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Are essential medicines available, reliable and affordable in low-middle income countries?

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ABSTRACT

A critical challenge for reducing the cancer survival disparity between children living in low-middle income countries (LMICs) and those in high income countries (HICs) is the apparent lack of consistent supplies of reliable, good quality, effective and affordable essential medicines for curative, supportive and palliative care in LMICs. Using a semi-structured 17 point questionnaire we asked ten paediatricians in nine countries for their perceptions of availability, accessibility, affordability and quality of the drugs they needed to treat their patients with cancer. All the countries needed to procure and import some or all of the required essential medicines. Despite their countries signing up to the latest World Health Organisation Essential Medicines Listing there were inconsistent supplies of key medicines. This occurred sometimes due to inadequate global production of some drugs but more often to failure of adequate registration, procurement, importation and distribution. Costs played a significant role regarding prompt importation in some of the countries and cheaper biosimilar drugs were procured often without certification of quality production and provenance. Where families carried the whole financial burden of drug costs the doctors cited it as a major but not the only reason for treatment refusal or subsequent abandonment. Only a concerted effort by each country, the WHO, ethical pharmaceutical companies and all worldwide medical and nursing groups, with the help of parent support organisations across the world can overcome the failure of access to, affordability of and ensured quality of these off -patent, generic drugs. This applies not just to childhood cancer but all medicines for communicable and non-communicable diseases.

1. Introduction

The gross disparity in survival of children and young adults with cancer in high income countries at 75–80% [1–3] and those in low-middle income countries at 10–30% [4,5] results from a number of causes. These include failure of patients, families and health care professionals, especially at primary care level, to recognise the significance of cancer signs and symptoms leading to the wrong diagnosis, delays in diagnosis and potential tumour progression [6–9]; perceptions of cancer incurability [6]; high rates of treatment refusal and abandonment [10–12]; advanced stage of disease at presentation; co-morbidities and a lack of trained staff, facilities and resources [4,6,7].

Even if a timely diagnosis is made, the lack of a reliable and consistent supply of affordable, quality-guaranteed, supportive, palliative

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and potentially curative World Health Organisation recommended medicines [13] is frequently cited as a major reason for treatment failures [14–18]. This is also cited as contributing to high rates of treatment refusal and abandonment [10–12].

We wished to explore with ten leading paediatricians in low and middle income – countries who were treating children with cancer what their perceptions were regarding drug availability, accessibility, reliability and affordability in each of their hospitals.

2. Methods (Appendix A)

We asked ten lead clinicians in January 2015 who were treating children with cancer and leukaemia in 9 countries; Bangladesh, Cameroon, Ghana, Malawi, Myanmar, Philippines, Colombia, Tanzania and Zambia, whether they would be willing to take part in a questionnaire (by email) about the availability, accessibility, reliability and affordability of essential medicines in their hospitals. A 17 item questionnaire was sent along with that email to the lead consultant in each hospital and all ten consented to take part in the study, completed the questionnaire and returned it by the end of February 2015. The timing was chosen to coincide with the review of the 2015 WHO Essential Medicines List. The responses were presented in an oral presentation at The International Society of Paediatric Oncology in October 2015 at Cape Town South Africa and at the World Cancer Congress in November 2016. A draft paper was written in early 2018, circulated to all participants for correcting any errors, incorrect facts and editing including any changes in issues regarding access to medicines.

In Ghana we sent it to two separate doctors /hospitals in Accra and Kumasi, both centres now in a shared care network. In Mindano Province in the Philippines there is a hub centre in Davao with 4 shared care hospital centres. Data supplied by the lead clinician covered all the 5 Hospitals. In Cameroon there are three small hospitals all working together and staffed by the same team so the lead clinician provided data for all three using their register which has been in place for more than 10 years.

The semi-structured questionnaire asked questions about; annual incidence in their hospital(s),rates of “curative” care intention, treatment refusal and abandonment rates, whether there was in country production of any of the required drugs, if not then from where essential medicines were obtained, costs of medicines and affordability/ who pays for them, if it is the family where they would buy them, if there were any family subsidies/and/or lower tariffs, availability of palliative care, and the major obstacles to providing good curative, supportive and palliative care. (Appendix A)

The first six countries listed are in long term twinning programmes created by World Child Cancer (WCC) linked to at least one and in five of the countries to two high income country hospitals. In all of those 7(2in Ghana) hospitals the doctors were able to provide reliable data from hospital based registers available for quantitative data for the questions on incidence, curative intent percentage, and treatment refusal and abandonment. The hospital in Bogota Colombia was previously in a partnership with Boston Children’s Hospital and WCC, and had a reliable data base. The hospitals in Tanzania and Zambia had requested help from WCC to develop their services and the lead clinicians were well known to WCC. And they also kept hospital- based registers. Consequently all of the data for questions [1] and [2] were available from primary data analyses using hospital based registers. No individual patient data was requested.

The countries selected were all in different stages of developing their services and represented a range of very low –income through to low-middle income status. Six of the hospitals are in the Country’s capital, in Ghana the Ashanti province capital Teaching Hospital was also included. In Malawi the hospital is in the commercial capital and in the Philippines the principal hospital is in the Mindano Provincial capital with the 4 shared care hospitals spread across the province. In the Cameroon the three hospitals are in the North and North-East of Cameroon.

No individual patient or family data was either requested in the questionnaire or needed in the study or paper. What is reported are the perceptions of the 10 clinicians regarding what happens in their own hospital and country.

