

# Global childhood cancer survival estimates and priority-setting – a simulation-based analysis

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## Abstract

**Background:** Accurate childhood cancer survival estimates are critical for policy-makers and clinicians for priority-setting and planning decisions. However, observed survival estimates are lacking for many countries, and where available, wide variation in outcomes is reported. Understanding the barriers to optimizing survival can help improve childhood cancer outcomes. We aimed to provide estimates of global childhood cancer survival, accounting for the impact of multiple factors that influence cancer outcomes.

**Methods:** We developed a microsimulation model to simulate childhood cancer survival for 200 countries/territories worldwide, taking into account clinical and epidemiologic factors, including country-specific treatment variables, such as availability of chemotherapy/radiation/surgery. To ensure model results were consistent with reported survival data, we calibrated the model to estimates from the CONCORD 2 and 3 studies using an Approximate Bayesian Computation approach. We estimated five-year net survival for diagnosed childhood cancer cases in each country/territory and estimated potential survival gains if seven policy interventions focused on improving treatment availability and delivery were implemented in isolation or as packages.

**Findings:** Our model estimates that global five-year net childhood cancer survival is currently 37.4% (95% uncertainty interval [UI] 34.7%-39.8%), with large variation by region, ranging from 8.1% (95% UI 4.4%-13.7%) in Eastern Africa to 83.0% (95% UI 81.6%-84.4%) in North America. Among the seven policy interventions modeled, each individually provided limited gains, increasing global five-year net survival to between 38.4% and 44.6%. When bundled into packages of interventions that either improved service delivery or expanded treatment access, five-year net survival increased to 50.2% (95% UI 47.3%-53.0%) and 54.1% (95% UI 50.1%-58.5%), respectively. A comprehensive systems approach consisting of all policy interventions yielded super-additive gains with global five-year net survival of 53.6% (95% UI 51.5%-55.6%) at 50% scale-up and 80.8% (95% UI 79.5%-82.1%) at full implementation.

**Interpretation:** Childhood cancer survival varies widely by region, with especially poor survival in Africa. While expanding access to treatment (chemotherapy/radiation/surgery) and addressing financial toxicity are essential, investments that improve the quality of care, at both the health system and facility-level, are needed to improve childhood cancer outcomes globally.

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**Research in context***Evidence before this study*

Recent population-based observed data of five-year net childhood cancer survival (ages 0-14 years) for acute lymphoblastic leukemia, lymphomas, and brain tumors from 322 cancer registries globally are provided by the CONCORD-3 study. The CONCORD-2 study previously provided similar population-based five-year net survival estimates for both acute lymphoblastic leukemia and acute myeloid leukemia. We searched PubMed for studies on global childhood cancer survival using the search terms “childhood cancer”, “survival”, and “global” on Feb 28, 2019, without language or publication date restrictions. We found no other estimates of global childhood cancer survival. While limited observed data from low- and lower middle-income countries are available, it is clear that reported survival varies considerably by region.

*Added value of this study*

With major geographic and histologic gaps in the observed five-year net survival statistics, there are no global estimates of how many children survive cancer. This study provides, to our knowledge, the first estimate of global childhood cancer survival, based on a simulation model for 200 countries and territories and 48 cancer diagnoses. We provide global, regional, and country-level estimates of five-year net cancer survival for all International Classification of Childhood Cancer (Third edition) subgroups and estimate the potential impact of various policy scenarios to help guide priority-setting efforts aimed at improving survival.

*Implications of all the available evidence*

The estimated gap in childhood cancer five-year net survival between high-income and low-income countries is over 70 percentage points. Thus, the most important prognostic factor for whether a child will survive cancer is where he or she lives. Our model-based findings suggest that while improving the availability of treatments and mitigating abandonment are necessary interventions to achieve high survival, they are insufficient if implemented alone. Concurrent improvements in health systems to achieve better quality of care will also be needed to substantially improve childhood cancer survival worldwide.

## 1 **Background**

2 Advances in treatment and supportive care over the past six decades have led to increases in five-year net  
3 survival for children diagnosed with cancer (ages 0-14 years) from nearly 0% to 80% in high-income  
4 countries (HIC) like Great Britain.<sup>1</sup> While it is generally known that children who develop cancer in low-  
5 income and middle-income countries (LMIC) have not experienced these gains,<sup>2</sup> the magnitude of the  
6 overall survival gap has not been quantified. The best available data, as observed in global population-  
7 based cancer registries, was recently published by the CONCORD study for a subset of childhood cancers:  
8 acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), lymphomas (as a group), and brain  
9 tumors.<sup>3-5</sup>

10 Highlighting the survival gap, CONCORD estimates of five-year net survival for ALL, the most common  
11 childhood cancer, range from less than 10% to over 90%.<sup>5</sup> However, due to the paucity of cancer registry  
12 data from resource-limited settings, only a small subset of CONCORD-3 data (7/322 registries) are from low-  
13 income and lower middle-income countries. Disparities in treatment access,<sup>6</sup> quality,<sup>2</sup> and financial toxicity<sup>7</sup>  
14 all contribute to the large global variations in childhood cancer outcomes.<sup>2-5,8,9</sup>

15 In order to quantify the survival gap and identify opportunities for intervention, we developed a simulation  
16 model that synthesizes clinical, epidemiologic, and health system data to estimate country-specific  
17 childhood cancer survival. Using the model, we estimate the potential survival gains that could be achieved  
18 by addressing barriers to successful treatment, such as availability of treatment modalities and quality of  
19 care. These estimates will be used to inform the Lancet Oncology Commission on Sustainable Paediatric  
20 Cancer Care, and can assist decision-makers as they prioritize policy interventions that have the potential to  
21 improve survival and reduce the number of deaths from childhood cancer.

