Supplementary Appendix

1. Countries and territories by regional sub groupings included in Table 1 (Estimated age-standardised incidence rates of childhood cancer per million population by world region, for 2018) in the main body of text

Africa, North	Algeria, Egypt, Libya, Morocco, Sudan, Tunisia, Western Sahara
Africa, Sub-Saharan	Burundi, Comoros, Djibouti, Eritrea, Ethiopia, France, La Réunion, Kenya, Madagascar, Malawi, Mauritius, Mayotte, Mozambique, Rwanda, Seychelles, Somalia, South Sudan, Tanzania, United Republic of, Uganda, Zambia, Zimbabwe, Angola, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of, Congo, Republic of, Equatorial Guinea, Gabon, Sao Tome and Principe, Botswana, Eswatini, Lesotho, Namibia, South Africa, Benin, Burkina Faso, Cabo Verde, Côte d'Ivoire, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Saint Helena, Senegal, Sierra Leone, The Republic of the Gambia, Togo
America, Caribbean	Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, British Virgin Islands, Carribean Netherlands, Cayman Islands, Cuba, Curaçao, Dominica, Dominican Republic, France, Guadeloupe, France, Martinique, Grenada, Haiti, Jamaica, Montserrat, Puerto Rico, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Sint Maarten (Dutch part), Trinidad and Tobago, Turks and Caicos Islands, United States Virgin Islands
America, South	Belize, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Argentina, Bolivia, Plurinational State of, Brazil, Chile, Colombia, Ecuador, Falkland Islands (Malvinas), French Guiana, Guyana, Paraguay, Peru, Suriname, Uruguay, Venezuela, Bolivarian Republic of
America, North	Bermuda, Canada, Greeland, Saint Pierre and Miquelon, United States of America
Asia, Eastern	China, Japan, Korea, Democratic Republic of, Korea, Republic of, Mongolia
Asia, South Central	Afghanistan, Bangladesh, Bhutan, India, Iran, Islamic Republic of, Kazakhstan, Kyrgyzstan, Maldives, Nepal, Pakistan, Sri Lanka, Tajikistan, Turkmenistan, Uzbekistan
Asia, South Eastern	Brunei, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, Viet Nam
Asia, Western	Armenia, Azerbaijan, Bahrain, Cyprus, Gaza Strip and West Bank, Georgia, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Turkey, United Arab Emirates, Yemen
Europe, Eastern	Belarus, Bulgaria, Czechia, Hungary, Poland, Republic of Moldova, Romania, Russian Federation, Slovakia, Ukraine
Europe, Northern	Channel Islands, Denmark, Estonia, Faeroe Islands, Finland, Iceland, Ireland, Isle of Man, Latvia, Lithuania, Norway, Sweden, United Kingdom
Europe, Southern	Albania, Andorra, Bosnia and Herzegovina, Croatia, Gibraltar, Greece, Holy See, Italy, Malta, Montenegro, Portugal, San Marino, Serbia, Slovenia, Spain, The former Yugoslav Republic of Macedonia
Europe, Western	Austria, Belgium, France, Germany, Liechtenstein, Luxembourg, Monaco, Switzerland, The Netherlands
Oceania	Australia, New Zealand, Fiji, France, New Caledonia, Papua New Guinea, Solomon Islands, Vanuatu, Guam, Kiribati, Marshall Islands, Micronesia (Federated States of), Nauru, Northern Mariana Islands, Palau, American Samoa, Cook Islands, French Polynesia, Niue, Samoa, Tokelau, Tonga, Tuvalu, Wallis and Futuna Islands

Source: http://gco.iarc.fr/today/fact-sheets-populations accessed September 18, 2019

2. Search Strategy for the Systematic Review of Survival of Children with a Solid Tumor in Low and Middle Income Countries

(((((("2011/01/01"[PDat] : "3000/12/31"[PDat])) AND (("children with cancer"[tiab] OR "child with cancer"[tiab] OR leukemia OR leukemi* OR leukaemi* OR ("precursor cell lymphoblastic leukemia-lymphoma"[MeSH] OR ("precursor"[tw] AND "cell"[tw] AND "lymphoblastic"[tw] AND "leukemia-lymphoma"[tw]) OR "precursor cell lymphoblastic leukemia-lymphoma"[tw] OR "childhood all"[tw]) OR AML OR acute myeloid leukemia OR acute lymphoblastic leukemia OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR (b-cell lymphoma[tiab] OR "leukemia, b-cell"[MeSH]) OR non-hodgkin OR sarcoma OR sarcom* OR "sarcoma, Ewing"[MeSH] OR Ewing* OR (Ewing's sarcoma*[tiab]) OR osteosarcoma OR osteosarcom* OR non-rhabdomyosarcoma OR Burkitt's lymphoma OR yolk sac tumor OR embryonal carcinoma OR choriocarcinoma OR germ cell tumor OR (germ cell tumo*[tiab]) OR ependymoma OR melanoma OR Astrocytoma OR Astrocytom* OR Glioblastoma OR glioblastoma* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR "neuroectodermal tumors, primitive"[MeSH] OR (primitive neuroectodermal tumo*[tiab]) OR retinoblastoma OR retinoblastom* OR glioma OR gliom* OR (pediatric oncology[tiab]) OR (paediatric oncology[tiab]) OR (childhood cancer[tiab]) OR (childhood cancers[tiab]) OR (childhood tumo*[tiab]) OR (brain tumo*[tiab]) OR brain neoplasms OR (central nervous system neoplasm*[tiab]) OR central nervous system neoplasms[MeSH] OR (central nervous system tumo*[tiab]) OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR (leukemia lymphocytic acute[tiab]) OR (acute lymphoblastic leukemia[tiab]) OR "Neoplasms/epidemiology"[Mesh])))) AND ("Developing Countries"[Mesh] OR "Poverty"[Mesh] OR developing countr*[tw] OR developing nation*[tw] OR developing world[tw] OR less developed world[tw] OR under developed countr*[tw] OR lmic*[tw] OR poor countr*[tw] OR poorer countr*[tw] OR poor nation*[tw] OR poorer nation*[tw] OR ((less developed[tw] OR underdeveloped[tw] OR (lower[tw] AND middle income[tw]) OR low income[tw] OR lower income[tw] OR low and middle income[tw] OR low middle income[tw] OR resource poor[tw] OR resource constrained[tw] OR low resource[tw] OR limited resource*[tw] OR resource limited[tw]) AND (country[tw] OR countries[tw] OR nation[tw] OR nations[tw] OR region[tw] OR regions[tw] OR setting*[tw] OR area[tw] OR areas[tw])) OR ((("Africa"[tiab] OR "Africa South of the Sahara"[MeSH] OR "Southern Africa"[tiab] OR "Africa, Western"[MeSH] OR "Africa, Southern"[MeSH] OR "Africa, Northern"[MeSH] OR "Africa, Eastern"[MeSH] OR "Africa, Central"[MeSH] OR "Namibia"[tiab] OR "Mozambique"[tiab]) OR "Cameroon"[tiab]) OR "Central African Republic"[tiab]) OR "Chad"[tiab]) OR "Democratic Republic of the Congo"[tiab]) OR "Equatorial Guinea"[tiab]) OR "Gabon"[tiab]) OR "Burundi"[tiab]) OR "Djibouti"[tiab]) OR "Eritrea"[tiab]) OR "Ethiopia"[tiab]) OR "Kenya"[tiab]) OR "Rwanda"[tiab]) OR "Somalia"[tiab]) OR "South Sudan"[tiab]) OR "Sudan"[tiab]) OR "Tanzania"[tiab]) OR "Uganda"[tiab]) OR "Angola"[tiab]) OR "Botswana"[tiab]) OR "Lesotho"[tiab]) OR "Malawi"[tiab] OR "South Africa"[tiab]) OR "Swaziland"[tiab]) OR "Zambia"[tiab]) OR "Zimbabwe"[tiab] OR "Benin"[tiab]) OR "Burkina Faso"[tiab]) OR "Cape Verde"[tiab]) OR "Gambia"[tiab]) OR "Ghana"[tiab]) OR "Guinea"[tiab]) OR "Guinea-Bissau"[tiab]) OR "Liberia"[tiab]) OR "Mali"[tiab]) OR "Mauritania"[tiab]) OR "Niger"[tiab]) OR "Nigeria"[tiab]) OR "Senegal"[tiab]) OR "Sierra Leone"[tiab]) OR "Togo"[tiab]) OR "Sub-Sahara"[tiab]) OR "sub-Saharan"[tiab]) OR "Western Africa"[tiab]) OR "Algeria"[tiab]) OR "Egypt"[tiab]) OR "Libya"[tiab]) OR "Morocco"[tiab]) OR "Tunisia"[tiab]) OR "Africa"[MeSH]) OR "Afrika"[tiab]) OR "Cote d'Ivoire"[tiab]) OR "Congo"[tiab])

