22</sup> Almost all Burkitt's lymphoma cases in Africa and more than half of Burkitt's lymphoma cases in the other low-income and middle-income countries from which data are available are linked with EBV.<sup>22</sup> Although EBV infection is ubiquitous, infection occurs in infancy in children with very low socioeconomic status, which could account for its more frequent association with



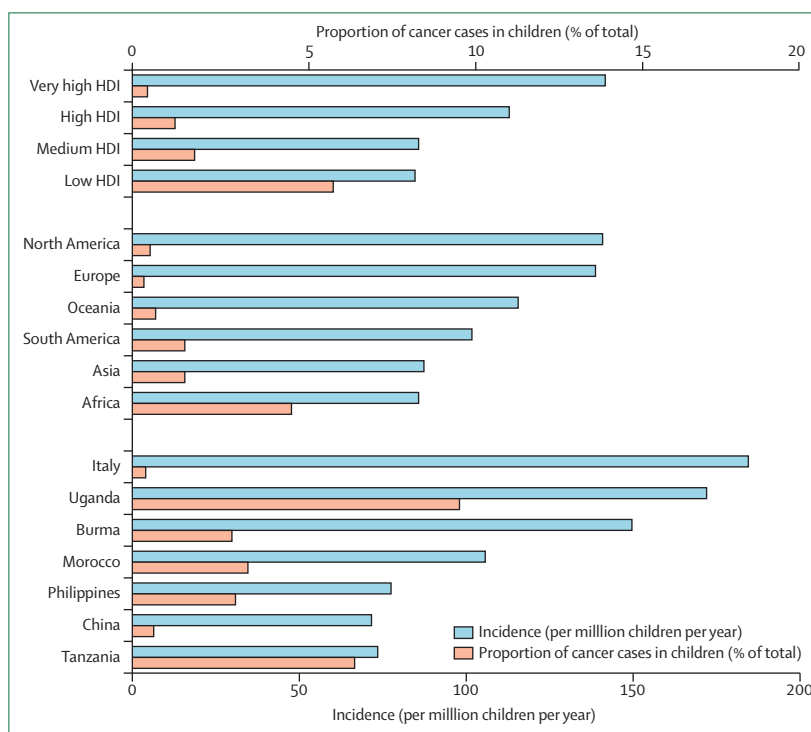
specific cancers in poorer countries. By contrast, in the wealthiest populations, where initial EBV infection occurs in adolescents and young adults, most cases of Burkitt's lymphoma are negative for EBV. The Berlin–Frankfurt–Münster cooperative group,<sup>23</sup> for example, reported that only 11% of the cases of Burkitt's lymphoma in their series were associated with EBV. The virus is also present in almost all cases of Hodgkin's lymphoma in children younger than 10 years in low-income and middle-income countries<sup>24,25</sup> and has been reported in NK/T-cell lymphomas in children in Peru,<sup>26</sup> T-cell lymphohistiocytosis in Asia (associated with haemophagocytic syndrome),<sup>27</sup> and in nasopharyngeal carcinoma, which is fairly common in children in north Africa and in south and southeast Asia.<sup>27,28</sup>

Malaria probably also predisposes people to Burkitt's lymphoma, at least in regions holoendemic for *Plasmodium falciparum*, which include equatorial Africa and Papua New Guinea.<sup>22</sup> Hepatocellular carcinoma, which is strongly associated with hepatitis B virus (HBV) and hepatitis C virus, is rare in children, but occurs at higher incidences in some regions, such as Taiwan, where it can be effectively prevented by vaccination against HBV.<sup>29,30</sup> Children co-infected with HIV and human herpesvirus type 8 are at an increased risk of Kaposi's sarcoma.<sup>30,33</sup> Although HIV infection has been shown to predispose people to B-cell lymphoma in many countries, the results of a 2010 study in Malawi<sup>31</sup> suggests that this is not the case for Burkitt's lymphoma in children in equatorial Africa.

