Improvements in Child Cancer Diagnostics and Treatment in Africa

Susan Horton, University of Waterloo

Sumit Gupta, Hematology/Oncology Hospital for Sick Children, Toronto

Avram Denburg, Hematology/Oncology Hospital for Sick Children, Toronto

Summary

In Africa, more than 50% of cases of childhood cancer go undiagnosed. Africa accounts for 146,000 of the projected 397,000 new cases globally per year (including both diagnosed and undiagnosed cases) (Ward et al, 2019a). Of the diagnosed cases, only 11.6% of children in Africa survive (Ward et al, 2019b). Based on the above modeling exercise, we estimate that only about one-third of those who are diagnosed actually receive treatment; no hard data are available. Increasing access to treatment will increase survival, although to reach survival rates comparable to high income countries, investments will also be needed to decrease treatment abandonment and improve quality of treatment (Ward et al, 2019b).We recommend investing to expand treatment of five key cancers that are both treatable and affordable. These five cancers together account for 40% of the burden of childhood cancer in Africa. Studies of cost per child treated in sub-Saharan Africa for three of the conditions (Burkitt lymphoma, nephroblastoma and early-stage retinoblastoma) were $1248, $1976 and $2202 USD respectively in various low- and lower-middle income countries in Africa. More conservatively, costs of a comprehensive cancer centre in one African country which achieved a projected 5-year survival rate of 35% for a cohort of children with multiple cancer types, were around $10,000 per child in 2018 USD, or around 6.5 times per capita GNI (see text below for all study references).

Benefit:cost ratios were estimated as 9.1 to 19.3 for the three diseases for which studies were available, and a more conservative 5.2:1 for a comprehensive centre which treats not only the priority diseases, but also provides treatment for other less-treatable conditions and palliative care to children for whom cure is not possible. Ratios would be a little lower (4.6:1) but still very attractive if indirect costs to families were included in treatment costs, and higher if non-profit organizations took the lead in small investments to reduce treatment abandonment rates, as has been done successfully in a number of low- and middle-income country (LMIC) contexts.

Expanding care from the estimated one-third of those diagnosed to all those currently diagnosed would cost $407m using the comprehensive cancer centre model. This amount would double, if 90% coverage of were attained (i.e. if 80% of all undiagnosed children could be diagnosed and linked to treatment). The value of the benefits would however be an estimated 5.2 times the costs, or $2116m. There are other potential unquantifiable benefits, such as helping to show that cancer is indeed curable and helping reduce the stigma associated with cancer in Africa, potentially leading adults with cancer to seek care earlier and improve their survival. In addition, improving capabilities to treat childhood cancers has the potential to strengthen health systems more broadly, by developing radiologic and pathologic services, medicines procurement and supply management, surgical facilities, health human resource training and retention, and supportive care capacities.

Scope of the problem

Childhood cancer is a leading non-communicable cause of death in children aged 0-14 years worldwide (Global Burden of Disease Cancer Collaboration, 2017; Bonaventure et al, 2017). Diagnosed cases of cancer accounts for the death of 140,000 children globally annually, 1.8% of the global total number of child deaths (Global Burden of Disease estimates): given that more than 50% of cases of childhood cancer go undiagnosed, the true child cancer death rates are more than twice this large. These undiagnosed child cancer deaths are currently attributed to other or unknown causes.

Childhood cancer differs from adult cancer in that there are no known methods for

prevention. In adults it is possible to reduce cancer risks by avoiding exposure to hazardous substances such as tobacco, by changing diet, and by becoming vaccinated against certain conditions such as hepatitis B and human papillomavirus. No such options exist for childhood cancer at present, and treatment is the key option. Moreover, childhood cancers are sufficiently uncommon that screening is also not a viable strategy. Early diagnosis linked to treatment is the main, and perhaps only route to reducing mortality.

More than 80% of diagnosed cases of childhood cancer occur in LMIC (Magrath et al, 2013), where access to diagnostics and treatment are limited (Farmer et al, 2010). The substantial improvements in pediatric cancer survival in high-income countries (HIC), where greater than 80% of children are cured, have not been realized in LMIC (Allemani et al, 2018). This stark survival gap has provoked global calls to prioritize childhood cancer in efforts to expand universal health coverage (UHC) and meet Sustainable Development Goal 3 targets. The recent launch of a World Health Organization Global Initiative on Childhood Cancer reflects mounting international commitment to addressing this significant, and remediable, loss of young lives (WHO, 2018).