3. Results

3.1. Patient numbers

Collectively the ten centres in the nine low-middle income countries (LMICs) annually reported that they receive between 2,000–2,500 new patients with childhood malignancies. Each unit does collect data on all presenting patients to their hospital but none of the nine countries in this study have a truly population-based cancer registry for children at present. Consequently it is not possible currently to accurately assess what percentage of all cases in each country these numbers represent.

The offer of potentially curative treatment for patients in the 10 centres ranged from 5 to 90% (median 65%). Reasons given by the clinicians for not treating a child included; very late presentation with advanced stage disease, initial family refusal of treatment, and/or their perception that all cancers are incurable, and/or a preference by the family for alternative traditional therapies provided nearer to their home.

3.2. Refusal and subsequent abandonment

The rates of treatment refusal and abandonment in the ten centres ranged from < 5%-50% (median of 20%). The reason cited in four of the hospitals was the cost of treatment where families had to find the money for all drugs, travel and parental accommodation at or near the hospital. In these centres the rate of failure to start or complete therapy ranged from < 5%-34%. At three of these hospitals, families are now receiving some subsidies for drug costs as part of International twinning partnerships funded by various charitable organisations. In Colombia and the Philippines the State is expected to cover all cytotoxic drug costs but some families still have to purchase some supportive drugs and sometimes also cytotoxics when supplies run out. Treatment abandonment was low at 5% in Colombia and higher, at 20–30% in the Philippines, but the lead clinician there did believed that the cost of drugs is only one of the many reasons for this higher rate of treatment abandonment. In Zambia chemotherapy drugs are obtained through a Governmental central medical stores system where there may be inconsistent supplies. As a result the treatment abandonment rate was reported to be high (45%). In Malawi initial refusal was reported to be rare now but still about 15% of children fail to complete all of their treatment. However, this was reported to be decreasing following increasing survival rates and a subsequent increase in community confidence in treatment. This has coincided, with increases in both external charitable and state funding for treatment. In Tanzania a variety of funding streams provide money for medicines and there is < 5% abandonment at the hospital surveyed in the capital city, Dar es Salaam. Recently a charity (called Tumainila Maisha, TLM) has started to provide chemotherapy to all centres treating children with cancer in Tanzania. Wherever subsidies were available, treatment refusal and abandonment was reported to be decreasing.

Drug costs were not the only cause of refusal and abandonment cited. Other reasons quoted included family perceptions of cancer incurability; cheaper and local alternative therapies delivered by traditional healers; difficulties in accessing the required medicines; the costs of travel to and from hospital and accommodation at both secondary and tertiary hospitals. Family disruption and loss of income because of the need for at least one family member to be with their child in the hospital was also reported.

3.3. Drug production and/or importation

Only Bangladesh has started to produce any cytotoxic drugs (vincristine, oral methotrexates, dexamethasone, 6-mercaptopurine) but still not all of those required for treating children with cancer. The other eight countries are totally dependent on procurement and importation of cancer drugs and five are also dependent on importation for some supportive and palliative medicines. In four countries production of some antibiotics, analgesics and antacids has recently started. All nine countries are therefore dependent on importation of some or all of the drugs required for treatment and supportive care of the children who present with cancer.

All of these countries were reported to have signed up to the World Health Organisation 2015 Essential Medicines List of cancer drugs and the governments are ultimately responsible for the procurement and importation of them. However in this study we found that only three of the nine governments were reported as doing that directly. In five countries, responsibility was delegated to specific pharmacies under a contract system and in one country to an adult cancer hospital. These contract arrangements were for a variable time and required renewal of the permission to import "contracts", sometimes resulting in disruption in the continuity of supply. Free market forces operated in Bangladesh enabling local pharmacies to import most drugs.

There were different importation regulations in each country and complex systems were part of the reason cited in all of the nine countries for inconsistent supplies of essential medicines. Failure to register drugs or renew licences to import in a timely fashion were cited in nearly all centres either in error or even deliberately if the importing pharmacy (in three countries) considered the specific drug to be of low priority or not financially worthwhile to import.

3.4. Source of essential medicines

The generic off-patent essential medicines were imported from a range of countries most commonly from India and China (some of the drugs produced in China were exported to India and further distributed mostly to Africa and Asia), but also from Argentina, Brazil, South Korea, Cyprus, and Malaysia. Drugs were rarely imported from Europe/UK or the United States, unless charities enabled sourcing from high income countries. When charities subsidise the cost of medicines, for example, in Tanzania at least some of the essential medicines are imported from high income countries with legal requirement for proof of production and provenance.

3.5. Special tariffs

Only the clinicians from the Philippines, Bangladesh and Malawi reported that they were aware of lower tariffs for the drugs they require. In Malawi there is a Central Medical Store which bulk orders medicines and in the Philippines the Department of Health takes responsibility for importation.

3.6. Is the supply consistent and reliable? (Table 1)

Table 1 shows that in each country a range of drugs were at times in short supply or not available at all. All of these drugs are required for the treatment of leukaemia and solid tumours including Non-Hodgkin lymphoma, Burkitt lymphoma, Wilms tumour and retinoblastoma. They are all on the 2015 WHO Essential Medicines List and are generic off-patent drugs.

3.7. Drug costs

In the two countries where the state covers the cost of most drugs the clinicians were not aware of those costs but parents still had to pay for some supportive medicines, transport and family accommodation. In five countries parents received some subsidy from internal or external agencies and the lead clinicians were aware of costs of all the drugs. In one country the clinician knew the cost only of subsidised drugs.