OR ((((((((((((("West Indies"[Mesh]) OR "Antigua and Barbuda"[Mesh]) OR "Cuba"[tiab]) OR "Dominica"[tiab]) OR "Dominican Republic"[tiab]) OR "Grenada"[tiab]) OR "Guadeloupe"[tiab]) OR "Haiti"[tiab]) OR "Jamaica"[tiab]) OR "Martinique"[tiab]) OR "Saint Kitts and Nevis"[Mesh]) OR "Saint Lucia"[Mesh]) OR "Saint Vincent and the Grenadines"[Mesh]) OR "Caribbean"[tiab]) OR ((((((((("Central America"[tiab]) OR "Belize"[tiab]) OR "Costa Rica"[tiab]) OR "El Salvador"[tiab]) OR "Guatemala"[tiab]) OR "Honduras"[tiab]) OR "Nicaragua"[tiab]) OR "Panama"[tiab]) OR "Latin America"[tiab]) OR "Mexico"[tiab]) OR ((((((((((((("South America"[tiab]) OR "South America"[Mesh]) OR "Argentina"[tiab]) OR "Bolivia"[tiab]) OR "Brazil"[tiab]) OR "Colombia"[tiab]) OR "Chile"[tiab]) OR "Ecuador"[tiab]) OR "French Guiana"[tiab]) OR "Guyana"[tiab]) OR "Paraguay"[tiab]) OR "Peru"[tiab]) OR "Suriname"[tiab]) OR "Uruguay"[tiab]) OR "Venezuela"[tiab]) OR ((((((((((((((("Asia"[Mesh:noexp]) OR "Asia, Central"[Mesh]) OR "Kazakhstan"[tiab]) OR "Kyrgyzstan"[tiab]) OR "Tajikistan"[tiab]) OR "Turkmenistan"[tiab]) OR "Uzbekistan"[tiab]) OR "Commonwealth of Independent States"[Mesh]) OR "Armenia"[tiab]) OR "Azerbaijan"[tiab]) OR "Georgia (Republic)"[Mesh]) OR "Moldova"[tiab]) OR "Russia"[tiab]) OR "Siberia"[tiab]) OR "Ukraine"[tiab]) OR "Transcaucasia"[Mesh]) OR "former soviet republic"[tiab]) OR ((((((((((((("Asia, Southeastern"[Mesh]) OR "Borneo"[tiab]) OR "Cambodia"[tiab]) OR "Indonesia"[tiab]) OR "Laos"[tiab]) OR "Malaysia"[tiab]) OR "Mekong Valley"[tiab]) OR "Myanmar"[tiab]) OR "Burma"[tiab]) OR "Philippines"[tiab]) OR "Thailand"[tiab]) OR "Timor-Leste"[tiab]) OR "Vietnam"[tiab]) OR "Southeast Asia"[tiab]) OR "Asia, Northern"[Mesh]) OR ((((((((((((((((("Asia, Western"[Mesh]) OR "Bangladesh"[tiab]) OR "Bhutan"[tiab]) OR "India"[Mesh]) OR "Middle East"[Mesh:noexp]) OR "Nepal"[Mesh]) OR "Pakistan"[tiab]) OR "Sri Lanka"[tiab]) OR "Afghanistan"[tiab]) OR "Iran"[tiab]) OR "Iraq"[tiab]) OR "Jordan"[Mesh]) OR "Lebanon"[tiab]) OR "Syria"[Mesh]) OR "Turkey"[Mesh]) OR "Yemen"[Mesh]) OR "Palestine"[tiab]) OR "Gaza"[tiab]) OR "West Bank"[tiab]) OR ((((((("Far East"[Mesh])) OR "China"[tiab]) OR "Tibet"[tiab]) OR "Mongolia"[tiab]) OR "Democratic People's Republic of Korea"[Mesh]) OR ((((((((((("Europe, Eastern"[Mesh]) OR "Albania"[tiab])) OR "Bosnia and Herzegovina"[tiab]) OR "Bulgaria"[tiab]) OR "Macedonia (Republic)"[Mesh]) OR "Kosovo"[tiab]) OR "Montenegro"[tiab]) OR "Republic of Belarus"[Mesh]) OR "Romania"[tiab]) OR "Serbia"[tiab]) OR ((((((((((((("Pacific Islands"[Mesh]) OR "Melanesia"[tiab]) OR "Fiji"[tiab]) OR "New Caledonia"[Mesh]) OR "Papua New Guinea"[tiab]) OR "Vanuatu"[tiab]) OR "Micronesia"[tiab]) OR "Palau"[tiab]) OR "Samoa"[tiab]) OR "American Samoa"[tiab]) OR "Independent State of Samoa"[Mesh]) OR "Tonga"[tiab]) OR "Australasia"[Mesh]) OR "Oceania"[Mesh]) OR (((((("Indian Ocean Islands"[Mesh]) OR "Comoros"[tiab]) OR "Mauritius"[tiab]) OR "Reunion"[Mesh]) OR "Madagascar"[tiab]) OR ("industrializing countries"[All Fields] OR "industrializing country"[All Fields])) OR "industrialising countries"[All Fields] OR ("industrialized countries"[All Fields] OR "industrialized country"[All Fields]) OR ("industrialised countries"[All Fields] OR "industrialised country"[All Fields]))) AND ((disease free survival OR Survival rate OR Survival analysis OR Survival OR Survival* OR Surviv* OR Survivor*) OR (Prognost* OR Prognostic methods OR Prognostic factors OR Prognostic factor OR Prognostic OR Prognos*) OR mortality)) AND (((Infant[MeSH] OR Infant*[tw] OR infancy[tw] OR Newborn*[tw] OR Baby[tw] OR Babies[tw] OR Child[MeSH] OR Child*[tiab] OR Childhood[tw] OR Schoolchild*[tw] OR School age*[tw] OR Preschool*[tw] OR Kid[tw] OR kids[tw] OR Toddler*[tw] OR Adolescent[MeSH] OR Adoles*[tw] OR Teen*[tw] OR "Boy"[tw] OR "Boys"[tw] OR "Girl"[tw] OR "Girls"[tw] OR "Boyhood"[tw] OR "Girlhood"[tw] OR "Juvenile"[tiab] OR "Youth"[tw] OR Minors[MeSH] OR Minors[tiab] OR Puberty[MeSH] OR Pubert*[tw] OR Pubescen*[tw] OR Prepubescen*[tw] OR Pediatrics[MeSH] OR Pediatric*[tiab] OR Paediatric*[tiab] OR Paediatric*[tiab])) NOT (animals[mh] NOT humans[mh]))

3. Methodology for systematic review of published studies on childhood cancer survival for solid tumours in low-income and middle-income countries

Data Sources

The search was first developed in the PubMed Medline format and subsequently translated into the formats of EMBASE, Web of Science, Cochrane Central Registry of Controlled Trials (Wiley), and the three regional databases: Index Medicus for the Eastern Mediterranean Region, SciELO[FL1] [FL2] (Latin America) and LILACS (Latin America and the Caribbean).

Article Selection

The full search strategy in the PubMed Medline format can be found in the Supplementary Appendix (pp 2-3). Included papers reported overall survival or event-free survival in children ages 0-14 years from a low-income or middle-income country as defined by the 2015 World Bank List of Economies[1] for all childhood cancer diagnoses. The search was then restricted to the following solid tumors: retinoblastoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, Kaposi sarcoma, neuroblastoma, Ewing sarcoma, osteosarcoma, germ cell tumors, Wilms tumor, or hepatoblastoma. The more "rare" types of childhood solid tumors, such as melanoma or adrenocortical carcinoma, were not included in this review.

For selection, the article was required to be either a sequential case series or a clinical trial and to include at least 20 pediatric patients ages 0-14 years in a single disease category. More than 50% of the patient sample in the article had to have

been treated after January 1, 2000. Median follow-up had to be at least one year. Additionally, because many articles reported only a subset of the expected disease incidence (e.g. only parameningeal rhabdomyosarcoma), we included only articles that reported on a selected population that would include at least 75% of the total population with disease. Conference proceedings and abstracts were excluded.

During the initial phase of the review, six teams were created consisting of one pediatric oncologist and one student each. Each team was responsible for one year of articles between 2011 and 2016: each member reviewed the abstracts independently, after which the two members resolved any conflicts or discordant abstracts. Any unresolved conflicts were reviewed by two senior reserachers. Subsequent full text review was performed in a similar fashion, except that each team was assigned the papers for a particular solid tumor.

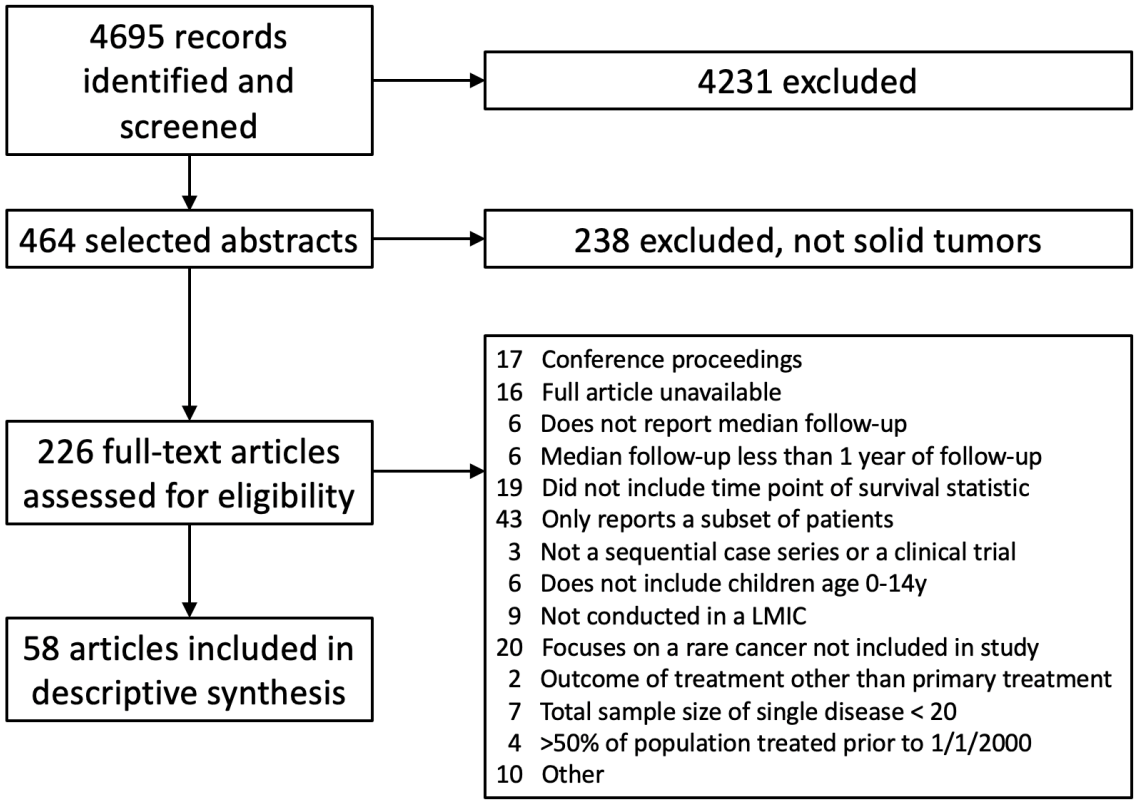
Data Abstraction

From the selected studies, the total number of patients in the article, the total number of patients under 14 years of age, the years the patients were treated, and the median and range of age at diagnosis were all recorded. The median and range of follow-up was abstracted, as well as the event-free survival and overall survival at every time point detailed in the selected study. If the survival was reported only by risk group, the results for each risk group were abstracted. Lastly, any Kaplan-Meier curve included in the article was abstracted.