22

## 23 **Methods**

24 *Study design and data sources*

25 We developed the Global Childhood Cancer (GCC) microsimulation model to simulate childhood cancer  
26 incidence<sup>10</sup> and survival for 200 countries/territories for 48 cancer subcategories defined by the  
27 International Classification of Childhood Cancer, Third edition (ICCC).<sup>11</sup> The survival module of the GCC  
28 model, described here, simulates the clinical course of childhood cancer from diagnosis to five years post-  
29 diagnosis, taking into account treatment availability, completion, and quality.

30 We fit the model to observed data by calibrating our model parameters so that our predicted survival  
31 estimates were consistent with population-based survival estimates for each cancer and country produced  
32 for this study by the CONCORD programme for the global surveillance of cancer survival.<sup>3-5</sup> We then used a  
33 hierarchical approach to infer parameters for countries/diagnoses for which no survival data are available.  
34 Using the calibrated model, we estimated current childhood cancer survival for all countries and projected  
35 survival gains from expanding access to each treatment modality and improving quality of care. We briefly  
36 describe our methods below and provide full details in the appendix.

37

### 38 *Procedures*

39 We developed a conceptual treatment cascade to account for multiple factors that impact cancer survival  
40 from the point of diagnosis to completion of therapy (Figure 1). We assume that a subset of children  
41 diagnosed with cancer will achieve five-year survival based on the availability, completion, and quality of  
42 treatment. If any required treatment modalities (chemotherapy/radiation/surgery) are unavailable, we  
43 assume the child will not survive. We also include a risk of abandoning treatment due to financial toxicity  
44 (i.e. financial distress related to the cost of medical care). Lastly, we assume that the quality of care, which  
45 depends on a functioning health system with supportive services (e.g. nursing standards, integrated referral  
46 and record-keeping) and facility-level activities (e.g. infection control, nutritional support), influences  
47 survival. We synthesized information from multiple sources to inform country-specific estimates for each  
48 step of the cascade (Table 1).

49 We used published estimates of diagnosed cancer cases by country and ICCC category from the GCC  
50 Incidence module.<sup>10</sup> These estimates, which take into account geographic variation in cancer incidence and  
51 country-specific factors such as demographic trends and health system barriers, are consistent with  
52 reported rates of diagnosed cancers in the International Incidence of Childhood Cancer, Volume III (IICC-  
53 3).<sup>12</sup> The GCC Incidence module also provides estimates for countries without registries.

54 For each ICCC diagnosis, we used expert opinion (based on the experience of clinicians with expertise in  
55 cancer care in LMIC and specializing in different cancer types (e.g. hematologic cancers, germ cell tumours,  
56 solid tumors, etc.)) to specify which treatment components (chemotherapy/radiation/surgical specialties)  
57 were necessary for survival. Because stage at diagnosis (which determines necessary treatments for some  
58 cancers) is not routinely collected in most cancer registries, as a proxy we estimated the probability of  
59 requiring chemotherapy/radiation based on reported treatment numbers from the Surveillance,  
60 Epidemiology, and End Results (SEER) program in the US. We also took into account heterogeneity in  
61 treatment needs for diagnoses for which a small proportion of patients require chemotherapy/radiation  
62 (Appendix pg 3-5).

63 To account for the curability of different cancer types we estimated maximum achievable survival  
64 probabilities using data from SEER 2010-2014 to inform the general level and variation of survival by  
65 diagnosis.<sup>13</sup> Because maximum achievable survival in the model assumes availability of all necessary  
66 treatment modalities, no abandonment, and optimal quality of care, we inflated the reported SEER  
67 estimates to account for the possibility of non-optimal service delivery in the US (Appendix pg 6-7).

68 As calibration targets we obtained country-specific survival estimates for 10 morphology groups from  
69 CONCORD (Appendix pg 8).<sup>3,5</sup> For three brain diagnoses (Astrocytoma, Embryonal, and Other), the  
70 CONCORD estimates of survival in the US were substantially higher than those reported in SEER.  
71 Specifically, SEER estimates of five-year survival were 80%, 68·4%, and 58·9%, respectively, compared to  
72 CONCORD estimates of 82·7%, 69·4%, and 96·9%. We therefore adjusted our prior probability distributions  
73 of maximum achievable survival for these groups to be consistent with the CONCORD estimates.

74 We used published country-specific estimates to inform the prior probability distributions of treatment  
75 variables in the model (Table 1). We estimated priors of the availability of chemotherapy agents based on  
76 reported data from a global survey of paediatric oncologists (Appendix pg 10-11).<sup>6</sup> Estimates of  
77 radiotherapy availability were based on coverage estimates from the Lancet Radiotherapy Commission  
78 (Appendix pg 12-13).<sup>14</sup>

79 Data for surgical specialties were drawn from multiple sources. For general surgery, we used estimates  
80 from a modeling study of the Lancet Surgery Commission (Appendix pg 14-15).<sup>15</sup> For neurosurgery, we  
81 used data on neurosurgeon density from the World Federation of Neurosurgical Societies (Appendix pg 16-  
82 17).<sup>16</sup> Finally, for ophthalmic surgery we used data on the density of ophthalmologists from the World  
83 Council of Ophthalmologists (Appendix 18-19).<sup>17</sup> When sampling country-specific surgery probabilities we  
84 assumed that general surgery was the most available type of surgery, followed by ophthalmic surgery, with  
85 neurosurgery the least likely to be available.

86 To estimate probabilities of treatment abandonment we used published data from a global survey of  
87 paediatric oncologists (Appendix pg 20-21).<sup>7</sup> We assumed that only patients requiring chemotherapy  
88 and/or radiation (thus excluding the few surgery-only groups) were at risk of abandoning treatment due to  
89 the prolonged nature of these modalities.