Radiation increases the risk of leukaemias and solid tumours in children, as shown by epidemiological studies done in children exposed prenatally or postnatally to radiation from the atomic bombs dropped on Japan in 1945, or after therapeutic radiation or diagnostic tests.<sup>32,33</sup> A high incidence of thyroid cancer was reported after the Chernobyl nuclear accident<sup>34,35</sup> and background environmental radiation also seems to increase the risk for leukaemia, probably without a low-dose threshold (ie, no one has been able to define a dose below which leukaemia does not occur).<sup>5,10,36</sup>

### Challenges for access to care

With the exception of hepatocellular carcinoma, for which a causal factor (HBV) has been identified and an effective vaccine exists, prevention of childhood cancer is not possible, and mortality can only be reduced through improvement of treatment outcomes. Cancer treatment needs many experts, infrastructure, equipment, and drugs, and can be costly, but a child with cancer should have the same rights to health care as any other child. The stark reality, however, is that access to treatment is very poor in low-income and middle-income countries. An unknown proportion of children with potentially curable cancers never receive treatment—not even palliative care—and most of those who do die. Minimisation of symptoms throughout the entire clinical course of cancer is of fundamental importance, but palliative-care services are at an early stage of development in many countries.

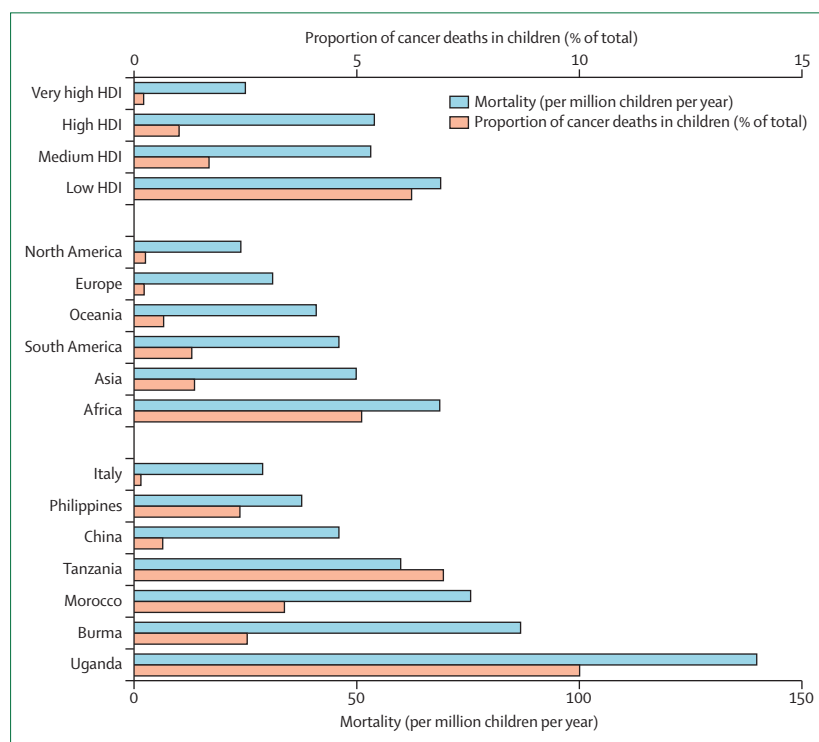


**Figure 3: Incidence of childhood cancer and childhood cancer as a percentage of total cancer cases in selected populations**

Childhood cancer is defined as cancer in people aged 0–14 years. All data are for both sexes. Populations are divided by human development index (HDI) classification and by continent. Data for a selection of individual countries are also shown. All data are from GLOBOCAN 2008.<sup>3</sup>

The expansion of hospital and community-based palliative care and access to pain medicines must be made high priorities for low-income and middle-income countries.<sup>37</sup>

The 36 low-income countries listed by the World Bank, although heterogeneous in many ways, share more similarities than differences with respect to the factors that affect access to health care. The vast majority of treatment centres are within the public sector, and referrals predominantly come through primary or secondary health-care providers, many of whom see very few childhood cancers in their entire professional lives. WHO strongly advocates the development of networks of primary health-care providers (wherein the access point to the health system is via an ambulatory generalist rather than a hospital) on the grounds that such networks would result in improved equity with respect to access to care.<sup>38</sup> However, the numbers of primary care providers in low-income countries and many middle-income countries (or regions within these countries) are often insufficient to serve the needs of the population, and most members of the public have little knowledge of cancer, particularly in children. As applies almost everywhere, the poorest people have the least access to health services. Many families consult traditional healers, who are more accessible in rural regions, but such practices can lead to delays in obtaining a medical consultation. Even primary



**Figure 4: Mortality from childhood cancer and deaths from childhood cancer as a percentage of total cancer deaths in selected populations**