3.8. How do families obtain the drugs?

The respondents from Colombia and the Philippines reported that there was a National Health Insurance Scheme (NHIS) which covers the cost of most medicines and families did not have to buy the chemotherapeutic drugs. However, supportive drugs are not always covered so there is still a degree of out of pocket expenditure for families. In Zambia the main way to obtain chemotherapy drugs is through the Government's central medical stores and now the adult hospital has taken over the management of childhood cancers. Only a few families who have company insurance schemes get their drugs free under those schemes, usually in Government hospitals. Ghana also has a National Health Insurance Scheme (NHIS) but at present it does not cover the drugs required for childhood tumours.

In Malawi there is a Governmental Central Medicines Store ("bulk-buying") and a Health Insurance Scheme, but also the hospital does have charity subsidies for some drugs which are procured separately from a range of countries. In Tanzania there is also a Governmental Central store and Health Insurance Scheme for adults with cancer but all required drugs for children with cancer are procured and funded by the TLM charity, some from the UK, Germany and the USA.

In the other hospitals in Cameroon, Bangladesh, Ghana and Myanmar parents have to buy most of the drugs but in each there is a degree of subsidy for some of the medicines and some help for procurement of rarer drugs.

Families in those hospitals will source the required drugs through both the hospital and external pharmacies and because of the subsidies the doctors do know the cost to parents. If the drugs are bought by the state then the doctors reported that they did not know the exact costs but could find out this information through the hospital pharmacy.

3.9. Quality of drugs

Just three of the clinicians felt that most of the drugs that they were using were reliable because they were purchased and imported with International Certifications of Production Quality. The remaining seven clinicians were not sure or expressed anxiety about quality and efficacy especially of some antibiotics and cheaper cytotoxic drugs from generic companies.

The reason for anxiety related to reported experiences of lower remission rates (for example for acute lymphoblastic leukaemia) when using documented successful therapeutic protocols developed in high income countries and also higher toxicity than expected when they used generic companies' imported products lacking quality certification. Parents in Bangladesh were reported to have a preference for drugs produced in high income countries compared with locally produced medicines.

3.10. Were there any subsidies for "out of pocket" expenses?

In 7 countries the doctors were able to receive funding for at least some drugs from internal or external charitable sources or directly as part of their NHIS schemes. In two countries clinicians could not currently access funding for drugs or other expenses. The sources of charitable money came from international twinning partnership support, parental support organisations and progressively from in-country local foundations, companies and charities. We asked if the doctors knew what percentage of out of pocket costs were due to the drugs required. Apart from the two countries with state funding and Tanzania where all drug costs are funded by a charity (TLM) only in Bangladesh did the doctors know for sure the cost of drugs due to a recent study

Table 1
Reported inconsistent and unreliable supplies of essential medicines for children with cancer by country.

Country	Reported Inconsistencies	
Bangladesh		Most not consistent; especially Cytarabine, L-Asparaginase, Morphine
Cameroon		All drugs; especially Doxorubicin, Actinomycin, Etoposide, Vincristine
Colombia		Methotrexate, 6-Mercaptopurine, Topotecan
Ghana	Frequently	6-Mercaptopurine, Carboplatin, Etoposide
	Occasionally	Methotrexate, Vincristine, L-Asparaginase
Malawi		Any drug if procured by Central Medical Supplies
		More consistently available if procured and distributed by charities
Myanmar	Intermittently	All drugs; especially L-Asparaginase
Philippines	Variable	L-Asparaginase, Methotrexate, Ifosfamide
Tanzania		L-Asparaginase, Actinomycin, 6-Mercaptopurine, intrathecal Methotrexate, Retinoic acid, Fluorouracil
Zambia	Intermittently	All drugs (supply chain related)

conducted there. Drug costs amounted to 48.6% of family out of pocket expenses in the hospital surveyed [18].

3.11. Challenges to overcome

The doctors were asked (in Question15) for their perception of all the challenges to ensure that every patient could be treated with reliable and affordable medicines for curative, supportive and palliative care.

3.11.1. For curative care (Table 2)

The cost of therapy,poor access to care, late presentation to hospitals, choice of local healers instead of conventional medical services, public perceptions that cancer was incurable and chemotherapy was “poison” did lead to higher rates of treatment refusal or subsequent abandonment. These were all cited as major obstacles to offering effective treatment in the nine countries surveyed. Premature cessation of treatment was not only a “cost issue” but it was reported that when a child was greatly improved after initial treatment families thought that their child was cured and did not need more treatment. Disruption of family life and structure often leading to loss of family income plus transport costs were all contributory factors cited by the respondents as an obstacle to curative care being fully delivered.

Interruptions to crucial drug supplies and anxiety about reliability of imported and/or locally produced drugs were highlighted by all ten paediatricians even on occasions in the three countries where the state took direct responsibility for procurement and importation. Some of these issues related to a global shortage of production of drugs like 6 M P, dactinomycin and asparaginase but most related to problems of procurement, importation and distribution within each country. The cost of drugs, even if relieved to some degree by subsidies, was emphasised as a major obstacle for many families in all the countries without state funding. Reliance on charitable donations was flagged as a risk for the future and not an optimum long term solution.

Table 2
Challenges to overcome for Curative Care.