90 Lastly, we included a parameter for ‘quality of care’, which has been defined as the “degree to which health  
91 services for individuals and populations increase the likelihood of desired health outcomes and are  
92 consistent with current professional knowledge”.<sup>18</sup> This parameter allows us to account for health system  
93 and facility-level factors, capturing residual differences in survival not explained by treatment access or  
94 abandonment (Appendix pg 22-23).

95 We used a modified Bayesian hierarchical framework<sup>19</sup> with three levels (World Bank income group, region,  
96 country) to synthesize all available estimates to generate prior probability distributions for all parameters  
97 described above. This approach allowed us to regularize the reported data and estimate priors for countries

98 with no data (see Appendix pg 24 for more details). These priors were used as initial sampling distributions  
99 during calibration.

100

### 101 *Outcomes*

102 For each country and territory, we modeled the effect of treatment variables on childhood cancer  
103 outcomes and estimated five-year net survival for each ICCO diagnosis. We also estimated what five-year  
104 net survival would be under various policy interventions aimed at improving survival. We report the mean  
105 and 95% uncertainty intervals (UI) calculated as the 2.5 and 97.5 percentiles of our simulation results.

106

### 107 *Statistical analysis*

108 Calibration involves comparing model predictions with observed data to identify parameter values that  
109 achieve a good fit.<sup>20</sup> We briefly describe this process here (see Appendix pg 25-56 for full details).

110 We calibrated to CONCORD country/diagnosis-specific five-year net survival estimates, providing 407

111 targets for model calibration. CONCORD-3 estimates of AML survival were reserved as a test set to assess

112 model validity and were not used in calibration. We used an Approximate Bayesian Computation (ABC)

113 approach to fit each country with CONCORD data (65 countries).<sup>21</sup> For each sampled parameter set we

114 simulated five-year net survival for the number of cancer cases reported for each CONCORD estimate. If the

115 simulated survival probability was within one percentage point of the reported survival estimate we

116 accepted the sampled parameters as a draw from the posterior distribution as per the ABC algorithm.<sup>21</sup> If a

117 parameter set was not accepted after one million iterations, the best-fitting parameter set for the country

118 was used. For computational efficiency we used simulated annealing<sup>22</sup> to direct the sampling.

119 For each country, we first tried to fit the model using overall probabilities of chemotherapy availability and

120 treatment abandonment across cancer diagnoses. If the model was unable to fit after 100,000 iterations we

121 allowed these probabilities to vary by diagnosis (see Appendix pg 10-11 and pg 20-21). Automatically

122 introducing flexibility in this way allowed us to fit parsimonious models where possible, while accounting



123 for variability in the availability and efficacy of diagnosis-specific chemotherapy regimens and  
124 abandonment if needed.

125 After fitting each country with calibration targets, we sampled from the posteriors of the hierarchical  
126 models to generate parameter values for countries with no CONCORD estimates. This approach allowed us  
127 to appropriately reflect country-specific parameter uncertainty while 'borrowing' information from similar  
128 countries (i.e. region and income group) when data were not available, similar to approaches used by the  
129 Global Burden of Disease and GLOBOCAN for data imputation.<sup>8,9</sup> This set of parameter values for all  
130 countries and cancers comprises a completed parameter set.

131 We repeated this process to generate 1,000 different parameter sets and scored each set based on how  
132 well the model predictions matched the survival targets (based on the distance squared), with each survival  
133 target weighted inversely proportional to the width of its confidence interval. We selected the top 100 sets  
134 for use in the final model to account for parameter uncertainty.

135 As a posterior predictive check<sup>19</sup> we compared our predicted survival from the final model to the reported  
136 survival estimates from CONCORD. Nearly all (99.0%) of our prediction intervals (i.e. 95% UI) overlapped  
137 with the 95% CIs of the CONCORD data, and our prediction intervals contained the reported point estimate  
138 87.2% of the time. Our mean predicted survival also fell within the CONCORD 95% CIs 86.4% of the time  
139 (Appendix pg 28-47).

140 As a further validity check we compared our predictions of AML survival to estimates for 48 countries from  
141 CONCORD-3. These estimates were not used to calibrate the model, so they can serve as an external  
142 validity check of our model predictions. Our prediction intervals (95% UI) overlapped with the CONCORD-3  
143 AML 95% CIs 97.9% of the time, contained the reported point estimate (i.e. coverage probability) 81.3% of  
144 time, and our mean predicted survival fell within the 95% CIs 77.0% of the time (Appendix pg 54-55).

145 Using the best-fitting 100 parameter sets we estimated five-year net cancer survival for each diagnosis. We  
146 ran 1,000 simulations from 2015 to 2019 to estimate survival over this period, in each iteration sampling a

147 good-fitting parameter set to account for parameter (second-order) uncertainty and simulating the number  
148 of diagnosed cases<sup>10</sup> and individual-level survival to account for first-order uncertainty.<sup>23</sup>

149 To explore the impact of treatment barriers (treatment availability, abandonment, and quality of care), we  
150 simulated counterfactual interventions in which we replaced the relevant parameter for each country with  
151 the mean estimated parameter among high income countries (Table 2). We also simulated packages of  
152 policy interventions to explore the relative impact of expanding treatment access vs. improving service  
153 delivery, and a comprehensive approach addressing all treatment barriers. We estimated five-year net  
154 childhood cancer survival for each scenario. The GCC model was coded in Java (version 1.8.0), and statistical  
155 analyses were performed in R (version 3.3.1).