Childhood cancer is defined as cancer in people aged 0–14 years. All data are for both sexes. Populations are divided by human development index (HDI) classification and by continent. Data for a selection of individual countries are also shown. All data are from GLOBOCAN 2008.<sup>3</sup>

care providers or specialists might not consider the possibility of cancer, and months can be wasted in futile treatment of an illness that a child does not have. Such delays in diagnosis results in more advanced disease and a worse prognosis. When children are sufficiently ill, parents might take them directly to a tertiary care centre, but the scarcity of such hospitals, either in the country as a whole (particularly low-income countries), or in large rural regions, means that for much of the population tertiary care centres are far from patients' homes. This situation creates several issues, including transportation costs, absence of parents from the home for long periods of time with detrimental effects on the rest of the family, and an unaffordable loss of income. A free hostel near the treatment centre where parents can stay while away from home can reduce abandonment of treatment,<sup>39</sup> but treatment costs often deter families from accepting care. With the exception of the few countries that have insurance coverage, families have to pay out of pocket for diagnosis and for much or all of treatment. Parents sometimes stop treatment when their money runs out or if they feel that they have to return home, even if to do so could result in the death of the child.

Ultimately, reaching a tertiary care centre is only of value if trained staff with experience in the treatment of childhood cancer, the necessary equipment and drugs

(nearly all of which are listed on WHO's list of essential drugs),<sup>40</sup> and standard treatment protocols are available. Even cheap, widely used drugs such as cyclophosphamide and vincristine might not be imported into some countries for periods of time (or be accessible to all hospitals able to provide care), and radiation therapy facilities, along with the staff needed to deliver radiotherapy, are totally insufficient in many countries—for example, the International Atomic Energy Agency's (IAEA) programme of action for cancer therapy has estimated that 80% of Africans do not have access to radiation therapy,<sup>41</sup> and more than 40 of the roughly 190 countries that report to the IAEA's directory of radiation therapy centres have no radiotherapy units at all. About 7000 additional radiotherapy machines are needed in developing countries around the world to treat patients with cancer, and the various experts—medical or otherwise—needed to ensure that well-organised health services are available are also either absent or are very few in number, which means that services are inaccessible to much of the population. Such deficits are worse in rural areas, and cancer centres vary substantially with respect to quality of care provided. Different ethnic and income groups can also experience unequal care, even in high-income countries, although differences are especially large in low-income and middle-income countries. Often wealthy individuals can access expensive treatment and obstetric care in well-equipped private hospitals in their own or other countries (not necessarily high-income countries), which is often paid for by their government.<sup>42</sup>

Although capacity for paediatric cancer care inevitably improves with development such that, overall, access to care is better in middle-income countries than in low-income countries, enormous variation in capacity exists, particularly in low-income countries, both within and between countries. Per-head income, for example, is ten times as high in some middle-income countries as in others, and this measure does not correspond to the quality or extent of health-care provision. A meaningful summary of access to care in middle-income countries as a whole is not possible, but, as with low-income countries, some commonalities do exist. Access to care is much better in the large urban regions that are developing rapidly, but in other areas the situation can differ little from that of low-income countries (eg, in China, India, and Brazil). This divide between urban and rural populations probably accounts for the absence of a change in mortality for all childhood cancers in 11 middle-income countries in Latin America between 1985 and 2007,<sup>43</sup> a period during which mortality was steadily falling in North America and Japan. Even now, cancer mortality in Latin America is twice that in North America. Many non-medical issues, such as access to secondary educational facilities, limits to the number of available university places, and incomplete coverage of academic disciplines (including medical specialties) affect the

availability of skilled health workers for childhood cancer care.<sup>44</sup> These factors are also related to economic development and vary substantially within and between countries.