Reported Challenges
Most common reason given is cost of therapy
Delayed or mis-diagnosis and lack of trained staff
Perception that cancer is “incurable”
Preference for local healers due to cheaper / affordable treatment
Public perception that chemotherapy is “poison”
High rates of treatment refusal/abandonment
Perception (of families) that when child goes into remission no more therapy required
Costs include not just drugs but travel, accommodation and disruption to families / loss of family income
Difficulties in accessing required drugs for families even when all costs are being met by them
Even if drugs are paid for by state or donors delays in procurement / importation / distribution and cost
Preference by medicine procurers to buy cheaper generic drugs often with no evidence of provenance
Lack of availability of essential medicines is due to worldwide inadequate production of drugs (e.g. 6 M P, Actinomycin and L-Asparaginase)
Even with state funding of most cancer drugs, families have “out of pocket” expenses for some supportive and curative drugs
Even with subsidies from donors, costs are still too much for many families
In some countries treatment of girls is reported as less likely than for boys
Wherever natural or man-made disasters occur treatment of children suffers or ceases

Treatment of girls was discouraged in some countries which is seen as a universal challenge regarding ethical care of all children. Lack of adequately trained staff, especially at nights, was cited by at least one centre as an issue. In all of these countries both natural and man-made disasters were reported to have been and will in the future remain an obstacle to providing a consistent service for children with cancer.

3.11.2. Supportive care (Table 3)

A lack of reliable supplies and the cost to families, of anti-emetics, antibiotics, steroids (especially for those with leukaemia) and anaesthetics (local and general) were a considerable obstacle to good practice and occurred in all countries to a varying degree.

Access to blood products, especially platelets, were difficult to access in over half of the units. Co-morbidities like malnutrition, malaria, infections and diarrhoea were all cited as a challenge when trying to treat children at these hospitals.

Overwhelming malnutrition in many countries in Africa and Asia, exacerbated by cancer and its treatment was cited as a very challenging issue requiring correction before and during treatment. The survey participants stated that if therapy was to be successful then good nutritional support for all patients was essential but not all units felt that at present they were able to provide that.

3.11.3. Palliative Care –can all patients receive symptom relief? (Table 4)

Six of the doctors reported that they were able to provide good palliative care within their unit. In Cameroon neither oral morphine nor intravenous morphine were consistently available. In Tanzania occasional non-availability of morphine was reported. In Bangladesh there was often a failure in the community to refer patients back when they needed palliative care, which is currently only available in major treatment centres. At the National Hospital in Bogota Colombia the lead

Table 3
Challenges to overcome for supportive care.

Reported Challenges
Lack of reliable supplies of anti-emetics, antibiotics, steroids and anaesthetics in all countries variably
Families are more likely to pay for these than for the cancer drugs
Access to blood products; especially platelets
Frequent co-morbidities complicate therapy
Malnutrition; not all units can provide nutritional support
Greater rates of toxicity and infections increase costs and contribute to treatment abandonment

Table 4
Challenges providing all patients with symptom relief.

Reported Challenges
Only one country reported being able to provide palliative care in hospital and in the community / home
Six countries surveyed can provide care in their hospital but could not guarantee such care at home / locally
Two countries experience very inconsistent supplies of oral and intravenous morphine
Factors preventing good quality palliation included families' distance from district hospitals and local clinics and poor transportation
All the doctors reported that lack of training and expertise in palliative care for all health workers was poor
Fear, anxiety and stigma was variably quoted for poor care
Anxiety about importation of opiates was cited by three doctors
Five doctors felt that there was fear/anxiety about distribution
Three felt prescribing, especially by junior staff, did cause them anxiety and fear of stigma for doing so
Five reported that there was anxiety about dispensing opiates
Reasons given for were fear of addiction, corruption, staff taking the drugs or the wrong patients might receive the drugs

paediatrician reported that patients could receive palliation of symptoms at home whilst in Ghana that depended on the patient's home locality and if there was adequate local medical or nursing expertise. All of the respondents stated that a number of factors influenced the ability to provide good palliation including; families' distance from district hospitals or even local clinics, poor transportation services, lack of expertise and training of health workers at the community level and anxieties associated with prescribing, dispensing and managing children with pain for whom strong analgesics, especially opiates, were required.

The questionnaire specifically asked for the clinician's perception as to whether there was fear, stigma, or anxiety regarding use of opiates at the level of procurement, importation, distribution, prescription, and dispensing. The common fear was that usage may lead to addiction in patients, overdosing, corruption and misuse by staff. Table 4 shows that anxiety was expressed in varying degrees regarding all stages of obtaining and using opiates. As a result of these worries supplies of morphine are not always available and often inadequate in amounts for the needs of all the children with severe pain. The specialist hospitals said they could procure opiates but once patients went home and/or attended local or district hospitals in eight countries delivery of WHO recommended palliative care for children was inadequate or impossible. Only one respondent stated that at or near home palliative care could be delivered fully. In eight countries there were very few staff outside teaching hospitals trained and experienced to relieve pain with opiates when it was needed. One of the respondents suggested that there was a need for national policies and guidelines in each country regarding pain control plus the correct training for all doctors regarding optimal palliative care.

4. Discussion

There are three crucial factors which are required for the potential cure of a child with any cancer; access to a timely and an accurate diagnosis, access to the most appropriate treatment and the efficacy of that therapy.

This study set out to explore the issues of supply, affordability and reliability of medicines needed for curative, supportive and palliative care for children in nine countries, all of which were involved in some form of international twinning partnership at the time. The perceptions of ten leading clinicians from 9 countries (Ghana, Mindano province of the Philippines, Tanzania, Myanmar, Colombia, Bangladesh, Zambia, Cameroon, Malawi was sought through a semi-structured 17 item questionnaire regarding availability, accessibility, affordability and quality of the essential medicines needed to treat children with leukaemia and solid tumours in their hospitals. This is clearly a small study and therefore we must be cautious about extrapolation to all such developing units in low-middle income countries (LMICs). It is also a qualitative perception study of ten lead clinicians working in varying local conditions. However some common themes have emerged.