The articles included in this systematic review are not population-based data, but instead represent more likely a sample of the best-reported facility-level possible outcomes within a country. The initial search identified 4695 articles, of which 4231 were excluded after review of the abstract for failing to meet initial inclusion criteria. . Of the 423 selected abstracts, 238 did not include data on survival of children with solid tumors and were excluded. For the remaining 226 abstracts full text articles were obtained and further screened for eligibility. Of these, 58 articles met the inclusion/exclusion criteria with close inspection (appendix pp. 6-12). Most of the articles that were included came from a limited set of upper-middle-income countries, such as Brazil (7), China (13), Argentina and Turkey. There were seven studies from low-income countries, including Botswana (1), Malawi (4), Senegal (1), and Uganda (1).

A meta-analysis of the published survival estimates was hampered by errors in reporting, limited articles in any one disease category, and inconsistent calculation and reporting methodologies. Hence descriptive statistics were generated. Further, reporting of follow up times, risk-group stratifications, and standard error of the estimate fluctuated in presence and methodology across the studies.

4. Survival from childhood cancers: PRISMA Diagram and the list of 58 studies included in the systematic review of published studies



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5. Appendix Table 1: Overall Survival of children with a solid tumor in low and middle income countries reported between 2011 and 2016

Disease	First Author	Year	Country	Overall Survival	
				OS	Stratification
Retinoblastoma	Bhavna Chawla	2016	India	83% at 1y	
				73% at 2y	
				68% at 3y	
				65% at 5y	
	Jingge Gao	2016	China	87.7% at 3y	
				81.4% at 5y	
				74.8% at 10y	
	Yi-Jin Gao	2011	China	98% at 5y	
	Kaan Gündüz	2013	Turkey	99.4% at y	
				78.7% at 1y	
				72.1% at 2y	
				61.8% at 4y	
				41.2% at 8y	
				33.3% at end of follow up	
	Dongsheng Huang	2013	China	95.13% at end of follow up	
	Farrah Islam	2013	Pakistan	66.2% at 1y	
	Simone G. A. Selistre	2016	Brazil	86.4% at y	
	M Kruger	2014	South Africa	68% at 5y	
	Sandra Luna-Fineman	2012	AHOPCA	48% at 5y	
	Xin LUO	2015	China	80.9% at 5y	
	D. Ossandón	2015	Chile	100% at y	
	Parag K. Shah	2015	India	93.1% at 1y	
				90.2% at 3y	
				89.2% at 5y	
	Shridevi Subramaniam	2014	Malaysia	94% at 1y	
	Keith M Waddell	2015	Uganda	65% at 2y	
				45% at 3y	
	Piyathida Wongmas	2015	Thailand	60% at end of follow up	
	Wang Yizhuo	2014	China	95.3% at 5y	
GCT	Fedhila, F	2016	Tunisia	82% at 2y	
				75% at 5y	
	Lopes LF	2016	Brazil	90% at 10y	intermediate risk, good response
				74.1% at 10y	intermediate risk, partial response
				66.8% at 10y	high risk, good response
				74.8% at 10y	high risk, partial response
Hepatoblastoma	Yuan X.	2016	China	83.3% at 6y	
	Aoun Tannuri AC	2015	Brazil	87.7% at 5y	
Rhabdomyosarcoma	Sezgin G	2015	Turkey	68.2% at 2y	
				78% at 2y	
				40% at 5y	
	Ma X	2015	China	65.3% at 10y	
	Babaei M	2015	Iran	94% at 0.5y	
				87% at 1y	
				69% at 3y	

				50% at 5y	
	Sidhom I	2015	Egypt	56.1% at 3y	
				35.3% at 3y	with anaplasia
				62% at 3y	without anaplasia
	Al-Jumaily U	2013	Jordan	72% at 4y	
	Badr MA	2012	Egypt	56.9% at 5y	
	Salman M	2012	Lebanon	83% at 5y	
Osteosarcoma	Pruksakorn, D.	2015	Thailand	37.9% at 5y	
				33.6% at 10y	
	Choeyprasert, W.	2014	Thailand	44.8% at 5y	
	Petrilli, A. S.	2013	Brazil	49% at 5y	
	Tan, P. X.	2012	China	61.8% at 5y	
				71.6% at 5y	received standard chemotherapy
Ewing Sarcoma	Brunetto, A. L.	2015	Brazil	54.5% at 5y	
	Abou Ali, B.	2014	Lebanon	69% at 5y	
Kaposi Sarcoma	El-Mallawany, N. K.	2016	Malawi	58% at 2y	
Neuroblastoma	Easton, J. C.	2016	Argentina	24% at 5y	high risk
	Moreno, F.	2016	Argentina	47% at 5y	
	Al-Tonbary, Y.	2015	Egypt	47.6% at 2y	males
				10.4% at 2y	females
	Bordbar, M.	2014	Iran	20% at 5y	
	Agarwala, S.	2014	India	60.7% at 3y	
	Li, K.	2012	China	80% at 5y	stage 1 and 2
				48.3% at 5y	stage 3
				20% at 5y	stage 4
Soft Tissue Sarcoma	Boam, T.	2016	Cambodia	58% at 1y	
				16% at 3y	
				10% at 5y	
	Farfalli, Germán Luis	2014	Argentina	72% at 5y	
Wilms Tumor	Tenge, C. N.	2016	Chile	89.9% at 10y	
	Rabeh, W.	2016	Lebanon	88.6% at 3y	
	Verma, N.	2016	India	74% at 5y	
	Stones, D. K.	2015	South Africa	66% at 5y	
	Fawzy, M.	2015	Egypt	75% at 3y	double LOH
				92% at 3y	16q
				93% at 3y	1p
				97% at 3y	negative LOH
	Pan, C.	2015	China	83% at 5y	
	Cai, J. Y.	2014	China	72% at 5y	
	Acipayam, C.	2014	Turkey	90% at 2y	carboplatin
				90% at 4y	carboplatin
				100% at 2y	non-carboplatin
				88% at 4y	non-carboplatin
	Israels, T.	2012	Malawi	46% at 3y	
	Yao, W.	2012	China	81% at 4y	

6. Modelling of Childhood Cancer Incidence and Survival – Appendix Panel 1: Methodology for the Global Childhood Cancer microsimulation model to estimate the global incidence of childhood cancer

The Global Childhood Cancer microsimulation model simulates the childhood cancer care cascade from incidence to diagnosis, referral and registration for all IICC-3 diagnoses in 200 countries and territories worldwide, taking into account trends in population growth, as estimated by the United Nations Population Division[2] and urbanicity, as measured by the United Nations[3], geographic variation in cancer incidence, and health system barriers that contribute to under-diagnosis.

The model assumes that for cancer cases to be diagnosed and recorded in a cancer registry, the patient must have access to primary health care and be appropriately referred to a specialist for care. By modeling this underlying process (using country-specific health system data from the Demographic and Health Surveys[4] and Multiple Indicator Cluster Surveys[5] as proxy indicators), the model estimates levels of under-diagnosis by accounting for the effects of the currently reported health system barriers on cancer diagnosis and registration.

We developed a Bayesian hierarchical modeling framework[6] to synthesize data on multiple indicators and to estimate parameters for countries lacking data on health system variables and/or cancer registries (three levels for health system variables [income group, region, country] and four levels for cancer incidence [global, continent, region, country]) and to ensure model predictions were consistent with data from cancer registries[7]. In our model the observed data are fixed and the

model parameters (cancer incidence and the probabilities of health system access and referral) are random variables.

Using the model, we ran 1000 simulations to estimate for children aged 0-14 years the total incidence of childhood cancer (diagnosed and undiagnosed) in each country and simulated projections of the global incidence of childhood cancer from 2020 to 2050. To portray uncertainty more fully, we report 95% uncertainty intervals (UI) for all outcomes.

7. Modelling of Childhood Cancer Incidence and Survival – Appendix Panel 2: Global Childhood Cancer Microsimulation Model: Survival Module

The survival module of the Global Childhood Cancer Microsimulation Model simulates the childhood cancer care cascade from the time of cancer diagnosis to 5-years after diagnosis (e.g., 5-year net survival) for all IICC-3 diagnoses[8] in 200 countries and territories worldwide.

To parameterise the model, we used data from CONCORD-2[9] and CONCORD-3[10] studies (which provide internationally comparable population-based cancer survival estimates for selected childhood cancers in over 70 countries), the Lancet Commission on Surgery (which provides estimates for coverage of surgical services globally)[11] and the Lancet Oncology Commission on Radiotherapy (which estimated current and future coverage of radiotherapy services globally)[12].

The current maximum achievable levels of 5-year survival for each type of cancer, given access to high-quality cancer care, were informed by estimates from the US Surveillance, Epidemiology, and End Results (SEER) Program.[13] These estimates were used as a proxy for the general level and variation of survival by diagnosis assuming access to all chemotherapy drugs for a given regimen[14 15], access to radiotherapy (if needed), and access to surgery and relevant surgical subspecialties (neurosurgery for central nervous system tumors, ophthalmology for retinoblastoma, and general surgery for all others if needed), social support services to minimize treatment abandonment, and high quality of care (appendix pp. 15-19).

We assumed that the observed differences between the levels of survival reported in the CONCORD studies and the corresponding SEER estimates were due to the lack of cancer treatment needed, abandonment of treatment, low quality of healthcare services, or a combination of these factors.