The migration of health workers to countries able to offer better professional and personal opportunities either before or after specialist training is another important issue. Training in high-income countries is often assumed to be advantageous, but many trainees stay abroad permanently. This practice is sufficiently widespread that WHO has issued guidelines on recruitment policies to be used by high-income countries.<sup>45</sup> Sometimes health-care providers are tempted to do fee-for-service work in their own countries, or to work in well-equipped private hospitals that provide care only for those who can afford to pay for it (costs in for-profit private systems are generally higher). These practices further reduce the workforce available to provide for poor people. Establishing professional societies, even if very small initially, can help to counteract such practices through improvement of job satisfaction—eg, by facilitating professional discussions among their members, promoting continuing education, fostering the development of research networks, and collaborating with similar organisations in neighbouring countries. For example, the Turkish Paediatric Oncology Group (*Türk Pediatrik Onkoloji Grubu*) has evolved from a small group of pediatric oncologists into a strong national force for education, research collaboration, and cancer registration.<sup>46</sup>

### Financing health systems

Universal insurance coverage with pooling of funds is strongly recommended by WHO as a means to finance health systems,<sup>47</sup> since it creates equity with respect to access to care. Insurance also overcomes the obstacle of the cost of diagnosis and treatment that is a major reason for late diagnosis and, consequently, advanced disease or refusal of care (WHO reports that 100 million people are pushed into poverty each year because they have to pay out of pocket for health care that they cannot afford). Some developing countries are therefore starting to build national insurance programmes.<sup>48–50</sup> In Mexico, the introduction by the government in 2006 of social health insurance for families previously excluded from health insurance coverage (50% of the population, most of whom are socioeconomically deprived), the development of standard treatment protocols, and the accreditation of 49 programmes for childhood cancer resulted in a reduction of treatment abandonment from 35% to 4%, although by 2010 a reduction in mortality had still not been seen.<sup>51–54</sup> Nigeria<sup>48</sup> and Rwanda<sup>49</sup> have also introduced national insurance programmes with tangible benefits such as improved access to health care, fewer patients failing to complete treatment, and improved follow-up. China has taken many actions to control medical costs and has greatly improved health insurance coverage, which was at more than 90% by the end of 2010.<sup>55,56</sup> These

examples show that more equitable access to care and a reduction in abandonment of treatment can be achieved with enough political will. However, insurance alone is not enough—it must be accompanied by improvements in health systems and the quality of care that can take many years.

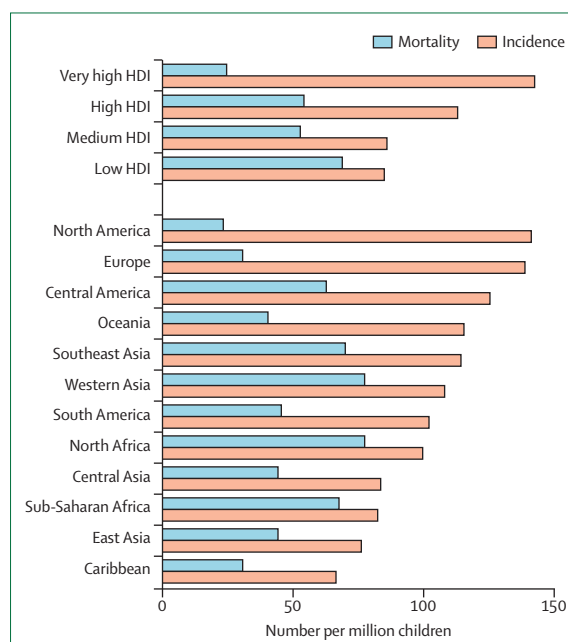


Figure 5: Estimated childhood cancer incidence and mortality in 2008, by human development index (HDI) classification and world region. All data are from GLOBOCAN 2008.<sup>3</sup>