156

#### 157 *Role of the funding source*

158 The funders of the study had no role in study design, data collection, data analysis, data interpretation, or  
159 writing of the report. All authors had full access to all the data used in the study. The corresponding author  
160 had final responsibility for the decision to submit for publication.

161

## 162 **Results**

163 We estimate that globally, for children diagnosed in 2015, five-year net survival for all cancers combined  
164 was 37.4% (95% UI 34.7%–39.8%), with large variation by region, ranging from 8.1% (95% UI 4.4%–13.7%)  
165 in Eastern Africa to 83.0% (95% UI 81.6%–84.4%) in North America (Figure 2). Detailed survival estimates by  
166 diagnosis and continent for all 48 ICCC categories are presented in Figure 3. These estimates reveal large  
167 variation within cancer-specific survival, with survival gaps of over 80 percentage points for cancers such as  
168 Hodgkin lymphoma and retinoblastoma that have high survival in North America but very poor survival in  
169 Africa. See Appendix pg 57-257 for complete country-/diagnosis-specific survival estimates.

170 We find that among individual policy interventions, efforts to improve the quality of care could yield the  
171 largest potential survival gains globally (five-year net survival of 44.6% [95% UI 41.7%–47.4%], an increase of

172 7.2%), followed by expanding access to general surgery (42.7% [95% UI 39.9%-45.6%], 5.3% increase) and  
173 chemotherapy (41.9% [95% UI 38.9%-45.0%], 4.5% increase) (Table 3). This general pattern is similar across  
174 most regions of the world.

175 Looking at policy intervention packages, we find that increasing the availability of all treatments to the level  
176 of HIC has a significant, though still relatively modest effect on global five-year net survival (54.1% [95% UI  
177 50.1%-58.5%]). Similarly, improving service delivery (i.e. simultaneously improving quality of care and  
178 reducing abandonment) yields important survival gains, but to a lesser extent (50.2% [95% UI 47.3%-  
179 53.0%]). We see however that improving both treatment access and service delivery has a super-additive  
180 effect. For example, closing the gap with HIC for all components by 50% is predicted to achieve similar or  
181 larger gains in global five-year net survival (53.6% [95% UI 51.5%-55.6%]) compared to 100% scale-up of  
182 treatment access or service delivery packages separately (Table 3). Full implementation of all interventions  
183 is estimated to increase global five-year net survival to 80.8% (95% UI 79.5%-82.1%).

184

## 185 **Discussion**

186 Using rigorous statistical and computational methods to synthesize estimates from multiple sources of  
187 data, we developed a model of childhood cancer survival for 200 countries/territories worldwide. We find  
188 that childhood cancer survival varies widely by country due to substantial differences in access to  
189 multidisciplinary treatment modalities, abandonment rates, and quality of care. As a result, our findings  
190 suggest that five-year net survival for all childhood cancers combined varies by up to 75 percentage points  
191 between World Health Organization (WHO) sub-regions (Table 3). Furthermore, as net survival only  
192 considers deaths from cancer, the gap in total survival is likely even larger given higher risks of competing  
193 mortality in LMIC. Although genetic variations are known to impact survival,<sup>24,25</sup> the most important  
194 prognostic factor today for whether a child diagnosed with cancer will survive is not related to cancer  
195 biology, but is instead the country where they receive treatment.

196 Beyond their importance for policy-making and informing health investment decisions by countries and  
197 development agencies, these estimates can provide a baseline assessment to help guide efforts to improve  
198 childhood cancer policies and those aimed at building stronger health systems. For example, the WHO  
199 Global Initiative for Childhood Cancer, announced in September 2018,<sup>26</sup> aims to increase global childhood  
200 cancer survival to 60% by 2030, as measured by six tracer cancer subtypes: ALL, Hodgkin lymphoma, Burkitt  
201 lymphoma, retinoblastoma, nephroblastoma, and low-grade gliomas. Our estimates of five-year net  
202 survival for ALL (56.1%) and Hodgkin lymphoma (44.6%) suggest moderate improvement is required for  
203 these cancers to achieve 60% survival. However, our survival estimates for the other cancers are much  
204 lower, with retinoblastoma, Burkitt, and nephroblastoma all around 25% (Figure 3). (It is not possible to  
205 estimate survival for low-grade gliomas with the current ICCC categories.)

206 In contrast, we estimate five-year net survival for these cancers to be 90% or higher in North America,  
207 highlighting both the opportunity to substantially increase survival and the challenge of achieving these  
208 gains in a relatively short period of time. However, given that nearly half of children with cancer may fail to  
209 be diagnosed in LMIC,<sup>10</sup> the true overall survival rate is likely even lower. Therefore, in addition to  
210 improving treatment, increased efforts to identify all cases in a population and develop stronger health  
211 systems with appropriate support services will also be needed to improve survival for all children with  
212 cancer.

213 To address the stark global disparities in childhood cancer survival, determining which policy interventions  
214 are likely to be most effective is a necessary first step. Individually, our model predicts that single policy  
215 interventions alone will yield limited survival gains. While efforts to address any one problem, such as  
216 financial toxicity, are necessary to achieve high survival, they are insufficient if implemented alone. In  
217 particular, we find that while reducing abandonment results in more children completing therapy, overall  
218 survival does not significantly improve due to interdependencies in the availability of treatment modalities  
219 and quality of care. Although abandonment represents an important actionable opportunity, ensuring

220 patient retention and completion of therapy is inefficient if the quality of care is not also improved to  
221 reduce treatment-related toxicity.

222 Our findings instead highlight the importance of complex interdependencies in childhood cancer treatment.

223 We find that comprehensive packages of policy interventions that improve both treatment access and  
224 service delivery yield synergistic survival gains. Thus, a key message is that a systems approach with  
225 packages of policy interventions including investments to expand access to multidisciplinary care, reduce  
226 financial toxicity, and improve service delivery are necessary to substantially improve cancer survival. In a  
227 follow-up analysis we are estimating the return on investment of implementing such a comprehensive  
228 approach, taking into account the costs of health system strengthening to improve care for children with  
229 cancer.