(1) Most low-middle income countries produce very few, if any drugs within their country especially anti-cancer medicines.
(2) Consequently there is a need to procure and import most or all of the required essential medicines for curative, supportive and palliative care.
(3) Inconsistent supplies of such essential drugs were reported by all ten lead clinicians in the nine countries
(4) Despite all the drugs being on the WHO Essential Medicines List to which each of these countries had signed up to, procurement and importation was not guaranteed and often erratic.
(5) All the drugs required are off-patent and generic but there were periodic episodes of lack of availability, accessibility, affordability (in some countries) of these drugs and clinical anxiety about drug quality depending upon from where drugs were procured.
(6) For some of the centres there was a perception that selective importation of off- patent generic medicines was taking place because of poor profit margins for the importing pharmacies and they felt this must be addressed and overcome.
(7) Uncertainty regarding the reliability, efficacy and safety of some imported drugs (especially those without international certification of production) from certain distributors was expressed.
(8) Where families had to cover all or most of the cost of drugs (in six / nine countries) it was frequently cited as the major reason for treatment refusal or subsequent abandonment of treatment.
(9) Sadly this leads to the deaths of children who could potentially be cured.
(10) Almost all the centres were unable to guarantee consistent and appropriate palliation of symptoms outside of their own hospital unit.

What steps can be taken to reduce and ameliorate these issues? Until the economic status of any low or middle income country improves there is little chance of it being able to produce in-country some or all of the essential medicines required to treat childhood cancer, even though they are generic drugs long off-patent. Currently only Bangladesh produces any cancer drugs (vincristine, oral methotrexate, and 6-mercaptopurine) but clearly not yet all of the required drugs. Consequently, all of these countries have to procure and import from overseas [14–17]. This survey has shown that only a minority of low income countries buy from the USA or Europe, due to the higher cost of drugs produced in these regions. The commonest sources for the countries surveyed were India and China for Africa, Asia and South America. Most of the major pharmaceutical companies who have developed cancer drugs over the last 50 years have sold off or stopped producing most of the basic essential drugs which can be used to treat and potentially cure at least 50% of childhood cancers and leukaemia. The original producers have found that it is not economically worth producing some of these essential medicines. Generic companies have taken over from them and produce biosimilar versions of those drugs. Often these are sold at lower cost with some selective tariffs which makes them more attractive to resource limited countries [19,20]. The proliferation of generic companies potentially opens up the market and should be able to increase availability of medicines worldwide. Major generic companies which ensure good provenance of their products and evidence of efficacy are warmly welcomed. However as this study has shown, doctors in LMICs are often anxious about using some branded drugs, particularly when they are not produced with evidence of production quality and efficacy. There is increasing evidence showing that the doctors are right to be worried about supplies of some such required essential medicines and their quality [21–25].

Recently multiple different brands, especially of difficult drugs to produce like the enzyme L-asparaginase (a crucial drug for treatment of acute lymphoblastic leukaemia (ALL)), have been shown to be contaminated and/or of low bioavailability [22,23] leading to low rates of remission and unacceptable early relapses. One brand, Leuginase, has been shown by mass spectrometry to contain at least 12 peptide contaminants including beta –lactamase with the potential risk of inactivating some antibiotics has the potential to reduce the efficacy. This agent has been procured in at least five South and Latin American countries because it is much cheaper than proven products. But it must be classified as a dangerous contaminated product. These experiences confirm, as the authors state, that monitoring the efficacy of agents like asparaginase (an enzyme) is essential to avoid this type of disaster [23].

There are clearly very good generic companies but they do not always have the capacity to produce what is required worldwide, hence the intermittent supplies of drugs such as Actinomycin- D (crucial for Wilms tumours and retinoblastoma), methotrexate (all forms) and 6-mercaptopurine tablets (for ALL remission treatment). There has been a reported 13% increase in childhood cancer between the decade 1980-89 to that in 2000–2010 and the trend looks to be continuing [26]. So adequate production of WHO essential medicines worldwide requires more attention if all children are to be able to access the appropriate cytotoxics to enable potential cure. The drugs must be efficacious, free of contaminants and not “false”. Sadly this is not currently guaranteed. This requires all genuine and high quality ethical pharmaceutical manufacturers to work together to ensure that guaranteed high quality essential medicines are available and accessible to all who need them no matter where they live.

Each of our ten respondents expressed anxieties about the systems of initial drug registration in their country and the procurement processes and importation of these drugs. It should be transparent, clear and timely. It was reported not to be so on occasion, even when the state took direct responsibility for the process. As Barr and Robertson reported [15] even if a country signs up to the concept of the WHO Essential Medicines Biennial List, it does not automatically ensure that any single drug will be included in the country’s National Formulary and/or the National Essential Medicines List. If a drug is not on national lists it is unlikely to be available for the general public and even if it is on the list it may not be available for children. Where countries have partial National Health Insurance schemes, for specific drugs there are anomalies. For example, doxorubicin, is freely available for women with breast cancer within the National Health Insurance Scheme in Ghana but for children the families have to pay. Such selective accessibility of any drug is no longer acceptable.

Affordability is a continuing challenge and as reported here it leads to treatment refusal and abandonment of treatment wherever families have to cover all drug costs [5,11,12,18,27–29]. There is evidence that with philanthropic subsidies the rates of treatment refusal and abandonment are decreasing and survival improving [6,7,29]. But such funding is not a long term sustainable solution [30]. Obviously universal health coverage [20] must be the ultimate goal for every country but it will be some time before most LMICs can achieve this. So internal and external public-private and charitable funding plus specific lower tariffs for medicines are needed for some years to come. It is also crucial that each country improves the infrastructure within their health services in order to manage the increasing incidence and prevalence of cancer not just in adults but also in children and young adults [26,28,29]. As already alluded to [22–25], unsafe or fake drugs bought because they are cheap must be identified and banned. Those who produce them and those who procure and import them without quality assessments should be held to account.