The African continent will become an epicenter of global childhood cancer mortality over the coming decade, as Africa currently accounts for 25% of the world's children, a share that will grow to 40% by 2050 (UNICEF, 2017). Indeed, modeling work by Ward et al. suggest that shortly after 2025, Africa will overtake Asia as the region with the highest number of childhood cancer cases (Ward et al. 2019a).The burden of childhood cancer is set to grow fastest in Africa: as national health systems expand their capability and reach, improved detection of childhood cancer will transform an epidemic of under-diagnosis into a signal health challenge for national governments. Presently, greater than 50% of childhood cancer cases throughout the continent remain undiagnosed. When accounting for under-diagnosis, estimates of age-standardized incidence rates of childhood cancer in western and sub-Saharan Africa are the highest of any in the world (Ward et al, 2019a).

Crucially, however, childhood cancer in Africa is a remediable problem, both in terms of scale and resources. Of the estimated 397,000 annual cases of childhood cancer globally (including both diagnosed and undiagnosed cases), roughly 146,000 occur in the African continent (Ward et al, 2019a). The majority of these cases are comprised of cancers that are highly treatable and for which treatment is very cost-effective. The five diseases that together account for 40% of childhood cancer incidence in Africa – acute lymphoblastic leukemia, non-Hodgkin lymphoma, nephroblastoma, Burkitt lymphoma, and retinoblastoma – are also the most curable, and at relatively low cost, representing a significant return on investment for health systems and societies.

Even when considering only those African children whose cancer is diagnosed, only a small proportion access treatment early enough to lead to a good outcome. Of those commencing treatment, a significant proportion abandon therapy, frequently due to health care costs and a lack of financial support for patients and their families (i.e. "financial toxicity"). Thus, though survival rates for all childhood cancers combined exceed 80% in North America, the survival rates for those diagnosed are only 8.1% and 8.5% in eastern and western Africa respectively, and only somewhat higher in southern and northern Africa (19.2% and 30.3% respectively: Ward et al, 2019b).

Proposed solution

We propose that for the first stage countries phase up treatment availability and financial support for the treatment of five highly curable childhood cancers, which represent relatively low cost and feasible interventions. These five cancers are: acute lymphoblastic leukemia (ALL), Burkitt lymphoma, nephroblastoma (also known as Wilms tumour), non-Hodgkin lymphoma, and early stage retinoblastoma.

These constitute five of the six WHO priority childhood cancers (WHO 2018); treatment of the sixth (low grade gliomas) is not as yet a widespread possibility in much of Africa. WHO's global goal is to achieve a 60% survival rate globally for childhood cancer by 2030, a

doubling of the current rate. To achieve this global goal, survival in Africa and South Asia (where cure rates are lowest) will need to increase significantly.

There are at least three important ways to improve survival. One is to expand availability of treatment, which includes specific treatment components (chemotherapy, radiotherapy, general surgery, and ophthalmic surgery); the second way is to reduce abandonment of therapy (which largely is a function of financial burden to the family); and the third way is to improve quality of care. Modelling by Ward et al (2019b) suggests that improving availability of treatment overall in Africa can increase survival from 11.6% (currently, across all four subregions) to 29.0%; decreasing abandonment can increase survival from 11.6% to 16.2% and increasing quality of care can increase survival from 11.6% to 21.0%. Ward et al (2019b) argue that there is "super-additivity" such that a combination of improvements in all three areas could increase survival in Africa to 80.9%. In high income countries, survival for ALL and lymphoma exceed 90% in several countries (Allemani et al, 2019) and are similarly high for early-stage cases of retinoblastoma and nephroblastoma.

We focus on the benefit:cost ratios for increased availability of treatment, since this is where most quantification has been done. We will make some suggestions regarding the likely benefit:cost of reducing treatment abandonment. Data are too limited to estimate the benefit:cost of improving treatment quality. Investments in the latter two areas will make investments to improve availability even more cost-effective.

Our results are most applicable to low- and lower-middle income countries in Africa, of which we identify 31 priority countries. The excluded countries are upper-middle income and high-income countries (10), small countries (5) and countries with life expectancy below 60 where advances in childhood cancer may be difficult to achieve due to conflict, infectious disease and other issues (9). The 31 priority countries account for more than 80% of the population of the continent and 82.1% of the incidences of childhood cancer (including both diagnosed and undiagnosed cases). We recommend that the upper-middle income countries continue to strengthen their treatment of childhood cancer, that the very small countries focus on diagnosing cases and linking children to treatment outside the country, and that the countries with lowest life expectancy start at least to educate healthcare providers about cancer. However we do not cost out interventions in the 24 countries excluded.