230 Beyond the interdependence of policy interventions, the model also highlights the importance that quality  
231 of care plays in improving childhood cancer outcomes. These findings are not unique to paediatric cancer,  
232 as the importance of quality is echoed in results from other areas of global health as well. For example, a  
233 conditional cash-transfer program incentivizing facility childbirth in India succeeded in substantially  
234 expanding access to healthcare, but failed to reduce maternal mortality due to a lack of focus on quality.<sup>27</sup>  
235 Similarly, improving childhood cancer outcomes worldwide will require paying attention to what happens  
236 once children reach healthcare facilities, with investments to measure and improve healthcare quality in  
237 addition to expanding access.<sup>28</sup>

238 The widespread impact of quality, from the patient level to the health system means that a broad range of  
239 initiatives is needed. For example, at the facility level, supportive care-related interventions (e.g. infection  
240 control and nutritional programs) designed to reduce death due to comorbidities are critical to improve  
241 service delivery and safety. Although generic guidelines promoting the importance of supportive care  
242 measures have been published,<sup>29</sup> specific quality improvement initiatives that reflect the local context need  
243 to be designed and evaluated. Improving the quality of care also requires higher-level improvements to the  
244 overall health system (e.g. workforce planning and efficient referral patterns). A focus on quality at all levels

245 of the health system is thus needed to achieve integrated care that is person-centered and responsive to  
246 the patient's needs.

247

#### 248 *Limitations*

249 While our modeling approach allows us to synthesize data from multiple sources in a way that is consistent  
250 with data on treatment availability and reported survival, there are a number of limitations due to the  
251 assumptions needed for model development. First, much of our data is based on cross-sectional surveys of  
252 treatment access and abandonment that may provide an incomplete snapshot of the reality on the ground.  
253 For example, our prior probabilities (i.e. pre-calibration) of abandonment are based on survey data which  
254 reported estimates for ALL only,<sup>7</sup> and the survey data used to inform chemotherapy priors may not be  
255 representative of the respondents' countries as a whole. However, our approach allowed us to account for  
256 uncertainty around all model parameters, as well as their joint distribution. Our 95% uncertainty intervals  
257 thus reflect the sensitivity of our results to different parameter estimates. However, it should be noted that  
258 while these intervals capture the statistical uncertainty around the model parameters and calibration  
259 targets, they do not include uncertainty due to other factors, such as our modelling assumptions and  
260 potential data quality issues in the calibration targets used to fit the model.

261 Second, although we used hierarchical models to incorporate all available observed data, the paucity of  
262 registries in LMIC and small sample sizes in some regions may have affected our results, and contribute to  
263 the wide uncertainty intervals we report for some cancers and countries. For example, CONCORD survival  
264 estimates were only available for two countries in sub-Saharan Africa (Nigeria and Lesotho), and then only  
265 for ALL.

266 Third, due to lack of data we used a single quality parameter per country as a proxy for many factors  
267 related to service delivery. In some countries this constraint meant it was not possible to fit all calibration  
268 targets. However, our approach allows us to refine and update our model as more specific data become  
269 available. While abstract, our estimates of quality are similar to other published estimates and are highly

270 correlated ( $r=0.83$ ) with the Global Burden of Disease Healthcare Access and Quality Index (HAQI)  
271 (Appendix pg 56).<sup>30</sup> Given that our quality parameters were inferred exclusively by model calibration this  
272 builds confidence in the convergent validity of our estimates.

273 Lastly, while calibration allowed us to align our model results with observed survival and induce appropriate  
274 covariance between model parameters, due to lack of data we assumed that the availability of each  
275 treatment modality was independent for each individual patient. In the future, facility-level data would  
276 help to refine this assumption and account for correlation between the availability of treatment options for  
277 a given patient. In addition, these types of data could also help inform more specific quality measures to  
278 include in the model to track progress more precisely.

279 Notwithstanding these limitations, using a model-based approach, we provide, to our knowledge, the first  
280 global estimate of childhood cancer survival and find large disparities in five-year net survival as a result of  
281 substantial differences in access to multidisciplinary treatment modalities, abandonment rates, and quality  
282 of care. Our findings suggest that while increasing access to treatment is necessary to achieve high survival,  
283 it is not sufficient. A comprehensive set of policy interventions, including expanding treatment access,  
284 reducing abandonment, and improving quality of care in health systems are needed to reduce the large  
285 disparities in childhood cancer survival and substantially reduce childhood cancer deaths worldwide.

## Contributors

ZJW, JMY, NB, ALF, and RA designed the study and acquired the data. FG provided insight on morphology groupings and additional survival estimates from the CONCORD programme. ZJW performed the analyses. All authors interpreted the results and contributed to the writing of the report.

## Declaration of interests

We declare no competing interests.