Evidence from this study of unfortunate delays leading to inconsistent availability and accessibility was a repetitive experience for most of the centres surveyed. Failure of initial drug registration; protracted procurement systems; and /or lack of the right to procure specific drugs; failure to renew import licences either by default or reluctance to import low volume or low profit drugs, were all cited as reasons for unreliable supplies of essential medicines. It would be ideal if there was a system to which all countries complied or at least did so on a loco-regional basis.

Collaboration across borders would help to develop consistency and facilitate “bulk buying” contracts with the potential for cost reduction and to improve availability and affordability. There are some initiatives doing just that for at least some essential medicines, for example through the Procurement and Supply Management Department (PRO) of the Pan American Health Organisation (PAHO) which purchases medicines for its member governments using a strategic fund. In the last year a number of collaborations have been announced linking hospitals and/or universities in high income countries along with charities or NGOs and pharmaceutical companies to try to ensure that essential medicines are available, accessible and affordable for children [31] and adults, and for some childhood tumours [32] mostly in Africa. Other pharmaceutical companies have assisted in the development of International Twinning Partnerships [33,34]. Collaborations across country borders regarding treatment of individual tumours have increased with the French-African Paediatric Oncology Group leading the way linking 18 Francophone countries and 23 hospitals (35,36)in specific tumour studies and more recently creation of a collaborative Wilms tumour collaboration between eight institutes in sub-Saharan Africa funded by World Child Cancer and the International Society of Paediatric Oncology-SIOP [37,38]. Such projects help to create more accurate diagnoses, consistent treatment and the opportunity for calculating more precisely the needs, quantities and opportunities for bulk buying of good quality medicines as demonstrated by PAHO. In August 2018 the World Health Organisation held a meeting in Geneva (with over 60 Stakeholders including SIOP, and Child Cancer International) to launch a 5 year Global Initiative to improve the care of children with cancer world-wide. One of its key objective is to address the issues of access to medicines and technologies.

Sadly this study has once again shown that at all stages from the production of opiates to delivery at the bedside required to control severe pain, is fraught with anxiety, stigma and failure of consistent provision. Palliation outside tertiary hospitals was reported to be very inconsistent or non-existent. This is unacceptable in the modern era. Education of all medical, nursing and pharmacy students and subsequently doctors, nurses and pharmacists regarding safe and appropriate use of opiates is essential to dispel the anxieties and stigmas reported across the world [39–41].Analyses of need for palliative care in children has been documented [40,41] and new developments are now being activated slowly and surely (42)

In all of the nine countries involved in this survey teams of doctors and nurses are working together to try to diagnose childhood cancer speedily and accurately; ensure that there are enough trained staff, facilities, and resources and are adapting well -tested treatment protocols pioneered in high income countries for each type of malignancy, suitable for the resources available. However the chance of curing children with cancer also requires the consistent availability, accessibility, affordability and above all of high quality essential medicines. Sadly the whole pathway of medicines from production to the bedside remains a big challenge. Despite the development of the new collaborations we have quoted most LMICs are still not receiving the help they need. We sincerely hope that the new WHO initiative will speed up progress in improving care for all children wherever they live and especially solve the issues encompassed in this study

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Appendix A

Survey of Drug Supply and Costs in 9 low-middle income countries

Q1	Total number of children with cancer seen at your centre each year	
	Total number/ % treated with curative intent	
Q2	Treatment refusal/ abandonment rate	
	Is cost of drugs the main reason for this	Yes / No
	Does your Country produce any of its own drugs?	Yes / No
	If **yes**:	Please specify:
	Cytotoxics?	
	Supportive agents?	
	Palliative care?	
Q4	If there is no in-country production:	
	Who is responsible for importation of drugs for example: *Ministry of Health/ Each hospital/ designated Pharmacy/ other agency*?	
	Please specify and add name of importer	
Q5	From which Country/ Company or Companies are drugs regularly imported?	
Q6	Do you know whether there is special tariff (cost) for cancer drugs imported to your country?	
	(Some countries obtain reduced costs by bulk ordering)	
Q7	Is the supply of drugs consistent and reliable	Yes / No
	If **no** does this apply to all drugs or just specific ones?	Yes / No
	If **yes** please specify for which drugs?	
Q8	Do you know what the cost of each drug is for your patients?	Yes / No
	If **yes** can you give some examples of drug costs	
	If **no** do you know the total cost of drugs on your unit for example per week or month or year?	
Q9	How families obtain the drugs for their children:	
	There is a National Health Insurance Scheme	Yes / No
	Some drugs are provided free but not cyto-toxics	Yes / No
	Parents have to buy all of the drugs	Yes / No
Q10	If parents have to buy the drugs from whom do they do that:	
	From a pharmacy inside the hospital	Yes / No
	Outside pharmacies	Yes / No
Q11	Do you know what such parental purchasing costs	Yes / No
Q12	Do you know if the drugs imported / purchased have reliable quality	Yes / No
Q13	Are you able to subsidise the out of pocket costs parents have to pay for their child's treatment:	
	Drug Costs	Yes / No
	Travel costs	Yes / No
	Accommodation costs	Yes / No
	Food costs	Yes / No
	If yes to any components from where does the money come?	
Q14	Do you know the % of out of pocket costs which families have to pay is due to drug costs?	Yes / No
	If **yes** do you record what data you have for all or any group of patients?	Yes / No
	If **no** is this something you would be able to explore in the future?	Yes / No
Q15	What other problems do you find in ensuring that each patient can be treated with reliable, affordable drugs for:	
	Curative care	
	Supportive care	
	Palliative care	
Q16	Can all children in your unit receive adequate relief of symptoms when an inpatient?	Yes / No
	If **no** why not?	
	Can they receive adequate palliation when they go home?	Yes / No
Q17	Is there a stigma associated with the use of opiates in your country for:	
	Importation	Yes / No
	Distribution	Yes / No
	Prescription	Yes / No
	Dispensing	Yes / No