Principal investment costs

Previous important work, such as that conducted by the Disease Control Priorities Project, has concluded that childhood cancer treatment is cost-effective and recommended that the treatment of select childhood cancers be included in any "best buy" package of cancer interventions in low- and middle-income countries (Gelband et al. 2016). These conclusions were however based mainly on theoretical reasoning, albeit strong. In this proposal, we attempt to use recent data to further support this assertion.

The estimated benefit:cost ratios for increased access to treatment are derived from African countries as much as possible. There are, however, cases where African data and not available. In addition, there is a bias in the costing literature for individual childhood cancers to omit key cost components, as demonstrated in a recent systematic review conducted by our group (Fung et al., 2019). Whenever possible, we have cited studies with "comprehensive" coverage of costs or have used adjusted data from other regions if necessary. We have focused on cost studies in low- and lower-middle income countries since these constitute the large majority of African countries.

Expanding treatment availability involves providing more of the essential inputs: training staff in pediatric oncology; funding chemotherapy and supportive care; training more surgeons in the more specialized care required for pediatric oncology. The most "lumpy" investment is in increasing access to radiotherapy (Atun et al, 2015); however the five priority cancers rely less on radiotherapy

precisely because availability is so poor in Africa. Building capacity (particularly human capacity and specialized healthcare resources such as radiotherapy equipment) takes time. For this reason, we assume a 12-year horizon to 2030 (the end-date for the WHO survival targets).

We use estimates from our group's work that cost per child treated in a comprehensive cancer centre is about 6.5 times per capita GNI (based on studies in Ghana and El Salvador). To treat the two thirds of children currently diagnosed in the 31 priority countries, we estimate the costs as $407m per year (Appendix 1: costs).

Benefits

The benefits of the investment are primarily in child survival. The cost-effectiveness of treatment of individual highly-treatable cancers is already comparable to that of the investments being made at the margin against childhood infections in Africa (such as rotavirus and pneumococcus).

Studies for Rwanda, Cote d'Ivoire, Democratic Republic of Congo and Uganda suggest that the benefit:cost of investments in treatment of nephroblastoma, retinoblastoma and Burkitt lymphoma range from 9.1:1 to 19.3:1 (Appendix 1). A study of a comprehensive cancer centre in Ghana found not surprisingly that benefit:cost ratios of a centre treating not only selected highly curable diseases at early stages, but providing care to a broader range of cancers (including palliative care for cases which are not amenable to cure) has a somewhat lower benefit:cost ratio of 5.2:1 (Appendix 1).

Our results are sensitive to assumptions made. The estimates of how costs vary across countries are based on two published studies for lower-middle income countries. We have other cost and survival estimates for four other African countries not yet published (including one low-income and three lower-middle income African countries) which suggest that these estimates are reasonable and generalizable.

Benefit:cost ratios would be slightly lower if indirect costs to families were included (travel, accommodation costs associated with seeking treatment; and lost work time of the parents). Quantitative data on this are scarce, but an older study for the US (Bloom et al, 1981) suggested that these costs could be as much as 70% of per capita income (no comparable data including lost income are available for Africa). If the 70% figure were applied in Africa, the benefit:cost ratio for the comprehensive cancer centre would reduce from 5.2:1 to 4.4:1.

Relatively small investments in reducing treatment abandonment could increase the benefit:cost ratio. The Hospital Nacional de Niños Benjamin Blum in El Salvador has a charitable foundation which pays for chemotherapy and supportive care for childhood cancer. The hospital also employs two social workers to track patients who do not attend scheduled appointments, operates a hostel which provides accommodation for families, and offers a per diem for those families of low means. The cost of the social workers plus hostel plus per diem costs amount to $773 per patient or 2.2% of overall costs and is paid for by the non-profit foundation. Undoubtedly the fact that the non-profit foundation covers the significant costs of chemotherapy, diagnostics and supportive care (and that radiotherapy is provided at no cost to non-members by the public contributory healthcare scheme) reduces treatment abandonment. However, the modest support of parental costs plus follow-up by social workers have also been cited as crucial factors in reducing treatment abandonment rates (Rossell et al, 2018). As governments in Africa move to include pediatric cancer treatment among the benefits provided by universal health coverage, there is also a role for national non-profit organizations to support parents and in doing so increase the benefit:cost of investments in the health sector.