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Table 1: Overview of GCC Survival Module country-specific data sources

<b>Model Parameter</b>	<b>Data Source</b>	<b># Model Countries Reported</b>	<b>Reference</b>
<i>Cancer Diagnosis</i>			
Diagnosed cancer cases	Estimated annual diagnosed cases by ICCC subgroup	200	GCC Incidence Module <sup>10</sup>
<i>Cancer Survival</i>			
Necessary treatment components	Expert opinion; SEER estimates of chemotherapy/radiation used as proxy for cancer stage	1 (US)	SEER <sup>13</sup> (Appendix pg 3-5)
Maximum achievable survival	SEER 2010-2014 five-year relative survival used as initial proxy	1 (US)	SEER <sup>13</sup> (Appendix pg 6-7)
Population-based survival	Five-year net survival by country, derived from cancer registry data	10-64 (varies by diagnosis)	CONCORD <sup>3,5</sup> (Appendix pg 8)
<i>Cancer Treatment</i>			
Chemotherapy availability	Reported availability of chemotherapy	94	Published survey data <sup>6</sup> (Appendix pg 10-11)
Radiation availability	Radiotherapy coverage	173	Lancet Radiotherapy Commission <sup>14</sup> (Appendix pg 12-13)
Surgery availability	Availability of general surgery	184	Lancet Global Surgery Commission <sup>15</sup> (Appendix pg 14-15)
	Neurosurgeon density	192	World Federation of Neurosurgical Societies <sup>16</sup> (Appendix pg 16-17)
	Ophthalmologist density	192	International Council of Ophthalmology <sup>17</sup> (Appendix pg 18-19)
Treatment abandonment	Probability of treatment abandonment	98	Published survey data <sup>7</sup> (Appendix pg 20-21)

Table 2: Policy Intervention Scenarios

<b>Scenario Name</b>	<b>Description of Policy Intervention</b>
Baseline	(No change from baseline)
<i>Individual Policy Intervention</i>	
Chemotherapy	Increase availability of chemotherapy to mean of HIC
Radiation	Increase availability of radiation to mean of HIC
General Surgery	Increase availability of general surgery to mean of HIC
Neurosurgery	Increase availability of neurosurgery to mean of HIC
Ophthalmology	Increase availability of ophthalmic surgery for Retinoblastoma to mean of HIC
Abandonment	Reduce treatment abandonment to mean of HIC
Quality of Care	Improve quality of care to mean of HIC
<i>Packages of Policy Interventions</i>	
Expand Treatment Access	Increase availability of all treatment modalities (chemotherapy, radiation, surgery and surgical subspecialties) to mean of HIC
Improve Service Delivery	Improve quality of care while reducing abandonment rates to mean of HIC
Comprehensive – 50%	Expand treatment access and improve service delivery to close the gap with mean of HIC by 50%
Comprehensive – 100%	Expand treatment access and improve service delivery to close the gap with mean of HIC by 100%

HIC = High Income Countries

Table 3: Estimated Childhood Cancer Five-Year Net Survival 2015-2019 (%) Under Various Policy Interventions\*