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References

[1] L.M. McGregor, M.L. Metzger, R. Sanders, V.M. Santana, Pediatric cancers in the new millennium: dramatic progress, new challenges, Oncology 21 (7) (2007) 809–820.

[2] K. Pritchard-Jones, R. Pieters, G.H. Reaman, L. Hjorth, P. Downie, G. Calaminus, et al., Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high income countries, Lancet Oncol. 14 (3) (2013) e95–e103, https://doi.org/10.1016/s1470-2045(13)70010-x.

[3] K. Pritchard-Jones, R. Sullivan, Children with cancer: driving the global agenda, Lancet Oncol. 14 (March) (2013) 189–191.

[4] I. Magrath, E. Steliarova-Foucher, S. Epelman, R.C. Ribeiro, M. Harif, C.-K. Li, et al., Pediatric cancer in low-income and middle-income countries, Lancet Oncol. 14 (3) (2013) e104–116, https://doi.org/10.1016/s1470-2045(13)70008-1.

[5] R.C. Ribeiro, E. Steliarova-Foucher, I. Magrath, J. Lemerle, T. Eden, C. Forget, et al., Baseline status of paediatric oncology care in ten low-income or middle –income countries receiving "My Child Matters" support: a descriptive study, Lancet Oncol. 9 (August (8)) (2008) 721–729.

[6] J. Hopkins, E. Burns, T. Eden, International twinning partnerships: an effective method of improving diagnosis, treatment and care for children with cancer in low-middle income countries, J. Cancer Policy (1-2) (2013) e8–e19, https://doi.org/10.1016/j.jcpo.2013.06.001.

[7] R.C. Ribeiro, C.-H. Pui, Saving the children: improving childhood cancer treatment in developing countries, New Engl. J. Med. 352 (2005) 2158–2160.

[8] S.C. Howard, J.A. Wilimas, Delays in diagnosis and treatment of childhood cancer :where in the world are they important? Pediatr. Blood Cancer 44 (2005) 3030–3034.

[9] D.C. Stefan, F. Siemonsma, Delay and causes of delay in the diagnosis of childhood cancer in Africa, Pediatr. Blood Cancer 56 (1) (2011) 80–85.

[10] R.S. Arora, T. Eden, B. Pizer, The problem of treatment abandonment in children from developing countries with cancer, Pediatr. Blood Cancer 49 (2007) 941–946.

[11] S. Mostert, R.S. Arora, M. Arreola, P. Bagai, P. Friedrich, S. Gupta, et al., Abandonment of treatment for childhood cancer: a position statement of a SIOP PODC Working Group, Lancet Oncol. 12 (August (8)) (2011) 719–720.

[12] S. Mostert, H. Sitaresami, C.M. Gundy, A.J. Veerman, Influence of socioeconomic status on childhood acute lymphoblastic leukaemia treatment in Indonesia, Pediatrics 118 (6) (2006) e1600–1606.

[13] World Health Organisation Model List of Essential Medicines for Children 5th List April 2015, (2015) amended August 2015 http://www.who.int/medicines/publication/essentialmedicines/en/.

[14] L.N. Shulman, C.M. Wagner, R. Barr, G. Lopes, G. Longo, J. Robertson, et al., Proposing Essential Medicines to Treat Cancer: Methodologies, Processes and Outcomes, J. Clin. Oncol. 34 (1) (2016) 69–76.

[15] R. Barr, J. Robertson, Access to Cytotoxic Medicines by Children with Cancer: a Focus on Low and Middle Income Countries, Pediatr. Blood Cancer (2015), https://doi.org/10.1002/pbc.25722.

[16] J. Robertson, R. Barr, L.N. Shulman, G.B. Forte, N. Magrini, Essential medicines for cancer: WHO recommendations and national priorities, Bull. World Health Organ. 94 (2016) 735–742 http//dx.doi.org./102471/BLT.15.163998.

[17] A. Denburg, R.S. Arora, C. Auste, P. Bagai, R. Barr, J. Challinor, et al., Access to Essential medicines for children with cancer: a joint SIOP-CCI position statement, Lancet Oncol. 18 (January (2017)) (2017) 20–22.

[18] A. Islam, A. Akhter, T. Eden, Cost of treatment for children with acute lymphoblastic leukaemia in Bangladesh, J. Cancer Policy 6 (2015) 37–43.

[19] The Lancet Oncology-Editorial. Generic drugs are they the future for affordable medicines? Lancet Oncol. 19 (2018) 149.

[20] V.J. Wirtz, H.V. Hogerzeil, A.L. Gray, M. Bigdeli, C.P. de Joncheere, M.A. Even, et al., Essential medicines for universal health coverage, Lancet Oncol. (November) (2016), https://doi.org/10.1016/s0140-6736(16)/31599-9 7th on line.

[21] F. Clark, Rise in online pharmacies sees counterfeit drugs go global, Lancet 386 (October (2015)) (2015) 1327–1328.