Using the three groups of childhood cancer included in CONCORD-2 and CONCORD-3 (the lymphomas, leukaemias, and brain tumors), we used an Approximate Bayesian Computation approach [16 17] to fit model parameters for each participating country that yielded predicted 5-year net survival estimates consistent with the survival estimates reported in CONCORD. We then used an empirical Bayes approach to estimate parameters for countries for which CONCORD estimates were not available, by using a hierarchical framework (income group, region, country) to synthesize the model parameters. This allowed us to leverage data from multiple sources on the availability of treatments required for each type of cancer (specifically, chemotherapy regimens[18], access to radiotherapy[12] and access to surgery and sub-specialties[19 20 21], and estimates of treatment abandonment[**18**]. Assuming model parameters fit to observed diagnoses (e.g., availability of chemotherapy regimens, radiation or surgery, treatment abandonment of treatment, and quality of care) were applicable to the types of cancer not included in CONCORD, we then used the calibrated model to project the numbers of deaths and survival outcomes for all countries and types of cancer.

8. Analysis of research funding for childhood cancers - Appendix panel 3: Data source and methodology for analysis of research funding for childhood cancers

We analysed global research funding for childhood cancers, incorporating data from 115 funders for 3414 research projects, in 35 countries from the Dimensions database.[22] Comparable data are available on grants listed individually including grant size, duration, start date, currency, funder and recipient; as well as the abstract associated with each grant outlining the nature of the research, allowing detailed objective analysis of patterns of funding, including trends over time.

In addition, using validated scientometric methods, we undertook analyses of the top funders of childhood cancer research by number of publications, the top ten largest public and philanthropic funders of health research worldwide (nine of which were included in the Dimensions database), funding from the International Cancer Research Partnership (a large cancer research funding network of more than 120 funders from Australia, Canada, France, Japan, the Netherlands, the United Kingdom, and the United States), organisations that have funded childhood cancer research and were not included in the Dimensions database, and the Cancer Prevention and Research Institute of Texas, a major public funder of childhood cancer research. The details of the data sources and methods are described comprehensively in a study published elsewhere.[23]

9. Prioritisation of childhood cancers in universal health coverage – Appendix Panel 4: Methodology for examining priority-setting on childhood cancer funding and care in El Salvador, Ghana, Guatemala, India, and the Philippines

We purposively selected five LMICs in different geographic regions, with varied socio-cultural economic and political settings to study factors which influence health system priority-setting on childhood cancer funding and care.

The research employed primary and secondary research. Primary research involved in-depth semi-structured interviews. Secondary research involved structured searches of the published and grey literature on the health system context and childhood cancer care in the five study countries, including academic articles, documents from governmental and non-governmental organisations, information from media sources, and websites of relevant health system organizations involved in health care for children with cancer.

For primary research a team of four researchers travelled to the five study countries in pairs or alone and worked with local counterparts to undertake interviews with key informants who were identified purposively and using snowballing methodology to establish a multi-level multi stakeholder sample. A total of 68 interviews were undertaken in El Salvador(19), Guatemala (13), India (14), Philippines (12) and Ghana (10).

Qualitative interviews were audiotaped, transcribed verbatim, and translated into English where relevant. Relevant literature and interview transcripts were imported

into and inductively coded using NVivo 11 software (QSR International Ltd.). Interviews were divided among the four researchers for coding and each interview was coded independently.

The researchers iteratively reviewed and compared coding systems. Random samples of the data from each country were double-coded to ensure broad consistency in approach to coding and analysis. Drawing on an interpretive grounded theory approach, the research team combined sequential phases of coding, moving from open through theoretical codes, with constant comparative methods employed to refine codes, establish analytic distinctions, and capture emergent themes. Interviews were conducted to explore in depth emerging themes until theoretical saturation was achieved.[24] The findings were discussed and reviewed with local investigators in each country for triangulation and to strengthen fidelity and reliability of the findings.

In analysing the data we used a framework that has been applied in global health to analyse generation of political priorities for health of women and children. This framework enables examination of the principal influences on priority-setting in four categories, namely, political contexts, actor power, ideas, and issue characteristics.[25] The study employed multiple case study design[26] to enable cross comparison and synthesis of findings from each of the five countries.

10. Cost and cost-effectiveness of treatments for childhood cancers – Appendix

Panel 5: Methodology for determining the institutional level cost of delivering childhood cancer care

Three childhood cancer treatment units were selected in countries of different stages of economic and health system development, GDP per capita and health expenditure per capita: Korle Bu Teaching Hospital (Accra, Ghana), Hospital Nacional de Niños Benjamin Bloom (San Salvador, El Salvador), and Hospital Civil de Guadalajara (Guadalajara, Mexico). The characteristics of three centers and settings are compared in the appendix table 2 (p 24).

We obtained data on the number of new diagnoses in a given year from each center. We also obtained survival data from the centers: two of the centers (Hospital Nacional de Niños Benjamin Bloom and Hospital Civil de Guadalajara) maintain registries or patient tracking systems and were able to provide 5-year survival information. For the third center in Korle Bu, as only one-year survival was available, we estimated 5-year survival by comparing it to 1-year survival by using data from another center with similar 1-year survival data.[27]

To summarize costs, we created a detailed abstraction tool that categorizes costs into pre-defined subgroups: personnel (medical and non-medical), ancillary services (diagnostic imaging, laboratory, pathology, radiation, blood bank), medications (chemotherapy and supportive), "hoteling" (costs associated with beds in the ward and the intensive care unit), operating room, outpatient clinic, and caregiver support (e.g. lodging, meals, and/or transportation provided by the center to family

members). Data for out of pocket costs were not collected. The sources of various cost data are available.[28]

Where the annual costs of shared services (e.g. pharmacy, blood bank, laboratory) attributable to childhood cancer cases were available, they were obtained directly from hospital accounts. Where such figures were not available, utilization of specific services (e.g. chest x-rays, blood tests) by paediatric oncology patients was captured retrospectively or tracked prospectively for a sample period of time, multiplied by unit costs, and converted to annual figures. Fixed costs related to hospital infrastructure and administrative personnel were collected directly where available, or determined by applying ratios of costs derived in other centres.

All costs were summed to determine the total annual operating cost of each center, the average cost per new diagnosis, and the cost per life year saved. We assumed a median length of one-year for treatment following discussion and consensus of the researchers, country teams and paediatric oncologists involved in the study, based on the assumption that treatment length for acute lymphoblastic leukaemia, the most common childhood cancer, is 2-3 years[29] while the duration of treatment for most of the other childhood malignancies is 6-12 months[30 31 32].

We used a discount rate of 3% for costs and benefits as recommended by WHO-CHOICE guidelines,[33] and WHO thresholds for cost-effectiveness, which suggest that interventions costing less than one per capita GDP per DALY averted are 'very cost-

effective', and those costing less than three times the per capita GDP per DALY averted are 'cost-effective.'[34] Cost-effectiveness of treatments was calculated by converting the cost per life saved to cost per DALY averted using each jurisdiction's life expectancy and a mean age at diagnosis of six years.

We conducted multiple sensitivity analyses at each centre, varying the discounting rate, the number of additional years survived to account for the impact of late effects of treatment, the five-year survival, and an age-dependent utility weight assigned to account for small health decrements associated with cancer survivorship. The sensitivity analyses did not change the results or conclusions at any centre, and are therefore not presented here.

There were several methodological limitations. First, we only included three centres due to data availability and time constraints, and hence, the results may not be generalisable. Second, in some analyses and for some line items, costs were determined over a relatively short, defined period of time, and then extrapolated to annual figures. This and other assumptions imply that the results should be taken as broad estimates. Indeed, the variation in data collection across the three centres, due to the difference in accounting systems, illustrates the complexity of this undertaking. Third, caregiver costs, which could be substantial, were not included. Fourth, the three centres where the study was undertaken are established childhood cancer treatment units, and creating new or expanding existing units would likely require substantial one-time fixed costs. Fifth, there are variations in

the percentage of overall cost associated with particular cost items, which are due to multiple factors and cannot be readily attributed to a single factor – such as the relative cost of personnel, or the cost of consumables, which vary from country to country. A further factor is the variation in the case mix, which influences the cost per patient. For example, in centres that treat a larger proportion of haematologic malignancies, the costs of chemotherapy, supportive care medication, and possibly personnel may be relatively higher as a proportion of total, whereas in centres the solid tumours account for a larger proportion of the patients treated will have greater costs related to surgery and operating rooms. As another example, blood bank costs would be low in centres that do not provide very intensive chemotherapy and where availability of such treatments is low. Another factor that leads to variability in costs is the differences in the use of nurses and doctors for treatment and the differences in nursing and physician ratios, which vary by countries. Further studies in a larger number of countries will help address such limitations.