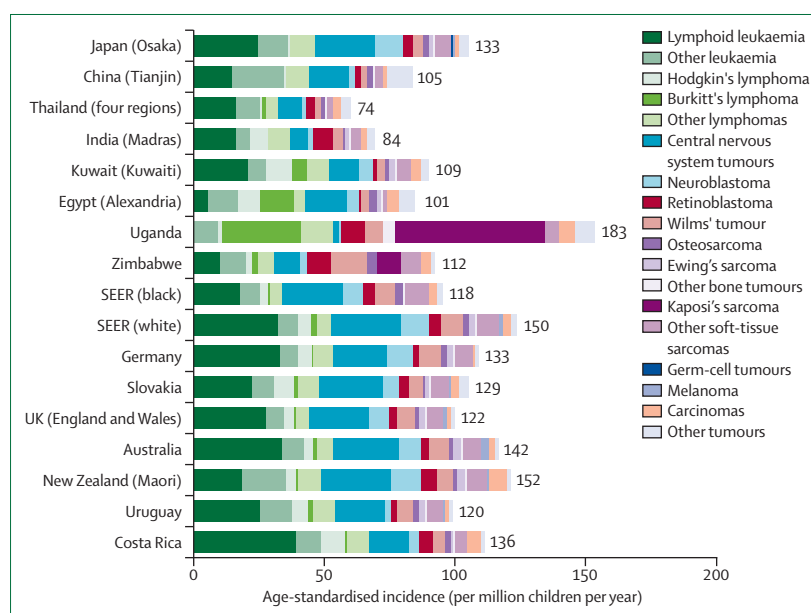


Figure 6: Incidences of childhood cancers in selected populations in the 1980s

Reproduced from reference 12, by permission of the International Agency for Research on Cancer. Figure is based on data from reference 5.

### Models of care and the need for research

Childhood cancer is one of the success stories in the history of cancer treatment, with 5-year survival of 80% or more now being achieved in high-income countries.<sup>57</sup> Because children have their entire lives ahead of them, saving the lives of children has a much greater effect on economic development than does cancer care for older people. Although the proportions of cancers that are cured are generally very low in low-income countries, treatment of curable childhood cancers is highly cost effective, even if it is only possible in a few institutions.<sup>58</sup> Essentially all countries, however poor, make some attempt to care for at least some children with cancer (eg, by focusing on specific types of cancer, such as Burkitt's lymphoma or acute lymphoblastic leukaemia), even though they might not have appropriately trained specialists. However, when trained medical and nursing staff are also scarce (eg, in low-income countries and many regions in middle-income countries), diagnosis and care can be poor or non-existent, even in major university hospitals.

Logical steps to address this situation are to first improve the quality of care in existing institutions that treat children with cancer, then to use these centres to train staff from centres elsewhere in the country, perhaps as part of a national cancer control plan (panel). An assessment of the present national situation is the first essential step, to be followed by a decision about whether to focus at first on one centre or one disease, for example, if that is all that is currently possible. Even one centre can provide a model, serve as a focal point for services and teaching activities, and initiate hospital networks that improve health systems.<sup>59</sup> Such plans can differ according to the available resources, and their chances of success are improved if they are supported by the government, a dedicated local leader, and by external support.<sup>60</sup> In middle-income countries, where high quality facilities might already exist, the approach is similar, except that the initial resources are probably better and external aid might not be needed.<sup>61</sup> Cancer control plans should include provision for prompt referral and early diagnosis, since these are essential to reduce the proportion of patients with advanced disease, and in some cases (eg, retinoblastoma) to preserve function.<sup>62-64</sup>

### Diagnosis

Correct diagnosis is the foundation on which all subsequent management rests. Unfortunately, the poorest countries have far too few pathologists to diagnose all cases of cancer, and even many middle-income countries have inadequate diagnostic capabilities, because health workers have not been trained in paediatric cancer diagnosis or because specific pathological techniques are unavailable. Although tissue blocks or slides are sometimes sent to centres in other countries for diagnosis, this practice is not a sustainable solution. Approaches to improve diagnosis might need to be focused initially, as with clinical care, on one or a few centres. Web-based

resources (telepathology) can facilitate this process and digital connections between local pathologists and international experts, or the use of telepathology in-country, can help greatly. Online educational resources can also be used to improve access to information for both doctors and patients, and can complement formal education.<sup>65,66</sup>

### Patient management

Paediatric oncology programmes can be located in cancer centres or hospitals with paediatric departments. If in general hospitals, physical separation of oncology inpatients from general hospital patients is important, since other patients might have infectious diseases that could be readily transmitted to neutropenic patients, with potentially fatal effects.<sup>67-71</sup> Overcrowding because of the few locations where children can be treated is a common issue, and hygienic facilities, standard procedures for disposal of contaminated materials, avoiding reuse of needles, and prompt recognition and treatment of the common toxic effects of chemotherapy are basic elements of care, without which avoidable deaths will be common. A system to ensure the availability of chemotherapy is essential, but very often in low-income countries, drug supplies are not stable. In some countries, haematologists will treat childhood leukaemias and lymphomas, thus providing more expertise for these cancers, which account for nearly half of all childhood malignancies. Social and psychosocial assistance provides family support and can decrease the risk of abandonment of treatment.<sup>72</sup>