Implications

Extrapolating from the few studies for low- and lower-middle income countries in Africa with reasonable data, we have calculated benefit:cost ratios for the treatment of several common childhood cancers as well as for a

comprehensive cancer centre as a combined intervention. These ratios vary from 5.2 (for the comprehensive centre) and from 9.2 to 19.3 for three selected high-priority conditions, showing that treatment of select childhood cancers in Africa represents a highly attractive investment. It is also important to note that these ratios likely represent conservative estimates, as most of the studies were conducted in inadequately resourced treatment centres. Low cost complementary interventions such as a social worker or provision of food to caregivers have been shown to dramatically decrease rates of treatment abandonment and increase rates of overall survival. Thus, adequately equipping new or existing childhood cancer centres in Africa with the appropriate interventions is likely to result in benefit:cost ratios even higher than those calculated above.

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Appendix 1: Cost and Benefit:cost calculations

Costs

We assume that costs of a comprehensive cancer centre are 6.5 times per capita GNI, consistent with data for lower-middle income countries Ghana (Renner et al, 2018) and El Salvador (Fuentes-Alabi et al, 2017). Current survival rates are 11.6% in Africa overall. Even in a lower-middle income country in Africa survival rates are projected at 35%. We therefore hypothesize that only one-third of those diagnosed, access appropriate treatment on average (hard data were not available).

The number of diagnosed cases in the 31 priority countries for our analysis is 126,671 (see Appendix 2). We estimate that currently one-third of these children are treated, and the untreated gap is two-thirds. To calculate cost of treating these cases, we multiply number of cases per country by 6.5 times per capita GNI, and estimate cost as $407m. By investing double this amount (plus an unspecified amount for educating healthcare workers and families to improve diagnosis) 80% of all cases (both those currently diagnosed, and those currently undiagnosed) could be treated.

Benefit-cost ratios

In all cases, we assume that the costs of treatment increase in proportion with per capita GNP, such that the benefit:cost estimates below apply across low- and lower-middle income countries in Africa. It is important to note however that although labour costs increase with per capita GNP, the cost of traded inputs (particularly chemotherapy, diagnostics and supportive care costs) may increase more slowly, making estimates from low-income countries such as Rwanda and Uganda conservative estimates of benefit:cost ratios in lower-middle income countries.

1. Burkitt lymphoma:

Cost per patient treated (health system perspective, i.e. excluding most indirect costs incurred by the family apart from travel, e.g. accommodation and lost income): $1241 USD of 2018, for Uganda (Denburg et al, 2019).

Of those treated, 97% completed treatment, and survival after 2 years was 55%. It is important to note that the treatment included significant interventions aimed at reducing treatment abandonment; the costs of these interventions were also included in this study. The average age at the conclusion of treatment was 10 years, yielding 50 life-years of benefits for children who were cured.

Estimated benefit:cost = (1.3 x per capita GNP X 50) x 0.55 x 0.97/1248 = 17.9.

2. Nephroblastoma:

Cost per patient in Rwanda was $1796 (early stage) and $2372 (advanced stage) (2018 USD) (Neal et al, 2018), where life expectancy is 67 years. Survival rate from an 8-country collaborative study (Paintsil et al, 2015) was 0.25. This rate assumed that all patients who abandoned treatment ultimately died due to their disease. The average age of diagnosis was 2.5 years and a treatment duration of 1 year was assumed. (Costs for another study for Rwanda by Kanyamuhunga et al, 2015, are similar but a little higher).

Estimated benefit:cost: (1.3 x 773 X 63.5) x 0.25/1796 = 9.1: 1

3. Retinoblastoma

No detailed cost-effectiveness estimates were available for Africa although studies have been conducted in China and South Africa. A study conducted in Cote d'Ivoire (11 patients) and Congo DRC (27 patients) (Lukamba et al, 2018). The treatment cost per patient was $1954 in 2013-2014, adjusted to $2202 in 2018 USD using US CPI); estimated survival was 0.47, average onset was at age 3 years. Life expectancy is 54 in Cote d'Ivoire and 60 in DRC, giving a weighted average of 53.2; and GNI per capita in 2018 was $1715 in Cote d'Ivoire and $561 in DRC, giving a weighted average of $1382 (weighted by share of patients).