11. Cost and cost-effectiveness of treatments for childhood cancers – Appendix

Table 2: Comparison of Center and Jurisdiction Characteristics

	Korle Bu Teaching Hospital	**Hospital Nacional de Ninos Benjamin Blum**	**Hospital Civil de Guadalajara**
Jurisdiction	Ghana	El Salvador	Jalisco, Mexico
GDP per capita (USD, 2016)	1,513	3,920	8,208
Population served, estimated	19.7 million	6 million	5 million
Other childhood cancer treatment units within jurisdiction	In addition to Korle Bu, a childhood cancer treatment unit exists in Kumasi serving the rest of Ghana's population	No	Two small private hospitals and one other public hospital estimated to reach the other 3 million people in Jalisco
Satellite centres	No	No	No
New childhood cancer cases each year	170	180	165
Age range	0-14 years	0-14 years	0-14 years
Paediatric oncology beds	30	24	31
Medical personnel, FTE	41	65	110
Average outpatient visits per day	7	90	57
Public financing of childhood cancer treatment	A National Health Insurance Authority exists but does not cover all medications and services. Private philanthropic funding also exists	Financing provided mainly by the Ministry of Health and the private non-profit foundation "Ayudame a Vivir"	Public insurance (Seguro Popular) covers pediatric cancer
Examples of caregiver medical costs not covered by public or philanthropic funds	Fundraising to expand hostel for parents of patients; Most parents have to cover costs of many diagnostics and treatment	Most costs are covered through government and philanthropic funding	Most costs covered by state and federal government, except for local housing for parents where foundation support is available
Treatment modalities available	Chemotherapy, surgery, radiation (limited)	Chemotherapy, surgery, radiation (not on-site)	Chemotherapy, surgery, radiation (not on-site), BMT
Five-year overall survival	35%*	49%	73%

*Estimated from one-year survival figures

12. Costs and Health and Economic Benefits of Scale-Up of Healthcare Services for Management of Childhood Cancers - Appendix Table 3: Values of the model parameters for health interventions (%) by World Bank Income Grouping (Mean value and 95% UI)

Income group	Model Parameters (%), mean (95% UI)								
	Access/Referral		Chemo-therapy	Radiation	Surgery			Treatment abandonment	Quality
	Rural	Urban			General	Neuro-surgery	Ophthalmology		
LIC	42.1 (40.4-43.8)	49.8 (47.8-51.8)	66.0 (59.3-71.4)	7.8 (5.5-10.4)	14.8 (12.9-16.8)	9.8 (7.9-11.7)	9.8 (8.3-11.4)	45.9 (32.9-60.3)	50.3 (37.1-64.0)
LMIC	46.6 (44.1-49.3)	52.3 (49.3-54.6)	75.4 (69.5-80.7)	38.0 (25.1-49.4)	38.1 (31.5-47.1)	22.2 (15.2-31.0)	22.5 (16.3-30.0)	22.4 (14.9-31.5)	68.1 (55.8-80.8)
UMIC	70.5 (63.0-77.6)	70.6 (64.9-75.3)	84.9 (79.0-93.1)	86.1 (76.4-93.0)	87.1 (76.6-93.8)	67.4 (55.5-77.9)	74.5 (61.6-84.9)	7.6 (3.6-13.2)	88.7 (77.8-94.6)
HIC	93.8 (91.2-96.0)	93.5 (90.8-95.5)	95.8 (94.9-96.7)	97.7 (97.0-98.4)	96.3 (94.8-97.3)	90.7 (89.2-92.3)	92.1 (90.2-94.1)	2.1 (1.4-3.3)	98.7 (98.2-99.1)

LIC: low income countries
LMIC: low middle income countries
UMIC: upper middle income countries
HIC: high income countries

For World Bank Income Groupings see World Bank Country and Lending Groups
https://datahelpdesk.worldbank.org/knowledgebase/articles/906519 (Accessed September 17, 2019

13. Appendix Table 4: Sensitivity analysis: Projected childhood cancer deaths averted and life years gained – no trends in background mortality rates

Income Group	Intervention Scenario	Projected Life Years Gained (No Trend in Background mortality), millions (95% UI)	
		Undiscounted	Discounted (3%)
Global	Access/Referral	50.94 (41.73-61.57)	15.07 (12.49-18.02)
	Abandon	11.69 (7.5-18.07)	3.34 (2.15-5.23)
	Treatment	98.98 (84.48-115.45)	27.8 (23.73-32.32)
	Comprehensive	307.9 (275.16-348.12)	86.58 (77.54-97.58)
LIC	Access/Referral	6.29 (4.48-8.96)	1.99 (1.46-2.73)
	Abandon	2.94 (1.69-4.8)	0.84 (0.49-1.37)
	Treatment	26.25 (20.93-32.85)	7.32 (5.84-9.14)
	Comprehensive	93.44 (79.89-111.59)	26.04 (22.34-31.03)
LMIC	Access/Referral	29.48 (21.97-38.71)	8.77 (6.64-11.42)
	Abandon	6.19 (2.85-11.47)	1.79 (0.82-3.34)
	Treatment	56.13 (45.23-69.07)	15.87 (12.92-19.45)
	Comprehensive	172.42 (146.68-200.23)	48.85 (41.78-56.41)
UMIC	Access/Referral	14.22 (10.61-19.08)	4.04 (3.03-5.42)
	Abandon	2.32 (0.88-4.65)	0.65 (0.24-1.28)
	Treatment	15.68 (11.49-20.37)	4.35 (3.22-5.6)
	Comprehensive	39.81 (32.86-47.63)	11.09 (9.22-13.23)
HIC	Access/Referral	0.96 (0.67-1.29)	0.26 (0.19-0.35)
	Abandon	0.23 (0.15-0.34)	0.06 (0.04-0.09)
	Treatment	0.92 (0.79-1.09)	0.25 (0.21-0.29)
	Comprehensive	2.23 (1.86-2.66)	0.61 (0.51-0.72)

14. Appendix Table 5: Projected (discounted) cumulative treatment costs ($ billions) and productivity gains (mean and 95%UI) – global and by country income group 2020, 2030 and 2050

Income Group	Projected Cumulative Costs/Gains ($ billions), mean (95% UI)		
	Year		
	2020	2030	2050
Globally			
Treatment	17.3 (16.9-17.6)	228.8 (220.7-237.0)	594.4 (563.1-626.7)
Productivity - 1xGDP	0.3 (0.3-0.3)	23.5 (22.8-24.2)	340.0 (327.1-353.8)
Productivity - 2.3xGDP (base case)	0.7 (0.6-0.7)	54.0 (52.5-55.6)	782.0 (752.3-813.8)
Productivity - 3xGDP	0.9 (0.8-0.9)	70.4 (68.5-72.6)	1020.0 (981.3-1061.5)
LIC			
Treatment	0.2 (0.2-0.2)	4.7 (4.2-5.4)	16.6 (14.3-19.4)
Productivity - 1xGDP	0 (0-0)	0 (0-0.1)	4.6 (4.0-5.4)
Productivity - 2.3xGDP (base case)	0 (0-0)	0.1 (0.1-0.2)	10.6 (9.1-12.5)
Productivity - 3xGDP	0 (0-0)	0.1 (0.1-0.2)	13.8 (11.9-16.2)
LMIC			
Treatment	1.9 (1.8-2.1)	38.7 (35.2-43.0)	121.8 (105.4-139.6)
Productivity - 1xGDP	0 (0-0)	1.1 (0.9-1.3)	42.6 (37.6-48.3)
Productivity - 2.3xGDP (base case)	0 (0-0)	2.5 (2.0-3.0)	97.9 (86.6-111.1)
Productivity - 3xGDP	0 (0-0)	3.2 (2.7-3.9)	127.7 (112.9-145.0)
UMIC			
Treatment	4.8 (4.6-4.9)	67.2 (61.9-73.1)	170.8 (150.8-193.0)
Productivity - 1xGDP	0.1 (0.1-0.1)	5.3 (4.9-5.7)	90.2 (82.3-98.8)
Productivity - 2.3xGDP (base case)	0.1 (0.1-0.2)	12.2 (11.2-13.1)	207.5 (189.3-227.2)
Productivity - 3xGDP	0.2 (0.2-0.2)	15.9 (14.6-17.1)	270.6 (246.9-296.3)
HIC			
Treatment	10.4 (10.1-10.6)	118.2 (114.0-122.4)	285.2 (269.5-300.7)
Productivity - 1xGDP	0.2 (0.2-0.2)	17.0 (16.5-17.6)	202.6 (195.6-210.0)
Productivity - 2.3xGDP (base case)	0.5 (0.5-0.5)	39.2 (38.0-40.6)	466.0 (449.9-482.9)
Productivity - 3xGDP	0.7 (0.6-0.7)	51.1 (49.6-52.9)	607.9 (586.8-629.9)

15. Appendix Table 6: Projected lifetime costs and productivity gains at different scale-up levels ($ billions) (mean and 95%UI)

Income Group	Projected Lifetime Costs/Gains ($ billions), mean (95% UI)					
	Scale-up, %					
	0%	20%	40%	60%	80%	100% (base case)
Globally						
Treatment	501.2 (477.5-527.2)	518.1 (493.6-545.1)	535.9 (509.7-563.9)	554.5 (526.6-583.6)	574 (544.3-604.6)	594.4 (563.1-626.7)
Productivity - 1xGDP	819.3 (778.1-859.5)	856.5 (813.5-898.9)	902.4 (858.9-947.3)	959.4 (912.6-1009.4)	1031.2 (978.9-1088.2)	1122 (1062.6-1185.2)
Productivity - 2.3xGDP (base case)	1884.4 (1789.6-1976.8)	1970 (1871-2067.5)	2075.4 (1975.6-2178.8)	2206.7 (2099-2321.7)	2371.6 (2251.5-2502.9)	2580.5 (2444-2726)
Productivity - 3xGDP	2457.9 (2334.3-2578.5)	2569.6 (2440.5-2696.7)	2707.1 (2576.8-2841.9)	2878.3 (2737.8-3028.3)	3093.5 (2936.7-3264.7)	3365.9 (3187.8-3555.7)
LIC						
Treatment	8.8 (7.7-10.1)	10.2 (8.9-11.7)	11.6 (10.1-13.4)	13.2 (11.4-15.3)	14.8 (12.8-17.3)	16.6 (14.3-19.4)
Productivity - 1xGDP	1.5 (0.9-2.4)	2.9 (2.1-4.1)	5.3 (4.1-6.8)	9.2 (7.5-11.3)	15.3 (13-18.2)	24.7 (21.1-29.3)
Productivity - 2.3xGDP (base case)	3.5 (2.1-5.4)	6.7 (4.7-9.3)	12.2 (9.4-15.6)	21.1 (17.3-25.9)	35.2 (30-41.8)	56.7 (48.5-67.3)
Productivity - 3xGDP	4.6 (2.8-7.1)	8.7 (6.2-12.2)	15.9 (12.3-20.3)	27.5 (22.6-33.8)	45.9 (39.1-54.5)	74 (63.2-87.8)
LMIC						
Treatment	70.8 (62.2-79.8)	79.8 (70.1-90.2)	89.4 (78.1-101.5)	99.6 (86.8-113.8)	110.4 (95.9-126.5)	121.8 (105.4-139.6)
Productivity - 1xGDP	39.4 (30.2-50.2)	53.7 (42.9-66.5)	73.8 (60.7-88.5)	101.4 (85.5-118.7)	139.1 (119.2-161.8)	190.1 (163.7-219.7)
Productivity - 2.3xGDP base case)	90.6 (69.6-115.4)	123.6 (98.8-153)	169.7 (139.7-203.6)	233.1 (196.6-273)	319.8 (274.1-372.1)	437.1 (376.4-505.4)
Productivity - 3xGDP	118.1 (90.7-150.5)	161.2 (128.8-199.6)	221.3 (182.2-265.6)	304.1 (256.4-356.1)	417.2 (357.6-485.4)	570.2 (491-659.2)
UMIC						
Treatment	140.7 (126.7-155.5)	146.4 (131.8-162.1)	152.3 (136.9-168.8)	158.3 (141.7-176.3)	164.5 (146.4-184.6)	170.8 (150.8-193)