Much research done in the USA and Europe in the second half of the 20th century identified patients with subsets or stages of cancers that can be treated with reduced therapy without detriment, on the one hand, or in whom standard therapy is inadequate, on the other. Unfortunately, in many low-income and middle-income countries, staging is imprecise because of poor access to imaging technologies or inadequate numbers of specialists trained in their use; ultrasound imaging is more widely available than more sophisticated equipment such as MRI, CT, or radionuclide imaging. However, the absence of precise staging does not mean that patients cannot be effectively treated, particularly when local therapy (surgery or radiation) is not involved. The same chemotherapy can be given to all patients with a specific diagnosis and their outcomes analysed to try to identify clinical or easily measured biochemical risk factors that can be used to triage future patients into different treatment groups.<sup>11,73</sup> Local staff and external experts should be aware that prognostic factors validated in high-income countries might have reduced predictive value in low-income and middle-income countries for several reasons: most patients have advanced disease; the biology and genetics of the tumour and the patient might be different; and comorbidities such as malnutrition and infections, including hepatitis, tuberculosis, and fungal infections, which lead to poor tolerance of treatment, are



**Panel: Elements that could be included in a model of paediatric cancer control in low-income and middle-income countries**

**Public health policy**

*National cancer control plan*

- Governmental plan to control cancer, including cancer in children
- Priorities to be set in wide consultation with health-care providers, professional and non-governmental organisations (NGOs), and international experts

*Cancer registration*

- Provision of data about cancer incidence relevant to local policy and research needs, from a population-based cancer registry
- Special attention should be paid to collection of data for both children and rural regions, neither of which are well represented at present
- International collaboration to make comparisons and improve methods

*Routine national statistics*

- Regular population counts and estimates and publication of detailed results, including for children and infants
- Death certification and reporting of causes of death to WHO
- Use of verbal autopsies to estimate cause-specific mortality where high-quality death registration is not available

*Health insurance coverage*

- Health insurance programme in which prepayment and pooling of risk ensures that families are not deterred from medical consultation because of cost
- Universal insurance is an important element of a sustainable health system
- Subsidisation of travel can ensure that financial concerns do not prevent early diagnosis

*Primary health care*

- Sufficient coverage by primary care providers to allow good access

*Referral pathway*

- Prompt referral to a tertiary care centre when necessary

*Centres of excellence*

- Centralisation of treatment, especially for rare cancers

**Health professionals**

*Primary care*

- Primary care providers educated in the signs and symptoms that could be caused by cancer and who know where to refer patients for further investigations

*Oncology team*

- Tertiary care facility with the necessary specialists, including paediatric oncologists, radiation therapists, surgical oncologists, and oncology nurses, as well as non-oncologists who deal with discrete sets of diseases (haematologists, neurologists, orthopaedic surgeons, neurosurgeons, etc)
- Multidisciplinary communication among all specialists through regular tumour board meetings, death conferences, and patient rounds to ensure that every patient gets the best treatment available

- The tumour board can also provide additional functions such as education of junior staff and trainees

*Training and professional support*

- Professional organisations that provide opportunities for continued education and a forum for discussion of relevant issues within the country, region, or local area, including issues such as abandonment of treatment, cancer registration, etc

**Diagnosis and risk stratification**

*Access to prompt biopsy of suspected cancer*

- Secondary care facilities with health professionals who are able to take biopsy samples when necessary and who understand the importance of prompt pathological diagnosis

*Pathology service*

- Access to a pathology service with well-trained pathologists and the necessary equipment and reagents to make accurate diagnoses
- Prompt reporting of pathology results to the clinician responsible
- Consultative network—eg, use of telepathology for education and discussion, as in INCTR's iPath or St Jude's international outreach programme

*Staging and risk stratification*

- Access to necessary imaging procedures to identify the stage or extent of spread of cancers
- Capability will vary substantially according to socioeconomic status of the country

**Treatment**

*Treatment protocols adapted to local conditions*

- Standard protocols agreed upon for all paediatric cancers
- Ideally, partnership in a disease-specific network or cooperative group capable of doing clinical research, even if mainly designed to assess suitability of regimens in the local setting

*Access to drugs and supportive care*

- An efficient pharmacy that procures drugs before they run out, and a national or regional system that ensures that all necessary drugs are available, including those needed for pain control, such as opioids