[22] P.P. Zenatti, N.A. Migita, N.M. Cury, R.A. Mendes-Silva, F.C. Gozzo, P.O. de Campos-Lima, et al., Low bioavailability and high immunogenicity of a new brand of E. coli L-asparaginase with active host contaminating proteins, EBioMedicines (2018), https://doi.org/10.1016/j.ebiom.2018.03.005.

[23] D.K. Cecconello, I.C.R. Werlang, A.P. Alegretti, M.C. Hahn, M.R. de Magalhaes, A.P. Battistel, et al., Monitoring asparaginase activity in middle-income countries, Lancet Oncol. (August (2)) (2018), https://doi.org/10.1016/s1470-2045(18)30584-9 published on line.

[24] B.J. Venhuis, A.E. Oostlander, D.D. Giorgio, R. Mosimann, I. du Plessis, Oncology drugs in the crosshairs of pharmaceutical crime, Lancet Oncol. (2018) e209–e217.

[25] G.H. Lyman, E. Balaban, M. Diaz, A. Ferris, A. Tsao, E. Voest, et al., American society of clinical oncology statement. Biosimilars in oncology, J. Clin. Oncol. 36 (12) (2018) 1260–1265.

[26] E. Steliarova-Foucher, M. Colombet, L.A.G. Ries, F. Moreno, A. Dolya, F. Bray, et al., International incidence of childhood cancer, 2001-10:a population –based registry study, Lancet Oncol. (2017), https://doi.org/10.1016/s1470-2045(17)30186-9.2.

[27] N. Ghatak, A. Trehan, D. Bansal, Financial burden of therapy in families with a child with acute lymphoblastic leukaemia: report from North India, Support. Care Cancer 24 (1) (2016) 103–108.

[28] G. Masera, Income matters: reducing the mortality gap, Lancet Oncol. 9 (2008) 703–704.

[29] S.C. Howard, A. Zaidi, X. Cao, O. Weil, P. Bey, C. Patte, et al., The My Child Matters programme : effect of public-private partnerships on paediatric cancer care in low-income and middle–income countries, Lancet Oncol. 19 (2018) e252–e266.

[30] Editorial Lancet Oncology-Cancer control in Africa: infrastructure, not philanthropy, Lancet Oncol. 18 (November (14)) (2017).

[31] First Comprehensive Hematology-Oncology Initiative Launched in Africa, Texas Children's Cancer and Hematology Centers,Baylor College of Medicine, Bristol-Myers Squibb and the Governments of Botswana, Uganda and Malawi, 2017 February http://www.accessaccelerated.org/first-comprehensive-pediatric-hematology-oncology-initiative-launched-africa/.

[32] Donald G. Mcneil Jr (Ed.), As Cancer Tears Through Africa, Drug Makers Draw Up a Battle Plan, The New York Times (Global Health), 2017October 7th, (linking the American Cancer Society, Pfizer USA and Cipla-India, and the Clinton Health Access Initiative and a network of 32 oncologists in 11 African Countries).

[33] T. Eden, K. Sandhu, Improving Childhood Cancer survival rates in developing countries, https://www.pmlive.com/May2018, pages 18–20.

[34] Making a difference for children with cancer. Online Access to Healthcare (https://www.sandoz.com/stories/access-healthcare).

[35] M. Harif, S. Barsaoui, S. Benchekroun, et al., Treatment of B-cell lymphoma with LMB modified protocols in Africa –report of the French-African Pediatric Oncology Group (GFAOP), Pediatr. Blood Cancer 50 (2008) 1138–1142.

[36] C. Moreira, M.N. Nachef, S. Ziamati, et al., Treatment of nephroblastoma in Africa: results of the first French African Pediatric Oncology Group (GFAOP) study, Pediatr. Blood Cancer 58 (2012) 37–42.

[37] V. Paintsil, H. David, J. Kambugu, L. Renner, F. Kouya, T. Eden, et al., The Collaborative Wilms Tumour Africa Project: baseline evaluation of Wilms tumour treatment and outcome in eight institutes in Sub-Saharan Africa, Eur. J. Cancer 51 (January (1)) (2015) 84–91 (doi:10.10.1016/j.ejca.2014.10.030.Epub 2014 Nov 19).

[38] T. Israels, V. Paintsil, D. Nyirenda, F. Kouya, G. Mbah, A. Fungchwi, P. Hesseling, et al., Improved outcome at end of treatment in the collaborative Wilms tumour Africa project, Pediatr. Blood Cancer 65 (May (5)) (2018) e26935.

[39] F.M. Knaul, P.E. Farmer, E.L. Krakauer, et al., Alleviating the access abyss in palliative care and pain relief-an imperative of universal health coverage: the Lancet Commission report, Lancet Oncol. (2017) published online https://doi.org/10.10.1016/S0140-6736(17)32513-8.

[40] S.R. Connor, J. Downing, J. Marston, Estimating the global need for palliative care for children: a cross –sectional analysis, J. Pain Symptom Manage. 53 (2) (2017) 171–177, https://doi.org/10.1016/j.jpainsymman. 2016.08.020.

[41] A.E.Caruso Brown, S.C. Howard, J.N. Baker, R.C. ibeiro, C.G. Lam, Reported availability and gaps of pediatric palliative care in low –and middle income countries: a systematic review of published data, J. Palliat. Med. 17 (12) (2014) 1369–1383, https://doi.org/10.1089/jpm.2014.0095.

[42] M. Doherty, C. Thabet, Development and implementation of a pediatric palliative program in a developing country, Front. Public Health 106 (April (6)) (2018) 1–7, https://doi.org/10.3389/fpubh.2018.00106.