Productivity - 1xGDP	196.4 (171.9-221.3)	214.4 (189.8-240.7)	234.2 (208.4-262.4)	256.1 (227.6-286.3)	280.3 (249.2-314.5)	306.9 (271.1-347.5)
Productivity - 2.3xGDP (base case)	451.8 (395.4-509)	493.1 (436.4-553.6)	538.7 (479.2-603.6)	589 (523.5-658.5)	644.6 (573.1-723.3)	705.9 (623.6-799.2)
Productivity - 3xGDP	589.3 (515.7-663.9)	643.1 (569.3-722.1)	702.6 (625.1-787.3)	768.3 (682.8-858.9)	840.8 (747.5-943.4)	920.7 (813.4-1042.5)
HIC						
Treatment	280.9 (265.5-296.5)	281.8 (266.2-297.4)	282.6 (267.1-298.2)	283.4 (267.9-299.1)	284.3 (268.7-299.9)	285.2 (269.5-300.7)
Productivity - 1xGDP	582 (553-612.1)	585.5 (556.1-615.5)	589.1 (559.7-619.2)	592.8 (563.4-622.8)	596.5 (567-626.7)	600.3 (570.7-631.1)
Productivity - 2.3xGDP (base case)	1338.5 (1271.8-1407.9)	1346.6 (1278.9-1415.6)	1354.9 (1287.2-1424.2)	1363.4 (1295.9-1432.3)	1372 (1304.1-1441.5)	1380.8 (1312.6-1451.5)
Productivity - 3xGDP	1745.9 (1658.9-1836.4)	1756.5 (1668.2-1846.4)	1767.3 (1679-1857.6)	1778.3 (1690.3-1868.3)	1789.6 (1700.9-1880.2)	1801 (1712.1-1893.3)

16. Appendix Table 7: Projected net benefits ($ billions) (mean and 95% UI) at different levels of scale up

Income Group	Projected Net Return on Investment ($ billions), mean (95% UI)					
	Scale-up, %					
	0%	20%	40%	60%	80%	100% (base case)
Globally						
Productivity - 1xGDP	318.1 (294-341)	338.4 (314.7-361.7)	366.5 (342.2-391)	404.9 (380-430.6)	457.1 (430.6-484.4)	527.6 (498.2-560.9)
Productivity - 2.3xGDP (base case)	1383.2 (1309.3-1458)	1451.9 (1375.5-1528.7)	1539.5 (1459.2-1620.7)	1652.1 (1567.9-1740.7)	1797.6 (1705.4-1899.4)	1986.1 (1884-2101.3)
Productivity - 3xGDP	1956.7 (1854.3-2058.3)	2051.5 (1943.6-2158.2)	2171.2 (2060.1-2282.9)	2323.7 (2206.3-2446)	2519.4 (2391.7-2659.9)	2771.5 (2630.2-2930.2)
LIC						
Productivity - 1xGDP	-7.3 (-8.6--6)	-7.2 (-8.7--5.9)	-6.3 (-7.8--4.9)	-4 (-5.4--2.7)	0.5 (-0.9-1.6)	8.1 (6.5-10)
Productivity - 2.3xGDP (base case)	-5.3 (-7--3.5)	-3.5 (-5.5--1.2)	0.5 (-2-3.2)	7.9 (4.9-11.3)	20.3 (16.4-25)	40.1 (34-47.8)
Productivity - 3xGDP	-4.2 (-6.2--1.9)	-1.4 (-4-1.4)	4.2 (1-8)	14.3 (10.3-19)	31 (25.6-37.7)	57.4 (48.7-68.4)
LMIC						
Productivity - 1xGDP	-31.4 (-41--21.7)	-26.1 (-36.5--16)	-15.6 (-26--5.4)	1.8 (-7.9-11.4)	28.7 (19.7-38.7)	68.2 (57-81)
Productivity - 2.3xGDP (base case)	19.8 (1.4-40.1)	43.8 (23.3-66.6)	80.3 (56.6-107.4)	133.5 (107.1-163.7)	209.4 (176.6-246.8)	315.3 (270.7-367.3)
Productivity - 3xGDP	47.3 (23.3-73.9)	81.4 (54.4-112.6)	131.9 (100.7-169.3)	204.5 (166.5-248.1)	306.8 (260.6-359.5)	448.4 (385.1-521.3)
UMIC						
Productivity - 1xGDP	55.8 (39.1-69.8)	68 (52.6-82.1)	82 (67-95.9)	97.8 (83.7-111.9)	115.8 (101.4-131.7)	136.1 (119.8-154.9)
Productivity - 2.3xGDP (base case)	311.1 (264.7-355.8)	346.7 (300.6-393.4)	386.4 (340.3-435.6)	430.8 (380-484.2)	480.2 (424.8-540)	535.1 (472.4-606.2)
Productivity - 3xGDP	448.6 (385.1-510.9)	496.7 (434-560.8)	550.4 (486.2-619.7)	610 (540.5-685.2)	676.3 (599.8-759.2)	749.9 (663.3-849.1)
HIC						
Productivity - 1xGDP	301	303.7	306.5	309.3	312.2	315.2

	(286.1-317.3)	(288.9-320.3)	(291.4-323)	(294-325.7)	(296.8-328.8)	(299.6-332)
Productivity - 2.3xGDP (base case)	1057.6 (1005.7-1112.9)	1064.9 (1012.6-1120.4)	1072.3 (1019.6-1128.4)	1079.9 (1026.6-1136.2)	1087.7 (1033.9-1143.8)	1095.6 (1041.9-1151.8)
Productivity - 3xGDP	1465 (1392.2-1539.9)	1474.7 (1402.5-1551)	1484.7 (1411.4-1561.1)	1494.9 (1421.7-1572.6)	1505.3 (1431.4-1582.9)	1515.9 (1441.1-1593.5)

17. Appendix Table 8: Projected cumulative treatment costs 2020-2050

Region	Projected Cumulative Costs ($ billions), mean (95% UI) – Treatment with 20% health system strengthening costs		
	2020	**2030**	**2050**
Globally	20.7 (20.3-21.1)	274.6 (264.9-284.4)	713.3 (675.7-752.1)
LIC	0.3 (0.2-0.3)	5.7 (5-6.5)	19.9 (17.2-23.3)
LMIC	2.3 (2.2-2.5)	46.5 (42.3-51.6)	146.2 (126.4-167.5)
UMIC	5.7 (5.5-5.9)	80.6 (74.3-87.7)	205.0 (181-231.5)
HIC	12.4 (12.2-12.7)	141.8 (136.8-146.9)	342.2 (323.4-360.9)