Area	Baseline	Single Intervention - Treatment Access					Single Intervention - Service Delivery		Intervention Packages			
		Chemotherapy	Radiation	General Surgery	Neuro-surgery	Ophthalmic Surgery	Abandonment	Quality of Care	Expand Treatment Access	Improve Service Delivery	Comprehensive - 50%+	Comprehensive - 100%+
<b>GLOBAL</b>	<b>37.4</b> <b>(34.7-39.8)</b>	<b>41.9</b> <b>(38.9-45.0)</b>	<b>39.1</b> <b>(36.4-41.5)</b>	<b>42.7</b> <b>(39.9-45.6)</b>	<b>39.0</b> <b>(36.3-41.6)</b>	<b>38.4</b> <b>(35.8-40.9)</b>	<b>41.1</b> <b>(37.8-44.4)</b>	<b>44.6</b> <b>(41.7-47.4)</b>	<b>54.1</b> <b>(50.1-58.5)</b>	<b>50.2</b> <b>(47.3-53.0)</b>	<b>53.6</b> <b>(51.5-55.6)</b>	<b>80.8</b> <b>(79.5-82.1)</b>
Low income	7.4 (5.0-10.7)	10.0 (6.6-14.5)	9.4 (6.4-13.4)	15.5 (10.8-20.6)	7.7 (5.2-11.1)	8.6 (5.9-12.1)	12.2 (8.7-16.5)	14.4 (11.0-18.2)	26.5 (18.3-35.4)	23.9 (20.0-27.8)	29.4 (25.8-33.4)	80.6 (77.2-83.3)
Lower middle income	24.0 (19.5-29.1)	29.2 (23.4-34.3)	26.1 (21.1-31.6)	31.9 (26.2-38.2)	26.0 (21.1-31.5)	25.5 (20.9-30.8)	28.5 (22.6-34.8)	33.6 (28.7-38.3)	46.5 (38.0-53.9)	40.8 (36.7-45.3)	45.4 (41.7-49.2)	80.6 (78.9-82.1)
Upper middle income	55.5 (51.5-58.9)	61.5 (55.6-67.1)	56.9 (52.8-60.5)	57.4 (54.1-60.6)	57.5 (54.0-60.4)	55.9 (52.1-59.2)	58.4 (53.7-63.1)	61.9 (55.9-68.1)	68.2 (61.7-73.5)	65.2 (59.5-71.5)	66.9 (64.4-69.1)	80.2 (78.8-81.6)
High income	79.8 (78.7-80.8)	80.6 (79.6-81.7)	80.0 (78.9-81.0)	80.2 (79.2-81.3)	80.3 (79.2-81.3)	79.9 (78.8-80.9)	80.4 (79.4-81.5)	80.2 (79.2-81.3)	81.7 (80.7-82.8)	80.9 (79.9-81.9)	81.3 (80.3-82.4)	82.9 (82.0-83.9)
<b>Africa</b>	<b>11.6</b> <b>(8.7-14.8)</b>	<b>14.1</b> <b>(10.5-18.1)</b>	<b>13.4</b> <b>(10.1-17.1)</b>	<b>19.0</b> <b>(13.9-25.1)</b>	<b>12.0</b> <b>(9.0-15.4)</b>	<b>13.1</b> <b>(9.8-16.9)</b>	<b>16.2</b> <b>(12.0-21.4)</b>	<b>21.0</b> <b>(18.0-24.5)</b>	<b>29.0</b> <b>(21.4-37.6)</b>	<b>30.4</b> <b>(26.8-34.0)</b>	<b>33.7</b> <b>(30.2-37.4)</b>	<b>80.9</b> <b>(77.9-83.5)</b>
Eastern Africa	8.1 (4.4-13.7)	10.5 (5.5-17.5)	10.7 (5.9-18.0)	15.3 (8.7-23.7)	8.3 (4.6-14.1)	8.8 (4.9-14.7)	13.0 (7.5-19.6)	15.4 (11.0-20.8)	26.3 (14.9-41.9)	25.1 (19.6-30.8)	29.7 (24.5-36.0)	80.2 (75.5-83.4)
Southern Africa	19.2 (11.9-26.1)	21.7 (13.9-30.1)	22.3 (14.6-30.5)	22.5 (14.6-31.4)	20.4 (12.8-27.6)	20.8 (13.2-28.2)	23.2 (15.0-31.0)	29.4 (24.8-34.1)	34.8 (24.3-53.3)	36.5 (32.0-41.1)	38.3 (32.7-45.0)	79.1 (75.7-81.7)
Western Africa	8.5 (4.9-13.0)	10.9 (6.3-17.3)	9.4 (5.5-14.4)	17.3 (9.7-28.1)	8.7 (5.0-13.2)	10.8 (6.1-16.7)	13.5 (7.1-22.2)	17.5 (13.4-23.1)	26.2 (15.2-40.3)	28.1 (22.8-34.3)	31.8 (26.4-38.1)	82.0 (78.1-85.0)
Northern Africa	30.3 (18.5-41.6)	33.9 (20.3-46.1)	32.9 (19.9-45.1)	34.8 (20.6-47.7)	32.0 (19.5-44.0)	30.9 (18.8-42.5)	33.3 (20.1-46.7)	47.0 (42.0-51.9)	45.4 (26.8-62.2)	51.8 (47.7-56.1)	50.3 (42.2-58.0)	79.2 (77.3-81.3)
<b>Asia</b>	<b>39.6</b> <b>(35.1-43.6)</b>	<b>45.8</b> <b>(40.8-50.8)</b>	<b>41.6</b> <b>(36.7-45.6)</b>	<b>45.2</b> <b>(40.5-50.4)</b>	<b>41.8</b> <b>(37.1-46.4)</b>	<b>40.6</b> <b>(36.1-44.8)</b>	<b>43.4</b> <b>(38.0-48.1)</b>	<b>46.9</b> <b>(42.3-50.9)</b>	<b>59.8</b> <b>(53.9-66.3)</b>	<b>51.9</b> <b>(47.1-56.4)</b>	<b>56.4</b> <b>(53.2-59.3)</b>	<b>80.1</b> <b>(78.9-81.2)</b>
Eastern Asia	53.8 (46.5-59.4)	61.3 (51.4-72.3)	55.2 (47.4-60.5)	55.7 (49.6-60.6)	55.7 (49.2-61.3)	54.3 (47.3-59.8)	57.0 (48.7-65.8)	59.5 (49.0-70.8)	67.9 (57.5-77.2)	63.0 (52.3-73.9)	65.6 (61.1-69.1)	79.4 (77.5-81.3)
South-Central Asia	31.3 (23.2-39.8)	38.0 (28.3-46.4)	33.7 (25.0-42.1)	40.2 (30.7-50.7)	34.3 (25.5-44.0)	32.6 (24.4-41.3)	34.8 (25.9-43.9)	38.8 (31.5-49.1)	58.4 (46.1-69.4)	43.5 (36.7-52.2)	51.5 (45.5-57.7)	80.5 (79.2-81.9)
South-Eastern Asia	28.8 (22.2-35.5)	33.6 (25.2-43.1)	30.7 (23.6-38.0)	34.0 (26.7-41.9)	30.0 (23.1-37.0)	30.1 (23.2-37.1)	34.7 (26.3-43.9)	39.0 (33.9-44.1)	46.9 (35.6-58.8)	47.2 (42.8-51.8)	48.4 (43.3-53.8)	79.3 (77.5-81.2)
Western Asia	56.7 (51.9-60.7)	58.7 (53.0-63.4)	58.5 (53.1-62.9)	58.3 (53.4-62.8)	57.8 (52.9-62.1)	56.9 (52.1-61.0)	60.5 (54.8-64.9)	63.8 (60.7-66.5)	64.5 (57.6-70.5)	68.8 (66.3-71.3)	67.1 (63.9-70.1)	81.4 (79.9-82.9)
<b>Europe</b>	<b>74.3</b> <b>(71.9-76.4)</b>	<b>75.4</b> <b>(72.9-77.5)</b>	<b>75.2</b> <b>(72.6-77.4)</b>	<b>74.9</b> <b>(72.7-76.9)</b>	<b>75.0</b> <b>(72.8-77.0)</b>	<b>74.4</b> <b>(72.0-76.4)</b>	<b>75.2</b> <b>(72.7-77.5)</b>	<b>76.6</b> <b>(74.8-78.3)</b>	<b>77.9</b> <b>(75.4-80.1)</b>	<b>77.8</b> <b>(76.0-79.3)</b>	<b>77.9</b> <b>(76.3-79.4)</b>	<b>82.2</b> <b>(81.0-83.3)</b>
Eastern Europe	65.7 (59.9-70.3)	67.4 (61.4-72.5)	67.5 (61.1-72.6)	66.9 (61.6-71.5)	67.1 (61.6-71.7)	65.9 (60.2-70.4)	67.4 (60.7-72.1)	70.4 (66.5-74.3)	72.4 (66.5-77.8)	72.6 (69.1-76.3)	72.7 (69.2-75.9)	81.3 (79.5-83.3)
Northern Europe	80.6 (78.3-82.7)	81.1 (78.9-83.3)	80.8 (78.5-82.9)	80.7 (78.6-82.8)	80.8 (78.6-82.9)	80.6 (78.3-82.7)	80.8 (78.5-82.9)	81.0 (78.7-83.1)	81.8 (79.7-83.8)	81.2 (79.0-83.4)	81.5 (79.5-83.5)	82.5 (80.4-84.6)
Southern Europe	76.2 (73.9-78.7)	77.3 (74.9-79.8)	76.9 (74.4-79.5)	76.5 (74.3-79.0)	76.6 (74.3-79.1)	76.3 (74.0-78.7)	77.2 (74.7-79.8)	78.3 (76.2-80.4)	78.8 (76.3-81.5)	79.4 (77.2-81.5)	79.1 (77.2-81.2)	82.3 (80.4-84.3)