**Support infrastructure**

*Psychosocial and financial*

- Psychosocial support with mechanisms to avoid lost earnings, local lodging when families live far away, and access to social assistance and advice
- Presence of a patient advocate to identify non-medical family and patient needs
- Subsidised travel and lodging to make access to tertiary care feasible

*Outcome assessment and quality improvement*

- A system of data collection that includes a hospital registry, necessary databases, and data managers able to collect data efficiently

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- A systematic approach and appropriate resources and personnel (eg, a tracking officer) to ensure that all patients are followed up to record the outcomes of treatments
- Collection of clinically relevant data
- Assessment of delays in cancer diagnosis and referral, abandonment pattern, etc
- Long-term follow-up of cancer patients and assessment of survival

#### **Advocacy and sustainability**

##### *Awareness of childhood cancer*

- A population educated in the signs and symptoms that could be caused by cancer and aware that early diagnosis is important
- Freedom from stigma associated with cancer

#### **NGOs**

- Local or national NGOs that advocate for paediatric cancer and might help to provide funding for necessary drugs, salaries, construction, etc
- Such NGOs can have an important role in ensuring the sustainability of the health system and advocating for improvements, and for the development of cancer control plans (and resources to enact them)

#### **External collaboration**

- Associations with international professional groups or organisations can lead to benefits with respect to drug prices (eg, through bulk purchasing), medical education, and political engagement
- Twinning programmes with other centres can facilitate development of specific services and treatment protocols
- Participation in international research studies

more common.<sup>11,68–71,74,75</sup> Remaining in hospital for long periods can also increase the risk of nosocomial infection and the potential for antibiotic resistance.<sup>11,69</sup> Some treatment approaches developed in high-income countries might be too intensive or toxic for use in lower-income countries, and will have to be adapted to local conditions and resources—eg, by reducing doses such that toxicity is more manageable, omitting or changing some drugs, or avoiding approaches that need close monitoring and additional equipment such as infusion therapy. Pilot studies—with good quality follow-up—are essential to document the toxic effects and efficacy of such adapted treatment protocols.

### **Institutional and national collaboration**

The extent of cooperation within an institution or between institutions is an important characteristic of paediatric oncology care. At the low end of the scale, specialists might act independently, rarely discussing care plans or causes of death with colleagues. If unaccountable, their knowledge could be out-of-date and they might have no awareness of the outcomes of their interventions. In many major centres, however, interdisciplinary meetings are routine (although this is much less often the case in low-income countries). Evidence-based approaches to care—a major factor in therapeutic advances made in Europe and the USA in the past several decades—might not be possible because of inadequate or non-existent training in research methods, the cost of research infrastructure, and low priority given to research for professional advancement. Until recently, little information was available with respect to clinical trials being done in low-income and middle-income countries. More recently, since investigators have been required to register clinical trials in publicly accessible databases, more comprehensive data have become available, even if incomplete.<sup>76</sup>

Most clinical studies that are undertaken in low-income and middle-income countries by academic institutions

are retrospective case series, often to explore the feasibility and efficacy of treatment protocols designed in high-income countries. Exceptions exist in some major universities and cancer institutes, particularly national cancer institutes in middle-income countries, where randomised studies are sometimes undertaken.<sup>70,74,77–80</sup> Yet unique research opportunities exist in low-income and middle-income countries, particularly with respect to epidemiological studies (which could lead to preventive measures) and the development of alternative approaches to elements of treatment from high-income countries that are not feasible in poorer countries (eg, high-dose treatments or infusion therapies).

### **International collaboration**

The greatest obstacle low-income countries face in the development of organised approaches to childhood cancer is the scarcity of skilled health professionals. As such, both service provision and education are generally rudimentary. Most middle-income countries have some paediatric cancer programmes, although much of the development that has taken place has ultimately come from direct or indirect collaboration with foreign institutions.<sup>11,73,81–85</sup> International experts can contribute directly to education efforts (eg, through a twinning programme or collaboration with an international organisation), take part in frequent online meetings, or provide web-based resources for distance learning. Translation of improvements in education to clinical results will initially be slow, but will accelerate as resource availability improves. Measurable 5-year survival outcomes, even if substantially less than those of high-income countries at first, will help to create a dynamic that is not easily ignored by politicians. International collaborators can also help with more general issues of health system strengthening, including hospital management, health-care infrastructure, and financing, and they can also create opportunities to participate in

international research, which can lead to more rapid completion of studies and an expansion of global research capacity.<sup>86,87</sup> In some cases, collaborators can help to provide capital funding—eg, for the purchase of radiotherapy equipment.<sup>88</sup>