18. Appendix Table 9: Projected Lifetime Treatment Costs – with 20% health system strengthening costs

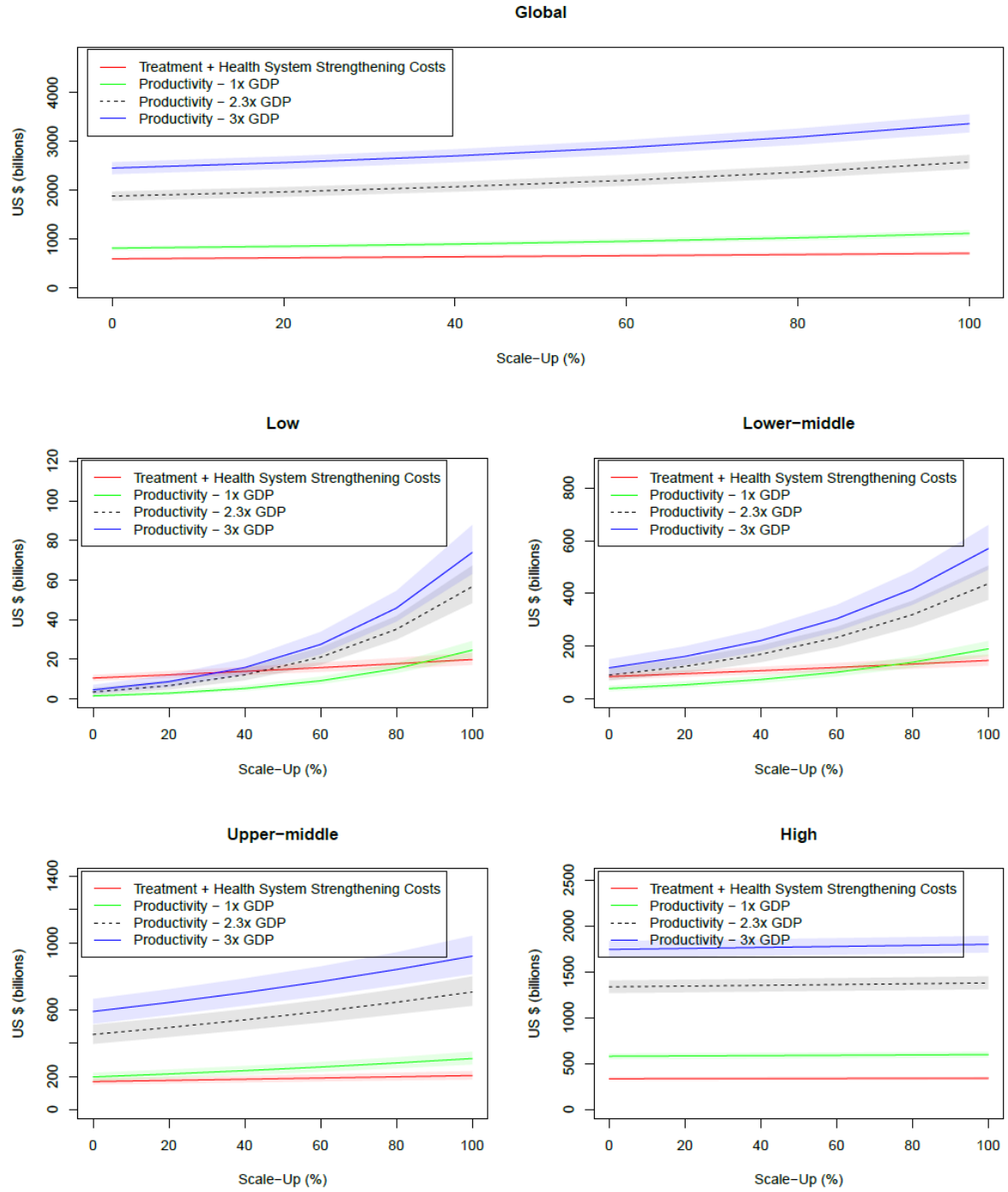
Region	Projected Lifetime Costs ($ billions), mean (95% UI) - Treatment with 20% health system strengthening costs					
	Scale-up, %					
	0%	20%	40%	60%	80%	100%
Globally	601.5 (573-632.7)	621.7 (592.4-654.1)	643.1 (611.6-676.6)	665.4 (631.9-700.3)	688.8 (653.2-725.5)	713.3 (675.7-752.1)
LIC	10.6 (9.2-12.1)	12.2 (10.6-14.1)	13.9 (12.2-16.1)	15.8 (13.7-18.3)	17.8 (15.4-20.7)	19.9 (17.2-23.3)
LMIC	85 (74.7-95.8)	95.8 (84.1-108.2)	107.3 (93.8-121.7)	119.5 (104.2-136.5)	132.5 (115.1-151.8)	146.2 (126.4-167.5)
UMIC	168.8 (152-186.6)	175.7 (158.2-194.6)	182.7 (164.3-202.6)	189.9 (170-211.5)	197.4 (175.7-221.5)	205 (181-231.5)
HIC	337.1 (318.6-355.8)	338.1 (319.5-356.9)	339.1 (320.5-357.9)	340.1 (321.5-359)	341.2 (322.5-359.9)	342.2 (323.4-360.9)

19. Appendix Table 10: Projected productivity gains (mean and 95%UI) at different scale up levels (global and by country income group) with additional 20% costs included for health system strengthening

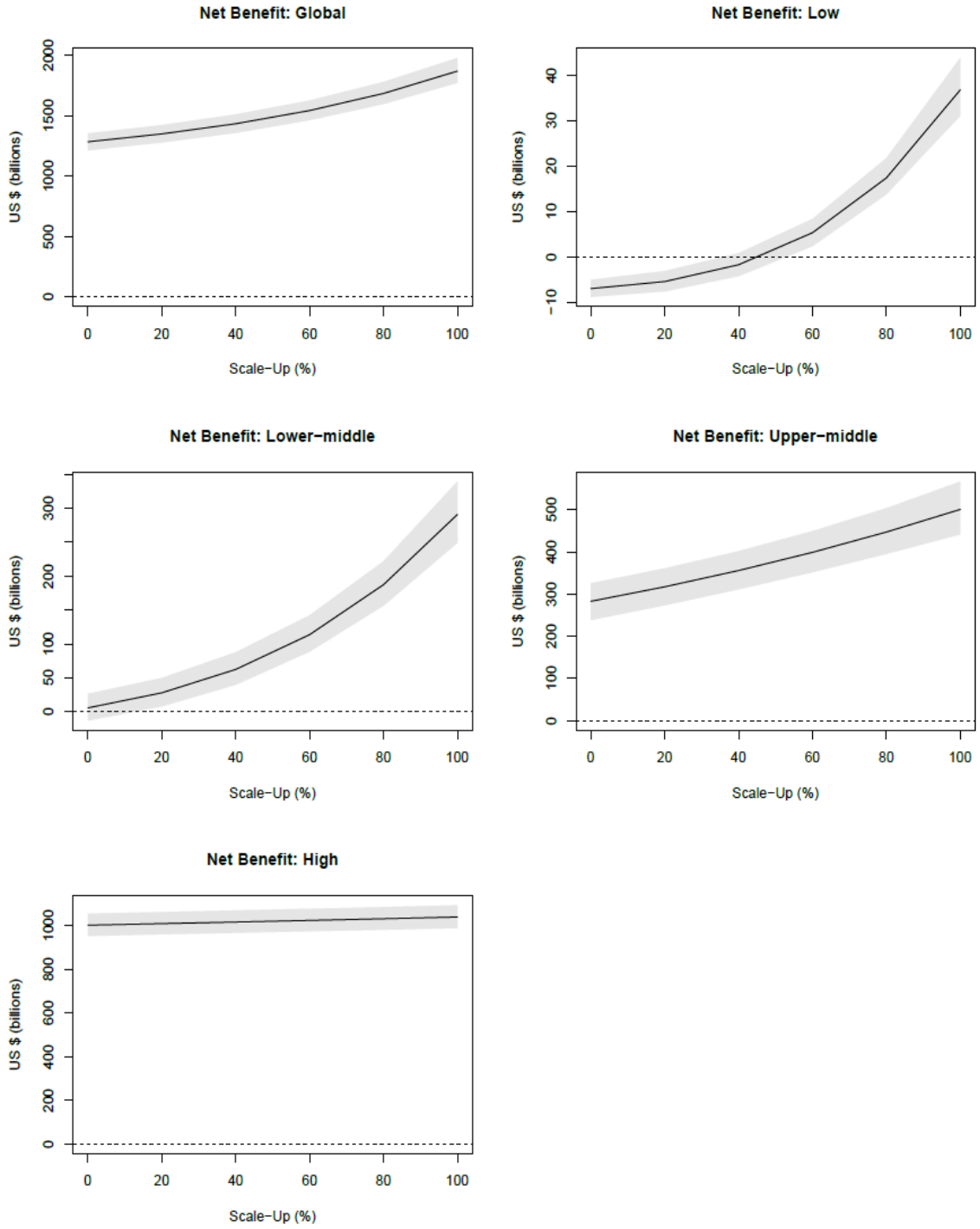
Income Group	Projected Net Return on Investment ($ billions), mean and 95% UI – Treatment with 20% health system strengthening costs					
	Scale-up, %					
	0%	20%	40%	60%	80%	100%
Globally						
Productivity - 1xGDP	217.8 (194-239.6)	234.8 (212-256.3)	259.3 (237.1-281.5)	294 (272.5-315.9)	342.3 (320.3-365.9)	408.7 (384.5-435.1)
Productivity - 2.3xGDP (base case)	1282.9 (1212.2-1352.9)	1348.3 (1277.1-1421.3)	1432.4 (1356.1-1509.7)	1541.2 (1461.7-1624.4)	1682.8 (1595.4-1778)	1867.2 (1770.5-1976.8)
Productivity - 3xGDP	1856.4 (1758-1955.8)	1947.8 (1844.3-2050.3)	2064 (1956.9-2171.9)	2212.8 (2099.7-2330.5)	2404.6 (2281.8-2540)	2652.6 (2516.7-2805.8)
LIC						
Productivity - 1xGDP	-9 (-10.6--7.6)	-9.3 (-11--7.7)	-8.7 (-10.5--7)	-6.6 (-8.3--5.1)	-2.5 (-4--1.4)	4.7 (3.4-6.2)
Productivity - 2.3xGDP (base case)	-7.1 (-8.9--5.1)	-5.5 (-7.7--3.2)	-1.8 (-4.3-0.8)	5.3 (2.3-8.3)	17.4 (13.8-21.7)	36.8 (31.1-43.9)
Productivity - 3xGDP	-6 (-8.1--3.6)	-3.5 (-6--0.6)	1.9 (-1.3-5.5)	11.7 (7.7-16.2)	28.1 (22.8-34.4)	54.1 (45.8-64.4)
LMIC						
Productivity - 1xGDP	-45.6 (-56.6--35.1)	-42 (-53.8--31)	-33.5 (-45.5--22.7)	-18.2 (-28.8--8.2)	6.6 (-1.9-15.3)	43.9 (35-53.4)
Productivity - 2.3xGDP (base case)	5.6 (-13.2-26.4)	27.8 (7.7-49.8)	62.4 (39.7-87.7)	113.6 (88.6-142.2)	187.4 (156.4-221.9)	290.9 (249.1-339.6)
Productivity - 3xGDP	33.2 (9.2-59.6)	65.5 (38.8-95.5)	114 (83-150.5)	184.6 (149-225.9)	284.7 (240.7-334.9)	424 (364.1-493.6)
UMIC						
Productivity - 1xGDP	27.6 (10.6-41)	38.7 (23.1-51.3)	51.5 (37.6-63.6)	66.2 (53.7-78)	82.9 (71.4-95.3)	101.9 (89.3-116.5)
Productivity - 2.3xGDP (base case)	283 (238.3-325.8)	317.4 (273.4-361.2)	356 (311.4-401.9)	399.1 (351.9-449.6)	447.3 (395.3-503.8)	500.9 (441.7-567)
Productivity - 3xGDP	420.5 (359.7-479.7)	467.5 (406.3-530)	519.9 (458.6-585.9)	578.4 (511.2-650)	643.5 (569.8-722.9)	715.7 (632.3-810.9)
HIC						
Productivity - 1xGDP	244.8	247.4	250	252.6	255.4	258.2