Western Europe	81.6 (79.4-83.6)	82.2 (80.0-84.1)	81.6 (79.5-83.6)	81.8 (79.8-83.7)	81.8 (79.8-83.8)	81.6 (79.4-83.6)	81.8 (79.7-83.8)	81.7 (79.5-83.7)	82.7 (80.9-84.5)	82.0 (79.9-83.9)	82.3 (80.5-84.1)	83.2 (81.6-84.7)
<b>Latin America/ Caribbean</b>	<b>55.0 (51.2-58.7)</b>	<b>60.6 (56.2-65.3)</b>	<b>55.9 (52.3-59.5)</b>	<b>57.8 (54.3-60.7)</b>	<b>57.8 (54.3-61.4)</b>	<b>55.6 (51.8-59.3)</b>	<b>58.2 (53.8-62.6)</b>	<b>61.2 (57.0-65.6)</b>	<b>68.4 (63.9-72.7)</b>	<b>64.8 (60.1-69.7)</b>	<b>66.9 (64.6-69.3)</b>	<b>81.0 (79.5-82.5)</b>
Caribbean	45.0 (36.3-54.1)	46.4 (37.5-56.1)	47.2 (37.5-58.1)	48.7 (38.6-59.4)	46.7 (37.7-56.5)	45.4 (36.7-55.0)	48.9 (38.8-57.8)	53.4 (46.5-59.4)	56.3 (43.5-71.5)	59.3 (54.1-64.2)	58.8 (51.8-66.0)	80.7 (77.9-83.3)
Central America	45.4 (35.9-54.1)	53.0 (41.5-62.8)	46.1 (36.6-55.2)	51.7 (46.4-57.3)	49.9 (42.0-57.4)	46.4 (37.6-54.7)	50.1 (40.5-61.1)	50.9 (42.5-58.4)	66.8 (58.8-74.3)	56.0 (46.8-65.7)	61.9 (56.1-66.8)	81.6 (79.4-83.5)
South America	60.2 (54.8-64.2)	65.3 (59.5-69.7)	61.1 (56.0-65.6)	61.3 (56.5-64.8)	62.2 (56.9-66.9)	60.5 (55.2-64.5)	62.6 (56.9-67.6)	66.6 (61.1-72.5)	70.0 (65.2-75.3)	69.3 (63.7-74.2)	69.9 (66.3-72.5)	80.7 (79.0-82.6)
<b>North America</b>	<b>83.0 (81.6-84.4)</b>	<b>83.8 (82.4-85.2)</b>	<b>83.0 (81.6-84.5)</b>	<b>83.0 (81.6-84.5)</b>	<b>83.1 (81.7-84.5)</b>	<b>83.0 (81.6-84.4)</b>	<b>83.1 (81.7-84.5)</b>	<b>83.0 (81.6-84.5)</b>	<b>84.0 (82.6-85.3)</b>	<b>83.1 (81.7-84.5)</b>	<b>83.5 (82.2-84.8)</b>	<b>84.1 (82.8-85.3)</b>
<b>Oceania</b>	<b>64.4 (58.9-69.2)</b>	<b>65.3 (59.5-70.3)</b>	<b>65.2 (59.4-70.3)</b>	<b>66.2 (60.5-71.3)</b>	<b>65.8 (59.9-70.5)</b>	<b>64.7 (59.2-69.6)</b>	<b>65.4 (59.4-70.5)</b>	<b>68.5 (64.1-73.2)</b>	<b>70.6 (63.6-76.8)</b>	<b>70.4 (66.5-74.6)</b>	<b>71.1 (66.4-75.2)</b>	<b>81.5 (78.6-84.5)</b>
Oceania (Region)	19.3 (6.7-33.3)	21.6 (7.4-37.1)	22.4 (7.9-38)	23.6 (8.1-40.0)	21.4 (7.6-36.6)	20.1 (7.1-34.2)	23.0 (7.6-39.7)	35.3 (26.3-45.6)	35.4 (11.7-58.2)	42.1 (33.2-51.7)	41.2 (29.5-53.1)	78.2 (72.5-83.7)
Australia/New Zealand	79.1 (74.8-83.4)	79.6 (75.3-83.7)	79.2 (74.9-83.4)	80.1 (76.4-83.9)	80.3 (76.2-84.4)	79.3 (75.0-83.7)	79.3 (75.2-83.6)	79.4 (75.3-83.7)	82.1 (78.5-85.6)	79.6 (75.6-83.8)	80.9 (77.3-84.5)	82.6 (79.7-85.8)

\* Policy interventions are defined in Table 2

+ Comprehensive 50%/100%: Expand treatment access and improve service delivery to close the gap with mean of HIC by 50%/100%