An increasing number of clinical trials related to drug development include both high-income countries and low-income and middle-income countries because the requisite number of patients can be more quickly accrued, but such trials should have relevance to the local population. Increased research infrastructure will doubtless be needed in low-income and middle-income countries as the already sizeable pharmaceutical industries of India, China, and many other countries develop more products.<sup>89</sup> Globalisation of pharmaceutical development, however, raises numerous questions about the comparability of results obtained in entirely different settings and different populations, intellectual property rights, and ethics (especially with respect to minors). Ethical issues in particular, some of which are unique to collaboration with low-income and middle-income countries, must be given a high priority. For example, taking tissue samples for molecular studies of interest to high-income countries from patients with a potentially curable disease for whom treatment is not available or not paid for, differences in ethical practices such as approval by ethics committees and informed consent procedures in different countries, and ensuring access of populations to those products that they have helped to develop but that may, if useful, prove to be beyond their financial means.<sup>86,87</sup>

## Conclusions

The first need of low-income and middle-income countries in the development of improved care for children with cancer is capacity building. Existing capacity, which can vary extensively between and within low-income and middle-income countries, must be taken into account and improvements should focus initially on ensuring that at least some patients are treated effectively. Care, however, begins in the community and a plan to improve childhood cancer care should link the public, primary care providers, a wide range of specialists, other health workers, and policy makers. The goal should be to incorporate, over time, the various elements listed in the panel at a rate and in a sequence that is tailored to each country's needs.

Unlike many other health challenges, paediatric cancer is a largely tractable problem that is, compared with other major global health issues, quite small. However, the fairly small numbers of patients is offset by the potential complexity and cost of diagnosis and treatment. The cost of treating one patient with acute lymphoblastic leukaemia in the Netherlands and the Nordic countries has been reported<sup>90,91</sup> to be in the region of US\$100 000, whereas in major cities in China the cost is about \$4000–12 000.<sup>92,93</sup> Although such calculations should be interpreted with caution, these estimates suggest that the total treatment costs for the 84% of childhood cancers that occur in low-

## Search strategy and selection criteria

We searched PubMed using the search strategy: "paediatric" OR "pediatric" OR "child" OR "children" AND "oncology" OR "cancer" OR "malignancy" OR "leukemia" OR "leukaemia" AND "international" OR "global" OR "developing" OR "low-income" OR "middle-income". Only articles published in English between 1965 and Feb 2, 2013 were included. Search results were supplemented by articles from our personal collections and by those identified from reference lists. References are illustrative of the authors' major points, and not intended to be exhaustive. We also use data from WHO, the International Agency for Research on Cancer, and the World Bank.

income and middle-income countries will probably be substantially lower than the costs associated with the treatment of the 16% of childhood cancers that occur in high-income countries. To make progress, however, governments of low-income and middle-income countries will need to increase expenditure on education and health care, with or without external aid, and to train the skilled workers necessary for sustainable socioeconomic development.<sup>94</sup> A survey of treatment outcomes in ten developing countries suggested that better results were achieved in countries in which gross domestic product, gross national income per head, the number of physicians and nurses per 1000 people, and, most importantly, per-head annual government expenditure on health care, were higher.<sup>95</sup> Investment in health-care systems, workers, and resources, and the establishment of international collaboration are essential to improve outcomes for children with cancer in low-income and middle-income countries.

## Contributors

IM contributed to the design and writing of the report; data collection, interpretation, and reconfiguration; and preparation of figures and tables. He also updated the report on the basis of comments from peer reviewers, and finalised revised versions for resubmission. ES-F contributed to the design and writing of the report, database searches, data analysis and interpretation, and preparation of figures. SE contributed to preparation of figures, design and writing of the report, database searches, and data analysis and interpretation. RCR and MH contributed to writing of the report and reviewed draft versions before submission. C-KL, RK, and SDM contributed to database searches, data interpretation, and writing of the report. SCH contributed to the preparation of figures, design and writing of the report, database searches, and data analysis and interpretation. All authors approved the final submitted version.

## Conflicts of interest

We declare that we have no conflicts of interest.

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