	232.7-258.6)	(235.1-261.3)	(237.7-264.1)	(240.3-266.7)	(243-269.3)	(245.8-272.2)
Productivity - 2.3xGDP (base case)	1001.4 (951.8-1053.7)	1008.5 (959.7-1061.3)	1015.8 (966.5-1068.9)	1023.2 (973.4-1076.5)	1030.8 (980.6-1084)	1038.6 (987.9-1092.5)
Productivity - 3xGDP	1408.8 (1339.2-1481.9)	1418.4 (1348.9-1492.4)	1428.2 (1357.9-1502.4)	1438.2 (1367-1513.1)	1448.4 (1376.9-1523.1)	1458.8 (1387.2-1533.5)

20. Appendix Figure 1: Sensitivity analysis: lifetime economic impact of comprehensive scale up - with 20% health system strengthening costs



21. Appendix Figure 2: Sensitivity analysis on net return on investment - with 20% health system strengthening costs



22. Addressing the Health Workforce Gap

Increasing anticipatory planning and scale-up of the workforce is a vital component of the national package for childhood cancer, and may provide a model for how specialty service workforce strategies can be contextualized and aligned with national health systems strengthening. The exact health workforce needs will vary depending on local burden of disease, current provider distribution and utilization, accessibility of alternative care settings, public demand and expectations, and at a systems level, organizational efficiency, health policies, regulations and standards, and technological and information systems capacity, as well as available financing.

In considering a potential national "reasonably achievable" target in LMICs for the most number of newly diagnosed pediatric cancer patients to be seen per year by one physician provider with specific training (leading to appropriate accreditation in the given country to clinically manage children with cancer), an initial reasonable target per consensus was 50 (approximately one new patient per week), with note of many caveats. Many provided current examples of in reality having more than 100 new children with cancer diagnosed per physician each year. Providers (physicians and nurses) for children with cancer in LMICs typically play many overlapping roles, often without the luxury of also having additional dedicated staff to attend to these roles as typically exist in HICs, including as: pharmacy technician, social worker, psychosocial counselor, palliative care provider, patient navigator, and fundraiser, among others. Differences in types and numbers of staff across shifts (morning/evening and

weekdays/weekends) are also noted to be common in many LMIC settings, affecting the role of the remaining team members. Worse, such ratios tended to be worse in more resource limited settings, where many have heavily fragmented health systems and more limited access to multidisciplinary care practice, translating to an even heavier burden for those providers in LMICs than those with similar ratios within strong health systems. The gap in workforce, including all the human elements required for the comprehensive care of the child with cancer in the entire continuum of care is significant, and a detailed analysis of the global needs and recommendations for addressing those were beyond the scope of the Delphi study.

Given the smaller numbers than many other pediatric chronic NCDs or adults cancers, strategic investments in childhood cancers' systems including in essential surgery and anatomic pathology where these are not already national priorities can demonstrate a model for scale-up, with early-wins that can in turn stimulate additional investments and donor interest for hospital-, network- and national-level developments in these integral services to benefit all patient populations, in the horizontal benefit framework described earlier. Given the context-specific variability of workforce demands, proposed strategies include setting progressive targets for workforce ratios based on local existing norms, as well as considering progressive percent reduction in the annual numbers of new patients safely managed per trained physician and progressively facilitating roles such as research and education to promote longer-term sustainability of the childhood cancer program. It is also important to contextualize metrics such as new patient-physician ratios while also considering potential disparities and access

concerns that may not be addressed even if these are improved, including attending to targeting increases overall in the annual number of patients effectively accessing cancer services across the country where appropriate.

Specialized training for the workforce dedicated to childhood cancer was strongly endorsed. Given that physician providers for children with cancer are not necessarily formally trained pediatric hematology-oncologists in many LMIC settings (including pediatricians that play valuable roles in many settings, and adult hematologists in the care of children with blood malignancies in a number of settings, including in some centers in Peru and in India), efforts for national workforce mapping should include local stakeholders' needs and expectations. Recommendations should reflect existing and achievable scenarios within the local context of undergraduate, graduate and continuing medical education, as well as professional licensure and specialization requirements, while being attentive to not alienate key provider groups. Close dialogue across the continuum of pediatric and adult, hematology and oncology providers, is essential, with in-country analyses and planning warranted for how continuity of care can best be promoted across settings, considering heterogeneous practices where care delivery may be divided by disease, discipline, and/or age (in some cases, with adult providers typically seeing all patients above age 14, as in India, or 12, as in Myanmar), or where pediatric providers may be expected to also care for adults (e.g. nurses in combined pediatric/adult cancer institutes, as in some settings in Armenia or in China).

Policies and provisions at a national and institutional level for specialized nurses who can be dedicated to childhood cancer (not rotating between services) were highly prioritized. Nurses should be given the opportunity for dedicated training, with competencies and professional development recognized, such that trained nurses can be retained and have a fulfilling career pathway as pediatric oncology nurses. Nurse educators should be an early investment, potentially with external/international support to start, but to be established as a local nurse educator program so that local/regional training can help increase skilled providers equipped to address the local patient burden and already familiarized with the care delivery context, and strengthen the workforce sustainably.[35] [36] As with physicians, remuneration for trained nurses should aim to adequately retain them in the public sector if possible, with appropriate incentives, retention and support mechanisms to be coordinated at a national level so that trained providers are appropriate distributed to facilitate patients' access, accounting for public/private and rural/urban disparities. Strategic public-private partnerships should also be considered where appropriate, and have successfully retained providers in Brazil and in different settings in Central America. Attention should also be paid to foster a conducive working environment, with administrative and information systems support, as well as accommodations for respite/work leave for professional development.[37]

23. Regional Collaboration Networks and Partnerships

Collaborative research through small consortia or large cooperative groups has contributed to advances experienced in paediatric oncology over the last decades.[38] [39]

International partnerships between institutions in high-income countries and LMICs that bring commitment from local governments, global health agencies, advocacy groups and local foundations, have helped to build paediatric oncology programmes in LMICs.[40]

These partnerships and regional networks include Indian Paediatric Oncology Group (InPOG) in the Indian sub-continent,[41] Central American Association of Pediatric Hematology and Oncology (AHOPCA), Grupo América Latina de Oncología Pediátrica (GALOP) and Consorcio Latinoamericano para Enfermedades (CLEHOP) in Central and South America, Groupe Franco-Africain d'oncologie Pédiatrique (GFAOP) and the Wilms tumor consortium in Africa, Pediatric Oncology East and Mediterranean Group (POEM) in the Eastern Mediterranean Region, VIVA-Asia in South East Asia and the China (acute lymphoblastic leukaemia) National ALL Group in China). These networks have offered new platforms for the design and conduct of clinical research focused on the epidemiologic, biologic, genetic, clinical, and psychosocial questions relevant to the advancement of local care, and the development of context-adapted treatment guidelines and interventions, and to guiding public health priorities.

The infrastructure, organizational culture, systems, and expertise developed through participation in cooperative clinical trials may have a favourable impact on patient care and outcomes.[42] Institutional and practitioner involvement with clinical trials helps to generate positive effects also on off study treatment through promoting familiarity with current knowledge on a given clinical issue, better monitoring of diagnosis and staging, compliance, deviations, and side effects.[43] Integrating collaborative research through the development of small consortia or regional cooperative groups may amplify the culture of higher standards and enhance research capacity in LMICs to improve outcomes of care for children with cancer.[44]

Established in 1998, AHOPCA has evolved as a successful model of paediatric oncology cooperative work and research in resource-limited settings. It currently includes the paediatric oncology programs of Central American countries, Dominican Republic, and Haiti.[45] Supported by institutions in North America and Europe, AHOPCA has grown to become a multidisciplinary cooperative group, with incorporation of nursing, surgery, pathology and laboratory medicine, nutrition, and psychosocial programmes to optimize treatments and foster the development of research capacity in abandonment, nutrition, nursing education, infection control, supportive care, and health related quality of life.

China provides an example of the coordinated efforts by multiple stakeholders to secure treatment for children with acute lymphoblastic leukaemia, where 10,000-12,000 children are diagnosed with the condition every year,[46] but only approximately

10% of the children with cancer received adequate treatment because of the lack of health insurance and the inability to pay.[47]

In 2004, a standardized, cost-efficient protocol was developed jointly by the Shanghai Children's Medical Center, the Beijing Children's Hospital, and St. Jude Children's Research Hospital to treat underprivileged children with low-risk and intermediate-risk acute lymphoblastic leukaemia with the support of a charitable foundation. In 2009, the effectiveness and the affordability (<$11,000 per patient) of the clinical trial were reported, [48]which drew the attention of the ministry of health of China which at that time, was developing a major health system reform, the New Rural Cooperative Medical Scheme, in which central and local governments provide health insurance to citizens with catastrophic diseases. In 2010, based on the success of the trial, childhood acute lymphoblastic leukaemia was selected as one the initial model diseases to test the new insurance model, with a financial package based on the same amount of the pilot clinical trial.[49] In the first year, access to treatment was provided to more than 7,000 children with low-risk or intermediate-risk acute lymphoblastic leukaemia whose families could not afford therapy. The insurance has since been extended to all children with acute lymphoblastic leukaemia, regardless of their disease risk.

In 2014 Shanghai Children's Medical Center undertook the initiative to develop the China National ALL Study Group. Twenty major hospitals and medical centers that covered 65% of the Chinese population participated. The China Children's Cancer Group ALL-2015 protocol was developed on the basis of the St Jude Total Therapy XV

study but modified per the treatment tolerance of Chinese patients. In 2014, the VIVA China Children's Cancer Foundation was formed to support state-of-the-art minimal residual disease measurements, data management, internal monitoring, external auditing, and data safety monitoring. Between November 2014 and September 2018, 5,225 patients were enrolled, and preliminary analyses report an estimated 3-year survival of 93.3%.[50]

24. Appendix References

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