Estimated benefit:cost: (1.3 x 1382 x 50.2 x .47)/2202 = 19.3: 1

4. ALL/non-Hodgkin Lymphoma

No studies for low- or lower-middle income Africa countries were located, other than for

Burkitt lymphoma which is less costly to treat than other non-Hodgkin Lymphoma. In high income countries ALL and non-Hodgkin lymphoma are among the more expensive childhood cancers to treat.

5. Comprehensive cancer centre

A recent study conducted by our group conceptualized the maintenance of a childhood cancer treatment unit in Accra, Ghana as a single intervention and costed both direct and indirect costs (Renner et al, 2018). The population receiving the intervention therefore consisted of all children with cancer (regardless of type) that presented to the centre. The cost per child diagnosed with cancer was calculated to be $10,540. The average age at diagnosis was 5 years, life expectancy in Ghana was 63 years, and survival for the overall cohort was estimated to be 0.35.

Estimated benefit:cost: (1.3 x 57 x 2130 x 0.35)/10,540 = 5.2: 1

Sensitivity analysis.

If indirect costs to the family amounted to 0.7 times per capita GNI, then the benefit:cost ratio would fall to (1.3 x 57 x 0.7 x 2130 x 0.35)/(10,540+1491) = 4.6:1

Appendix 2: Applicability by country

Country	Category	No. incident cases 2015
Algeria	UMI	2417
Angola		1472
Benin		1998
Botswana	UMI	78
Burkina Faso		3596
Burundi	Low life expect	1329
Cabo Verde	Small	58
Cameroon		4135
Cantral Af Rep	Low life expect	824
Chad		2934
Comoros	Small	74
Congo		831
Cote d'Ivoire		4227
Dem Rp Congo	Low life expect	9495
Djibouti	Small	67
Egypt		6628
Eq. Guinea	UMI	136
Eritrea		586
Ethiopia		11192
Gabon	UMI	268
Gambia		389
Ghana		4720
Guinea		2337
Guinea Bissau	Low life expect	315
Kenya		4821
Lesotho		85
Liberia		810
Libya	UMI	392
Madagascar		2712
Malawi		949
Mali	Low life expect	3254
Mauritania		706
Mauritius	UMI	52
Morocco		1995
Mozambique	Low life expect	1589
Namibia	UMI	102
Niger		4387
Nigeria		34854
Rwanda		1268
Sao Tome & Pr	Small	26
Senegal		2804
Seychelles	High income	2
Sierra Leone	Low life expect	1186
Somalia	Low life expect	1345
South Africa	UMI	1733
South Sudan	Low life expect	1385
Sudan		3554
Swaziland	UMI	49
Togo		1336
Tunisia		556
Uganda		4911
UR Tanzania		6513
Zambia		2002
Zimbabwe		802

Note: Saharwi Arab Republic is not listed above (no cancer incidence data) – also small size.

Shading indicates priority countries (31). There is 1 high income and 9 upper-middle income countries where coverage of treatment of the more treatable conditions is likely better; there are 5 countries below 1 million in size where scale economies mean that it may be appropriate to identify children with cancer but send out of the country for treatment (including Sahrawi Arab Republic); and 9 countries with life expectancy below 60, where conflict/low income/infectious disease priorities may make childhood cancer a lower priority.

These data are Wade et al's (2019a) modelled estimates of childhood cancer incidence which include undiagnosed cases. IARC's GLOBOCAN data (Ferlay et al, 2019) are generally

considered as the authoritative source. However, GLOBOCAN data of course rely on cancer registry data that in turn capture only those children who are properly diagnosed and registered. Children who do not access healthcare, access healthcare but are are undiagnosed, or are diagnosed but not registered, will not be included in GLOBOCAN estimates. To overcome this issue, Ward and colleagues employed microsimulation modeling to estimate the total burden of childhood cancer across LMICs, taking into account health system barriers to access and referral. The model was calibrated to publicly available cancer registry data using a Bayesian approach with multiple model parameters as random variables.

The country specific estimates are what are illustrated in Appendix 2. Importantly, posterior predictive checks of the calibrated model comparing the model predictions of diagnosed incidence of specific malignancies to registry-reported incidence found that the prediction intervals of the former overlapped with the confidence intervals of the latter 99.3% of the time.

The priority countries account for 126,671 incident cases of pediatric cancer (age 0-14) in 2015 (87% of the cases for all African Union countries: calculated from Ward et al, 2019a).